
**IN THE HIGH COURT OF NEW ZEALAND
WELLINGTON REGISTRY**

**I TE KŌTI MATUA O AOTEAROA
TE WHANGANUI-A-TARA ROHE**

CIV-2021-485-13

UNDER THE	Judicial Review Procedure Act 2016
IN THE MATTER OF	of an application for judicial review of a decision made under the Medicines Act 1981
BETWEEN	MKD and others Applicants
AND	MINISTER OF HEALTH First Respondent
AND	GROUP MANAGER OF THE NEW ZEALAND MEDICAL DEVICES SAFETY AUTHORITY (MEDSAFE) Second Respondent
AND	MINISTER FOR COVID-19 RESPONSE Third Respondent

SECOND AFFIDAVIT OF GEORGE IAN TOWN

10 June 2022

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I, George Ian Town, of Christchurch, Chief Science Advisor, Ministry of Health,
affirm:

Introduction

1. My full name is George Ian Town. I am presently the Chief Science Advisor at the Ministry of Health.
2. I have previously affirmed an affidavit in these proceedings dated 25 January 2022 (**first affidavit**). Unless otherwise stated, this affidavit uses the same defined terms that I used in my first affidavit.
3. My first affidavit set out my opinion that the Paediatric Vaccine is both safe and effective and responded to a number of the claims made by the applicants' witnesses concerning COVID-19, the Paediatric Vaccine and the Parent Product.
4. The purpose of this affidavit is to:
 - 4.1 provide the Court with additional detail on some of the topics covered in my first affidavit (which was prepared under urgency);
 - 4.2 provide additional information on the safety and efficacy of the Paediatric Vaccine that has become available since my first affidavit; and
 - 4.3 respond to some of the points made by the applicants' expert witnesses.
5. I again confirm that I have read, understood and complied with the High Court's Code of Conduct for Expert Witnesses and that the evidence in this affidavit is within my area of expertise.

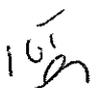
Evidence

My role as Chief Science Advisor and the ongoing review of all evidence on the safety and efficacy of the Paediatric Vaccine

6. I am the Chief Science Advisor at the Ministry of Health. My role is to help ensure that robust credible science is at the core of decision making. My work is supported by scientists within the Ministry of Health's Scientific and Technical Advisory Team. The team includes experienced immunologists and epidemiologists.



7. I, and the Ministry's Scientific and Technical Advisory Team, ensure that all emerging evidence on the safety and effectiveness of the Paediatric Vaccine, the Parent Product and other COVID-19 vaccines is kept under close review, to ensure that the advice I provide to the Director-General of Health and others remains accurate. This includes closely monitoring communiques from the World Health Organisation and other international medical bodies as well as from the relevant scientific institutions of other governments. For example, the Australian Technical Advisory Group on Immunisation (**ATAGI**), the United States Centre for Disease Control (**CDC**), the European Centre for Disease Prevention and Control, and the United Kingdom Health Security Agency.
8. The Ministry's Science and Technical Advisory Group issues a regular update on current COVID-19 variants. These updates include analysis of the current COVID-19 variants that are circulating and, amongst other matters, discusses vaccine effectiveness and therapeutic effectiveness against those variants. A copy of the most recent update, dated 23 May 2022, is exhibited at **GT-4**. A copy of the updates issued in the first part of December 2021 are attached as **GT-5**.
9. Throughout the pandemic the Ministry's Science and Technical Advisory Team has produced evidence summaries for each for each of the COVID-19 vaccines in New Zealand's portfolio. These are updated on a regular basis. Recently the Ministry has engaged an external data gathering agency to produce these summaries on a fortnightly basis. Evidence summaries are prepared adhering to the basic principles of systematic reviews, with the goal of producing unbiased summaries of all available evidence.
10. Additionally, any major studies concerning any of the COVID-19 vaccines in New Zealand's portfolio, are reviewed by me, the Ministry's Science and Technical Advisory Team and the members of CV-TAG. Any credible evidence which suggested that the risks of any COVID-19 vaccine were greater than previously known would be quickly brought to my attention. As I said in my first affidavit (at [62]), there is no risk that significant developments relating to the Paediatric Vaccine (or the Parent Product) and its safety or effectiveness are going unnoticed by me or the Ministry's



Science and Technical Advisory Team.

11. The scale at which the Paediatric Vaccine and other COVID-19 vaccines have been simultaneously rolled out in a large number of countries across the world and the number of studies in relation to the safety and effectiveness of those vaccines have given rise to a substantial volume of data. To ensure a clear view of all available evidence is being obtained, in addition to consideration of individual studies, the Ministry's Science and Technical Advisory Team consider systematically conducted, frequently updated reviews, which enables us to assess trends and patterns arising from multiple studies, so alerting us to any particular issues of repeated concern. This ensures that we do not over-rely on any one individual study.
12. I believe the system of review described above ensures that the safety and effectiveness of the Paediatric Vaccine (and other COVID-19 vaccines in New Zealand's vaccine portfolio) is subject to robust, informed discussion and review that is essential for the formulation of sound scientific advice.

CV-TAG

13. In my first affidavit (at [56] – [61]) I discuss CV-TAG and CV-TAG's December 2021 recommendation that the Government expand the COVID-19 vaccine rollout to include the Paediatric Vaccine for children aged five to 11. To help facilitate CV-TAG's consideration detailed advice was provided to the Group from the Ministry's Science and Technical Advisory Group. This document is referred to as a "Request for Advice" or "RFA". Drafts of this advice were provided to CV-TAG on 23 November, 30 November, 7 December, and 14 December 2021. A copy of the final version of that advice is exhibited at **GT-6**.
14. CV-TAG was established during the pandemic to provide science advice on all aspects of the COVID-19 vaccine rollout in New Zealand. There are currently 14 members of CV-TAG. I am the only member of CV-TAG working for the Ministry of Health. All other members are practising medical practitioners and/or academics with a range of specialities including immunology, vaccinology and paediatrics. Members include professors from the University of Otago, University of Auckland, University of

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Queensland, the Chair of the Immunisation Subcommittee of the Pharmacology and Therapeutics Advisory Committee, the Medical Director of the Immunisation Advisory Centre and several paediatricians and general practitioners.

Formal review of safety data in February 2022

15. As discussed in my first affidavit at [61], as part of ongoing monitoring, CV-TAG was to undertake a formal review of the safety data for the Paediatric Vaccine and to report back on our findings in February 2022. CV-TAG undertook this formal review and met on 1, 8 and 15 February 2022 to consider the available data. Following which, I, and the other members of CV-TAG, were satisfied that the Paediatric Vaccine was safe and confirmed our previous recommendation that children aged 5 to 11 should have at least eight weeks between their first and second doses.
16. As part of that review, CV-TAG considered the real-world safety data collected from over 8 million doses of the Pfizer vaccine that had been administered to children in the United States and were satisfied that no significant safety concerns had been identified. The data available from the United States did identify that VAERS had received two reports of death from children following administration of the Paediatric Vaccine. Both children had complicated medical histories and were in a fragile health before vaccination and none of the available data suggested a causal association between death and vaccination.
17. CV-TAG also considered the preliminary unpublished data available from Medsafe about reports to CARM following administration of the Paediatric Vaccine. At that time Medafe indicated there had been 352 adverse events following immunisation reported from 17 January to 30 January 2022. Of these 341 were classified as non-serious. Of those 11 other cases, six were reported as recovered or recovering, one was ongoing, and four had unknown outcome. Only one of the 11 was admitted to hospital for observation (no evidence of myocarditis but was reporting chest discomfort).
18. CV-TAG had also been advised by Medsafe, who is in regular contact with

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other regulators overseas, that none of those regulators had drawn their attention to anything of concern regarding the safety profile of the Paediatric Vaccine.

19. I reported on the outcome of CV-TAG's review by a memorandum to the Director-General of Health dated 16 February 2022. A copy of that memorandum is exhibited as **GT-7**

Severely immunocompromised 5 to 11 year olds

20. In March 2022, CV-TAG considered whether a third primary dose of the Paediatric Vaccine should be made available for severely immunocompromised 5 to 11 year olds. At this time some other jurisdictions (Australia, Canada, the United Kingdom and the United States) were already recommending that severely immunocompromised children receive a third primary dose of the COVID-19 vaccine, in line with other severely immunocompromised age cohorts. To help facilitate CV-TAG's consideration detailed advice was provided to the Group from the Ministry's Science and Technical Advisory Group. A copy of that advice is exhibited at **GT-8**.
21. On 22 March 2022, CV-TAG recommended that those aged 5 to 11 years old who are severely immunocompromised should be offered a third primary dose of the Paediatric Vaccine. A copy of that advice is exhibited as **GT-9**.

COVID-19 Vaccine Independent Safety Monitoring Board

22. The COVID-19 Vaccine Independent Safety Monitoring Board (**CV-ISMB**) is another COVID-19 focused group/committee that I have been involved with during the pandemic. Until February of this year, I was an ex-officio member of CV-ISMB but have since delegated that role to the Clinical Lead of the National Immunisation Programme, Dr Juliet Rumball-Smith.
23. CV-ISMB is an independent board that meets regularly to review and discuss the safety data for all COVID-19 vaccines, including the Parent Product and the Paediatric Vaccine. A copy of the CV-ISMB's interim report on adverse events reported in 2021 is exhibited as **GT-10**.

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Further evidence on the effects of COVID-19 on 5 to 11 year olds (disease burden)

24. In my first affidavit (at [15] – [36]) I discuss the effects of COVID-19 on 5 to 11 year olds. Since my first affidavit, evidence continues to emerge on the effects of COVID-19 on 5 to 11 year olds.

Omicron in New Zealand

25. At the time of writing my first affidavit, Omicron had just been detected in the community in New Zealand. Since then there has been a widespread outbreak of Omicron, with more than a million confirmed cases.¹ The number of confirmed cases contrasts starkly to the position in New Zealand before the arrival of Omicron, where less than 15,000 cases of COVID-19 had been confirmed over 2020 and 2021 combined.²

26. With the significant increase in cases, there has also been a significant increase in the number of deaths reported from COVID-19. At the time of writing my first affidavit 52 people were reported as dying with COVID-19 since the first case of COVID-19 in New Zealand (acknowledging that in some of these cases, the underlying cause of death may be unrelated to COVID-19). This contrasts starkly with the number of reported deaths with COVID-19 while Omicron has been in the New Zealand community.

27. As at 25 May 2022, 1057 people are reported to have died with COVID-19 (this includes the 52 people mentioned in my first affidavit).³ In some of those cases the underlying cause of death is unrelated to COVID-19. The Ministry of Health is undertaking an ongoing process of formally coding whether COVID-19 was the cause or contributing factor of death or whether COVID-19 was unrelated. On 18 May 2022, the Ministry of Health released an update on this process, noting as at the morning of 18 May 2022:⁴

27.1 447 people have died with COVID-19 as the underlying cause of

¹ As at 8 June 2022, 1,221,724 cases have been confirmed (<https://www.health.govt.nz/covid-19-novel-coronavirus/covid-19-data-and-statistics/covid-19-current-cases>).

² <https://www.health.govt.nz/covid-19-novel-coronavirus/covid-19-data-and-statistics/covid-19-source-cases-2020-and-2021>

³ <https://www.health.govt.nz/covid-19-novel-coronavirus/covid-19-data-and-statistics/covid-19-current-cases>

⁴ “COVID-19 deaths reporting update”, 18 May 2022 (available here: <https://www.health.govt.nz/news-media/news-items/covid-19-deaths-reporting-update>).

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- death;
- 27.2 231 people have died with COVID-19 as a contributing cause of death;
- 27.3 161 people had a cause of death unrelated to COVID-19; and
- 27.4 138 people who died within 28 days of being a reported case of COVID-19 had yet to be classified.
28. These statistics evidence that any suggestion the Omicron variant only causes a mild infection is inaccurate. The position is more complex. The Omicron variant is highly transmissible. People can and do develop severe disease from Omicron and in some cases Omicron is fatal.
29. Looking at the impact on children and adolescents specifically, in New Zealand, as at 8 June 2022, since 16 August 2021 there has been:⁵
- 29.1 140,396 confirmed cases of COVID-19 amongst 0 to 9 year olds, with 878 of those cases hospitalised; and
- 29.2 207,100 confirmed cases of COVID-19 amongst 10 to 19 year olds with 717 of those cases hospitalised.
30. The overwhelming majority of these infections and hospitalisations occurred during the current Omicron wave.
31. Since the first case of COVID-19 in New Zealand in March 2020, as at 8 June 2022:⁶
- 31.1 0 – 9 year olds make up 11.5% of all confirmed COVID-19 cases in New Zealand;
- 31.2 10 to 19 year olds make up 17% of all confirmed COVID-19 cases in New Zealand;
- 31.3 20 to 29 year olds make up 18.6% of all confirmed COVID-19 cases in New Zealand;

⁵ <https://www.health.govt.nz/covid-19-novel-coronavirus/covid-19-data-and-statistics/covid-19-case-demographics>

⁶ <https://www.health.govt.nz/covid-19-novel-coronavirus/covid-19-data-and-statistics/covid-19-case-demographics#hospitalisations>

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- 31.4 30 to 39 year olds make up 17.6% of all confirmed COVID-19 cases in New Zealand;
- 31.5 40 to 49 years olds make up 14.4% of all confirmed COVID-19 cases in New Zealand;
- 31.6 50 to 59 year olds make up 10.5% of all confirmed COVID-19 cases in New Zealand;
- 31.7 60 to 69 year olds make up 6.2% of all confirmed COVID-19 cases in New Zealand;
- 31.8 70 to 79 year olds make up 2.9% of all confirmed COVID-19 cases in New Zealand;
- 31.9 80 to 89 year olds make up 1.1% of all confirmed COVID-19 cases in New Zealand; and
- 31.10 those aged 90 and older make up 0.3% of all confirmed COVID-19 cases in New Zealand.
32. Since the first case of COVID-19 in New Zealand in March 2020, four children aged between 0 to 9 have died with COVID-19 and four adolescents aged between 10 to 19 have died with COVID-19.⁷
33. For the data above, I have not included some data to protect privacy. For examples, for the eight children/adolescents aged 0 to 19 who have died with COVID-19, I have not specified whether it is known if COVID-19 was the underlying cause or contributory cause of death. I have not provided this detail as the Ministry's approach is not to reveal data on cases or deaths when disclosure of that data could identify a specific individual and breach their privacy or their family's privacy. I can confirm that some of the publicly notified deaths in the 0 to 9 age bracket are yet to be classified and some of the deaths in the 10 to 19 age bracket have been classified as "COVID as contributory".

⁷ <https://www.health.govt.nz/covid-19-novel-coronavirus/covid-19-data-and-statistics/covid-19-case-demographics#age-gender>

Internationally

34. Internationally, COVID-19 is continuing to spread, with Omicron the predominant variant. Data from UNICEF is that as at March 2022, among the 3.7 million COVID-19 deaths reported globally, 0.4% (over 13,400) occurred in children and adolescents under 20 years of age.⁸ With 58% of those deaths occurring among adolescents aged 10 to 19 and 42% occurring among children aged 0 to 9.
35. Data from the United States shows that children aged 5 to 11 years can suffer from severe disease from Omicron. During the peak of the winter Omicron outbreak in the United States (December 2021 and February 2022), weekly hospitalization rates of children aged 5 to 11 years peaked during the week ending 22 January 2022.⁹ At that time 2.8 per 100,000 children aged 5 to 11 years old were hospitalized with COVID-19 in the United States. This was 2.3 times higher than the peak during the Delta outbreak (which peaked at 1.2 per 100,000 children aged 5 to 11 years old).¹⁰ Among children who were hospitalized during the Omicron-predominant period in the United States, 19% required ICU admission, including 15% with no underlying medical conditions.¹¹ A copy of the CDC's report on this data is attached as **GT-11**.
36. As at 25 May 2022, the CDC reports that 359 5 to 11 year olds have died with COVID-19 in the United States.¹²
37. As at 2 June 2022, in Australia, eight children aged 0 to 9 and six children/adolescents aged 10 to 19 have been reported as a COVID-19 associated death.¹³

⁸ <https://data.unicef.org/topic/child-survival/covid-19/>

⁹ Shi DS, Whitaker M, Marks KJ, et al. Hospitalizations of Children Aged 5–11 Years with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 2020–February 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:574-581 (available here: https://www.cdc.gov/mmwr/volumes/71/wr/mm7116e1.htm?s_cid=mm7116e1_w).

¹⁰ Shi DS, Whitaker M, Marks KJ, et al. Hospitalizations of Children Aged 5–11 Years with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 2020–February 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:574-581 (available here: https://www.cdc.gov/mmwr/volumes/71/wr/mm7116e1.htm?s_cid=mm7116e1_w).

¹¹ Shi DS, Whitaker M, Marks KJ, et al. Hospitalizations of Children Aged 5–11 Years with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 2020–February 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:574-581 (available here: https://www.cdc.gov/mmwr/volumes/71/wr/mm7116e1.htm?s_cid=mm7116e1_w).

¹² "Demographic Trends of COVID-19 cases and deaths in the US reported to CDC" (United States) (available here: https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html#demographics).

¹³ "Coronavirus (COVID-19) case numbers and statistics" (Australia) (available here: <https://www.health.gov.au/health-alerts/covid-19/case-numbers-and-statistics#cases-and-deaths-by-age-and-sex>).

38. In the United Kingdom, for the period from 1 March 2021 to 28 February 2022:¹⁴
- 38.1 less than 10 children aged 5 to 9 died within 60 days of a laboratory-confirmed case of COVID-19; and
- 38.2 75 children/adolescents aged 10 to 19 died within 60 days of a laboratory -confirmed case of COVID-19.

Updated evidence on the safety and efficacy of the Paediatric Vaccine

39. In my first affidavit (at [40] – [49]) I discuss the safety and efficacy of the Paediatric Vaccine. Since my first affidavit, evidence continues to emerge demonstrating that the Paediatric Vaccine is safe and effective.

Vaccine effectiveness against Omicron

40. A pre-print study by the New York State Department of Health (dated 25 February 2022) found that effectiveness of the paediatric vaccine against COVID-19 infection was 12% for 5 to 11 year olds (observed during the Omicron wave (13 December 2021 to 30 January 2022)).¹⁵ The pre-print study is mentioned in the RFA provided to CV-TAG in March 2022 (attached as exhibit **GT-8**). The focus of the study was on vaccine effectiveness against infection (in relation to Omicron). Vaccine effectiveness against hospitalisation and severe disease was significantly higher (which is notable as protection against severe disease is the primary goal of immunisation). The authors of that study conclude that the paediatric vaccine for 5 to 11 year olds was protective against severe disease. I note the study has since been peer reviewed and published and no longer provides any statements about vaccine effectiveness (but the underlying data is still provided).¹⁶
41. In the United States, on 19 May 2022, the Advisory Committee on

¹⁴ “COVID-19 confirmed deaths in England (to 28 February 2022): report” (available here: <https://www.gov.uk/government/publications/covid-19-reported-sars-cov-2-deaths-in-england/covid-19-confirmed-deaths-in-england-to-28-february-2022-report>).

¹⁵ Dorabawila V, Hoefler D, Bauer UE, Bassett MT, Lutterloh E, Rosenberg ES, Effectiveness of the BNT162B2 vaccine among children 5-11 and 12-17 years in New York after the emergency of the Omicron variant, 28 February 2022 (available here: <https://www.medrxiv.org/content/10.1101/2022.02.25.22271454v1>). This article is a preprint.

¹⁶ Dorabawila V, Hoefler D, Bauer UE, Bassett MT, Lutterloh E, Rosenberg ES. Risk of Infection and Hospitalization Among Vaccinated and Unvaccinated Children and Adolescents in New York After the Emergence of the Omicron Variant. *JAMA*. Published online May 13, 2022 (available here: <https://jamanetwork.com/journals/jama/fullarticle/2792525>).

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Immunisation Practices (**ACIP**) COVID-19 Vaccines Work Group released an update on the safety of COVID-19 vaccines for children aged 5 to 11. The ACIP COVID-19 Vaccines Work Group is a working group within the CDC.

42. On vaccine effectiveness against the Omicron variant, the ACIP COVID-19 Vaccines Work Group reported the following in relation to the Paediatric Vaccine's effectiveness in children aged 5 to 11:¹⁷
 - 42.1 Infections were reduced by 43% in vaccinated compared to unvaccinated 5 to 11 year olds in the first two months after vaccination. This appears to reduce with time, but it is not yet clear how rapidly. This is nevertheless a meaningful protection against infection.
 - 42.2 Symptomatic infections were reduced by 60% in vaccinated compared to unvaccinated 5 to 11 year olds in the first month after vaccination. This reduced to around 30% in the subsequent two months. No data beyond two months after vaccination were available in the reported study to assess how rapidly waning occurs after two months. However, it likely follows the pattern seen in adults against symptomatic infection, with continued waning in effectiveness.
 - 42.3 Hospitalisations were reduced by 68% in vaccinated compared to unvaccinated 5 to 11 year olds (and 74% in a second study, but confidence intervals were wide around this estimate and the analysis included non-omicron variants which made up around one third of the cases). There wasn't yet enough data available to assess the waning of the vaccine effectiveness against hospitalisation in this age group. If following the trajectory for severe diseases as seen in adults, waning of vaccine effectiveness against severe disease would be slower than waning of vaccine effectiveness against infections.
43. A copy of the ACIP COVID-19 Vaccines Work Group' update is exhibited as

¹⁷ ACIP, COVID-19 vaccine effectiveness during Omicron for children and adolescents, 19 May 2022 (available here: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-05-19/02-COVID-Link-Gelles-508.pdf>).

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GT-12.

44. I also attach at **GT-13** a copy of a recent study in the United States that discusses in detail vaccine effectiveness against hospitalisations in relation to Omicron among children aged 5 to 11. That study found the Paediatric Vaccine was 68% effective at preventing hospitalisations in that age group.
45. These findings are all consistent with the Parent Product, with studies indicating that the effectiveness of the Parent Product after completion of the primary course wanes and is lower against Omicron than Delta but it does still provide protection.¹⁸ It is important to note that if, for example, vaccine effectiveness against severe disease is 50% that means hospitalisations have been halved. This is a substantial and meaningful reduction and of great benefit to individual and public health in New Zealand.

Safety of the Paediatric Vaccine

46. Emerging evidence since my first affidavit has not identified any significant safety concerns with the Paediatric Vaccine.

New Zealand

47. In New Zealand, as at 7 June 2022, 263,265 first doses and 126,282 second doses of the Paediatric Vaccine have been administered.¹⁹ In total this is in excess of 385,000 doses. As at 30 April 2022, 776 adverse events have been reported to the CARM.²⁰ The overwhelming majority of these adverse events are not serious. As at 30 April 2022, there were no cases in New Zealand where myocarditis or pericarditis has been medically confirmed in a child between 5 to 11 years following immunisation with the Paediatric Vaccine or where the Paediatric Vaccine has been identified as the cause or contributing factor in the death of a child between 5 and 11 years.

United States

48. On 19 May 2022, the ACIP COVID-19 Vaccines Work Group reported, while

¹⁸ A M Price, S M Olson, M M Newhams et al, BNT162b2 Protection against the Omicron Variant in children and Adolescents, 19 May 2022, N Engl J Med 2022; 386:1899-1909 (available here: <https://www.nejm.org/doi/full/10.1056/NEJMoa2202826>).

¹⁹ <https://www.health.govt.nz/covid-19-novel-coronavirus/covid-19-data-and-statistics/covid-19-vaccine-data>

²⁰ "Adverse events following immunisations with COVID-19 vaccines: Safety Report #43 – 30 April 2022" (available here: <https://www.medsafe.govt.nz/COVID-19/safety-report-43.asp>).

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discussing the safety and efficacy of the Paediatric Vaccine, that as at 24 April 2022:²¹

- 48.1 18,182,496 million doses of the Paediatric Vaccine had been administered in the United States;
 - 48.2 9001 reports of adverse reactions were made to VAERS in relation to the Paediatric Vaccine;
 - 48.3 97% of those reports to VAERS were non-serious, with several thousand of those reports relating to issues with vaccinators preparing and administering the Paediatric Vaccine rather than a clinical response to the vaccine;
 - 48.4 3% of the reports to VAERS are classified as severe adverse events, the most common of which was fever (84 reports), vomiting (54 reports) and Multisystem Inflammatory Syndrome (45 reports);
 - 48.5 20 children aged 5 to 11 suffered myocarditis after receiving the Paediatric Vaccine. 17 of those children were hospitalised with 14 having recovered as at 24 April 2022; and
 - 48.6 One child died 13 days after receiving their first dose of the Paediatric Vaccine with histopathological evidence of myocarditis on autopsy. This death is still under review by the CDC. As I noted in my first affidavit (at [49]), bodies like the CDC that monitor safety are conservative and cautious and will take their time to do a thorough review, so final assessment of this child's cause of death will take some time.
49. It is important to note that just because an adverse event is reported to VAERS (or any other similar spontaneous reporting system) does not mean that there is a causal link between the event and the vaccine. For example, I am not aware that there have been any proven cases of MIS-C following vaccination. There is one patient in the United States who presented with MIS-C who had no evidence of past or recent infection with COVID-19 but

²¹ ACIP, COVID-19 vaccine safety updated: primary series in children ages 5 – 11 years, 19 May 2022 (available here: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-05-19/03-COVID-Shimabukuro-508.pdf>).

had received two doses of the Comirnaty vaccine 12 and 8 weeks prior, raising the possibility that MIS-C was related to their vaccination.²² The patient has since recovered.

Australia

50. In Australia, as at 29 May 2022, 1,460 adverse events have been reported from the more than 1.9 million doses of the Paediatric Vaccine and the Moderna COVID-19 vaccine that have been administered to 5 to 11 year olds.²³ The most common reactions reported included chest pain, vomiting, fever, headache and abdominal pain. 33 reports of suspected myocarditis and/or pericarditis have been made, with four of those determined to likely represent myocarditis and six of those determined to likely represent pericarditis.²⁴

Update on international rollout of the Paediatric Vaccine

51. New Zealand is not the only country rolling out the Paediatric Vaccine. In my first affidavit (at [50] – [51]), I discussed the international vaccination of children over five years of age against COVID-19, noting in particular approximately 42 countries, including New Zealand, had approved and/or started vaccinating children over the age of five years against COVID-19 and that New Zealand's approach aligned with Australia where the rollout of the Paediatric Vaccine commenced on 10 January 2022. To the best of my knowledge no countries have stopped the rollout of the Pfizer Paediatric Vaccine.
52. I discuss below briefly, by way of example only, the rollout of the Paediatric Vaccine in the United States, the United Kingdom, Australia and Canada to illustrate examples of other countries with similarly rigorous regulatory processes who are rolling out the Paediatric Vaccine to give a snapshot of the volume of paediatric doses administered worldwide. I also discuss the situation in Sweden and Denmark which was commented on by the

²² Wangu Z, Swartz H, Doherty M, Multisystem inflammatory syndrome in children (MIS-C) possibly secondary to COVID-19 mRNA vaccination, *BMJ Case Reports CP* 2022;15:e247176 (available here: <https://casereports.bmj.com/content/15/3/e247176>).

²³ "COVID-19 vaccine weekly safety report" (Australia) (available here: <https://www.tga.gov.au/periodic/covid-19-vaccine-weekly-safety-report-02-06-2022#vaccine-safety-in-children-and-adolescents>).

²⁴ "COVID-19 vaccine weekly safety report" (Australia) (available here: <https://www.tga.gov.au/periodic/covid-19-vaccine-weekly-safety-report-02-06-2022#vaccine-safety-in-children-and-adolescents>).

applicants' witnesses.

United States

53. I have discussed the rollout of the Paediatric Vaccine in the United States above at [35], [36], [40] – [44] and [48]. As noted above at [48.1], more than 18 million doses of the Paediatric Vaccine have been administered in the United States as at 24 April 2022.

United Kingdom

54. In my first affidavit (at [77] – [79]), I discussed the rollout of the Paediatric Vaccine in the United Kingdom. At the time of my first affidavit the JCVI only recommended medically vulnerable children and children who are household contacts of immunosuppressed people get the Paediatric Vaccine in the United Kingdom. The JCVI provides advice to UK health departments on immunisations (akin to the role of ATAGI). As I noted in my first affidavit, Medsafe's equivalent in the United Kingdom, the Medicines and Healthcare Regulatory Agency, had approved the use of the Paediatric Vaccine for all five to 11 years. It was only the JCVI recommendation that the Paediatric Vaccine rollout be limited to certain high-risk children in that age group.

55. On 16 February 2022 the JCVI provided updated advice, recommending that the Paediatric Vaccine be made available to all children aged 5 to 11.²⁵ Adopting that advice, the Paediatric Vaccine is now available to all children aged 5 to 11 in the United Kingdom. As at 1 June 2022, 456,918 doses of the Paediatric Vaccine have been administered in the United Kingdom.²⁶

Australia

56. In Australia, the Paediatric Vaccine has been available since 10 January 2022. As at 26 May 2022, more than 1.9 million doses of the Paediatric Vaccine and the Moderna COVID-19 vaccine have been administered in Australia in 5 to 11 year olds.²⁷

²⁵ JCVI statement on vaccination of children aged 5 to 11 years (UK), 16 February 2022 (available here: <https://www.gov.uk/government/publications/jcvi-update-on-advice-for-covid-19-vaccination-of-children-aged-5-to-11/jcvi-statement-on-vaccination-of-children-aged-5-to-11-years-old>).

²⁶ <https://www.england.nhs.uk/statistics/statistical-work-areas/covid-19-vaccinations/>

²⁷ https://www.health.gov.au/sites/default/files/documents/2022/05/covid-19-vaccine-rollout-update-26-may-2022_0.pdf

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57. The decision in Australia to rollout the Paediatric Vaccine was informed by a recommendation from ATAGI (following the Therapeutic Goods Administration provisionally approving the vaccine). ATAGI, amongst other matters, provides advice to the Minister for Health on the administration of vaccines available in Australia. During the COVID-19 pandemic that role has included providing advice on all aspects of Australia's COVID-19 immunisation programme. ATAGI recommended the use of the Paediatric Vaccine in children aged 5 to 11 in Australia in December 2021. This advice was updated on 21 February 2022 to, amongst other matters, recommend that a third primary dose of the Paediatric Vaccine be available for children aged 5 to 11 years who are severely immunocompromised. A copy of the updated ATAGI advice is exhibited as **GT-14**.²⁸

Canada

58. In Canada, the Paediatric Vaccine was approved for use on 19 November 2022 and has been available since late November 2021. As at 8 May 2022, more than 1.2 million doses of the Paediatric Vaccine have been administered in Canada.²⁹ Canada's decision to rollout the Paediatric Vaccine was informed by a recommendation of the National Advisory Committee on Immunisation, issued on 19 November 2021.³⁰ A copy of that recommendation is exhibited as **GT-15**.

Sweden and Denmark

59. One of the applicants' witnesses, Dr Philip Altman (at [182] and [183] of his affidavit) discusses that the Swedish drug regulator decided against recommending COVID-19 vaccines for children aged 5 to 11 in Sweden and that in Denmark the COVID-19 vaccination programme has been suspended. There are a couple of observations I want to make about these decisions.
60. First, in Sweden the decision was not to initiate a general rollout of COVID-

²⁸ ATAGI recommendations on the use of the paediatric vaccine in children aged 5 to 11 years in Australia (available here: <https://www.health.gov.au/sites/default/files/documents/2022/02/atagi-recommendations-on-pfizer-covid-19-vaccine-use-in-children-aged-5-to-11-years.pdf>).

²⁹ <https://health-infobase.canada.ca/covid-19/vaccination-coverage/>

³⁰ Recommendation on the use of the Pfizer-BioNTech COVID-19 vaccine (10mcg) in children 5-11 years of age (Canada (available here: <https://www.canada.ca/content/dam/phac-aspc/documents/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines/pfizer-biontech-10-mcg-children-5-11-years-age/pfizer-biontech-10-mcg-children-5-11-years-age.pdf>).

19 vaccines for children under 12 years of age. It was not a decision to pause an existing rollout to that age group. That decision was made in the context of COVID-19 in Sweden where there has been widespread outbreak of COVID-19 for some time and where Sweden's response to the pandemic has often diverged from other countries. It should be noted that since 21 December 2021, children aged 5 to 11 who are at high risk of suffering severe disease from COVID-19 infection have been recommended by the Swedish drug regulator to receive a COVID-19 vaccination.³¹

61. Second, Denmark has recently paused its general COVID-19 vaccination programme to all age groups. This decision to pause was made because of Denmark's high vaccine coverage and that coming into spring, the epidemic was judged to be under control in Denmark.³² The decision was not made because of a safety concern of any of the COVID-19 vaccines in Denmark's vaccine portfolio. The effect of the pause is that formal vaccination invitations are no longer being sent out but COVID-19 vaccines are still available to anyone who wishes to receive a vaccine. In particular, the Danish drug regulator still recommends that people complete their started vaccination course.³³ The Danish drug regulator has also indicated the formal COVID-19 vaccination programme will resume in autumn.³⁴ It should be noted that the Paediatric Vaccine has been available for children aged 5 to 11 in Denmark since the end of November 2021.³⁵

Update on Omicron

62. When the Paediatric Vaccine was given provisional consent and Cabinet subsequently decided to make the Paediatric Vaccine available in New Zealand, Delta was the prevalent variant. Omicron had only recently been detected in South Africa and was not yet in New Zealand.

³¹ <https://www.reuters.com/world/europe/swedish-health-agency-recommends-covid-shots-some-5-11-year-olds-2021-12-21/>

³² <https://abcnews.go.com/Health/denmark-announces-temporarily-pausing-covid-vaccination-campaign/story?id=84369102>

³³ <https://apnews.com/article/fact-checking-541482118776>

³⁴ <https://abcnews.go.com/Health/denmark-announces-temporarily-pausing-covid-vaccination-campaign/story?id=84369102>

³⁵ <https://www.sst.dk/en/english/news/2021/vaccination-of-5-11-year-old-children-is-to-help-stop-infection>

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63. Since Omicron was first detected in South Africa in November 2021, it has become the dominant COVID-19 variant circulating globally. Like other variants, the Omicron variant (B.1.1.529) comprises a number of lineages and sub-lineages (generally referred to as subvariants). Variant BA.1 was responsible for the initial Omicron surge seen globally in December 2021 and January 2022. This has now been replaced by variant BA.2 as the predominant subvariant.³⁶
64. The emerging data to date indicates that hospitalisations and death rates are lower with Omicron than Delta, taking into account vaccination status and the risk for severe disease. However, as discussed above people and children are still suffering severe COVID-19 from Omicron infection. In particular, there remains a higher risk of severe disease in the unvaccinated, as noted by the World Health Organisation in its weekly COVID-19 update published on 12 April 2022:³⁷

Unlike previous waves, the most recent wave due to Omicron can be characterized by a decoupling between the number of cases, hospitalizations (particularly for intensive care) and deaths in many countries. However, data continue to show that those who are unvaccinated remain at higher risk of severe disease following infection with Omicron as compared to those who have been vaccinated. Despite the reduction in severity, the massive increases in cases with Omicron have led to large numbers of hospitalizations, putting further pressure on the healthcare systems, and in some countries, similar or high numbers of deaths when compared to previous peaks.

65. Looking at the BA.2 subvariant in particular, a Hong Kong study of an uninfected and unvaccinated population of children, investigated the severity of BA.2.³⁸ The study investigated severe outcomes among 1,147 children aged 11 and younger who were hospitalised between 5 February

³⁶ World Health Organisation, COVID-19 Weekly Epidemiological Update (published 18 May 2022). Available here: file:///C:/Users/andersonk/Downloads/20220518_Weekly_Epi_Update_92.pdf

³⁷ World Health Organisation, COVID-19 Weekly Epidemiological Update (published 12 April 2022). Available here: file:///C:/Users/andersonk/Downloads/20220412_Weekly_Epi_Update_87.pdf

³⁸ Tso, W., et al. *Intrinsic Severity of SARS-CoV-2 Omicron BA.2 in Uninfected, Unvaccinated Children: A Population-Based, Case-Control Study on Hospital Complications*. 2022 21 Mar 2022.

and 28 February 2022 (a BA.2 dominant period). The authors of the study concluded that the intrinsic severity of BA.2 in children who had no past COVID-19 infection or vaccination is not mild.

66. Two new variants within the Omicron lineage have recently been identified, BA.4 and BA.5, and their presence in the New Zealand community was first reported on 3 June 2022. Data is limited on BA.4 and BA.5. Preliminary evidence from overseas has indicated that the presence of subvariants BA.4 and BA.4 in the community appears to be resulting in an increase in the number of cases.³⁹ However, given the current low prevalence of BA.4 and BA.5 it is unknown whether these subvariants have different disease characteristics or severity to other Omicron subvariants.
67. The emergence of these subvariants illustrates that the COVID-19 pandemic is continuing to evolve. All emerging evidence on COVID-19 and the effectiveness and safety of COVID-19 vaccines is subject to robust and regular review by myself, the Ministry's Scientific and Technical Advisory Team and CV-TAG. If there was any robust emerging evidence that raised material concerns about the efficacy or safety of the Paediatric Vaccine, I would advise the Director-General of Health accordingly, so that any necessary decisions on the inclusion of the Paediatric Vaccine in the national COVID-19 Immunisation Programme could be made.

Applicants' claims

68. I have read the applicants' amended statement of claim and the affidavits of Dr Peter McCullough, Dr Simon Brown (April 2022 affidavit), Dr Geert Vanden Bossche, Dr Phillip Altman and Professor Nikolai Petrovsky (reply affidavit of January 2022). This is in addition to the affidavits I read prior to giving my first affidavit. As I said in my first affidavit, I am familiar with the types of views and concerns these witnesses raise. Their views represent a very small minority of scientific opinion particularly when viewed in the light of the significant number of well-regarded scientific bodies and organisations in favour of providing COVID-19 vaccines to 5 to 11 year olds. Nothing in the aforementioned affidavits nor the affidavits I read prior to

³⁹ World Health Organisation, COVID-19 Weekly Epidemiological Update (published 18 May 2022) (available here: file:///C:/Users/andersonk/Downloads/20220518_Weekly_Epi_Update_92.pdf).

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my first affidavit makes me concerned about the rollout of Paediatric Vaccine in New Zealand.

69. I respond below to some of the key points raised by the applicants' witnesses to the extent that they are not already addressed by my preceding comments or my first affidavit. The fact that I do not respond to a particular point made by the applicants' witnesses does not mean that I agree with it.

mRNA technology and development of the Comirnaty vaccines

70. The applicants' experts raise concerns that mRNA technology is new and untested, and that the Comirnaty vaccine has been developed too quickly. I note in particular the comments of Dr Altman at [21] – [23] and [48] of his affidavit and Professor Petrovsky at [51] – [62] of his first affidavit.
71. It is true that COVID-19 vaccines are the first widely administered vaccines to be based on mRNA technology. But mRNA technology for vaccines is not new. It has been studied for decades. I attach as **GT-16** a 2018 article discussing the development of mRNA vaccines. This article notes that a number of recent reports had demonstrated the potency and versatility of mRNA to protect against a wide variety of infectious pathogens, including influenza virus, Ebola virus, and Zika virus.
72. There are a number of advantages with mRNA vaccines as compared with vaccines based on live attenuated viruses: mRNA is non-infectious, it is a non-integrating platform; mRNA is degraded by normal cellular processes; and it is easier to manufacture large quantities quickly.
73. The time taken for a pharmaceutical company to develop a new medicine and bring it to market will be dependent on a number of factors, including the level of investment and how much priority that potential medicine is given. At [46] of his affidavit Dr Altman refers to a publication by Young et al about the length of time taken to develop vaccines, suggesting that it usually takes about seven years to develop a conventional vaccine. The point that this paper appears to be making is that there is a lack of investment for developing vaccines for non-first world disease. Following the outbreak of the COVID-19 pandemic, there has been a huge

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international scientific effort and financial investment in the development of safe and effective COVID-19 vaccines. You would expect that vaccine development would take a shorter amount of time if significant investment and effort is made over that time.

Messenger RNA vaccines are not a gene therapy

74. The applicants' evidence suggests that the Paediatric Vaccine, and all mRNA vaccines are a gene therapy, claiming that this results in permanent changes to a person's DNA that is passed down generations. Noting in particular the comments of Dr Vanden Bossche at [11] – [13] and Dr Altman at [20] – [27].
75. I disagree. Messenger RNA vaccines, like the Paediatric Vaccine, are not gene therapies. They do not alter a person's genes.
76. A gene therapy is a technique that modifies a person's genes to treat or cure disease.⁴⁰ It involves making deliberate changes to a person's DNA in order to treat or cure a particular disease.⁴¹ Gene therapies can work in several ways:
- 76.1 Replacing a disease-causing gene with a healthy copy of the gene.
- 76.2 Inactivating or disabling a disease-causing gene that is not functioning properly.
- 76.3 Introducing a new or modified gene into the body to help treat a disease.
77. If a person has a disease caused by a mutation of a gene (i.e. cystic fibrosis) then to treat that disease gene therapy can be used by replacing the disease causing gene with a healthy copy of that gene.
78. This is not what mRNA vaccines do. They do not change a person's genetic makeup. COVID-19 mRNA vaccines teach a person's cells how to make a protein that will trigger an immune response inside that person's body when exposed to the COVID-19 virus. They do not enter the nucleus of a

⁴⁰ "What is a gene therapy?" FDA (available here: <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy>).

⁴¹ "What is a gene therapy?" FDA (available here: <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy>).

human cells nor does the vaccine interact with a person's DNA.

79. Some types of virus like the influenza virus are transported into the nucleus. Those viruses have proteins (called ribonucleoproteins) associated with their genome that help transport their genomic RNA into the nucleus.⁴² The mRNA from the Parent Product and the Paediatric Vaccine do not have any of these proteins.

Messenger RNA contained in the Comirnaty vaccines cannot be reverse transcribed into DNA

80. Dr Altman refers to a recent paper raising the theoretical possibility that the mRNA contained in the Comirnaty vaccines could be reverse transcribed into DNA (see his comments at [179] of his affidavit).
81. The point raised by Dr Altman, and the paper he refers to, is only a theoretical concern. There is no credible evidence to support this theoretical concern. Messenger RNA does not transcribe back into DNA.
- 81.1 The only known mechanism by which RNA can integrate into the host genome requires the presence of a complex containing reverse transcriptase and integrase. These are not present in the mRNA for the Parent Product or Paediatric Vaccine.
- 81.2 Another reason is geography. Messenger RNA is in an entirely separate compartment of a cell from the DNA with no simple means to get to it.
- 81.3 The mRNA in the Parent Product and Paediatric Vaccine degrades within a relatively short time once taken up by the body's cells, as does the cell's own mRNA. During that entire time, the mRNA vaccine remains in the cytoplasm (i.e. outside the nucleus of the cell), where it will be translated and then degraded by normal cellular mechanisms.
82. So far as the particular paper referred to by Dr Altman is concerned, I note that a comment has been published in response, describing this study as

⁴² S Huet, S V Avilov, L Feritz, N Daigle et al, Nuclear import and assembly of Influenza A Virus RNA Polymerase studied in live cells by fluorescence cross-correlation spectroscopy, 1 February 2010 (available here: <https://journals.asm.org/doi/full/10.1128/JVI.01533-09>).

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“scientifically incompetent” to evaluate the genotoxicity of mRNA therapeutics, including the Paediatric Vaccine and the Parent Product.⁴³ Noting in particular the difference between an *in vitro* environment, where a study is undertaken in a test tube or petri dish (which is how the study Dr Altman refers to was conducted) and an *in vivo* environment, where a study is undertaken in a living organism.

Messenger RNA vaccines do not cause negative vaccine effectiveness

83. The applicants’ witnesses suggest the Paediatric Vaccine and Parent Product are causing negative vaccine effectiveness. In essence that those vaccines are negatively impacting a person’s ability to amount an immune response to Omicron and that this is evidenced by the fact vaccinated persons have materially higher rates of Omicron infection than unvaccinated persons. Noting in particular the comments of Dr McCullough in his affidavit at [44] – [50] and Dr Brown in his April 2022 affidavit at [59] – [63].
84. I disagree. Real world studies, particularly unrandomized observational trials, cannot control for all the variables which influence the rate of infection. The Danish study referred to by Dr Brown which he says indicates that Pfizer vaccination results in negative vaccine efficacy has been cherry picked and mis-interpreted. The overwhelming evidence (as presented above) indicates that vaccination decreases the risk of infection and the risk of severe disease. The authors of the Danish study state:⁴⁴

The negative estimates in the final period arguably suggest different behaviour and/or exposure patterns in the vaccinated and unvaccinated cohorts causing underestimation of the VE. This was likely the result of Omicron spreading rapidly initially through single (super-spreading) events causing many infections among young, vaccinated individuals.

⁴³ Merchant HA. Comment on Aldén et al. Intracellular Reverse Transcription of Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 In Vitro in Human Liver Cell Line. *Curr. Issues Mol. Biol.* 2022, 44, 1115–1126. *Current Issues in Molecular Biology*. 2022; 44(4):1661-1663 (available here: <https://www.mdpi.com/1467-3045/44/4/113/htm>).

⁴⁴ C H Hansen, A B Schelde et al, Vaccine effectiveness against SS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162B2 or mRNA-1273 vaccination series: a Danish cohort study (available here: <https://www.medrxiv.org/content/10.1101/2021.12.20.21267966v3.full.pdf>).

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The extent to which previous COVID-19 infection provides effective immunisation is complex

85. Some of the applicants' witnesses suggest that having been infected with COVID-19 provides effective immunity from future infection. Noting in particular the comments of Dr Vanden Bossche in his affidavit at [35] – [42]. In my view the position is more complex.
86. Previous infection with COVID-19 can induce an immune response that provides some immunity and protection against subsequent COVID-19 infection.⁴⁵ However, there is no correlate of protection that can be reliably used to assess whether an individual is protected from COVID-19 infection or severe COVID-19.⁴⁶
87. The first time a person is infected with COVID-19, it can take several days or weeks for their body to produce the necessary antibodies to fight the infection. After infection, for the vast majority of people, their immune system will "remember" the COVID-19 virus and has the capacity to respond quickly if the body encounters COVID-19 again. It is the presence of these antibodies that means a person has some protection from reinfection. However, this immunity is far from perfect.
88. The level of natural immune response as a result of COVID-19 infection can be widely variable. Multiple factors appear to impact the degree of immunity provided following an infection. Most notably those who experience more severe COVID-19 symptoms tend to have a higher degree of immunity. In comparison, immune responses to vaccination tend to be more consistent from person to person.
89. Similar to vaccination, a person's natural immune response as a result of a COVID-19 vaccination tends to wane over time.
90. Research into the impacts of natural immune response is ongoing. In November 2021, the CDC examined hospitalizations in adults with COVID-

⁴⁵ "Science Brief: SARS-CoV-2 Infection-induced and vaccine-induced immunity", 29 October 2021 (available here: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/vaccine-induced-immunity.html>).

⁴⁶ "Interim statement on the use of additional booster doses of Emergency Use Listed mRNA vaccines against COVID-19", 17 May 2022 (World Health Organization) (available here: <https://www.who.int/news/item/17-05-2022-interim-statement-on-the-use-of-additional-booster-doses-of-emergency-use-listed-mrna-vaccines-against-covid-19>).

19-like illness and compared the odds of testing positive for COVID-19 between patients who were unvaccinated but had been infected with COVID-19 90 – 179 days prior and those patients who were fully vaccinated with an mRNA COVID-19 vaccine 90 – 179 days prior. The odds of an unvaccinated patient testing positive for COVID-19 was 5.49-fold higher than the odds of a vaccinated patient testing positive for COVID-19.⁴⁷

91. Studies also suggest that people with previous COVID-19 infections who are vaccinated (known as hybrid immunity) demonstrate stronger immune responses to COVID-19. A study of Kentucky (US) residents found that being unvaccinated was associated with 2.34 times the odds of reinfection compared with being fully vaccinated.⁴⁸
92. Other studies from the United Kingdom, the United States, Canada, the Netherlands and Qatar have demonstrated that a person who has completed a primary course of vaccination plus a booster appears to provide broadly similar protection against subsequent Omicron infection to that provided by a combination of primary vaccination and prior infection (with a previous variant).⁴⁹ However, there is a lack of studies directly comparing duration of this effect in both of these groups. Indirect comparisons (where different studies used to examine duration of protection in each group) suggest that the protection against reinfection after two doses plus infection with a previous variant might decline more

⁴⁷ Bozio CH, Grannis SJ, Naleway AL, et al. Laboratory-Confirmed COVID-19 Among Adults Hospitalized with COVID-19–Like Illness with Infection-Induced or mRNA Vaccine-Induced SARS-CoV-2 Immunity — Nine States, January–September 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1539–1544 (available here: <https://www.cdc.gov/mmwr/volumes/70/wr/mm7044e1.htm>).

⁴⁸ Cavanaugh AM, Spicer KB, Thoroughman D, Glick C, Winter K. Reduced Risk of Reinfection with SARS-CoV-2 After COVID-19 Vaccination — Kentucky, May–June 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1081–1083 (available here: <https://www.cdc.gov/mmwr/volumes/70/wr/mm7032e1.htm#:~:text=Among%20Kentucky%20residents%20infected%20with,compared%20with%20being%20fully%20vaccinated>).

⁴⁹ UK Health Security Agency. *SARS-CoV-2 variants of concern and variants under investigation in England. Technical briefing* 34. 14 January 2022; Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1046853/technical-briefing-34-14-january-2022.pdf; Carazo, S., et al. *Protection against Omicron re-infection conferred by prior heterologous SARS-CoV-2 infection, with and without mRNA vaccination*. 3 May 2022; Available from: <https://www.medrxiv.org/content/10.1101/2022.04.29.22274455v2>; Altarawneh, H.N., et al. *Effect of prior infection, vaccination, and hybrid immunity against symptomatic BA.1 and BA.2 Omicron infections and severe COVID-19 in Qatar*. *medRxiv* 22 March 2022; 2022.03.22.22272745]. Available from: <https://www.medrxiv.org/content/10.1101/2022.03.22.22272745v1>; Andeweg, S.P., et al. *Protection of COVID-19 vaccination and previous infection against Omicron BA.1 and Delta SARS-CoV-2 infections*. 12 May 2022; Available from: <https://www.medrxiv.org/content/10.1101/2022.02.06.22270457v3>; and Lind, M.L., et al. *Effectiveness of Primary and Booster COVID-19 mRNA Vaccination against Omicron Variant SARS-CoV-2 Infection in People with a Prior SARS-CoV-2 Infection*. 25 April 2022; Available from: <https://www.medrxiv.org/content/10.1101/2022.04.19.22274056v3>.

slowly than with three doses of vaccine.

Children with underlying conditions are at greater risk of severe COVID-19

93. The applicants' witnesses suggest that there is no reliable evidence that children with underlying conditions are at greater risk of severe COVID-19. Noting in particular the comments of Dr Altman in his affidavit at [88].
94. I disagree. In my first affidavit (at [19] – [20]) I discuss that children living with pre-existing health conditions and comorbidities have a greater risk of severe disease from COVID-19. There is significant evidence that children with underlying conditions are at greater risk of severe COVID-19. By way of example:
- 94.1 As discussed in my first affidavit (at [20]), CDC surveillance data from November 2021 shows that of the children who have developed severe illness from COVID-19 in the United States most have underlying health conditions (like asthma and obesity). 68% of hospitalisations of children with COVID-19, at that time, had underlying conditions.
- 94.2 During the peak Omicron period in the United States (December 2021 – February 2022), the majority of children hospitalised (70%) with COVID-19 had underlying medical conditions.⁵⁰ During the same period the evidence from the United States is that children with diabetes and obesity were more likely to experience severe COVID-19.⁵¹
- 94.3 In a large meta-analysis, pre-existing obesity, chronic pulmonary disease, congenital heart disease and neurological disease were found to increase the odds of death due to COVID-19 approximately 9-fold compared with children with no risk conditions.⁵²

⁵⁰ Shi DS, Whitaker M, Marks KJ, et al. Hospitalizations of Children Aged 5–11 Years with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 2020–February 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:574-581 (available here: https://www.cdc.gov/mmwr/volumes/71/wr/mm7116e1.htm?s_cid=mm7116e1_w).

⁵¹ Shi DS, Whitaker M, Marks KJ, et al. Hospitalizations of Children Aged 5–11 Years with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 2020–February 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:574-581 (available here: https://www.cdc.gov/mmwr/volumes/71/wr/mm7116e1.htm?s_cid=mm7116e1_w).

⁵² Shi Q, Wang Z, Liu J, et al. Risk factors for poor prognosis in children and adolescents with COVID-19: A systematic review and meta-analysis. *EClinicalMedicine* 2021;41:101155.

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94.4 In another study among 43,465 patients with COVID-19 aged 18 years or younger (with the median age in the study being 12) found a higher risk of severe COVID-19 illness among children with medical complexity and certain underlying conditions, such as type 1 diabetes, cardiac and circulatory congenital anomalies and obesity.⁵³

95. That is not to say that healthy children don't suffer from serious illness from COVID-19. They can and do but the evidence clearly demonstrates that children with underlying conditions are at a greater risk.

Children aged 5 to 11 have no greater risk of serious illness with Omicron than the seasonal flu

96. The applicants' witnesses suggest that children aged 5 to 11 have no greater risk of serious illness with Omicron than influenza. Noting in particular the comments of Dr Brown in his affidavit at [22] and Dr Altman in his affidavit at [73].

97. I disagree. These statements are based on an assumption that influenza is not a problem in children and that it is not necessary to attempt to prevent influenza in children. This is incorrect. Influenza, like COVID-19, can be a severe illness in children and adults. It is also incorrect to suggest that COVID-19 is not a severe illness for some children. As discussed above, the risk of severe disease from COVID-19 in children in Hong Kong was not considered minimal.

There has been a significant increase in reported potential vaccine deaths to VAERS

98. The applicants' witnesses suggest that there has been a significant increase in reported potential vaccine deaths to VAERS with the introduction of COVID-19 vaccines and that there have been more adverse events attributed to COVID-19 than any other vaccine in history. Noting in particular the comments of Dr McCullough in his affidavit at [60] and [61] and Dr Altman in his affidavit at [128] – [134] and [149]. I understand Christopher James is responding to these claims in detail so I only make

⁵³ Kompaniyets L, Agathis N, Nelson J. Underlying Medical Conditions Associated With Severe COVID-19 Illness Among Children. JAMA Netw Open 2021;4:e2111182.

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two brief comments in response:

98.1 First, it is important to note that cases are notified to VAERS because an adverse event occurs after vaccination. Serious events are always occurring to individuals in the population and it is inevitable that adverse events will occur at some time after a vaccination. This does not indicate that the vaccine caused the adverse event. However, from these adverse events, patterns of complications can be identified, and the observed rate of complications can be compared to the expected rate of adverse events occurring in the population.

98.2 Second, it is not surprising that there has been an increase in the number of adverse events reported to VAERS. This is entirely to be expected when you consider the number of COVID-19 vaccine doses that have been administered. Worldwide it is in excess of 11.7 billion doses. This is more than 10 times the number of influenza vaccines that would be administered worldwide in an ordinary year. It is therefore entirely expected, and not of any particular concern, that VAERS is receiving more reports about adverse events from immunisation than it did before the COVID-19 pandemic.

PCR tests

99. Dr Altman makes a number of claims about the reliability and accuracy of polymerase chain reaction tests, more commonly known as PCR tests. In particular that PCR tests cannot distinguish between influenza and COVID-19. See Dr Altman's comments at [58] – [64] and [162] – [165] of his affidavit.

100. I strongly disagree with Dr Altman. PCR tests are very accurate in identifying COVID-19. They will only give a positive result if SARS-CoV-2 is present, being the virus that causes COVID-19. They do not conflate the presence of influenza and SARS-CoV-2. The narrative that PCR tests produce false positives has arisen because these tests are so effective at the identification of SARS-CoV-2 viral particles. Because PCR is so sensitive,

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some individuals may remain positive when tested by PCR for some time after they are no longer infectious. This fact is well understood and recognised in the use of PCR in the management of individuals with COVID-19 and is why the production of a negative PCR test is not required for individuals to leave isolation or quarantine.

101. Dr Altman (at [162] of his affidavit) refers to the fact the CDC has withdrawn the PCR test as a valid test for identifying COVID-19 suggesting this was done because the PCR test was inaccurate. That is entirely incorrect. At the end of last year, the CDC switched to using multiplexed PCR tests rather than the original PCR tests that had been used up to that point.⁵⁴ The multiplexed PCR tests, can detect more than just the presence of SARS-CoV-2 but also influenza. For each virus the multiplexed PCR test will give either a positive or negative result. That is, the multiplexed PCR test can detect both viruses at the same time, saving a patient from having to be tested twice.
102. Some PCR tests have been able to not only detect SARS-CoV-2 (the virus that causes COVID-19), but additionally differentiate between Omicron (some sub-lineages) and previous variants. The remaining PCR tests have been able to detect both Omicron and other variants (like Delta) but not differentiate between them. This is not a failure of these tests, rather that some other tests have an unexpected additional benefit. For the avoidance of doubt, all PCR tests are able to detect with a high level of accuracy the presence of SARS-CoV-2 and PCR tests remain the gold standard test for detection of COVID-19.

Predetermination

103. I understand the applicants are alleging the decision to give provisional consent to the Paediatric Vaccine and the subsequent decision to rollout the Paediatric Vaccine were both predetermined because of the government's vaccination strategy, or political objectives, or contractual arrangements with Pfizer.
104. I did not make either of those decisions. However, I had a role in providing

⁵⁴ https://www.cdc.gov/csels/dls/locs/2021/07-21-2021-lab-alert-Changes_CDC_RT-PCR_SARS-CoV-2_Testing_1.html

advice to the Director-General of Health that helped to inform Cabinet’s decision to rollout the Paediatric Vaccine in my capacity as a member, and Chair, of CV-TAG. As previously discussed, CV-TAG recommended the Government expand the COVID-19 vaccine rollout to include the Paediatric Vaccine and children aged 5 to 11.

105. My understanding is that the applicants are not directly alleging that CV-TAG’s recommendation to the Government was predetermined. For the avoidance of doubt, I would emphatically reject any suggestion that it was. I am a trained physician and scientist. My role, as Chief Science Advisor and a member of CV-TAG, is to provide robust credible science advice to assist decision-makers. I am focused on the scientific evidence of the efficacy and safety of the Paediatric Vaccine (and other COVID-19 vaccines). CV-TAG’s recommendation on the Paediatric Vaccine was formed entirely in reliance of the available scientific evidence.

AFFIRMED

at Christchurch this 10th day of)
June 2022)
before me:)

George Ian Town


A Solicitor of the High Court of New Zealand

Emma Louise Sprott
Solicitor
Christchurch

Date published: 23 May 2022

About the SARS-CoV-2 Variants Update

The purpose of this document is to provide an overview of recent developments with respect to the identification of new variants or further detail about the properties of already identified variants. Characteristics of current circulating variants are monitored including: growth advantage/transmissibility; disease course/viral dynamics; clinical features (symptoms and severity); immune evasion, vaccine effectiveness and therapeutics effectiveness; and detection/testing.

All viruses, including SARS-CoV-2, change over time. Most of these changes have little to no impact on the properties of the virus, but some may affect properties such as: how easily it spreads, the associated disease severity, the performance of vaccines, therapeutic medicines, diagnostic tools, or the performance of other public health and social measures. Nomenclature systems for naming and tracking SARS-CoV-2 genetic lineages have been established by GISAID, Nextstrain and Pango. To assist with public discussions of variants, an expert group convened by WHO recommended using letters of the Greek Alphabet, i.e., Alpha, Beta, Gamma, Delta etc.[2]

About this update

A selected sub-set of topic areas are comprehensively updated in each issue of this document. The dates stated for section updates relate to when a comprehensive update was performed, although additional data might have been added in the interim. New information included since the previous update is provided in red text.

This issue retains the separate table for the BA.2 sub-lineage of Omicron, as it continues to replace the previously dominant BA.1 sub-lineage of Omicron.[4]

Key documents published recently

In addition to selected recent pre-prints and published studies, key reports used in this update include:

- UKHSA: SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing 41, 6 May 2022 [5]
- UKHSA: Risk assessment for SARS-CoV-2 variants V-22APR-03 and V-22APR-04, 28 April [6]
- WHO: Weekly epidemiological update on COVID-19 - 11 May 2022 [7]
- WHO: Weekly epidemiological update on COVID-19 - 4 May 2022 [8]
- ECDC: Communicable Disease Threats Report - Week 19, 8-14 May 2022 [9]

This is the exhibit marked "GT-4" referred to in the annexed Affidavit of **GEORGE IAN TOWN** affirmed at **Christchurch** this 10th day of **June 2022** before me:


Solicitor of the High Court of New Zealand

Emma Louise Sprott
Solicitor
Christchurch

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Date: 23 May 2022

Key new information in this update

- The Omicron Variant of Concern remains the dominant variant circulating globally, accounting for nearly all sequences recently reported to GISAID.
- BA.4 and BA.5 are Omicron sub-lineages that were first detected in South Africa in January and February 2022 respectively, and are now the dominant variants there. BA.4 and BA.5 remain at a low prevalence globally, but their geographic distribution implies they are spreading successfully. They have now been detected in over 20 countries, including at the New Zealand border. BA.4 and BA.5 appear to have a growth advantage, though no evidence regarding impact on transmissibility has been reported. BA.5 has an estimated daily growth advantage over BA.2 of 13% in Portugal and 12% in South Africa. The growth advantage for BA.4 and BA.5 is thought to be likely due to their ability to evade immune protection induced by prior infection and/or vaccination, particularly if this has waned over time. There is currently no evidence to suggest an effect on severity of illness.
- Although the UK Health Security no longer classifies Delta as a Variant of Concern, the WHO retains this designation. A recently published study on waste-water surveillance in Israel found that Delta is highly resilient and continued to be detected at low levels even at the height of the Omicron wave. The authors raise concern that such 'cryptic circulation' could possibly result in the re-emergence of a Delta wave of generation of a new variant.
- A World Health Organization report included an updated summary of evidence on Omicron, including for vaccine effectiveness (VE). Lower vaccine effectiveness of a primary vaccine series has been observed for severe disease, symptomatic disease, and infection against the Omicron compared to the previous four VOCs. However, importantly, in the majority of studies VE estimates against the Omicron variant remain higher for severe disease than for other outcomes. Booster vaccination substantially improves VE for all outcomes, but studies that assess VE of booster vaccination beyond 6 months are needed to evaluate the longer duration of protection.

Overview of variants

Section updated: 24 April 2022

Many agencies monitor existing and emerging variants, including the World Health Organization (WHO) and the UK Health Security Agency (UKHSA). Surveillance, classification, and reporting varies between countries and agencies.

Changes to UK Health Security Agency (UKHSA) variant classification system [1]:

From 1 April 2022, the UKHSA amended its variant classification system to give a clearer indication of which variants have potentially significant changes in biological properties compared to current dominant variant(s).[3] These variants with potentially significant changes may pose a risk to public health in the UK although at the time of identification it may be difficult to predict the extent of the impact.

In the new system, the Variant of Concern (VOC) label is assigned to variants which are currently emerging or circulating, and for which the UKHSA have confirmed or can predict:

- a detrimental change in biological properties (changes in transmissibility, severity or immune evasion) compared to the current dominant variant(s); and
- a growth rate potentially compatible with maintaining transmission and/or displacing the current dominant variant.

There will be no other categorisation of variants, and there will be no variant under investigation (VUI) category. UKHSA will continue to designate new variants based on genomic features and growth, and these will receive a variant number (V-date-number) and will have routine characterisation analyses once biological materials are available and/or sufficient cases accrue.[3] Previous variants of concern which no longer meet the criteria have been redesignated.[1]

Different national authorities may designate variants differently depending on their definitions and the risk posed to their country.[8] Table 1 outlines the currently circulating known variants of public health interest. It displays the various nomenclature for the different variants, including UKHSA labels, WHO designations and Phylogenetic Assignment of Named Global Outbreak Lineages (Pangolin lineages), **European Centre for Disease Control and Prevention (ECDC) designation**, as well as the date/location of earliest documented samples. It also indicates the classification level given by the UKHSA (VOCs, variants (V-date-number), and 'signals in monitoring') if applicable. Red text indicates new or updated information since the previous Variants Update.

As of **16 May 2022**, Delta and Omicron¹ were the only circulating Variants of Concern as designated by the WHO.[\(link\)](#) There were no currently circulating Variants of Interest as designated by the WHO at that time. As of 16 May, the WHO listed two variants under monitoring: B.1.640 and XD.[10]

Recently designated variants include the following, which were classified by the UKHSA Variant Technical Group (VTG) on 6 April 2022²[1]:

- Recombinant XD was classified V-22APR-01
- Recombinant XE was classified V-22APR-02

¹ Includes BA.1, BA.2, BA.3, BA.4, BA.5 and descendent lineages. It also includes BA.1/BA.2 circulating recombinant forms such as XE.

² Whilst recombinant lineages generally are monitored through horizon scanning, UKHSA has classified XD and XE recombinant lineages as variants V-22APR-01 and V-22APR-02, respectively. XD has been classified a variant (V) on the basis of the data published from France, suggesting that it may be biologically distinct. XE has been classified a variant (V) based on apparent continued growth within the UK.

- Omicron sub-lineage BA.4 was classified V-22APR-03
- Omicron sub-lineage BA.5 was classified V-22APR-04.

Table 1 now also includes European Centre for Disease Prevention and Control (ECDC) classifications. The ECDC uses the label 'variant of concern' when clear evidence is available for a variant indicating a significant impact on transmissibility, severity and/or immunity that is likely to have an impact on the epidemiological situation in the EU/EEA.[11]

Note that whilst BA.4 and BA.5 were both first detected in South Africa, the country performs a high rate of whole genome sequencing, and it is possible the variants first emerged (but was not detected) somewhere else.[12]

SARS-CoV-2 Variants Update

Table 1: Overview of SARS-CoV-2 variants of public health interest

Table updated: 16 May 2022

Pango lineage	WHO label	UKHSA label	UKHSA designation	ECDC designation	Earliest documented samples	Distribution
B.1.1.7	Alpha	V-20DEC-01 (previously VOC-20DEC-01)	Variant (previously a variant of concern)	De-escalated variant	United Kingdom, Sep-2020	Detected in the UK in the past 12 weeks as at 6 May.[5]
B.1.617.2 and sub-lineages	Delta	V-21APR-02 (previously VOC-21APR-02)	Variant (previously a variant of concern)	Variant of Concern[11]	India, Oct-2020	Detected in the UK in the past 12 weeks as at 6 May.[5]
B.1.1.529/BA.1	Omicron	VOC-21NOV-01	Variant of concern	Variant of Concern[11]		Detected in the UK in the past 12 weeks as at 6 May.[5]
B.1.1.529/BA.2	Omicron	VOC-22JAN-01	Variant of concern (previously a variant under investigation)	Variant of Concern[11]		Detected in the UK in the past 12 weeks as at 6 May.[5]
AY.4.2		V-21OCT-01 (previously VUI-21OCT-01)	Variant (previously a variant under investigation) - *AY.4.2 is a sub-lineage within Delta that has been assigned as a distinct variant by UKHSA.	De-escalated but monitored under Delta VOC		Detected in the UK in the past 12 weeks as at 6 May.[5]
B.1.640	-	-	Signal in monitoring (previously Variant in monitoring)		Multiple countries, Sep-2021	Detected in GISAID, but not in the UK, in the past 12 weeks as at 6 May.[5]
BA.3	-	-	Signal in monitoring (previously Variant in monitoring)	Variant under monitoring [11]	South Africa [11]	Detected in the UK in the past 12 weeks as at 6 May.[5] As of 16 May 2022, most BA.3 cases reported were in South Africa (81%) and the US (5%).(link)
Delta and Omicron recombinant lineages (UK)	-	-	Signal in monitoring (previously Variant in monitoring)		United Kingdom, Feb-2022	Detected in the UK in the past 12 weeks as at 6 May.[5]

SARS-CoV-2 Variants Update

Pango lineage	WHO label	UKHSA label	UKHSA designation	ECDC designation	Earliest documented samples	Distribution
B.1.351	Beta	V-20DEC-02	<i>Variant of Concern (last report unclear designation)</i>		South Africa, May-2020	Detected in GISAID, but not in the UK, in the past 12 weeks as at 6 May.[5]
P.1		Removed from UKHSA list	Removed from UKHSA list		Brazil, Nov-2020	
B.1.621	Mu	V-21JUL-01 (previously VUI-21JUL-01)	<i>Variant (previously Variant under investigation)</i>		Colombia, Jan-2021	Detected in GISAID, but not in the UK, in the past 12 weeks as at 6 May.[5]
AY.119.2/BA.1.1 Recombinant			Signal under monitoring			Detected in GISAID, but not in the UK, in the past 12 weeks as at 6 May.[5]
XD Recombinant (Delta x BA.1)		V-22APR-01	<i>Variant (previously signal under monitoring)</i>		France, Jan-2022	Detected in GISAID, but not in the UK, in the past 12 weeks as at 6 May.[5]
XE Recombinant (BA.1 x BA.2)		V-22APR-02	Variant		First case detected on 19 January 2022. [3, 13]	Detected in the UK in the past 12 weeks as at 6 May.[5]
B.1.617.3		V-21APR-03	Variant			Detected in GISAID, but not in the UK, in the past 12 weeks as at 6 May.[5]
BA.1/BA.2 Recombinant (with unique mutation C3583T)			Signal in monitoring			Detected in the UK in the past 12 weeks as at 6 May.[5]
XF Recombinant			Signal in monitoring			Detected in the UK in the past 12 weeks as at 6 May.[5]
B.1.1.529/ BA.4	Omicron sub-lineage BA.4	V-22APR-03	Variant	Variant of Concern as of 12 May 2022 (previously variant of interest)[14]	South Africa, January 2022. [12]	Detected in the UK in the past 12 weeks as at 6 May.[5] Dominant in South Africa along with BA.5.[14]

SARS-CoV-2 Variants Update

Pango lineage	WHO label	UKHSA label	UKHSA designation	ECDC designation	Earliest documented samples	Distribution
B.1.1.529/ BA.5	Omicron sub-lineage BA.5	V-22APR-04	Variant	Variant of Concern as of 12 May 2022 (previously variant of interest)[14]	South Africa, February 2022. [12]	Detected in the UK in the past 12 weeks as at 6 May.[5] Dominant in South Africa along with BA.4. Increasing trend in the variant proportions for BA.5 observed in Portugal in recent weeks.[14] As of 6 May UKHSA reported it had been detected in 17 countries, with highest numbers in South Africa, Portugal, Germany and the UK.[5]
BA.2.12.1			Signal in monitoring			Detected in the UK in the past 12 weeks as at 6 May.[5]

Delta

The UKHSA no longer classifies Delta as a Variant of Concern, however the WHO does. A recently published peer-reviewed study has raised concerns that Delta could continue to pose a larger threat than widely assumed. ([link](#)) Previous variants have tended to diminish and vanish fully, being over-powered by the next variant. However, waste-water surveillance in Israel found that the Delta variant is highly resilient – even at the height of the Omicron wave, the Delta variant was still detected at low levels.[15] Their modelling suggests that Omicron levels may decrease until it is eliminated, while the Delta variant could maintain its ‘cryptic circulation’, possibly resulting in the re-emergence of a Delta wave or generation of a new variant.

Omicron Overview

Section updated: 16 May 2022

The Omicron variant has quickly become dominant across the world, displacing the previously dominant Delta variant.[16] It has spread rapidly even in regions with high levels of population immunity.[17] Omicron was first detected in November 2021 and was associated with a rapid resurgence of COVID-19 cases in South Africa.[17] Within three days of the first genome being uploaded, the WHO had designated it as the fifth variant of concern of SARS-CoV-2 (Omicron, B.1.1.529).[17] Within three weeks the variant had been identified in 87 countries.[17] Compared to the previous four VOCs (Alpha, Beta, Gamma, and Delta), the Omicron variant was noted to have the greatest number of mutations; 50 mutations accumulated throughout the genome.[18] This included at least 32 mutations in the spike protein (twice as many as Delta),[18] enabling highly efficient evasion from neutralising antibodies.[16] Omicron has continued to evolve, leading to further variants with slightly different genetic constellations of mutations.[8]

The Omicron variant (B.1.1.529) comprises a number of lineages and sub-lineages.[19] This includes BA.1, BA.2, BA.3, BA.4, BA.5 and descendent lineages, as well as BA.1/BA.2 circulating recombinant forms such as XE.[10] There are a large number of mutations differentiating Omicron variants from other known SARS-CoV-2 lineages.[17] BA.2 and BA.3 are evolutionarily linked to BA.1[17] and BA.4 and BA.5 are evolutionarily linked to BA.2.[1]

BA.1 and BA.2

In early December 2021, Pango announced it was designating two genetically distinct sub-lineages of B.1.1.529 as BA.1 (B.1.1.529.1) and BA.2 (B.1.1.529.2)[20]: BA.1 for the original globally distributed lineage, and BA.2 for the new outlier lineage. The prefix BA was then an alias for B.1.1.529.[20] BA.2 was designated a variant under investigation (VUI) by UKHSA on 21 January 2022. UKHSA’s latest BA.2 risk assessment was published on 23 March 2022.[21] BA.2 contains 29 mutations in the spike protein and a deletion at 25-27. Some of the mutations in the spike protein are shared with BA.1.[22]

Definitive differentiation of BA.1 from BA.2 requires whole genome sequencing (WGS). However, as the Omicron genome (lineage BA.1) contains the spike deletion at position 69-70 which is associated with S-gene target failure (SGTF) in some widely used PCR tests, SGTF patterns have been used to assess the spread of Omicron lineage BA.1. The BA.2 genome generally is S-gene target positive, but as of 30 March 2022, the UKHSA reported that 0.16% of BA.2 samples sequenced had the deletion at position 69-70.[1] **The UKHSA is no longer reporting SGTF patterns. A change in UK testing policy on 1 April resulted in a substantial reduction in tests processed through assays which can report SGTF. Therefore, SGTF is no longer a reliable representation of variants in the population, and the UKHSA will not be reporting it going forward.**[5]

BA.3

Omicron sub-lineage BA.3 continues to be very rare, with 107 sequences noted in cov-lineages.org as of 16 May 2022. It has been most commonly reported in South Africa (81% of BA.3 global cases) followed by Poland (5%) and the US (5%). BA.3 has the SGTF deletion (Δ 69-70) so can be detected using PCR tests that detect SGTF, and has a combination of the mutations found in BA.1 and BA.2 spike proteins.[23]

BA.4 and BA.5

Two new variants within the Omicron lineage have been recently identified and named BA.4 and BA.5. These were classified by the VTG on 6 April 2022 as V-22APR-03 and V-22APR-04, respectively.[1] On 12 April 2022, WHO announced that BA.4 and BA.5 had been added to their list of variants for monitoring. The ECDC classified both as variants of concern on 12 May.[14] At this stage it is unknown what effect on transmissibility or severity of disease these subvariants have, but both appear to have a growth advantage over BA.2.[12] Further information about these two subvariants is provided later in this document.

Prevalence of Omicron and its sub-lineages

The highly transmissible Omicron variant continues to be the dominant variant circulating globally, and has rapidly replaced all other circulating variants in almost all countries in which it has been reported.[24] The WHO Weekly Epidemiological Update on 11 May [7] reported that:

“The Omicron VOC remains the dominant variant circulating globally, accounting for nearly all sequences reported to GISAID in the last 30 days. Of note is the very low proportions of ‘previously circulating VOCs’ and of the Delta VOC. With variant diversification, Omicron sublineages have continued to be identified; however, only a few of these sublineages appear to have a growth advantage. These findings need to be interpreted with caution, as differences in sequence capacity across regions and countries may confound such interpretations and global distributions.”[7]

BA.1 was responsible for the initial Omicron surge and is now being replaced by BA.2 globally.[4]

- As of 16 May 2022, BA.2 was most commonly reported in the UK (40% of reported global BA.2 cases), Denmark (16%), Germany (13%), the US(7%), and France (4%).(link) 797 891 sequences had been assigned BA.2 globally.
- A WHO report from 27 April noted that among the 257 337 sequences uploaded to GISAID with specimens collected in the last 30 days, 256 684 (99.7%) were Omicron, 47 (<0.1%) were Delta, and 555 (0.2%) sequences were not assigned to a Pango lineage. WHO comments that while the decrease in sequences is consistent with the overall decreasing trend in new cases reported globally, it may also reflect changes in epidemiological surveillance policies in some countries, including changes in sampling and sequencing strategies.[25]
- **UK:** VOC-22JAN-01 (Omicron sub-lineage BA.2) remains dominant in the United Kingdom (UK) based on sequencing data.[5] The UKHSA also notes that some diversity is developing within this variant, based on both lineage and mutation surveillance. Of the sequenced episodes from 24 April to 1 May 2022, 91.9% were Omicron lineage BA.2 (VOC-22JAN-01) and 8.1% were Omicron lineage BA.1 (VOC-21NOV-01).[5]
- **US:** CDC projections for the week ending April 30, 2022, estimated that 100% of lineages in the United states are Omicron,[26] as with projections for the week ending April 9.[27] The predominant Omicron lineage in the United States is BA.2. The national proportion of BA.2 is projected to be 61.9% , BA.2.12.1 is projected to be 36.5%, BA.1.1 is projected to be 1.3% and B.1.1.529 (BA.1, BA.3, BA.4 and BA.5) is projected to be 0.1%.[26]

Data on BA.2 is summarised in Table 2 below. BA.2 data has been highlighted due to its increasing dominance worldwide. For current information about BA.2 in sections not updated in this version, see the most recent UKHSA technical briefing.[1]

Table 2: Characteristics of Omicron BA.2

Characteristic	Data
<p>Growth advantage/ transmissibility</p> <p>Section updated: 15 March 2022†</p>	<p>There is evidence of a growth advantage of BA.2 relative to BA.1. WHO have stated that a relative increase in BA.2 has been observed in multiple countries. BA.2 may have between 30-50% greater transmissibility compared to BA.1.</p> <p>BA.2 has now been reported in 85 countries and there has been a continuing relative increase in Omicron sequences that are BA.2 according to WHO.[28]</p> <p>UKHSA states that there is evidence of a growth advantage for BA.2 compared to BA.1 in more than one country.[29] The growth rate advantage observed in England, in areas where there are sufficient cases to assess, is supported by increased household SARs in preliminary UK data.[29] The UKHSA Risk Assessment of 26 January 2022 noted that given the high SAR observed for BA.2 and “lack of apparent immune evasion” (presumably relative to BA.1), it is plausible that a change in transmissibility is contributing to the growth advantage.[29] In the latest UKHSA Risk Assessment (9 February 2022), the potential role of the shorter serial interval for BA.2 in conferring the growth advantage is noted.[30]</p> <p>Scientists from Heidelberg University have shared data on Twitter which suggests a BA.2 growth advantage over Delta of approximately 20% per day and a BA.1 growth advantage over Delta of approximately 15% per day.(link)</p> <p>Data from the UKHSA [31] and Denmark [32] suggests BA.2 may have 30-50% greater transmissibility than BA.1. Two papers have reported a higher estimated effective reproduction number of BA.2 compared to BA.1 – in one pre-print paper 1.26-fold higher, [33] in the other paper (now published) 1.40-fold higher.[34]</p> <p><u>Household transmission</u></p> <p>UKHSA reported that the crude SAR for BA.2 is 30% higher, compared to BA.1 for household contacts.[31] Analysis of routine contact tracing data showed SAR for household contacts as 13.4% (10.7%-16.8%) for BA.2 and 10.3% (10.1%-10.4%) for BA.1.[31] SAR analysis was not adjusted for vaccination status and only included close contacts named by the original case to NHS Test and Trace, (household members, face-to-face contact, people within one metre of the case for one minute or longer, or people within 2 metres for 15 minutes).[31]</p> <p>Non peer-reviewed analysis from the Danish Statens Serum Institut suggests a 50% increase in transmissibility for BA.2 compared to BA.1, with the estimated SAR of 29% for BA.1; and 39% SAR for BA.2 across households infected with Omicron.[32]</p>

SARS-CoV-2 Variants Update

Characteristic	Data
<p>Disease course/Viral dynamics</p> <p>Section updated: 15 March 2022†</p>	<p>Preliminary UK data gives a mean serial interval for BA.2 of 3.27 days, with 95% of serial intervals expected to be less than or equal to 7.56 - 8.40 days after primary case symptom onset.</p> <p><u>Serial interval</u></p> <p>UKHSA preliminary analysis of contact-tracing data shows the mean serial interval for BA.2 is 3.27 days (95% CI: 3.09 - 3.46), around half a day shorter than BA.1 (3.72; 95% CI: 3.62 - 3.80).[35] Similarly, BA.2 has a shorter median serial interval (2.68 days 95% CI: 2.50 - 2.87) compared to BA.1 (3.27 days; 95% CI: 3.17-3.36). For BA.2, 95% of serial intervals are expected to be less than or equal to 7.56 - 8.4 days after primary case symptom onset. This is similar to BA.1, with 95% of serial intervals expected to be less than or equal to 8.21 - 8.57 days after primary case symptom onset.[35]</p> <p><u>Viral load</u></p> <p>A Danish pre-print found no difference in viral load between BA.1 and BA.2 across 58,015 samples.[36] However, a study from Qatar reported that BA.2 demonstrated greater infectiousness than BA.1 on the basis of lower cycle threshold (Ct) values (mean of -3.53 cycles compared with BA.1) on PCR tests of over 150,000 samples.[37]</p> <p>A pre-print reporting Omicron breakthrough infections in triple vaccinated HCWs (within the Stockholm COMMUNITY study) found viral load peaked at day 3 after first PCR-positive sample and viral load did not differ significantly between BA.2 and BA.1 or BA.1.1 infections.[38] Live virus was detected for up to 9 days after first PCR-positive sample. Of note, this report documents only 82 breakthrough infections in total, with 24 BA.2 breakthrough infections included in the analysis.</p> <p>A large Swedish study analysing 174,933 clinical nasopharyngeal swab samples at a time of transition between BA.1 and BA.2 has reported a nearly two-fold higher (1.9) level of viral RNA in cases with BA.2.[39] The authors suggest that this increased viral load in the upper pharynx may explain the growth advantage of BA.2 over BA.1.</p>

SARS-CoV-2 Variants Update

Characteristic	Data
<p>Clinical features (symptoms and severity)</p> <p><i>Section updated: 15 March 2022†</i></p>	<p>There are insufficient data to determine the severity of BA.2 infections. Preliminary analyses show no differences in frequency of hospitalisation for BA.2 compared to BA.1</p> <p>Danish Statens Serum Institut has stated that preliminary analysis shows no differences in hospitalisations for BA.2 compared to BA.1 and those analyses are ongoing.[40] There continue to be insufficient data to assess the severity of BA.2.[30]</p> <p>Preliminary analysis of South African data suggest the odds of being hospitalised does not differ between BA.1 and BA.2 and that the severity of clinical illness remains similar for both sub-lineages. [41] A report of Omicron cases from Rajasthan, India also reported no difference in clinical profile for BA.1 and BA.2.[42]</p> <p>Early data regarding Omicron in children suggested that symptoms appeared to be less severe than previous variants, and paediatric deaths were rare. However, these data were from populations in which a majority were already protected from past infection, vaccination or both.[43] A large study of an uninfected and unvaccinated population of children, investigated the intrinsic severity of BA.2. The population-based case control study investigated severe outcomes among 1,147 children aged 11 years or below who were hospitalised between 5 February and 28 February 2022 (a BA.2-dominant period). The authors concluded that the intrinsic severity of BA.2 in children who had no past COVID-19 or vaccination is not mild. Four deaths (0.35%) occurred during the Omicron wave, resulting in a higher in-hospital case fatality rate than other SARS-CoV-2 variants (0%), influenza (0.05%) and parainfluenza (0.04%). The mortality estimates are based on very small sample sizes. Children hospitalised during the BA.2 dominant period had higher odds of PICU admissions, mechanical ventilation and oxygen use. BA.2 was reported to be more neuropathogenic than previous SARS-CoV-2 variants, influenza and parainfluenza viruses, resulting in more seizures. One notable limitation of the study was the lack of viral genome sequencing data verifying that all infections in February 2022 were caused only by the BA.2 variant. However, epidemiological data suggested that the BA.2 variant was dominant right from the start of the latest surge. The authors also suggest caution regarding the in-hospital CFR of 0.35%, as it is likely an overestimate of fatality because of under-detection of milder cases. The results of this Hong Kong study could have particular relevance for New Zealand, given that this age group have similarly largely escaped infection with previous variants, with children under the age of 5 without access to vaccination. The authors of the study note that the lack of exposure to seasonal human coronaviruses in the past 2 years, resulting in lack of cross-reactive immunity.[43]</p>

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Immune evasion/vaccine effectiveness/therapeutics

Section updated: 15 March 2022†

Based on early data BA.2 does not appear to have a greater capacity for immune evasion than BA.1.

Neutralisation assays

UKHSA states that a preliminary pseudovirus neutralisation study does not suggest a difference in neutralisation between BA.2 and BA.1, using sera from vaccinated individuals.[29] A further pseudovirus neutralisation study using sera from Pfizer vaccinated individuals (3 doses) found similar neutralisation rates for BA.1 and BA.2.[44] Another neutralisation study found greater neutralisation of BA.2 than BA.1 for sera from Pfizer vaccinated individuals whether single, two-dose or three-dose vaccinated sera.[45]

Vaccine effectiveness

A preprint study of UK data posted in March 2022 estimates the effectiveness of booster vaccination against symptomatic disease caused by the BA.2 sub-lineage of the Omicron (B.1.1.529) variant.[46] Preliminary analysis from the UKHSA found no statistical difference in the vaccine effectiveness for BA.2 compared to BA.1.[31] Analysis included Pfizer, Moderna and AstraZeneca vaccines (combined data). After 2 doses, vaccine effectiveness was 9% (7 to 10%) and 13% (-26 to 40%) respectively for BA.1 and BA.2, after 25+ weeks. This increased to 63% (63 to 64%) for BA.1 and 70% (58 to 79%) for BA.2 at 2 weeks following a booster vaccine.[31] UKHSA will continue to analyse this data.

Reinfection

A pre-print reporting on reinfection with BA.2 in Qatar found a higher rate of BA.2 infection in previously uninfected people than those previously infected with BA.1.[47] Limitations of the study included the definition of reinfection as infection ≥ 35 days and variation in testing strategies (differing PCR tests and use of rapid antigen tests) and assignment of sub-lineage. Vaccination status was adjusted for in the analysis.

UK data on BA.2 reinfection is being monitored as part of the SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) study of NHS healthcare workers and is summarised in UKHSA reports.[3, 48] The UKHSA Risk Assessment for BA.2 reported on 23 March 2022 notes that a small number of sequence-confirmed BA.2 reinfections after BA.1 infection have been identified and that these reinfections have been predominantly in unvaccinated people.[48] The SIREN study defines reinfection as: new PCR positive infections 90 days after a previous PCR positive date or 28 days after antibody positivity consistent with prior infection.[3] Notably, the latest UKHSA Technical Briefing 39 of 25 March 2022 states that they are at the start of the 90-day period for possible reinfection following a BA.1 infection, so limited information is available about the frequency of BA.2 infection following a BA.1 infection.[3]

The UKHSA Risk Assessment for BA.2 also reports that neutralisation studies support protection from BA.2 reinfection after BA.1 infection in those vaccinated.[48] A cross-neutralisation study using human sera from unvaccinated individuals infected with BA.1 showed similar, but slightly lower neutralisation activity of BA.1 sera against BA.2 (and BA.3).[4]

Therapeutics

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Characteristic	Data
	<p>Antivirals - evidence from <i>in vitro</i> studies and animal studies (for molnupiravir only to date) show remdesivir, molnupiravir and nirmatrelvir (the active component of Paxlovid) demonstrate similar activity against BA.2 as for earlier variants.</p> <p>Monoclonal antibody treatments – recent <i>in vitro</i> studies suggest differing neutralisation activity for some monoclonal antibodies against BA.2 compared to other sub-lineages. Notably, sotrovimab has been shown to have some reduced activity against BA.2 and there is some preliminary evidence that imdevimab (one of the components of Ronapreve) may have some retained activity against BA.2.</p> <p>As recent studies document the evidence against sub-lineages together and to avoid repetition, detail of recent therapeutics studies can be found in Table 3.</p>
<p>Detection</p> <p>Section updated: 22 February 2022†</p>	<p>Most observational studies have relied on SGTF as a proxy for Omicron, which would generally identify BA.1 but not BA.2. Therefore, caution is required when interpreting comparative analyses which use S-gene target results as the only determinant of Omicron and Delta.</p> <p>Unlike BA.1, the BA.2 lineage generally does not have the spike deletion at 69-70 that causes S-gene target failure (SGTF).[49] Because of this, it is being called the “stealth” version of Omicron as it cannot be detected using PCR tests that detect SGTF, such as Thermo Fisher’s TaqPath. (link) This has implications on using PCR tests that detect SGTF as a proxy for rapidly detecting Omicron cases. It should be noted that as at 30 March 2022, the UKHSA reported that 0.16% of BA.2 samples sequenced had the deletion at position 69-70.[11]</p> <p>Data is emerging for BA.2. Most observational studies have relied on SGTF as a proxy for Omicron, which would generally identify BA.1 but not BA.2. Therefore, caution is required when interpreting comparative analyses which use S-gene target results as the only determinant of Omicron and Delta.</p>

† See Table 3 for updates on non-BA.2 lineages

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Table 3 below highlights data relating to various characteristics of the Omicron variant as a whole. This includes non-BA.2 related information, as well as data where Omicron is specified but not the sub-lineage. For data specific to Omicron BA.2 sub-lineage please see Table 2 above.

Table 3: Characteristics of Omicron and its sub-lineages

Characteristic	Data
<p>Growth advantage/ transmissibility</p> <p>Section updated: 22 February 2022</p>	<p>Omicron is more transmissible and has a higher secondary attack rate than Delta</p> <p>One analysis has estimated that Omicron had a growth advantage that corresponds to a 5.4-fold (95% CI = 3.1–10.1) weekly increase in cases compared with Delta.[17] The authors suggest that the growth advantage of Omicron is likely to be mediated by (1) an increase relative to other variants in its intrinsic transmissibility, (2) an increase relative to other variants in its ability to infect, and be transmitted from, previously infected and vaccinated individuals; or (3) both.[17]</p> <p>Using data from Denmark (to 18th Dec 2021), the effective (instantaneous) reproduction number of Omicron is 3.19 (95%CI 2.82–3.61) times greater than that of Delta under the same epidemiological conditions.[50] In Canada, initial modelling estimates of R_{eff} for Omicron is 1.5 (90%CI 0.78–2.34).[51]</p> <p>Data to 20 December 2021 reported by UKHSA show that, relative to Delta, Omicron is currently more concentrated in young adult age groups (20 to 29) and is less prevalent in children.[52] Of the 1,063 cases in one region of Canada, 59% of 1,063 cases were 18-24 years old and 27% were 25-39 years old, corresponding with the main outbreak environments being in post-secondary education and food/beverage settings.[51]</p> <p>Scientists from Heidelberg University have shared data on Twitter which suggests a BA.1 growth advantage over Delta of approximately 15% per day.(link)</p> <p>Data from a US health provider in Houston, Texas, indicated a case-doubling time for Omicron of 1.8 days, three times faster than for Delta in this area.[53] Preprint data from South Africa found Omicron was more associated with asymptomatic infection and transmission than Beta and Delta.[54] In England, contact tracing data show a greater proportion of transmission happening outside the household for Omicron than for Delta.[52]</p> <p>Emerging data from the UK estimated a shorter generation time (interval between infection events in an infector-infectee pair) for Omicron during late November to December 2021, with a mean of 1.5-3.2 days (standard deviation [SD] 1.3-4.6 days), compared to a mean of 2.5-4 days (SD 1.9-3 days) for Delta.[14] This translated to a transmission advantage of 160%-210% for Omicron. However, the study is subject to bias from factors such as differences in the populations the variants were present in, differences in immune escape between variants, and using test to test distribution as a proxy for the generation time distribution.</p>

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Characteristic	Data
	<p>UKHSA preliminary analysis of contact-tracing data shows the mean serial interval for BA.1 is 3.72 days (95% CI: 3.62 - 3.80).[35] BA.1 has a median serial interval of 3.27 days (95% CI: 3.17-3.36). For BA.1, 95% of serial intervals are expected to be less than or equal to 8.21 - 8.57 days after primary case symptom onset.[35]</p> <p><u>Household transmission</u></p> <p>Non peer-reviewed analysis from the Danish Statens Serum Institut estimates a SAR of 29% for BA.1 (compared with an SAR of 39% for BA.2) across households infected with Omicron.[32]</p> <p>South Korea [55]: secondary attack rate in a small study of 25 households was 50.0%</p> <p>Danish data [56]:</p> <ul style="list-style-type: none"> • Overall, household SAR was 31% for Omicron and 21% for Delta. • Household SAR for unvaccinated individuals was 29% for Omicron and 28% for Delta. • Household SAR for fully vaccinated (defined according to each vaccine) individuals was 32% for Omicron and 19% for Delta. • Household SAR for booster-vaccinated individuals was 25% for Omicron and 11% for Delta. <p>UK data [52]: The UKHSA Technical Briefing 33 (23 December 2021) reported that household SAR was 13.6% (95% CI: 13.1-14.1) for Omicron and 10.1% (95% CI: 10.0-10.2) for Delta. SAR in non-household settings was 7.6% (95% CI: 7.2-8.0) for Omicron and 2.8% (95% CI: 2.7-2.9) for Delta. However, this data has not been stratified by vaccination status.</p> <p><u>Other data</u></p> <p>Japan [57]: A study investigated the differences in viral environmental stability between the SARS-CoV-2 Wuhan strain and all VOCs on plastic and skin surfaces. The Omicron variant has the longest survival time of 21.1 hours (95% CI: 15.8–27.6) compared to 16.8 hours (95% CI: 13.1–21.1) for Delta. The high environmental stability of Omicron could increase the risk of contact transmission and contribute to its spread.</p> <p>Canada [58]: A study found that initial testing of HCWs if they had a household positive case in majority of instances was sufficient to prevent nosocomial transmission to patients. On initial testing 196 of 475 HCWs were positive and were quarantined. Only 42 (15%) of 279 HCWs that were initially asymptomatic and allowed to work became positive a median of 4 days after the initial test, but no further transmission was detected. Absence of symptoms at initial evaluation (OR 3.8, 95% CI 2.5-5.7) and having received a third vaccine dose more than 7 days before (OR 1.88, 95% CI 1.3 – 2.8) were associated with increased odds of remaining negative.</p>

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Characteristic	Data
	Non-omicron, novel transmission data: A human challenge study (n=36) using pre-alpha wild-type virus found that a dosage of 10 TCID ₅₀ (very low dose) was sufficient to result in an infection. Also, they found that viral shedding occurs in both the nose and throat at high levels irrespective of symptom severity.[59]
<p>Disease course/Viral dynamics</p> <p>Section updated: 22 February 2022</p>	<p>Median or mean incubation period 3-4 days, maximum incubation unclear (6-8 days reported). Omicron may have a shorter serial interval than Delta.</p> <p><i>NOTE: Incubation period refers to the time from infection until symptom development. The serial interval refers to the time from illness onset in the primary case to illness onset in the secondary case. The latent period refers to the time from infection until the person becomes infectious (and more likely to test positive)</i></p> <p><u>Incubation period</u></p> <p>Single exposure event data (assumes participants infected at event):</p> <ul style="list-style-type: none"> • Faroe Islands [60]: Observed incubation period was short, ranging from 2 to 6 days, with a mean incubation period of 3.24 days (95% CI 2.87-3.60). All had had 3 doses of Pfizer (2 primary, and booster in last 2.5 months) • Norway [61]: Estimated incubation period was 0 to 8 days, median of 3 days (interquartile range: 3–4).[61] Almost all participants interviewed had received 2 doses of an mRNA vaccine. The incubation period was consistent with another study (median 3 days for both Delta and Omicron variants) • USA [62]: Incubation period (6 cases only) of approximately 3 days (73 hours, range = 33–75 hours).[62] • Netherlands [63]: Mean incubation period 3.2 days (SD = 2.2 days) for SGTF cases (Omicron BA.1) <p>Human challenge studies (non- omicron, novel transmission data)</p> <ul style="list-style-type: none"> • Incubation period of 2 to 4 days after inoculation with wild-type virus.[59] Viral load (VL) rose steeply and peaked around day 4-5. <p><u>Serial Interval</u></p> <ul style="list-style-type: none"> • Spain [64]: The mean serial interval was significantly shorter for Omicron (4.8 days) versus Delta (5.4 days), corresponding to a difference of -0.6 (95% CI: -1 to -0.15). • Netherlands [63]: Within households, a mean serial interval of 3.4 days was observed for SGTF (proxy for Omicron) and 3.9 days for non-SGTF (proxy for Delta) cases.

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Characteristic	Data
	<ul style="list-style-type: none"> South Korea [55]: mean: 2.5-4.3 days, and median was 3-4 days (based on small sample size of 12 transmission pairs). Belgium [65]: overall Omicron mean 2.75 days (SD=2.54). Within household mean 2.8 (SD=2.6), between household mean 2.72 (SD=2.44) <p><u>Latent period:</u></p> <p>Human challenge studies (non- omicron, novel transmission data)</p> <ul style="list-style-type: none"> Viral shedding by qPCR became quantifiable in throat swabs from 40 hours (95% CI [40,52]) (~1.67 days) post-inoculation, significantly earlier than in the nose (p=0.0225, where initial viral quantifiable detection occurred at 58 hours (95% CI [40,76]) (~2.4 days) post-inoculation.[59] Viral load (VL) rose steeply and peaked around day 4-5. <p><u>Duration of infectiousness</u></p> <p>Data predominantly from vaccinated people:</p> <ul style="list-style-type: none"> Japan [66]: Preliminary data from the National Institute of Infectious Diseases suggest that the amount of viral RNA in specimens from Omicron infections (19 vaccinated and 2 unvaccinated cases) was highest 3-6 days after diagnosis or symptom onset and then decreased gradually, with a marked decrease 10 days after diagnosis or symptom onset. A similar trend was seen for viral isolates, with no infectious virus detected in the respiratory samples 10 days post diagnosis or symptom onset. Switzerland [67]: A study investigating viral shedding dynamics included a small number of Omicron breakthrough infections (n=18) and showed similar infectious viral titres in nasopharyngeal samples for breakthrough Omicron and Delta (n=17 for this comparison) infections. Samples were gathered in the first 5 days post symptoms. US [68]: Preliminary data from a longitudinal study (National Basketball Association’s [NBA] occupational health programme) in a largely vaccinated cohort suggest that Omicron may have a lower peak viral load (Ct 23.3 for Omicron vs Ct 20.5 for Delta) and shorter clearance time (5.35 days for Omicron vs 6.23 days for Delta) than Delta. However, the rate of clearance (3.13 Ct/day for Omicron vs 3.15 Ct/day for Delta) and total mean duration of infection is similar (10 days for Omicron vs 11 days for Delta). These data are only from a small number of infections, so more is needed to understand the viral dynamics of Omicron and how they are affected by vaccination.

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Characteristic	Data
	<ul style="list-style-type: none"> Singapore [69]: Ct value at presentation was significantly higher for Omicron compared with Delta infections (20.7 [IQR 17.9 – 28.5] vs. 19.1 [15.4 – 21.1], $p < 0.001$). Pattern of viral shedding was comparable for Omicron and Delta, with an increase in viral load over the first 2-3 days of illness, and significant decline from Day 8. Trough and illness onset median Ct values were similar for Omicron between those with primary vaccination or booster vaccination doses. Switzerland[70]: A small study in Delta (n=17) and Omicron patients (n=18) found that Delta and Omicron have comparable genome copies ($p=0.3345$) but Omicron patients had slightly but not significantly lower infectious viral titres compared to Delta patients ($p=0.1033$). <p>Human challenge studies (non- omicron, novel transmission data)</p> <p>Some clinical participants still shed culturable virus ~10 days after symptom onset but the sample size is small (n=36).[59]</p> <p><u>Duration of illness</u></p> <ul style="list-style-type: none"> Faroe Islands [60]: Time to resolution of symptoms varied, and at the end of follow-up, five individuals still reported symptoms, while the rest (16 individuals) reported symptoms lasting 1 to 9 days. Singapore [69]: Negative viral cultures were obtained starting from day 2 of illness and no positive viral cultures were obtained for patients beyond day 5 of illness or with Ct values >26 based on 14 patients. For time to hospitalisation and death, see “severity” section above. Data on the disease course remains limited at present, with few quantitative studies to date.
<p>Clinical features (symptoms and severity)</p> <p><i>Section updated: 22 February 2022</i></p>	<p>Severity – data to date indicates hospitalisation and death rates are lower than Delta, taking into account vaccination status and risk for severe disease.</p> <p>As of 10 April 2022, the WHO provided the following summary: “Unlike previous waves, the most recent wave due to Omicron can be characterized by a decoupling between the number of cases, hospitalizations (particularly for intensive care) and deaths in many countries. However, data continue to show that those who are unvaccinated remain at higher risk of severe disease following infection with Omicron as compared to those who have been vaccinated. Despite the reduction in severity, the massive increases in cases with Omicron have led to large numbers of hospitalizations, putting further pressure on healthcare systems, and in some countries, similar or higher numbers of deaths when compared to previous peaks.”[24]</p>

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Characteristic	Data
	<p>A pre-print posted in March 2022 has proposed that the particular interactions of Omicron within the mucosal surfaces of the respiratory tract could contribute to its reduced lung involvement and clinical severity.[71] They found that replication of Omicron in lung tissues is highly restricted compared to other VOC, whereas it remains relatively unchanged in nasal tissues. In addition, Omicron induced a much stronger antiviral interferon response in infected tissues compared to Delta and earlier VOC – particularly in the lung tissues, where the innate immune response to all other SARS-CoV-2 VOC was blunted.[71]</p> <p>Hospitalisation</p> <p><u>Hospitalisation frequency for Omicron relative to Delta</u></p> <p>Adjusted for vaccination status (important for understanding basic differences in severity as it can remove differences in vaccine effectiveness from assessment. However, residual confounding for vaccination status may still occur):</p> <ul style="list-style-type: none"> • A preprint Swedish study (N= 1 384 531) comparing Omicron period vs Delta found that risk of severe disease was lower with Omicron by 40% for unvaccinated and 71% less for vaccinated individuals. Also, the risk for severe COVID-19 remained high among unvaccinated, first-time-infected cases of both sexes during the Omicron period in the age group 65+, and also among males in the age group 40-64 years with two or more comorbidities.[72] • US study comparing healthcare utilisation in high transmission periods of Omicron vs Delta found a relative increase in ED visits (86%) and hospitalisations (76%) compared to the Delta period due to the higher volume of cases but a relative decrease in the length of stay in hospitals (-27%).[73] • A preprint US study comparing Omicron period vs Delta period found that among hospitalised omicron patients (41% vaccinated) they were less likely to require ICU or die. [74] • A Norwegian study (n= 91005) found that cases infected with Omicron were 73% lower risk of hospitalisations compared with delta infection.[75] • A preprint study from France looked at 39 Hospitals in the Paris area to measure the risk of ICU admission. It found risk of hospitalisation with Omicron was reduced by 64% compared to Delta. [76] • Canadian data: risk of hospitalisation or death was 54% lower (Hazard Ratio =0.46, 95% CI: 0.27-0.77)³. [77] • Scottish data: risk of hospitalisation 68% lower (observed/expected ratio of 0.32, 95% CI: 0.19-0.52).⁴[78]

³ adjusted for vaccination status and region

⁴ adjusted for age, sex, socioeconomic status, vaccination status and clinical risk factors.

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Characteristic	Data
	<ul style="list-style-type: none"> UK data: risk of presentation to emergency care or hospital admission 50% lower than with Delta (Hazard Ratio 0.53, 95% CI: 0.50 to 0.57). The risk of hospital admission from emergency departments was approximately 67% lower than with Delta (Hazard Ratio 0.33, 95% CI: 0.30-0.37).⁵ [79] A pre-print from South Africa showed that much of the severity reduction observed for Omicron relative to Delta was due to prior infection and vaccination. Intrinsically reduced virulence accounted for a ~25% reduced risk of hospitalization/death compared to Delta. [80] A US study in veterans found that infection by Omicron has a 45% (95% CI: 26-58) lower likelihood of resulting in hospitalisation than infection by Delta.[81] UK data in long term care facility residents: risk of hospitalisation much lower, 10.8% for Delta and 4.0% for Omicron (Hazard Ratio 0.50, 95% CI: 0.29-0.87).[82] This paper by Krutikov and colleagues, part of the VIVALDI study, is also reported in the UKHSA Technical Briefing 35. [31] Portugal data: risk of hospitalisation lower, 1.6% for Delta and 0.2% for Omicron (Hazard ratio 0.25, 95% CI: 0.15-0.43). [83] Danish data [84] stratified rather than adjusted by vaccination status: <ul style="list-style-type: none"> Among those with <2 doses: 43% lower risk of hospitalisation (RR = 0.57, 95% CI: 0.44-0.75) Among those with 2 doses: 29% lower risk of hospitalisation (RR = 0.71, 95% CI: 0.60-0.86) Among those with 3 doses: 50% lower risk of hospitalisation (RR = 0.50, 95% CI: 0.32-0.76) <p>Unadjusted for vaccination status (provides indication of burden on healthcare at the level of vaccination in country where study conducted):</p> <ul style="list-style-type: none"> UK data (adjusted to some extent for prior infection): reduction in hospitalisation of 38% (95%CI 31-45%) for emergency department attendance or admission, and 62% (95% CI 50-70%) for admission, [52] or (from a different group analysing same data, with different methods for prior infection) 20-25% lower for attendance at hospital, and 40-45% for hospital admission.[85] US data (unclear if adjusted for vaccination/infection): 53% reduction in hospitalisation (hazard ratio for symptomatic hospital admission relative to Delta was 0.47 (95% CI: 0.35-0.62))⁶ [86] Danish data [84]: Overall, 36% lower risk of hospitalisation (RR = 0.64, 95% CI: 0.56, 0.75) <p><u>Hospitalisation frequency (not compared to Delta)</u></p>

⁵ Controlled for date of specimen and area of residence and further adjusted for age, sex, ethnicity, local area deprivation, international travel, vaccination status. Also adjusted for whether the current infection is a known reinfection, although as reinfections are substantially under-ascertained, the adjustment may not have fully accounted for the effect of reinfections.

⁶ adjusted for age, sex, race/ethnicity, and neighborhood-level median household income, as well as clinical risk factors recorded within the prior year (including history of smoking, body mass index, Charlson comorbidity index, and healthcare utilization across outpatient, emergency department, and inpatient settings)

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Characteristic	Data
	<p>UK data:</p> <p>England: ICU admissions with a valid sequencing result for Omicron increased from 9% week commencing 15 December 2021 to 50% in week commencing 12 January 2022.[31]</p> <p>England: To 29th December, 815 Omicron hospitalisations had been reported. To the same date, around 650,000 Omicron cases had been reported, but there are lags in hospitalisation reporting and many recent cases are unlikely to have had sufficient observation time to be admitted to hospital (i.e., hospitalisation likely to be underestimated). [79] Some crude data available by day but vary substantially each day, and likely affected by lack of follow up time (people testing positive most recently only followed up for 7 days), and lack of adjustment for age or vaccination status.[85]</p> <p>Scotland: Did not report as numbers too small.[78]</p> <p>Canadian data:</p> <p>Ontario: 29,594 cases to December 25th, of whom 75 (0.25%) hospitalised (or died). Again this is likely to be an underestimate due to very short follow up of those diagnosed later.[77]</p> <p>US data:</p> <p>California: 52,297 cases to January 1, 2022, of whom 182 (0.35%) were admitted to hospital with symptoms.[86]</p> <p>Indian data:</p> <p>New Delhi: 82 cases to December 23rd, 3 (3.6%) of whom required hospitalisation. This could be biased due to the short follow up time since diagnosis, or underdiagnosis of cases.[87]</p> <p>French data:</p> <p>Marseille: 1,119 cases between November 28 to December 31, 21 (1.9%) of whom were admitted to the hospital.[88]</p> <p><u>Paediatric data</u></p> <p>South Africa: Rapid increases in paediatric COVID-19 cases and hospitalisations were reported in the Tshwane District, mirroring high community transmission of SARS-CoV-2 (Omicron variant).[89]</p>

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Characteristic	Data
	<p>US: According to news reports, the CDC says since mid-December the hospital admission rate for those under 5 has increased to more than 4 in 100,000 children, up from 2.5 per 100,000, while the rate among children aged 5 to 17 years is about 1 per 100,000 (link). However, the overall hospitalisation rate among children and teens is still lower than that of other age groups, and they account for less than 5 per cent of average new daily hospital admissions, according to the CDC. A US study in children under 5 years found a significantly lower risk for severe clinical outcomes in the 3-day time-window following initial Omicron infection compared to Delta.[90] Risk for ED visits was 18.83% (vs 26.67%), hospitalisation was 1.04% (vs 3.14%), ICU admissions was 0.14% (vs 0.43%), and mechanical ventilation was 0.33% (vs 1.15%).</p> <p>UK: Pediatric admissions began to rise from 26 December 2021, with a 3-fold increase in 2 weeks.[49] The rise is most rapid among children under 5 years, and highest in infants aged under 1 year (based on data for all variants, but Omicron represents over 90% of sequenced samples in the UK). A clinical case review of a small number of Omicron admissions in infants found those admitted were not severely unwell. [49, 91] Preliminary data from the UK during the Omicron wave (14 December 2021 to 6 January 2022) indicate less severe outcomes in children aged under 1 year compared to previous waves.[92] In the current wave, 12.7% required oxygen use compared to 22.5% in the first wave of the pandemic. 16% required admission to intensive care (vs 14%), 3.9% required use of mechanical ventilation (vs 5.8%), 1.3% required use of non-invasive ventilation (vs 7.2%), and mean length of stay was 1.9 days (vs 6.6 days).</p> <p>A preprint study from the US states that paediatric acute upper airway infection (UAI) cases have increased during the Omicron variant surge, with many developing severe disease.[93] The retrospective cohort study suggests that Omicron replicates more efficiently in the conducting airways, increasing the risk of a croup phenotype in children as they have smaller airway calibres. The study compares data within the National COVID Cohort Collaborative before and during the rise of Omicron. It was observed that in December 2021, as Omicron became dominant in the US, SARS-CoV-2 positive UAI cases increased to the highest number per month (N = 170) and 1.5% (234/15,806) of hospitalized children with SARSCoV-2, had an UAI diagnosis.</p> <p><u>Risk factors for hospitalisation with Omicron:</u></p> <p>In the UK, the age range of individuals admitted with Omicron to 29 December 2021 was 0 to 100 years (median: 45.5 years); 496 (60.9%) were aged 40 years or more; 30.8% were aged 70 years or more. [79]</p> <p>Public Health Scotland data reported on hospital admissions for COVID-19 (week of 22-28 December 2021) shows approximately 44% were in people 60 plus years of age, and 21% of admissions were in people aged 80 plus.[94] Of note, most cases of COVID-19 at this time in Scotland were Omicron but the proportion of cases of the Omicron variant for each age-group hospitalised are not reported.</p> <p><u>Time to hospitalisation with Omicron:</u> no data found.</p>

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Characteristic	Data
	<p>Time in hospital with Omicron: median length of stay reported as 2.8 days but strong potential bias as included only those already discharged at 3 weeks after start of Omicron wave (i.e., those with longer stays might not be included).[53] A South African study also found median hospital length stay was significantly lower for Omicron than other variants, but possibly suffers from similar bias.[95] Preliminary analysis of South African hospital admissions in Gauteng Province (includes Johannesburg and Tshwane) reported a median hospital stay of 4 days (inter-quartile range 2-6 days) during an Omicron-dominant period. [96] A US study estimated that the median duration of stay for patients with Omicron variant infections experiencing symptomatic hospitalisations was 1.5 (1.3-1.6) days, with 90% of patients expected to complete hospitalisations within 3.1 (2.7-3.6) days, corresponding to a 69.6% (95% CI: 64.0-74.5%) shorter median length of hospital stay compared to patients with Delta infections.[86] However, a key limitation in some of these studies is that longer stays will have been missed for Omicron (biasing median duration downward) due to short follow up times. A US study in veterans found that among COVID hospitalisations, Omicron is associated with a 2-day (95% CI: 1-2) shorter stay than Delta. The average length of stay was 6 days (95% CI: 5-7).[81] A Portuguese study found the length of stay in hospital for Omicron was significantly shorter than for Delta (confounding-adjusted difference⁷ -4.0 days (95% CI -7.2 to -0.8).[83]</p> <p>ICU admission</p> <p>Severe/ICU/ventilated frequency relative to Delta</p> <p>Adjusted for vaccination status (important for understanding basic differences in severity as removes differences in vaccine effectiveness from assessment. However, residual confounding for vaccination status may still occur):</p> <ul style="list-style-type: none"> • South African data: Among <i>hospitalised</i> individuals, after controlling for factors associated with severe disease⁸, the odds of severe disease did not differ between S-Gene Target-Failure (SGTF, interpreted as Omicron) infected individuals compared to non-SGTF individuals diagnosed during the same time period (aOR 0.7, 95% CI 0.3-1.4).[97] Compared to earlier Delta infections, after controlling for factors associated with severe disease⁹, SGTF-infected individuals had lower odds of severe disease (aOR 0.3, 95% CI 0.2-0.5). • A US study in veterans found that Omicron is associated with a 73% (95% CI: 28-92) lower risk of ICU admission than Delta.[81] <p>Unadjusted for vaccination status (provides indication of burden on healthcare at the level of vaccination in country where study conducted):</p> <ul style="list-style-type: none"> • US data: Unadjusted hazard ratios for ICU admission associated with Omicron variant infection was 0.26 (95% CI: 0.10-0.73), a 74% reduction.[86]

⁷ adjusted for sex, age, previous infection and vaccination status

⁸ controlled for factors known to be associated with severity (age, presence of comorbidity, sex, province and healthcare sector) and adjusted for the number of days between the date of specimen collection and date of hospital admission, known prior SARS-CoV-2 infection and SARS-CoV-2 vaccination status.

⁹ controlled for factors known to be associated with disease severity (age, presence of co-morbidity, sex, province and healthcare sector), and adjusted for number of days between date of specimen collection and date of hospital admission, known prior SARS-CoV-2 infection and SARS-CoV-2 vaccination status.

SARS-CoV-2 Variants Update

Characteristic	Data												
	<p><u>Severe/ICU/ventilated frequency (not compared to Delta)</u></p> <p>In Texas, among 862 people who tested positive for Omicron (mainly symptomatic people presenting to healthcare facilities),[53] the maximum ventilatory support required was:</p> <table border="1"> <tbody> <tr> <td>Extracorporeal membrane oxygenation</td> <td>1 (0.7% of 134 hospitalised, 0.1% of 862 testing positive for Omicron)</td> </tr> <tr> <td>Mechanical ventilation</td> <td>6 (4.5%, 0.7%)</td> </tr> <tr> <td>Non-invasive ventilation</td> <td>9 (6.7%, 1.0%)</td> </tr> <tr> <td>High flow oxygen</td> <td>12 (9.0%, 1.4%)</td> </tr> <tr> <td>Low flow oxygen</td> <td>42 (31%, 4.9%)</td> </tr> <tr> <td>Room air (but hospitalised)</td> <td>64 (48%, 7.4%)</td> </tr> </tbody> </table> <p>A total of 19.7% (875/4438) of hospital admissions required supplemental oxygen (not further specified) and 6.9% were treated in ICU (308/4438) in an analysis of data from Gauteng Province, South Africa during an Omicron-dominated period. [96]</p> <p>Californian data: The daily risk of mechanical ventilation among patients (unclear if analysis restricted to hospital inpatients) with Omicron infections was significantly lower than for Delta (0 vs 0.04 per 1000 person-days at risk).[86]</p> <p><u>Risk factors for ICU/ventilation:</u> no data.</p> <p><u>Time to ICU/ventilation:</u> no data.</p> <p>Death</p> <p><u>Death frequency relative to Delta</u></p> <p>UK data: To 29 December 2021, a total of 57 people were reported to have died within 28 days of an Omicron COVID-19 diagnosis (198,348 confirmed cases of Omicron).[79]</p> <p>South African data: After adjusting for age, sex, comorbidities, and subdistrict, the hazard ratio was 0.27 (95% CI: 0.19-0.38), a 73% reduction relative to Delta, but the extent of reduction was attenuated when prior infections and vaccination were also considered (HR: 0.72, a 28% reduction relative to Delta).[80]</p>	Extracorporeal membrane oxygenation	1 (0.7% of 134 hospitalised, 0.1% of 862 testing positive for Omicron)	Mechanical ventilation	6 (4.5%, 0.7%)	Non-invasive ventilation	9 (6.7%, 1.0%)	High flow oxygen	12 (9.0%, 1.4%)	Low flow oxygen	42 (31%, 4.9%)	Room air (but hospitalised)	64 (48%, 7.4%)
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Characteristic	Data
	<p>US data: Unadjusted hazard ratios for mortality associated with Omicron variant infection was 0.09 (95% CI : 0.01-0.75)[86] but unadjusted ratios could be confounded by many factors, and the short follow up time might bias results.</p> <p>UK data in long term care facility residents: Reduced risk of death within 28 days of a new diagnosis in the Omicron dominant period (1.1 deaths / 1000 person-days, 95% CI: 0.6-2.2) compared to the pre-Omicron period (3.8 deaths / 1000 person-days, 95% CI: 2.8-5.2).[82]</p> <p>Portugal data: The odds of death were 0.14 (95% CI: 0.0011-1.12), representing a reduction in the risk of death of 86% for Omicron compared with Delta.[83]</p> <p><u>Risk factors for death:</u> UK data: Of 57 people who died within 28 days of Omicron diagnosis (to 29th December 2021) the age of those dying ranged from 41 to 99 years.[79]</p> <p><u>Time to death:</u> UK data: median time from Omicron specimen date to death was 5 days (range 0 to 14).[79] Note that specimen date might not reflect date of symptom onset.</p> <p>Symptomatology</p> <p>Non-peer reviewed studies (pre-prints) have shown that in hamster and mouse models, Omicron poorly infects the lung, leads to lower viral loads, and produces milder clinical signs of infection compared to those observed with previous strains. [98-100] Data from a study using ex-vivo human lung and bronchus tissue show similar results, with slower Omicron replication observed in the lung and faster in the bronchus compared to previous strains.[101] Clinical symptoms were largely absent in hamsters that were re-infected with Omicron, suggesting that immunity raised against the ancestral strain was protective against Omicron.[99] The characteristics of the antibody-mediated protection observed within this study is of interest while we wait for further studies in humans confirm the relevance of these findings.</p> <p>Symptoms – Symptoms may be milder in previously infected and/or vaccinated individuals. Recent UK data suggests a substantial proportion of Omicron cases may be asymptomatic – estimates range from 25-54%. The most common symptoms reported are sore throat, cough, runny/stuffy nose, and fatigue. Additional data supports earlier reports that loss of smell and taste is less commonly reported by Omicron cases than for Delta, and that sore throat is more commonly reported.</p> <p>The most common symptoms reported in early data were: cough; runny/stuffy nose; and fatigue.[51, 61, 102, 103] The COVID Symptoms Study (by health science company Zoe and Kings College London) reports that headache and sneezing are also common symptoms of Omicron infection. [104] Preliminary information suggests no difference in symptoms between vaccinated and unvaccinated cases of COVID-19 infection but milder and of shorter duration in vaccinated cases (data likely to include both Omicron and Delta cases). (link) A study from Canada of 1,063</p>

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Characteristic	Data
	<p>cases of Omicron (confirmed or suspected) found that only 10% reported shortness of breath.[51] Symptoms reported in paediatric cases in South Africa have included fever, vomiting, diarrhoea and convulsions.[89]</p> <p>UKHSA Technical Briefing 34 compares Omicron to Delta symptoms. The report provides a recent analysis of NHS Test and Trace data of 182,133 confirmed Omicron cases and 87,920 confirmed Delta cases in the period between 01 December to 28 December 2021. Adjusted odds ratio analysis showed that Omicron cases were less likely to report loss of smell and taste compared to Delta cases (13% of Omicron cases, 34% of Delta cases, odds ratio 0.22, 95% CI: 0.21-0.23). However, Omicron cases were more likely to report a sore throat than Delta cases (53% of Omicron cases, 34% of Delta cases, odds ratio 1.93, 95% CI: 1.88-1.98). Adjustments were made for age group, sex, ethnicity, self-reported vaccination status (two or more doses, one or no dose, or missing data), geographical region of residence, and the week in which symptoms began. UKHSA states that the findings relating to reports of sore throat could be incidental and suggests that sore throat may not be a specific predictor of Omicron infection, as another recent study led by Oxford University and the Office for National Statistics [105] found increased reports of sore throat in both PCR-positives and symptomatic PCR-negative cases. More data are required to understand which symptoms may be used to identify Omicron infections.</p> <p>A study from Korea investigated the clinical and epidemiological characteristics of 40 patients with Omicron (42.5% were fully vaccinated) and found that half of the patients (19, 47.5%) were asymptomatic, while the others had mild symptoms.[106] The most common symptoms were sore throat (25%), fever (20%), headache (15%), cough (12.5%), and sputum production (12.5%). While these findings are consistent with recent reports of mild symptoms from other sources, given the small size and low median age of the study (39.5), more data are required to understand symptoms and determine the severity of Omicron.</p> <p>A Singapore study compared the symptoms between Omicron and Delta found having sore throat was significantly more common in Omicron patients (sore throat 46.0 vs 23.0%, p=0.005) and less likely to develop pneumonia (3.4 vs 16.1%, p=0.005). Median neutrophil count, C-reactive protein and lactate dehydrogenase levels were lower in Omicron infections. Patients with booster vaccination were significantly older and had higher anti-spike antibody but were similar in clinical and laboratory features including median initial and lowest PCR cycle threshold values.[69]</p> <p>A study from Jordan showed that the most frequent symptoms for Omicron were fever, cough, sore throat, runny nose, joint and muscle pain, and general fatigue. Loss of taste and smell was only reported in 1.2% of patients.[107]</p> <p>Recent UK data reported from the REal-time Assessment of Community Transmission-1 (REACT-1) survey (Round 17; 99% Omicron cases) found a substantial proportion (approximately 25%) of positive tests were in asymptomatic people.[108] Vaccine status of individuals within this group was not included in the report.</p> <p>A preprint study that analysed data from the UK COVID-19 Infection Survey found Omicron infections were associated with fewer lower, and more upper, respiratory tract symptoms.[109] There was a marked reduction in reports of loss of taste/smell, from high levels observed in the</p>

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Characteristic	Data																																
	<p>Delta period, e.g. 44%/44% on 1 December 2021, to 16%/13% on 31 December 2021. Loss of taste/smell were previously highly specific symptoms.[109] Increases in sore throat were reported, from 45% to 57% in symptomatic PCR-positive infection episodes during December 2021 decreasing slightly to 54% by 15 January 2022. However, data should be interpreted with caution as sore throat also increased from 40% to 43% in symptomatic PCR-negative visits during December 2021 and then decreased to 35% by 15 January 2022. The UK COVID-19 Infection Survey collects data on characteristics of people testing positive for COVID-19, including data on symptoms for those who had strong positive tests - Ct value under 30 (see imbedded table below). These data are provisional, reflect infections reported in the community, and exclude infections reported in hospitals, care homes, or other institutional settings. The below imbedded table is taken from the 19 January 2022 edition of this dataset.[110] The Delta variant was dominant in the UK in the November period and Omicron was becoming dominant in the December period.</p> <p>While the December data provide an indication of the common symptoms of the Omicron variant, Omicron was not dominant for the whole of December, so these data are not a complete representation and further information is required. Recent data from the UK COVID-19 Infection Survey which reported on what can be considered the beginning of the 'Omicron period' (20 December 2021 23 January 2022) indicates that approximately 54% of participants did not report any symptoms (within 35 days after first observed positive test), considered asymptomatic.[111]</p> <table border="1"> <thead> <tr> <th rowspan="2">Symptoms</th> <th colspan="2">Percentage of people with this symptom within 35 days of a positive PCR, among those people with a Ct value under 30</th> </tr> <tr> <th>November 2021</th> <th>December 2021</th> </tr> </thead> <tbody> <tr> <td>Any symptoms</td> <td>65.00</td> <td>58.16</td> </tr> <tr> <td>No symptoms (asymptomatic)</td> <td>35.00</td> <td>41.84</td> </tr> <tr> <td>Classic symptoms (cough, fever, shortness of breath, loss of taste, loss of smell)</td> <td>56.86</td> <td>48.42</td> </tr> <tr> <td>Loss of taste or smell</td> <td>30.52</td> <td>15.55</td> </tr> <tr> <td>Gastrointestinal symptoms (abdominal pain, nausea or vomiting, diarrhoea)</td> <td>17.38</td> <td>13.31</td> </tr> <tr> <td>Cough</td> <td>45.65</td> <td>39.88</td> </tr> <tr> <td>Fatigue (weakness)</td> <td>39.96</td> <td>32.09</td> </tr> <tr> <td>Headache</td> <td>40.45</td> <td>34.39</td> </tr> <tr> <td>Sore throat</td> <td>29.62</td> <td>32.71</td> </tr> </tbody> </table>	Symptoms	Percentage of people with this symptom within 35 days of a positive PCR, among those people with a Ct value under 30		November 2021	December 2021	Any symptoms	65.00	58.16	No symptoms (asymptomatic)	35.00	41.84	Classic symptoms (cough, fever, shortness of breath, loss of taste, loss of smell)	56.86	48.42	Loss of taste or smell	30.52	15.55	Gastrointestinal symptoms (abdominal pain, nausea or vomiting, diarrhoea)	17.38	13.31	Cough	45.65	39.88	Fatigue (weakness)	39.96	32.09	Headache	40.45	34.39	Sore throat	29.62	32.71
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Characteristic	Data		
	Fever	25.19	21.95
	Loss of smell	25.96	12.29
	Muscle ache (myalgia)	27.83	23.07
	Loss of taste	25.14	12.62
	Shortness of breath	13.82	9.84
	Nausea or vomiting	10.29	7.35
	Abdominal pain	7.94	5.84
	Diarrhoea	5.86	5.42
Immune evasion/vaccine effectiveness/therapeutics Section updated: 16 May 2022	<p>Vaccine effectiveness (VE) – VE against infection with Omicron is approximately 50% soon after 2 doses of Pfizer. This wanes to levels unlikely reduce transmission within 5-6 months of the second dose. VE against infection with Omicron is around 55-70% after a booster dose of Pfizer, but also wanes. VE against hospitalisation is around 60-70% after a primary vaccine course of Pfizer but declines to ~45% from 25 weeks after second dose. VE against hospitalisation increases to ~90% after a Pfizer booster dose (including in those over 65 years of age) and remains at above 70% 3 months after the booster. Duration of effectiveness of Pfizer vaccine against hospitalisation after a booster dose has not been fully established, but effects remain higher for longer than for protection against infection.</p> <p>(Note: Pfizer and BioNTech have begun enrolment for a clinical trial to test the safety, tolerability, and immunogenicity of an Omicron-based vaccine candidate in 1,420 healthy adults aged 18-55 years. link Pfizer is hoping to be able to deliver the vaccine in (southern hemisphere) Spring 2022. However, testing in primates has shown no advantage of an Omicron specific mRNA (Moderna) booster over a booster with the regular Moderna vaccine (link). All data described below relate to the standard vaccine (not the Omicron-based vaccine candidate).</p> <p>Data from reviews (all vaccines)</p> <p>A recent WHO weekly epidemiological report (11 May 2022) included an updated summary of evidence on Omicron, including for vaccine effectiveness.[7] The WHO notes that results of vaccine effectiveness (VE) studies should be interpreted with caution because estimates vary with the type of vaccine administered and the number of doses and scheduling (sequential administration of different vaccines).[7] Some key points from the WHO interpretation of results of VE for the Omicron variant include:</p> <ul style="list-style-type: none"> • To date, 23 studies from ten countries have assessed the duration of protection of five vaccines against the Omicron variant. • Findings from these studies show reduced VE of primary vaccine series against the Omicron variant than has been observed for previous variants, for all outcomes (severe disease, symptomatic disease, and infection). • However, in the majority of studies VE estimates against the Omicron variant remain higher for severe disease. • VE estimates against symptomatic disease and infection within the first three months of primary series vaccination tended to be lower than those against severe disease, and VE decreased more substantially over time. 		

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Characteristic	Data	
	<ul style="list-style-type: none"> Booster vaccination substantially improves VE for all outcomes, but studies that assess VE of booster vaccination beyond 6 months are needed to evaluate the longer duration of protection. <p>A more detailed summary of the WHO VE interpretation is below, highlighting results particularly for mRNA vaccines and AstraZeneca.</p>	
	Outcome	Timing
	Severe disease	Within first three months of primary series vaccination
		Beyond three months after vaccination
		Between 14 days and three months after receipt of booster
		Three to six months post mRNA booster
	Symptomatic disease	Within first three months of primary series vaccination
		Beyond three months after vaccination
		Between 14 days and three months post booster
		Three to six months following receipt of an mRNA booster dose
	Infection	
	<p>WHO summary of VE results for Omicron (as at 11 May 2022)</p> <p>mRNA vaccines: seven of 12 (58%) VE estimates were $\geq 70\%$ AstraZeneca: one study reported VE of $< 70\%$</p> <p>mRNA vaccines: 12 of 27 (44%) VE estimates for the mRNA vaccines were $\geq 70\%$ while 18 (77%) were $\geq 50\%$ AstraZeneca: one of the 12 (8%) VE estimates was $\geq 70\%$ while eight (67%) were $\geq 50\%$</p> <p>A booster dose improved VE estimates against severe disease in all studies, with only one estimate for Pfizer as the booster dose below 70%.</p> <p>18 of 20 (90%) estimates showed VE $\geq 70\%$ (an mRNA vaccine was given as the primary series in 13 of the 20 estimates while AstraZeneca-Vaxzevria and Sinovac-CoronaVac were given as the primary series for six and one of the twenty estimates, respectively).</p> <p>Only three of 13 (23%) VE estimates for the mRNA vaccines were $\geq 70\%$, and seven (54%) were $\geq 50\%$; all the three (100%) VE estimates for AstraZeneca were below 50%.</p> <p>None of the VE estimates were $\geq 50\%$ (20 estimates evaluated mRNA vaccines, six evaluated AstraZeneca)</p> <p>An mRNA booster after completion of a primary series of an mRNA vaccine, AstraZeneca-Vaxzevria, or Sinovac-CoronaVac, improved VE estimates against symptomatic disease, with four of 21 (19%) VE estimates $\geq 70\%$ and 16 (76%) estimates $\geq 50\%$, between 14 days and three months post booster.</p> <p>Booster dose protection declined with time since vaccination, with only one of twelve (8%) available estimates indicating a VE of $\geq 50\%$ at three to six months following receipt of an mRNA booster dose. Estimates for a booster dose of AstraZeneca-Vaxzevria (one estimate) and Sinovac-CoronaVac (one estimate) three to six months post vaccination indicated VE of $< 50\%$.</p> <p>VE estimates against infection showed a similar pattern as those against symptomatic disease.</p>	

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	<p><u>Data from individual studies (Pfizer where available)</u></p> <p><u>VE against infection, symptomatic infection and onward transmission</u></p> <p>Summary of the international data:</p> <ul style="list-style-type: none"> • VE against infection with Omicron is 40- 55% soon after 2 doses of Pfizer. This represents an epidemiologically important reduction in transmission. • VE against infection with Omicron wanes to levels unlikely reduce transmission within 5-6 months of the second dose • VE against infection with Omicron is around 55-69% after a booster dose of Pfizer. This also represents an epidemiologically important reduction in transmission. Although there is some indication of waning after a booster dose, data about symptomatic infection in the UK suggests this occurs more slowly after a booster dose than after a primary course of Pfizer, with VE against symptomatic infection remaining above 50% in those that had received a booster more than 10 weeks prior. • Data about onward transmission are scarce and are only available for “all vaccines” and not Pfizer alone. Non-peer-reviewed data from a small study suggest that vaccinated people infect fewer people in their household (a setting where many “exposure events” are likely to occur, generally resulting in lower “vaccine efficacy” than in settings with less intense contact) <p><i>Vaccine effectiveness on transmission related parameters in the Omicron era</i></p> <table border="1"> <thead> <tr> <th rowspan="2">Vaccine</th> <th rowspan="2">Outcome</th> <th colspan="3">2 doses (95% CI in brackets)</th> <th colspan="3">3 doses (95% CI in brackets)</th> </tr> <tr> <th>Soon after</th> <th>Later effect</th> <th>Data not reported by time since 2nd dose</th> <th>Soon after</th> <th>Later effect</th> <th>Data not reported by time since 3rd dose</th> </tr> </thead> <tbody> <tr> <td>Pfizer (all doses)</td> <td>Infection</td> <td>Denmark[112]*: 1-30 days 55% (24- 74%) 31-60 days 16% (-21 – 42%) 61-90 days 10% (-10 – 26%)</td> <td>Denmark[112]*: 91-150 days -76% (-95 - - 60)</td> <td></td> <td>Denmark[112]*: 1-30d 55% (30- 70%)</td> <td></td> <td></td> </tr> </tbody> </table>	Vaccine	Outcome	2 doses (95% CI in brackets)			3 doses (95% CI in brackets)			Soon after	Later effect	Data not reported by time since 2nd dose	Soon after	Later effect	Data not reported by time since 3rd dose	Pfizer (all doses)	Infection	Denmark[112]*: 1-30 days 55% (24- 74%) 31-60 days 16% (-21 – 42%) 61-90 days 10% (-10 – 26%)	Denmark[112]*: 91-150 days -76% (-95 - - 60)		Denmark[112]*: 1-30d 55% (30- 70%)		
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Characteristic		Data					
		Denmark [113] 14-30 days 40% (38-41%)	Denmark [113] >120 days 13% (13-14%)	Portugal[114]*: 28% (12-41%)†	Denmark [113] 14-30 days 55% (55-56%)	Denmark [113] >120 days 50% (47-53%)	Portugal[114]*: 69% (46-82%)†
	Symptomatic infection**	UKHSA [49]: 14-28d \forall 64% (62-66%)	UKHSA [49]: 70-98d \forall 29% (27-30%) >180d \forall 14% (12-16%)		UKHSA [49]: 14-28d \forall 68% (66-70%)	UKHSA [49]: >70d \forall 54% (52-56%)	USA [115]: 65% (62-68%), estimate vs. 2 doses almost identical. Qatar[116]*: Only VE relative to primary course (shows booster prevents 50% (47-53%) of symptomatic infections that occur with only a primary course).
	Onward transmission	No Data			No Data		
mRNA (Moderna,	Infection	USA [117]: 14-90 days	USA [117]: 91-180 days	USA [117]:	USA [117]: 14-60 days	USA [117]: >60 days	USA [117]:

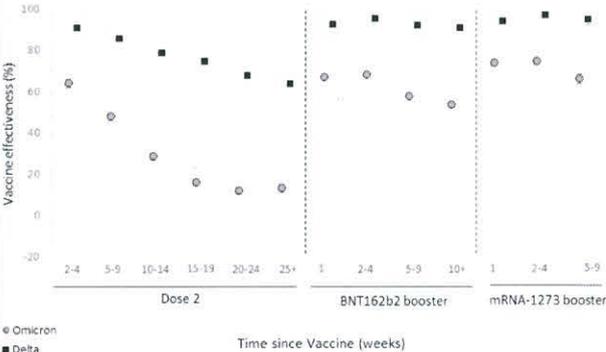
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Characteristic		Data							
or Moderna and Pfizer)		44% (35-52%)	24% (16-30%) 181-270 days 14% (10-17%) >270 days 6% (0.4 - 11%)	14% (11 – 17%)	72% (70-73%)	47% (41-54%)	70% (68% - 79%)	USA [81]*: 25% (20 – 30%)	USA [81]*: 62% (59 – 65%)
	Symptomatic infection	No data			No Data				
	Onward transmission	No data				No Data			
All vaccines	Infection			UKHSA (SIREN study) [49]: 32% (-6-57%)§ Netherlands: [118]* 33% (31-35%) Norway[119]*: 27% (6 – 49%)‡				UKHSA (SIREN study) [49]: 62% (41-75%)§ Netherlands: [118]* 68% (67-69%) Norway[119]*: 45% (26 – 57%)‡ Spain [120]*: Only VE relative to primary course (shows booster prevents 51% (50-52%) of infections that occur with only a primary course).	
	Symptomatic infection	No Data			No Data				
	Onward transmission			Norway[119]*:				Norway[119]*: % house contacts infected by:	

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Characteristic	Data
	<p>% house contacts infected by:</p> <ul style="list-style-type: none"> Unvaccinated 57% (51 -62%) Partial primary 42% (34 – 49%) Full primary 51% (47 – 55%)
	<p>Unvaccinated 57% (51 – 62%) Boosted 46% (36 – 55%) ‡</p> <p>* pre-print. Findings not peer reviewed so may change **additional data available from Hong Kong but appears to exclude those with severe disease. [121] VE 31% (2%-52%) after 2 doses, VE after 3 doses 20-59 years 72% (55-82%), 60+ years 72% (43%-86%) † Indirect calculation of VE by multiplication of estimates ‡pre-print with substantial changes in estimates since first posted. Note that study looks at transmission within households, where frequency of contact is higher, often resulting in lower VE estimates than for "per contact" VE estimates (for "leaky vaccines") ‡ Data points not reported in text. Estimates read from graph, below (Figure 1) § Data reported are for those with no prior COVID-19 infection. For those with prior infection these values are 60% (95% CI: 36-75) after 2 doses and 71% (95% CI: 56-82) after 3 doses</p> <p>In terms of VE against Omicron in comparison to VE against Delta, data from multiple studies [49, 52, 78, 79, 112, 122-124] all suggest reduced VE for 2-dose Pfizer vaccine regimens against symptomatic disease caused by Omicron compared with Delta.</p>

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Characteristic	Data
	<p data-bbox="459 824 944 846">Two doses of BNT162b2 with a BNT162b2 or mRNA-1273 booster dose</p>  <p data-bbox="375 1220 1289 1249">Figure 1: Pfizer vaccine effectiveness against symptomatic disease by period after 2 doses and after a booster[49]</p> <p data-bbox="375 1303 715 1326"><u>VE against hospitalisation / severe disease</u></p> <p data-bbox="375 1344 1364 1366">UKHSA COVID-19 Vaccine Surveillance Report from 27 January reported estimates from a test-negative case control study:</p> <ul data-bbox="402 1377 1492 1429" style="list-style-type: none"> • Protection against hospitalisation remained high, particularly after 3 doses. For a Pfizer booster (after either Pfizer or AstraZeneca primary 2 doses), VE against hospitalisation started at around 90% dropping to around 75% after 10 to 14 weeks.[125] <p data-bbox="375 1440 766 1462">South African data for VE against hospitalisation:</p> <ul data-bbox="402 1478 1540 1608" style="list-style-type: none"> • VE against hospitalisation for two doses of Pfizer was 70% (95%CI 62-76) during Omicron dominance (Delta dominance (93% [95%CI 90-94]) in South Africa.[126] Data were adjusted for age, sex, previous infection, surveillance week, geographic location, and CDC risk factors. • Results from another South African study show that VE against hospitalisation for the Janssen vaccine increased over time since the second (booster) dose. [127]

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Characteristic	Data
	<p>UK data for VE against hospitalisation (all vaccines combined):</p> <ul style="list-style-type: none"> For adults 18+ years, VE was 64% (95% CI: 54-71) 2 to 24 weeks after dose 2, declining to 44% (95%CI: 30-54) at 25+ weeks. VE increased to 92% (95% CI: 89-94) 2+ weeks after a booster dose, declining to 83% (95% CI: 78-87) at 10+ weeks.[49] For elderly aged 65+ years, booster VE was 94% (95% CI: 89-97) 2 to 9 weeks after a booster dose and 89% (95% CI: 80-95) at 10 weeks. VE after two doses was not reported in this analysis. [128] <p>US data:</p> <ul style="list-style-type: none"> VE against Omicron-related hospitalisation for two doses of Pfizer was 68% (95% CI: 58–75), and VE for three doses of Pfizer was 89% (95% CI: 84–92). VE against omicron-related hospitalisation after two or three doses remained steady for several months.[129] VE against Omicron-related ED admission for two doses of Pfizer was 60% (95% CI: 43–72) at <3 months and declined to 41% (95% CI: 32–50) at ≥6 months.[129] VE against Omicron-related ED admission for three doses of Pfizer was 78% (95% CI: 73–82) at <3 months and declined to 48% (95% CI: 14–69) at ≥3 months.[129] VE against Omicron-related hospitalisation for mRNA vaccines was 81% 14–179 days after dose 2, 57% ≥180 days after dose 2, and 90% ≥14 days after dose 3.[130] VE against Omicron-related ED and UC encounters for mRNA vaccines was 52% 14–179 days after dose 2, 38% ≥180 days after dose 2, and 82% ≥14 days after dose 3.[130] An evaluation of VE against infection from Omicron of those who received an extra primary dose or booster dose of a COVID-19 vaccine in residents in aged-care facilities, found that VE was 47% (45-59%) compared to those who only received a primary course of vaccination.[131] <p>Denmark data:</p> <ul style="list-style-type: none"> VE for two doses against hospitalisation 14-30 days post-vaccination during Omicron dominance was 62% (95% CI 46-74%), and 66% (95% CI 62-69%) at >120 days.[113] VE for three doses against hospitalisation 14-30 days post-vaccination during Omicron dominance <ul style="list-style-type: none"> 18-59 year old was 90% (95% CI 88-91%).[113] 60+ year olds was 94% (95% CI 93-96%).[113] VE for three doses against hospitalisation >120 days post-vaccination during Omicron dominance

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Characteristic	Data
	<ul style="list-style-type: none"> ○ 18–59-year-old was 33% (95% CI 1-55%). Note the large confidence interval as only 34 cases in a relatively small sample population (6,415) were included in this category. [113] ○ 60+ year olds was 77% (95% CI 71-82%).[113] <p>Hong Kong data for VE against severe COVID-19:</p> <ul style="list-style-type: none"> • Two doses of Pfizer for 20-59 years 95% (93-94%), 60-69 years 91% (85-95%), 70-79 years 89% (83-93%), 80+ years 85% (76-90%).[121] • Three doses of Pfizer for 20-59 years 99% (96-99%), 60-69 years 99% (97-100%), 70-79 years 100% (96-100%), 80+ years 96% (89-98%).[121] • Relative VE (compared to the primary course) against severe disease for 20-59 years was 68% (10-89%), 60-69 years 91% (61-98%), 70-79 years 95% (61-99%), and 80+ years 72% (25--90%).[121] The relative benefit of a booster was therefore greatest for those aged 60+ particularly those aged 70-79.[121] <p>VE against death</p> <p>Qatar: relative VE (compared to the primary course) against any severe, critical, or fatal COVID-19 for a Pfizer booster dose was estimated at 100.0% (95% CI: 71.4-100.0). [116]</p> <p>Hong Kong: relative VE (compared to the primary course) against mortality for 20-59 years was 83% (-29-98%), 60-69 years 82% (20-96%), 80+ years 66% (-1.3-89%).[121]</p> <p>Use of second booster dose (fourth dose)</p> <p>Some countries have begun recommending the administration of a second booster dose to elderly populations or individuals at increased risk of severe disease or exposure.</p> <ul style="list-style-type: none"> ○ <i>Israel:</i> On 22 January 2022, Israel's vaccine advisory committee recommended that those aged 18 and over be offered a fourth vaccine dose at least five months after their third dose or after recovering from the disease. (link) • The marginal VE against infection of a fourth dose, increased from second week after inoculation, peaking at 64% (62-66%) during the third week compared to those vaccinated with three doses of the Pfizer vaccine. However, VE begins to decline four weeks after inoculation, dropping to 29% (18-39%) after nine weeks.[132] • A study analysing clinical data from 1,049 adult patients with severe/critical COVID-19 admitted to hospital in January 2022 during Israel's Omicron wave, showed a fourth dose (administered ~2 weeks prior) conferred significant protection against mechanical ventilation or in-hospital death with an odds ratio of 0.51 (0.3-0.9%).[133]

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Characteristic	Data
	<ul style="list-style-type: none"> • Another study validated the efficacy of a fourth dose compared to three doses.[134] <ul style="list-style-type: none"> ▪ VE against PCR confirmed infection after days 7-30 post-vaccination was 45% (44-47%) and 14-30 days was 52% (49-54%). ▪ VE against symptomatic infection after days 7-30 post-vaccination was 55% (53-58%) and 14-30 days was 61% (58-64%). ▪ VE against hospitalisation after days 7-30 post-vaccination was 68% (59-74%) and 14-30 days was 72% (63-69%). ▪ VE against Death after days 7-30 post-vaccination was 74% (50-90%) and 14-30 days was 76% (48-91%). ○ Evaluation of VE of a fourth dose in people aged 60+ found that VE against infection relative to a third dose, peaked 3 to 4 weeks post-vaccination at an adjusted rate ratio of 2.1 (2.0 to 2.1).[135] <ul style="list-style-type: none"> ▪ The effect of a fourth dose against severe illness was even greater, providing significantly enhanced protection that peaked between weeks 4 to 6 post-vaccination with adjusted rate ratios ranging from 3.4 (2.5-4.7) to 4.3 (2.6-7.1).[135] ○ <i>UK:</i> The Joint Committee on Vaccination and Immunisation (JCVI) has advised an additional spring booster dose be given for the most vulnerable individuals in the population. (link) ○ <i>Europe:</i> The European Medical Authority are yet to receive any application for a second booster dose, though the Head of Vaccine Strategy has been reported in the media to say there is not yet enough evidence on its need (link). In May 2022 the ECDC noted it had recently deemed that the public health benefit of administering a second mRNA COVID-19 booster dose was clearest in those aged 80 years and above and immediate administration of a second booster dose in this population was found to be optimal in situations of continued high or increasing viral circulation.[9] ○ <i>Chile:</i> Media reports have stated that from 7 February 2022, eligibility for a fourth dose will be extended to people aged over 55 years who had a third vaccine dose at least 6 months prior. (link) ○ <i>Hungary:</i> In January 2022, Hungary made a fourth COVID-19 vaccine shot available to people who ask for it, after a consultation with a doctor, in order to combat growing Omicron infections. (link) ○ <i>South Korea:</i> In February 2022, populations that are at increased risk of severe disease (the elderly and immunocompromised) or at increased risk of exposure (healthcare workers) became eligible for a fourth dose. (link)

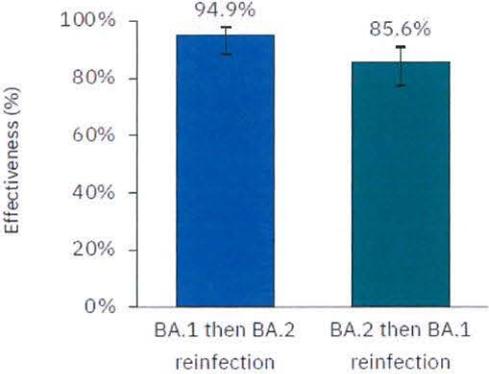
SARS-CoV-2 Variants Update

Characteristic	Data
	<p>Neutralising assays</p> <p>Neutralisation studies provided initial data predicting lower vaccine effectiveness against Omicron.[136-141] These data have now been superseded by effectiveness data.</p> <p>Cell-mediated responses</p> <p>While data remain preliminary, an increasing number of studies indicate that vaccination provides a durable T-cell response to Omicron infection.[136, 142-145]</p> <p>Immunopathological characteristics</p> <p>Omicron breakthrough patients had a more robust IFN-γ response (critical for viral clearance) and lower concentration of proinflammatory cytokines at the acute phase of infection. They also had lower frequency of immature neutrophils indicating milder inflammatory response.[69]</p> <p>Prior Infection</p> <p>A Qatar study estimated effectiveness of prior infection against preventing Omicron symptomatic re-infection at 61.9% (95% CI: 48.2-72.0) after excluding vaccinated individuals. Effectiveness against hospitalisation/death was 87.8% (95% CI: 47.5-97.1), however both vaccinated and unvaccinated individuals were included in this analysis. [146]</p> <p>The UKHSA reported an unadjusted effectiveness of 44% (95% CI: 4-67) against infection in unvaccinated healthcare workers (SIREN cohort) who had a prior infection.[49]</p> <p>The Imperial College London COVID-19 Response Team (Report 49 Updated 20 December 2021) estimated that Omicron was associated with a 5.41-fold (95% CI: 4.87-6.00) higher risk of reinfection than Delta, controlling for vaccination, age, and ethnicity. The relative risks were 6.36 (95% CI: 5.23-7.74) and 5.02 (95% CI: 4.47-5.67) when estimated separately for unvaccinated and vaccinated cases, respectively. It was estimated that the protection prior infection (with most likely a non-Omicron variant) provides against reinfection with Omicron is 19% (95%CI: 0-27%). The data analysed was UKSA and NHS data from PCR-confirmed SARS-CoV-2 cases with no history of recent travel.[147]</p> <p>A New Zealand study investigated neutralising antibody activity over time using sera from a cohort of Southern District Health Board PCR-confirmed cases infected between 11 March and 5 April 2020. Neutralising antibody activity was assessed to Omicron and earlier variants, including Delta, at 11 months post infection, with a key finding being the limited cross-neutralisation of Omicron from a previous non-Omicron infection.[148]</p>

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Characteristic	Data
	<p><u>Omicron reinfection</u></p> <p>UK data from the COVID-19 Infection Survey reported in February 2022 that there were more reinfections in a month when Omicron became the dominant variant (764 reinfections), than in the previous 18 months (586 reinfections).[149] The reinfection rate was reported as increasing from 11.7 to 180.3 per 100,000 people since Omicron became the dominant variant (proportion vaccinated not specified).</p> <p>Earlier COVID Infection Survey reported in January stated that unvaccinated people were approximately twice as likely to be re-infected than people who had their second vaccine 14 to 89 days previously. Of note, this data was drawn from both Delta-dominant and Omicron-dominant periods.[149]</p> <p>A study of neutralising antibody activity found that Delta breakthrough infections showed 10.8 times higher antibody titres against ancestral wild type virus compared to Omicron breakthrough infections. Following either Delta or Omicron breakthrough infection, limited variant-specific cross-neutralizing immunity was observed. The authors concluded that the results suggest Omicron breakthrough infections are less immunogenic than Delta breakthrough infections and therefore provide reduced protection against reinfection.[150]</p> <p>Data from Qatar indicate strong protection against Omicron sub-lineage reinfection provided by a previous Omicron infection (regardless of the sub-lineage causing the primary infection) with an effectiveness of over 85%.[47].</p>

SARS-CoV-2 Variants Update

Characteristic	Data						
	<p data-bbox="517 853 935 898">Effectiveness of Omicron sub-lineage infection against subsequent Omicron reinfection</p>  <table border="1" data-bbox="395 927 884 1301"> <thead> <tr> <th>Reinfection Scenario</th> <th>Effectiveness (%)</th> </tr> </thead> <tbody> <tr> <td>BA.1 then BA.2 reinfection</td> <td>94.9%</td> </tr> <tr> <td>BA.2 then BA.1 reinfection</td> <td>85.6%</td> </tr> </tbody> </table> <p data-bbox="368 1384 1493 1458">Therapeutics - Oral antivirals and remdesivir have been shown to be effective in recent <i>in vitro</i> studies, and their use is increasing internationally. The activity of monoclonal antibodies against Omicron appears to vary according to Omicron sublineage on the basis of emerging data.</p> <p data-bbox="368 1476 520 1498"><u>Antibody products</u></p> <p data-bbox="368 1516 1517 1563">The FDA (statement of 24 January) have revised authorisations for two monoclonal antibody treatments – bamlanivimab and etesevimab (administered together) and REGEN-COV (casirivimab and imdevimab; Ronapreve). These treatments are not authorised for use at present in</p>	Reinfection Scenario	Effectiveness (%)	BA.1 then BA.2 reinfection	94.9%	BA.2 then BA.1 reinfection	85.6%
Reinfection Scenario	Effectiveness (%)						
BA.1 then BA.2 reinfection	94.9%						
BA.2 then BA.1 reinfection	85.6%						

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Characteristic	Data
	<p>any U.S. states, territories, or jurisdictions due to Omicron being estimated to comprise more than 99% of US COVID-19 cases as of January. (Link)</p> <p>Evusheld (cilgavimab + tixagevimab) has an FDA emergency use authorisation (EUA) as pre-exposure prophylaxis for prevention of COVID-19. The FDA have recently authorised an increase in the dose of both cilgavimab and tixagevimab for this indication from 150mg to 300mg on the basis of data suggesting the higher dose was more likely to be effective against the Omicron sublineages BA.1 and BA.1.1. (link)</p> <p>A number of laboratory studies have now investigated the activity of commercially available monoclonal antibodies and products in development against the Omicron variant.</p> <p>Early <i>in vitro</i> studies showed Omicron was resistant to neutralisation by a number of monoclonal antibodies including casirivimab + imdevimab (Ronapreve) [151-156], while studies indicated that sotrovimab retained some neutralisation activity against Omicron <i>in vitro</i>. [151-156] An animal study (mice) from the University of Liverpool investigating the virological efficacy of casirivimab + imdevimab (Ronapreve) showed no reduction in viral RNA in lung and nasal turbinate tissue compared to saline for Omicron but a reduction for Delta. [157]</p> <p>Recent <i>in vitro</i> studies suggest a differential activity of monoclonal antibodies to specific Omicron sublineages BA.1, BA.1.1 and BA.2, with sotrovimab reported as retaining some 'appreciable' activity against BA.1 [158] [159] and BA.1.1. [158], but BA.2 showing greater resistance to sotrovimab. [158] [159] Iketani et al. investigated 19 monoclonal antibodies and report that the recently FDA authorised monoclonal antibody LY-CoV1404 (bebtelovimab) is the only clinically approved/authorised monoclonal antibody treatment to have adequate activity against all three main Omicron sublineages. [158]</p> <p>The Ohashi et al. <i>in vitro</i> study also found that imdevimab (but not casirivimab) showed 'minor activity' against BA.2, but not against BA.1. [159] An additional Japanese study by Takashita et al was reported in a letter to the Editor of the New England Journal of Medicine (NEJM) published on March 9. The authors reported activity of imdevimab and some activity of casirivimab against BA.2 but not BA.1. [160] They found that for casirivimab, the titre required for BA.2 was higher than for earlier variants, including Delta. These reports in the literature are an interesting development for the New Zealand context, as casirivimab + imdevimab (Ronapreve) has previously received Medsafe approval as a COVID-19 treatment, with stock available in the country. Prior to these reports, the evidence has indicated casirivimab + imdevimab (Ronapreve) is ineffective as a treatment against Omicron.</p> <p><u>Antivirals</u></p>

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Characteristic	Data
	<p>Antiviral agents including remdesivir and newer oral antivirals are expected to be effective against the Omicron variant on the basis of their mode of action. <i>In vitro</i> studies provide experimental evidence of preserved effect of remdesivir, molnupiravir and Paxlovid against Omicron, including the Omicron sub-lineages.</p> <p>A non-peer reviewed cell-culture study showed that the antiviral drugs molnupiravir (Legevrio), Paxlovid, remdesivir, acriflavine, and AT-527 will likely retain efficacy for the omicron variant.[161] An <i>in vitro</i> study using live virus collected from nasal swab specimens demonstrated that the activity of the antivirals remdesivir, molnupiravir (specifically, its active metabolite EIDD-19331) and PF-07321332 (nirmatrelvir) was preserved against Omicron.[162] Antiviral assays completed in a Belgian study similarly reported retained effect of remdesivir, EIDD-19331 and nirmatrelvir against all variants studied, including Omicron. [163] Note that the oral antiviral Paxlovid is a combination of PF-07321332 and ritonavir, with the PF-07321332 responsible for blocking viral replication (whereas ritonavir acts to slow the breakdown of PF-07321332). Further <i>in vitro</i> studies supported by Pfizer showing that nirmatrelvir is effective against Omicron have also recently been reported as pre-prints.[164, 165] (Link) <i>In vitro</i> data from Japan reported in a January 26 NEJM editorial showed preserved effect of remdesivir, molnupiravir and PF-07394814 (active component of Paxlovid) against Omicron.</p> <p>A further <i>in vitro</i> study using a cell culture infection assay demonstrated that nirmatrelvir and also EIDD-1931 (molnupiravir's active metabolite) achieved a dose-dependent reduction in viral RNA for all variants studies, including Omicron BA.1 and BA.2 sublineages.[159] Takashita et al reported findings of an <i>in vitro</i> study showing that BA.2 had similar susceptibility to remdesivir, molnupiravir and nirmatrelvir as the ancestral strain and other variants of concern.[160] An animal study (hamsters) demonstrated that molnupiravir treatment significantly reduced Omicron viral replication and shedding. [166] Another study reported that molnupiravir and nirmatrelvir reduced viral infection in the respiratory organs of hamsters infected with BA.2.[167]</p>

SARS-CoV-2 Variants Update

Detection

Section updated: 15 March
2022

More PCR tests recognised as unable to detect Omicron. Saliva testing might offer advantages for Omicron over nasal swabs. RATs under spotlight but evidence is mixed for reduced analytical sensitivity, including two NZ approved RATs.

PCR

PCR tests continue to be appropriate for diagnosis of SARS CoV-2.[168] On 23 December, the World Health Organization stated that PCR tests that include multiple gene targets are unlikely to be affected and should continue to be used to detect SARS-CoV-2 infection, including the Omicron variant.[169] However, the FDA has identified three COVID-19 molecular tests (from Applied DA Sciences, Meridian Bioscience and Tide Laboratories) that are not able to detect the Omicron variant because they target genes with deletions in Omicron. [170] ThermoFisher TaqPath PCR test can detect S gene target failure - an early marker to distinguish between Omicron and Delta, pending sequencing confirmation.[168] The PCR proxy marker RNA-dependent RNA polymerase (RdRp) target delay was associated with a lower risk of hospital admission.[171] To account for the changing receptor binding domain of the SARS-CoV-2 spike protein, assays capable of rapidly and accurately identifying variants including Omicron are being reported to have discriminated against a S-gene dropout Delta specimen.[172] A Malaysian study evaluated the Allplex SARS-Cov-2 Master Assay and Variant Assay and found that the assays should detect Omicron (B.1.1.529).[173]

Two pre-print studies suggest saliva testing might detect more infections (and possibly earlier) than nasal swabs in PCR testing.[174, 175]

RATs

Evidence on the performance of RATs is of two main types: analytical studies that use stored/'spiked' samples of the virus; and clinical studies that measure real-world performance. It is generally understood that laboratory experiments cannot fully replicate the real-world application of a test kit and clinical performance studies are required.

Due to the time needed to establish and perform research studies the current evidence base contains more analytical than clinical studies, refers to the BA.1 variant, and is mostly from pre-print sources. Summary of current evidence on detection of the Omicron variant:

- Published analytical studies - four investigated the performance of various RATs. Three found similar sensitivities for both Omicron and Delta [176-178], and one found reduced sensitivity for Omicron.
- Pre-print analytical studies - four (one using CareStart, and one using Clintest RATs that are authorised in NZ,) found no change in sensitivity between Omicron and Delta [179-182], and one reported some reduced sensitivity. [183]
- Pre-print clinical performance study - a good quality study using BinaxNOW (not currently authorised in NZ) found sensitivity of only 52.1% compared to RT-PCR in Omicron cases confirmed by whole genome sequencing. [184] However, sensitivity could be improved to 75.7% by changing the RT-PCR positivity threshold from Ct of 40 to Ct of 30. Unfortunately, this study did not compare sensitivity with other variants. A low quality study found two RATs (neither authorised in NZ) yielded higher false negative rates. [175] A moderate

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Characteristic	Data
	<p>quality study found the performance of 3 RATs (including BD Veritor that is authorised in NZ) in detecting Omicron was not inferior to Delta.[185]</p> <ul style="list-style-type: none"> • <u>Pre-print studies on swab sample site</u> - four addressed the issue of whether sensitivity varies by swab sample site. All assumed cases were Omicron during large community outbreaks. Three studies used the Abbott Panbio RAT (which is authorised in NZ) and found that mid-turbinate swabs perform better than buccal. [186] The second study used a RAT not currently authorised in NZ and found oral cheek specimen was significantly less sensitive than nasal swab. The third study compared nasal, throat, and combined nasal/throat swabs and found support for the combined method is self-perceived asymptomatic individuals.[187] The fourth compared sensitivity for MT (66.7%), OP (82.2%) and saliva (72.5%) specimens, concluding the data do not support a preferred sample type for Omicron [188]. • <u>Government reports</u> – The UKHSA published a preliminary analysis of the performance of four RATs with Omicron on 17 December 2021. [168] One of these is authorised in NZ (Orient Gene). They reported the RATS “all of which target the nucleocapsid protein, have detected the new Omicron variant that contains 4 amino acid changes from the original viral sequence.” The FDA state they are working on the issue of Rat performance [189], the ECDC’s latest guidance is pre-Omicron [190], and the WHO reported in December 2021 that no reduction in RAT sensitivity has been reported so far.[191] • <u>Manufacturer statements</u> - most RAT manufacturers have issued statements about the ability of their products to detect Omicron.[192-194] Unfortunately, these tend to lack supporting evidence, and can therefore be considered very low quality. <p><u>Summary</u> - Overall, it is known that rapid antigen tests (RATs) are less sensitive and less likely to detect very early infections. Most analytical studies (six versus two) indicate that RATs detect Omicron with similar sensitivity to Delta. There are very few clinical studies available to date. However, one study using a RAT authorised in NZ found that detection of Omicron is not inferior to Delta.</p> <p>Available evidence indicates that nasal swabs may slightly be superior to throat swabs, and one study suggests a combined sample may be even better. However, the available evidence does not seem to support changing current testing practices at this time.</p> <p>To date there is a paucity of evidence about RATs and the BA.2 variant or newer lineages. This summary is therefore limited to detection of BA.1.</p>

New signals

The risk of clinically significant emerging variants is considered to be high, according to the WHO.[195] The WHO has expressed concern that during recent months, some countries have significantly reduced SARS-CoV-2 testing. They caution that unless robust surveillance systems are retained, countries may lose the ability to accurately interpret epidemiological trends, implement the appropriate measures necessary to reduce transmission and monitor and assess the evolution of the virus.[24]

This section covers BA.4/BA.5 and then BA.2.12/ BA.2.12.1/ BA.2.12.2.

BA.4 and BA.5

BA.4 and BA.5 are Omicron sub-lineages that were first detected in South Africa in January and February 2022 respectively, and are now the dominant variants there.[9] They have now been detected in over 20 countries. The WHO began tracking these sub-variants in mid-April. Both BA.4 and BA.5 had been identified at the NZ border as of 4 May 2022.[196]

BA.4 and BA.5 have many mutations in common with the original Omicron variant, but have more in common with the BA.2 variant.[12] They also have a number of additional mutations. The BA.4 and BA.5 sub-variants tend to be discussed together because the mutations in their spike protein gene are identical (though they differ in mutations found elsewhere in the genome).[12] Both lineages contain the amino-acid substitutions L452R, F486V, and R493Q in the spike receptor binding domain compared to BA.2.[9] SGTF is present in BA.4 and BA.5.[8] There have been limited studies on BA.4 and BA.5 to date, and so far none of them have been peer-reviewed.[12] Preliminary studies suggest that BA.4 and BA.5 have a significant change in antigenic properties compared to BA.1 and BA.2, especially compared to BA.1.[9]

BA.4 and BA.5 are driving a spike in new COVID-19 cases in South Africa, and they both seem to have a growth advantage over other sub-lineages of Omicron, according to the WHO.[\(link\)](#) The estimated daily growth advantage for BA.5 over BA.2 is 13% in Portugal, similar to the 12% daily growth advantage previously reported by South Africa.[9] The growth advantage for BA.4 and BA.5 is thought to be likely due to their ability to evade immune protection induced by prior infection and/or vaccination, particularly if this has waned over time.[9] The ECDC has noted that the high growth advantages reported for BA.4/BA.5 suggest that these variants will become dominant in the EU/EEA in coming months, although the current proportion of these variants is currently low. Although there is currently no indication of any change in severity for BA.4/BA.5 compared to previous Omicron lineages, if COVID-19 case numbers increase substantially, the ECDC cautions that some level of increased hospital and ICU admissions is likely to follow.[9] Limited available data indicates that both BA.4 and BA.5 are capable of escaping immune protection induced by infection with BA.1.[9] One study, (not yet peer-reviewed) isolated live BA.4 and BA.5 virus and tested for neutralizing immunity using blood samples from participants previously infected with BA.1 and with or without vaccination.[197] The vaccinated group (3 doses) showed approximately 5-fold increased neutralization capacity of BA.4/BA.5 when compared to the unvaccinated group. This indicates better protection in vaccinated individuals, although it is likely this protection will decrease over time with waning.[197] The ECDC has noted there is currently no evidence regarding impact on transmissibility for BA.4 and BA.5.[11]

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The number of countries reporting detection of the BA.4 and BA.5 variants is rising, along with the number of cases.[12] The WHO has noted that the limited evidence to date does not indicate a rise in hospital admissions or other signs of increased severity with BA.4 and BA.5, however at this stage the preliminary data and short follow-up of cases does not allow for conclusions on disease severity to be drawn at this stage.[8]

Omicron subvariants BA.4 and BA.5 are generally still circulating at low levels, with <700 cases of BA.4 detected across at least 16 countries and >300 cases of BA.5 detected across at least 17 countries as of mid-May.(link) BA.4 and BA.5 appear to be growing in prevalence. [12]The WHO weekly report from 4 May reported that the Africa Region had showed an increase in cases for the second consecutive week following a decreasing trend observed since January 2022. The highest number of new weekly cases were reported from South Africa (approx. 32,000 new cases, +67%).[8] Although the number of sequences reported is low, the UKHSA warns that the apparent geographic spread suggests that the variant is transmitting successfully.[5]

Table 4: BA.4 and BA.5

Variant	Genomic features	Geographic distribution and prevalence	Characteristics/ possible impact
BA.4	<p>BA.4 shares all mutations and deletions with the BA.2 lineage except the following:[5]</p> <ul style="list-style-type: none"> S: 69/70 deletion; R408 (WT, wild type)*, L452R, F486V, Q493 (WT); ORF 7b: L11F; N: P151S; Synonymous SNP G12160A. E484A. <p>*Note, only a subset of BA.4 samples have the S: R408S mutation.</p>	<p>BA.4 has been found in multiple countries, with the highest prevalence in South Africa where the first known sample was collected on the 10 Jan 2022. [1]</p> <p>According to data by cov-lineages.org as of 16 May 2022, BA.4 was most commonly reported in South Africa (69% of global BA.4 cases), followed by Austria (7%), the UK (6%), the US (5%), and Denmark (3%).</p> <p>NZ: As of 4 May 2022, two cases of BA.4 had been detected at the New Zealand border, with the first case reported on 25 April.</p> <p>ESR notes that wastewater analysis for the period 17 to 30 April did not detect BA.4,</p>	<p>Although the number of cases of BA.4 is relatively low, the geographic spread indicates that the variant is successfully transmitting. [1]</p> <p>In an informal report from Gauteng, BA.4 was observed to have a 0.09 per day growth rate, similar to BA.2.(link) A preprint similarly reported a growth advantage of approximately 0.08 (95% CI: 0.07 – 0.09) compared to BA.2 in South Africa.[198]</p> <p>The mutation on the spike (69/70 deletion) is associated with S-gene target failure. This will have implications for detection. [1]</p> <p>Spike L452R has been associated with increased infectivity and increased cell fusion.[199] Mutations to L452R spike protein in BA.4 have been seen other variants including Delta, Epsilon, Kappa and BA.5. This mutation appeared to play a role in the increased spread of Delta.</p> <p>The mutations to E484A and F486V have been associated with immune-system escape. F486V mutation may provide a key site for escape of antibodies that are produced by both vaccine/infection induced immunity.[197]</p>

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Variant	Genomic features	Geographic distribution and prevalence	Characteristics/ possible impact
		indicating no community cases of BA.4 at this stage.[196]	Although data showed BA.4 to be able to escape BA.1 infection elicited neutralising immunity[197] (see study in overview of this section for more details), there is currently no evidence that this is also true for BA.2 past infections. This is relevant in the New Zealand context where >80% of Omicron infections in New Zealand have been BA.2.[196] Ongoing studies from other countries that experienced a BA.2 wave would help inform on the potential impact of BA.4 in the New Zealand context.[196]
BA.5	Shares all the same mutations/deletions as BA.2 except the following:[5] S: 69/70 deletion, R408 (WT) L452R, F486V, Q493 (WT); ORF6:D61 (WT) M: D3N; synonymous SNPs: A27038G, G12160A, and C27889T.	According to data by cov-lineages.org as of 16 May 2022, BA.5 was most commonly reported in South Africa (45% of global cases), Germany (22%), Portugal (13%), the UK (9%) and the US (3%). The Portuguese National Institute of Health estimated that BA.5 accounted for ~37% of positive cases as of 8 May 2022. BA.5 is predicted to become the dominant variant in Portugal by 22 May 2022.[9] As of May 2022 BA.5 has been detected at the New Zealand border. (link) ESR has noted that no BA.5 was identified in wastewater testing in NZ for the period of 17-30 April, indicating negligible community cases.[196]	Due to the similarities in mutations, BA.5 has similar implications to BA.4. BA.5 does not have the geographic spread of BA.4 at this stage.[1] It does have a similar observed growth rate of 0.11 in the location of primary focus. This was also reported in a preprint, which reported a growth advantage of approximately 0.12 (95% CI: 0.09 – 0.15) compared to BA.2 in South Africa.[198] This is comparable to growth rates seen in BA.4 and BA.2. The Portuguese National Institute of Health has estimated a daily growth advantage for BA.5 over BA.2 of 13%, which is similar to the 12% daily growth advantage previously reported by South Africa.[9] BA.5 has identical spike proteins to BA.4, therefore it is likely to behave similarly.[198] It has the mutations to E484A and F486V, which have been associated with immune escape as well as the L452R mutation, associated with increase affinity for receptor binding, and therefore cell entry.[198] Like BA.4, BA.5 has shown the neutralisation evasion against vaccination (3-doses) and vaccination with prior BA.1 infection.[197] This has not been shown in prior BA.2 infections which have accounted for the majority of New Zealand omicron infections.



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BA.2.12, BA.2.12.1 and BA.2.12.2

On 13 April the New York State Department of Health announced the emergence of two Omicron subvariants in New York State, BA.2.12 and BA.2.12.1, both sub-lineages of BA.2.[200] The subvariants have been estimated to have a 23% – 27% growth advantage above the original BA.2 variant. State officials had determined that these highly contagious new variants were likely contributing to the higher-than-average infection rates in Central New York over the previous few weeks. The Department's findings are the first reported instances of significant community spread due to the new subvariants in the United States. The Department reported no evidence of increased disease severity by these subvariants.[200]

The [CDC](#) estimated 36.5% (95% PI 28.9-44.9%) of COVID-19 cases in the United States to be BA.2.12.2 as of 30 April 2022.

BA.2.12.1 has been shown to have a substitution mutation at the L452 location (L452Q). This is very similar to BA.4/B.5 which have L452R.[198] A mutation to L452 location has arisen independently in other variants including Delta, Epsilon, Kappa. This mutation is linked to immune evasion and cell binding, making it a mutation of interest in new variants.[201] BA.2.12.1 has been reported to have increased ACE2-binding affinities in comparison to BA.1, implying increased cell binding.

BA.12.2 has been shown to have increased immune evasion abilities when compared to BA.2.[201] A pre-print posted on 2 May found that BA.12.2 has strong neutralising evasion against plasma taken from people with previous BA.1 infection (both 3-dose vaccinated and unvaccinated).[201] This neutralising evasion was also seen in other Omicron subvariants, including BA.4/BA.5.

BA.2.12.1 and BA.2.12.2 have been detected in New Zealand from travellers returning 11 and 15 April respectively.

Recombinants

Section updated: 25 April 2022

What are recombinants and how are they formed?

Viruses naturally evolve and are continuously changing as a result of genetic selection.[202] They can undergo minor genetic changes through mutation, as well as major genetic changes through recombination.[202] Mutation occurs when an error is incorporated in the viral genome, and recombination occurs when two viruses infect the same host cell and exchange genetic information, creating a novel virus. Recombinants can emerge when more than one variant infects the same person (or animal) at the same time ('co-infection') – this allows the variants to interact during replication, mixing their genetic material and forming new combinations.[173]

Genetic recombination is a common evolutionary mechanism among coronaviruses and is thought to be critical for coronavirus diversity and the emergence of SARS-CoV-2, MERS-CoV, SARS-CoV, and other zoonotic coronaviruses.[203] Genetic recombination events occur often in natural reservoirs, leading to the emergence of new viruses. The possibility for coronaviruses to transmit between species makes the emergence of novel viruses a particular threat to human and animal health.[204] Recombination allows viruses to overcome selective pressure and adapt to new hosts and environments.[205] Many recombinants will never be spread, but some do. It has been recently proposed that the prototype Omicron variant B.1.1.529 may have been generated by genomic recombination of two early SARS-CoV-2 lineages in the spike protein Coding Sequence.[205]

Recombinant events become more likely when case numbers are higher.[206] Liu et al (2022) note that the rapid and extensive spread of SARS-CoV-2 in humans has contributed additional mutational variability in this genome, increasing opportunities for future recombination.[205] The frequency of creation of recombinants between two variants depends on the duration of their co-circulation, the time until viral clearance, and the number of people exposed to both viruses.[207]

Collaborations between scientists are essential to verify possible new variants. For example, a supposed Delta-Omicron recombinant found in January in Cyprus turned out to be likely due to laboratory contamination.[208]

Of note, several of the emerging recombinants have been referred to as Deltacron, however this term is also being widely used in popular press as an umbrella term referring to any Delta/Omicron recombinants. 'Deltacron' is a non-scientific and simplistic term because there are many possible recombinants of various parts of Omicron and Delta genomes (i.e. different versions of Deltacron). Having two variants recombine does not necessarily mean they will share the most severe or concerning features of each variant.

The WHO continues to closely monitor and assess the public health risk associated with recombinant variants, alongside other SARS-CoV-2 variants, and will provide updates as further evidence becomes available.[195] The Pango dynamic nomenclature system gives recombinant viruses a two-letter abbreviation starting with X.

Three SARS-CoV-2 recombinant variants with evidence of person-to-person transmission have been reported: XD (AY.4/BA.1 recombinant, where AY.4 is Delta), XE (BA.1/BA.2 recombinant) and XF (another AY.4/BA.1 recombinant). XE was first reported in New Zealand on 23 April 2022.[209] The latest sequencing data from ESR had not found any of the other known recombinant variants, or an original recombination variant, in New Zealand. The significance of the existing recombinants, and potential future recombinants is not yet known.

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Table 5 below outlines the recombinant lineages designated by Pangolin which are currently being monitored by the UKHSA as part of horizon scanning.[3] These recombinants are XD, XE, and XF.

Table 5: Recombinant lineages XD, XE and XF

Recombinant lineage	Parents	Genomic features	Geographic distribution and prevalence	Characteristics/ possible impact
XE	Omicron BA.1 and Omicron BA.2	XE contains BA.1 mutations for NSP1-6 and BA.2 mutations for the remainder of the genome. It also has three mutations that are not present in BA.1 or BA.2 sequences: NSP3 C3241T and V1069I, and NSP12 C14599T.[1]	XE has predominantly been isolated and sequenced in the UK, with the first case detected on 19 January 2022. [3, 13] As of 3 May 2022, a total of 1,399 episodes of V-22APR-02 have been reported in England.[5] XE shows evidence of community transmission within England,[1] however it remains at a low prevalence - between 3 April 2022 and 3 May 2022, XE accounted for 0.7% of sequenced cases reported in England.[5] XE was first reported in New Zealand on 23 April 2022.[209]	A UKHSA analysis using data up to 30 March 2022 found XE has a growth rate 12.6% above that of BA.2.[1] UKHSA notes this estimate has not remained consistent as new data have been added and cannot be interpreted as an accurate estimate of growth advantage.[1] WHO stated on April 5 th that XE has been estimated at having a ~10% transmission advantage compared to BA.2, however this finding requires further confirmation.[210]
XD [206]	Delta and Omicron BA.1	The XD recombinant lineage is a Delta AY.4 genome that has acquired an Omicron BA.1 spike sequence (nucleotide positions 21,643 to 25,581). XD contains the unique mutation NSP2: E172D.[3]	XD is present in several European countries but as of 01 April it had not been detected in the UK.[1] The earliest collection date for XD samples is January 2022. UKHSA reported that total of 68 XD samples in GISAID met the XD definition on 01 April, of which 66 were from France, one from the Netherlands, and one from Belgium.[1]	The WHO weekly epidemiological report of 29 March stated that no new evidence indicates that XD is associated with higher transmissibility or more severe outcomes.[195] XD, which has an Omicron S gene incorporated into a Delta genome, is present primarily in France but has not been detected in the UK. Whilst the total number of genomes is still small, it has been designated on the

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				basis that data published from France suggests that it may be biologically distinct.[1]
XF	Delta and Omicron BA.1	The XF lineage is a recombinant of Delta and BA.1 with a break point near the end of NSP3 (nucleotide 5,386).	In the UK, 39 sequences samples have been identified and validated as part of the XF lineage since 7 January 2022.[3] XF caused a small cluster in the UK but has not been detected since mid- February.[3] There is currently no evidence for XF samples from non-UK countries on GISAID.	Given the lack of evidence for recent UK samples from this lineage it is thought unlikely to be associated with sustained community growth.[3]

The UKHSA also continues to list a BA.1/BA.2 recombinant (with unique mutation C3583T) as a signal currently under monitoring and investigation.[5]

Effectiveness of infection prevention and control/ public health measures

Section updated: 13 May 2022

This section outlines some of the available literature about the effectiveness of infection prevention and control (IPC) and public health measures. It is not intended to be a systematic review of all available evidence, but to provide an overview of available evidence. Papers that relate to SARS-CoV-2 in general or earlier variants are in the 'general' section. This is followed by a section which includes papers specific to Omicron. However it is worth noting that "while these subvariants are new, the tools to combat them are not" (New York State Health Commissioner).[200]

General

- A modelling study estimating remaining burden of COVID-19 hospitalisations and deaths in European countries found that there could be still more than 3 million hospitalisations and 640,000 deaths, but that burden varies between countries, with much higher potential remaining burdens in countries that have experienced less transmission so far and/or have lower vaccine coverage and/or have older populations.[211] Furthermore, that non-pharmaceutical interventions are required to limit severe COVID-19 outcomes.
- An observational study on the impact of contact tracing and testing on controlling COVID-19 without lockdown in Hong Kong found that restoring social distancing measures without maintaining tracing and testing efficiency was not enough to prevent growth of the outbreak; ii) a rise in number of daily cases increased the probability of confirmation delay among contact-traced cases; iii) testing at-risk groups reduced the probability and the duration of confirmation delay among contact-traced cases.[212]
- A cross-sectional study comparing OECD countries in evaluating economic outcomes found that non-pharmaceutical interventions effectively contained the outbreaks and had positive impacts in lowering unemployment rates.[213]
- A modelling study points to the role of super-spreader events in the contribution of novel variant predominance. Suggesting that from a public health perspective the results give weight to the need to focus NPIs on preventing large super-spreader events (10 or 20 secondary infections from single infected individual).[214]
- A preprint study on social gatherings and transmission found that small gatherings, due to their frequency, can be important contributors to transmission dynamics and that because gathering size distributions are "heavy-tailed", a meaningful reduction in new cases only occurs once restrictions are set quite low (to achieve reduction in cases of 50% or more, restrictions must be set below 30 in most settings).[215]
- Transmission of SARS-CoV-2 and the effectiveness of NPIs depend strongly on age related factors, including differences in contact patterns and pathophysiology.[216] A recently published modelling study found that the risk of a local outbreak depends on the age of the index case, and explored the effects of non-pharmaceutical interventions (NPIs) targeting individuals of different ages. Social distancing policies that reduce contacts outside of schools and workplaces and target individuals of all ages were predicted to reduce local outbreak risks substantially, whereas school closures were predicted have a more limited impact. The authors note that when different NPIs are used in combination, the risk of local outbreaks can be eliminated. In addition, the authors state that heightened detection of infectious individuals reduces the level of NPIs required to prevent local

outbreaks, particularly if enhanced detection symptomatic cases is combined with efforts to find and isolate non-symptomatic infected individuals.[216]

- A recently published Australian study aimed to establish a predictive model to assist stakeholders in decision-making regarding timely and effective interventions based on limited surveillance data in the early stages of an outbreak. It is reportedly the first of its kind to integrate existing public health interventions and epidemic severity to quantify the risk of COVID-19 resurgence. The model integrates existing public health interventions, population vaccination coverage, and the transmissibility of variants. Non-pharmaceutical interventions (NPIs) are important tools for COVID-19 control, and experience has demonstrated that early intervention results in more effective control of outbreaks.[173] However, the emergence of new, more transmissible SARS-CoV-2 variants has changed the thresholds for public health interventions. The study found that in the early phase of an outbreak, containing a wildtype-dominant epidemic to a low level (≤ 10 cases/day) would require effective combinations of social distancing and face mask use interventions to be commenced before the number of daily reported cases reaches 6. Containing an Alpha-dominant epidemic would require more stringent interventions that commence earlier. For the Delta variant, public health interventions alone would not contain the epidemic unless the vaccination coverage was $\geq 70\%$.[217]
- An Australian study on digital contact tracing found the COVIDSafe app was not sufficiently effective to make a meaningful contribution to the COVID-19 response in New South Wales (Australia's most populous state) over a 6-month period (May to November 2020).[218]
- A preprint study suggested that mobility restriction and testing were effective interventions even in the presence of vaccination in India.[219]
- A German modelling study found indicate that local containment of outbreaks and maintenance of low overall incidence of COVID-19 is possible even in densely populated and highly connected regions. They also found that if less strict public health interventions are used, substantially increased testing rates are needed to compensate.[220]
- A Canadian study found although vaccinations helped to control the COVID-19 infection rate, the stay-at-home order (April 7th 2021) resulted in approximately a 37% reduction in COVID-19 prevalence one week after the intervention's effective date. Therefore, Ontario's strict lockdown policy, including several NPIs, mitigated the COVID-19 surge during the third wave.[221]
- A systematic review of economic evaluations of COVID-19 interventions found that treatment, public information campaigns, quarantining identified contacts/cases, cancelling public events, and social distancing were deemed highly cost-effective. The authors also concluded that accounting for broad non-health impacts and distributional effects is essential for a comprehensive assessment of interventions' value.[222]
- Results of an Italian study imply that school reopening generated an increase of one third in cases.[223]

Papers specific to Omicron

- A modelling study suggests that in contrast to Delta, infection prevention control settings in South Africa and UK will be insufficient to control the Omicron outbreak in those countries.[224]
- A French study discussed the significance of a higher viral load on airborne transmission within the context of COVID-19 with new variants and its implication for health policies.[225] Their conclusion was that the present norms of ventilation, already insufficient, are not respected, especially in a variety of public premises, leading to high risk of contamination.

Zoonotic reservoirs of SARS-CoV-2

- SARS-CoV-2 is a zoonotic virus, which means that it can spread between humans and animal.[226]
- It most likely has a natural reservoir in bats, as suggested by its close genomic sequence identity to other SARS-CoV viruses.[227, 228]
- SARS-CoV-2 has an RBD that specifically targets specifically ACE2 receptors. ACE2 receptors share a large degree of similarity amongst many mammalian animal species, resulting in a broad range of potential zoonotic reservoirs.[229]
- Early comparisons identified 17 potential host species including animals belonging to a number of groups (by examining proteins involved in binding SARS-CoV-2): Primates (monkey), Lagomorpha (rabbit), Pholidota (Malayan pangolin), Carnivora (cat, civet, fox, dog, and raccoon dog), Perissodactyla (horse), Artiodactyla (pig, wild Bactrian camel, alpaca, bovine, goat, and sheep), and Chiroptera (little brown bat and fulvous fruit bat).[230]
- Large-scale outbreaks have been reported in farms across the world, with particular outbreaks of note being in Denmark, Netherlands and the USA.[231] Infection of minks in the Netherlands was determined to be introduced by infected farm workers.[232]
- WGS of SARS-CoV-2 from infected minks and infected employees at the farms indicated that SARS-CoV-2 had likely from humans to minks and, at least once, back to humans.[232]
- Mink-selected SARS-CoV-2 variants carrying the Y453F/D614G mutation displayed an increased affinity for human ACE2 and escaped neutralisation by one monoclonal antibody.[233] This demonstrates the potential for interspecies infection to be evolutionary routes for emergence of novel variants of SARS-CoV-2.
- Controlled studies on transmission of SARS-CoV-2 to livestock species are limited, but experiments using a sample of 6 cattle showed that it was possible to achieve infection and subsequent viral replications when the cattle were intranasally inoculated.[234] Transmission from infected cattle to uninoculated cattle was not observed, however.
- Experiments with rabbits that have been inoculated with SARS-CoV-2, showed a lack of any clinical symptoms but active infectious viral shedding from their nose and throat, indicative of a potential zoonotic reservoir.[235]
- Domestic cats have been experimentally infected with SARS-CoV-2 and have been shown to be able to transmit it to one another through respiratory droplets.[236, 237] A viral survey of a household of two humans and three cats suggested that cats may shed SARS-CoV-2 for a shorter duration than humans [238] but due to the small sample size, this must be interpreted with caution. Close viral genomic similarity between SARS-CoV-2 from pet cats and their respective owners indicates a mode of direct human to animal transmission.[238]
- Dogs can also be infected with SARS-CoV-2 but appear to shed little to no virus, making them less likely to be able to transmit it.[239] Although data is limited, dogs do not appear to be symptomatic with SARS-CoV-2 infection [240] and appear to be a low risk for transmission of the virus.
- Widespread infection of free-ranging white-tailed deer has been documented in the USA, with more than a third of nasal swabs (129/360) collected from northeast Ohio in early 2021 testing positive for SARS-CoV-2.[241]
- Three separate lineages (B.1.2, B.1.582 and B.1.596) were detected, which correlated with the high prevalence of B.1.2 variant that was dominant amongst humans in Ohio at the time, suggesting direct human-to-deer transmission. Probable deer-to-deer transmission was detected for these three variants, allowing for amino acid substitutions in the RBD and ORF1 that were observed infrequently in humans.[20]
- The high prevalence of SARS-CoV-2 amongst white-tailed deer populations in the USA at the time of sampling suggests that deer could potentially act as a zoonotic reservoir for further spillback events back into human populations. A preprint article from February 2022 identified a potential spillback

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event in Canada, where a high diversity of viral lineages was noted in SARS-CoV-2 genomic sequences from white-tailed deer and one such lineage was identified in a human sample isolate from Ontario.[242]

- This highlights the interdependence of human, animal and ecosystem health and reinforce the importance of One Health approaches in addressing emerging zoonotic diseases.[243-245] One Health approaches promote collaboration between human, animal and environmental health stakeholders in order to improve health and well-being through prevention and mitigation of risks at the interface between humans, animals and the environment.[244]

ENDS

Glossary of Terms

The AstraZeneca vaccine	AZD1222 or ChAdOx1
The Pfizer/BioNTech vaccine	Comirnaty/BNT162b2
Global Initiative on Sharing Avian Influenza Data (GISAID)	This is a consortium that promotes and provides open access to SARS-CoV-2 genomic sequence data. Its original purpose was for sharing data on avian (bird) flu.
Immune escape	The ability of the virus to evade our body's immune response. See also Immune response.
Immune response	The response of our immune system to an infection. It includes development of specific antibodies to the virus and also cell-mediated responses (triggered by T cells).
Mutation	Small change made to the pattern of nucleotides that make up the virus. These occur as the virus spreads and replicates. Most do not confer a benefit to the virus.
Naming mutations	Mutation nomenclature (i.e., how they are named), describes what occurred at a specific location of the genome. For example, the 'E484K' mutation means that at the position 484, the amino acid changed from glutamic acid (E) to lysine (K). When a deletion occurs, the location is provided (e.g., deletion 144).
N-terminal domain	Part of the spike protein of the SARS-CoV-2 virus.
R₀, Reproductive number	The reproductive number R ₀ (R-naught), is a measure of how contagious a disease is. It is the average number of people who would catch a disease from one infected individual when there are no control measures in place, e.g., vaccination, lockdowns.
R_{eff}, Effective reproductive number	The 'effective R' (R _{eff}) is the R observed when control measures are in place. R _{eff} can therefore change depending on the control measures currently enacted in a particular population. In general, whenever R is less than 1, i.e., an infected person goes on to infect less than one person on average, then the prevalence of the disease would be expected to decrease.
Secondary attack rate	The probability that an infection occurs among persons within a reasonable incubation period after known contact with an infectious person in household or other close-contact environments.
Serial interval	The time from symptom onset of a case to symptom onset in their identified contacts.
SGTF / SGTP	"The Omicron genome (lineage BA.1) contains the spike deletion at position 69/70 which is associated with S-gene target failure (SGTF) in some widely used PCR tests. Such PCR tests evaluate the presence of 3 SARS-CoV-2 genes: Spike (S), nucleocapsid (N) and ORF1ab. SGTF is defined as a PCR test where the N and ORF1ab genes are detected (with Ct values less than or equal to 30) but the S-gene is not. SGTF patterns can be used to assess the spread of Omicron lineage BA.1. The Omicron lineage BA.2, VOC-22JAN-01, does not generally contain the spike gene deletion and is S-gene target positive (SGTP)." [1]
Variant	Viruses with mutations are referred to as variants of the original virus. New variants of SARS-CoV-2 have been emerging as the virus has spread and evolved.
Variant of Concern (VOC)	WHO definition: A SARS-CoV-2 variant that meets the definition of a VOI (see below) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:

	<ul style="list-style-type: none"> • Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR • Increase in virulence or change in clinical disease presentation; OR • Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.
Variant of Interest (VOI)	<p>WHO definition: A SARS-CoV-2 variant:</p> <ul style="list-style-type: none"> • with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND • Identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.
Variant under Investigation (VUI)	<p>UKHSA definition: SARS-CoV-2 variants, if considered to have concerning epidemiological, immunological or pathogenic properties, are raised for formal investigation. At this point they are designated Variant Under Investigation (VUI) with a year, month, and number. Following a risk assessment with the relevant expert committee, they may be designated Variant of Concern (VOC).</p>

Abbreviations

CDC: Centers for Disease Control and Prevention

Ct: Cycle Threshold

E: Glutamic Acid

GSAID: Global Initiative on Sharing Avian Influenza Data

ICU: Intensive Care Unit

IPC: Infection Prevention and Control

L: Lysine

mRNA: messenger RNA

N: Nucleocapsid (Protein)

NPI: Non-pharmaceutical intervention

PCR: Polymerase Chain Reaction

RBD: Receptor binding domain (of the virus spike protein)

RAT: Rapid Antigen Test

R_{eff}: 'Effective R', the effective reproductive number

R₀: 'R-naught', the baseline reproductive number

RNA: Ribonucleic Acid

S: Spike (Protein)

UKHSA: UK Health Security Agency

UAI: Upper Airway Infection

VE: Vaccine effectiveness

VTG: Variant Technical Group

WHO: World Health Organisation

Useful Links

US CDC – SARS CoV-2 variant classifications and definitions	CDC classification of variants
Outbreak Info	Outbreak Info
WHO - Tracking SARS-CoV-2 variants	WHO Variant Tracking
UK Health Security Agency Technical Briefings (from October 2021 onwards)	Investigation of SARS-CoV-2 variants: technical briefings
Public Health England Technical Briefings	Investigation of SARS-CoV-2 variants: technical briefings

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"GT-5"



STA COVID-19 Pātaka Knowledge Hub

PUBLICLY ACCESSIBLE DOCUMENT

This is the exhibit marked "GT-5" referred to in the annexed Affidavit of **GEORGE IAN TOWN** affirmed at **Christchurch** this 10th day of **June 2022** before me:


Solicitor of the High Court of New Zealand

Emma Louise Spratt
Solicitor
Christchurch

COVID-19 Variants Update

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COVID-19 Variants Update

Date: 3 December 2021

About this update

During the COVID-19 pandemic, the Ministry of Health has seen high interest in all aspects of the virus from the scientific and healthcare community, and the general public. This update is produced fortnightly and is designed to provide new information on the variants of concern or that are of interest.

The format of this report has changed. The document now contains three sections: 1) Key Points; 2) Omicron variant summary table; 3) Delta variant summary table; 4) Other variants summary table.

Key points

Omicron

- On 26 November 2021, the World Health Organisation (WHO) designated variant B.1.1.529 a variant of concern, named Omicron. This decision was made because the Omicron variant has several mutations in the spike protein that could influence how it behaves.
- As at 02 December 2021, Omicron is present in at least 30 countries around the world. Although there is limited evidence currently available for this variant, several countries globally have implemented stricter border measures to minimise risk of spread.
- PCR tests continue to detect Omicron infection. Studies are ongoing to determine whether there is any impact on other types of tests, including rapid antigen detection tests.
- Preliminary data from South Africa shows that the risk of reinfection has increased in the era of Omicron. This suggests that Omicron could have increased evasion of immunity following prior infection. However, this is not yet confirmed, and it is not yet clear if Omicron can evade vaccine-induced immunity.
- Many characteristics of Omicron are still unclear. More robust data are required to determine:
 - if Omicron presents with different symptoms and if there are any changes to disease severity. Data reported over the next 1-2 months will be important.
 - if Omicron is more transmissible than Delta. Data reported over the next 2-4 weeks will be important.
 - if Omicron can escape vaccine-induced immunity. Laboratory data are expected over the next 1-2 weeks.

Delta

- Delta continues to be the dominant variant of concern (VOC) globally. It is substantially more transmissible than previous variants, with a higher secondary attack rate.
- Two doses of Pfizer vaccine remain effective against infection, symptomatic disease and hospitalisation for cases associated with Delta. However, protection against infection wanes over time, indicating the need for a third (booster) dose after several months.
- Preliminary evidence indicates that COVID-19 vaccination reduces onwards transmission of Delta (i.e., both the chance of becoming infected and the likelihood of an infected person transmitting to another person), but this impact reduces over time.

Omicron (B.1.1.529) Variant of Concern

Characteristic	Data
Identification and global prevalence	<ul style="list-style-type: none"> The B.1.1.529 variant was first detected in samples collected on 11 November 2021 in Botswana and on 14 November 2021 in South Africa.[1] B.1.1.529 was first reported to WHO from South Africa on 24 November 2021. This variant was named 'Omicron' and designated a variant of concern on 26 November 2021 by WHO's Technical Advisory Group on Virus Evolution due to the high number of mutations in the spike protein.[2] Omicron is the most divergent variant detected so far, which raises concerns that it may be associated with increased transmissibility, significant reduction in vaccine effectiveness, and increased risk for reinfection. As at 02 December 2021, Omicron is present in at least 30 countries around the world, including Australia, the US, UK, Canada, Israel, and the Netherlands. Although there is limited evidence currently available for this variant, several countries globally have implemented stricter border measures to minimise risk of spread.
Spike protein mutations	<p>Summary: Omicron contains many mutations in the spike protein, some of which have been associated with increased transmissibility and immune escape.</p> <ul style="list-style-type: none"> In comparison to the original strain, Omicron contains at least 30 mutations in the spike protein, including three deletions and one small insertion.[1, 2] Of these, 15 are located within the receptor binding domain (RBD). A particular cluster of mutations at the S1-S2 furin cleavage site (H655Y, N679K, P681H) are associated with more efficient cell entry, which may indicate an increase in transmissibility.[3] These mutations have been identified in other variants, but never reported together in one variant. For example, P681H is seen in Alpha and Mu; Delta contains P681R; and N679K is seen in C.1.2. The large number of mutations in the RBD, including K417N and E484A, may indicate an increased potential for immune escape.[3]
Testing and detection	<p>Summary: PCR tests continue to detect Omicron infection. Studies are ongoing to determine whether there is any impact on other types of tests, including rapid antigen detection tests.</p> <ul style="list-style-type: none"> Omicron has a deletion $\Delta 69-70$ in the Spike protein (similar to Alpha, but different to Delta). One PCR test, ThermoFisher TaqPath, can detect the lack of this target gene (called S gene dropout or S gene target failure) [1, 2] and therefore this test can be used as an early marker to distinguish between Omicron and Delta, pending sequencing confirmation. It is unknown how rapid antigen tests will perform on Omicron. Since many tests in the market (but not all) target the nucleocapsid protein rather than the spike protein, they are expected to continue to work. Studies are ongoing to assess if rapid antigen tests may be impacted.[1, 2]
Symptoms and severity of disease	<p>Summary: More robust data is required to determine whether this variant presents with different symptoms and to understand the extent of disease severity. Data reported over the next 1-2 months will be important.</p> <ul style="list-style-type: none"> Preliminary information from South Africa indicates that there are currently no unusual symptoms associated with Omicron. As seen with other variants, some individuals are asymptomatic.[4] There have been some anecdotal reports from doctors in South Africa stating that Omicron causes milder symptoms and less severe illness.[5] However, these milder cases were in younger people. Therefore, it is too early to draw any conclusions on disease severity until more data for different age groups, especially the elderly, become available. Data for severity and mortality is expected to become available in the next 1-2 months, once outcomes for hospitalised cases are evaluated.
Transmission	<p>Summary: It is unclear whether Omicron is more transmissible than Delta. Data reported over the next 2-4 weeks will be important.</p> <ul style="list-style-type: none"> Early data shared on Twitter by Dr Tulio de Oliveira from the Center for Epidemic Response and Innovation in South Africa showed that prevalence of Omicron in samples has increased to 75% in less than 2 weeks, indicating that this variant could potentially outcompete Delta.[6] The variant is now spreading quickly in South Africa, with over 180 confirmed cases, as at 02 December 2021. It should be noted that vaccine coverage is very low in South Africa, with only around 24% of people fully vaccinated.[7] More robust data are required to understand whether Omicron has increased transmissibility over other variants. If the variant has been seeded by several visitors to the country in different locations at the same time, then this could appear to be an increase in transmissibility initially, but then not be borne out by the data over time. International data on transmissibility over the next 2-4 weeks will therefore be very important to confirm these early observations.
Vaccine/immune escape	<p>Summary: Preliminary data from South Africa suggests that Omicron could have increased evasion of immunity following prior infection. It is unclear whether Omicron can escape vaccine-induced immunity. Laboratory data are expected over the next 1-2 weeks.</p> <ul style="list-style-type: none"> A pre-print from South Africa looking at infection trends in routine surveillance data found that Omicron is associated with a high risk of reinfection.[8] Reinfection was defined in the study as two positive tests (PCR or antigen detection), at least 90 days apart. The relative hazard ratio (reinfection versus primary infection) for the Omicron period versus the first wave of infection was 2.39 (95% CI: 1.88-3.11). These preliminary data suggest that Omicron has increased immune evasion to prior infection, but it is not yet clear if time since previous infection could have influenced these findings. It is also not clear if Omicron can evade vaccine-induced immunity. No robust data are available on binding or neutralising antibody responses yet, but these are expected in the next two weeks.[9, 10] Despite uncertainties, vaccine developers and scientists are expecting that the COVID-19 vaccines will still offer protection against severe disease and death.[10, 11] Pfizer have begun the production of an upgraded vaccine to target the Omicron variant.[10] The Pfizer CEO has stated that if needed, an initial batch of 25-50 million doses would take about 100 days to produce, provided regulators are satisfied. A media report from Israel[12] states that the Pfizer vaccine "is just slightly less effective in preventing infection with Omicron than with Delta – 90% as opposed to 95% – while it is as effective – around 93% – in preventing serious symptoms at least for those vaccinated with a booster." The report also states that "the ability of the variant to infect is higher than Delta but not as much as feared – around 1.3 times higher." However, the data to support these statements are yet to be published, so they should be treated with caution.

Delta (B.1.617.2) Variant of Concern

Characteristic	Data for unvaccinated	Data for vaccinated																																			
Viral dynamics (Note: It is difficult to estimate viral dynamics accurately due to differences in study methodologies. For example, results may vary depending on the contact tracing system of the country, on the timing that cases are isolated, or on the number of exposure events in a transmission study.)																																					
Latency period time from exposure to start of infectious period	<p>Summary: Evidence is limited. Delta may have the same or shorter latency period than other variants. Approximately 4 days.</p> <ul style="list-style-type: none"> One study reported the mean latency was 4 days.[13] Another study reported a time window of approximately 3.7 days.[14] 	No data available																																			
Incubation period time from exposure to symptom onset	<p>Summary: Evidence is limited. Delta may have a shorter incubation period than other variants. Range is approximately 4-6 days.</p> <ul style="list-style-type: none"> One study reported the mean incubation period was 5.8 days.[13] Another study reported a significantly shorter incubation period for Delta compared with the wild-type strain (4 versus 6 days).[15] 	No data available																																			
Serial Interval time from onset of symptoms in the primary case to onset of symptoms in the secondary case	<p>Summary: The serial interval for Delta is approximately 2.5-3.3 days.[16-18]</p> <ul style="list-style-type: none"> One study reported that the serial interval was not different for Delta and non-Delta cases.[16] However, a study of an outbreak in South Korea found the mean serial interval declined from 4.0 days to 2.5 days as Delta became more prevalent (of note, Delta only accounted for ~40% of cases during this time).[17] A Korean contact tracing study reported a serial interval of 3.26 days.[18] 	No data available																																			
Duration of infectious period	<p>Summary: Evidence is limited on whether Delta has a longer infectious period.</p> <ul style="list-style-type: none"> Low cycle threshold (Ct) values correspond to high viral load. Ct values are used as a surrogate for infectiousness and may not correlate with risk of transmission. Ct values stay ≤30 for 18 days for severe/hospitalised cases.[19] However, some studies report similar values for non-Delta variants. This is likely an upper limit of infectious period given the data was based on hospitalised cases and total viral load (rather than total infectious virus). A Chinese study reported a longer duration of viral shedding in upper respiratory tract samples compared with the wild-type strain (14 versus 8 days).[15] 	<p>Summary: Evidence on duration of infection period in breakthrough infections is limited.</p> <ul style="list-style-type: none"> A US study of 8 Delta breakthrough infections found longer duration of viral shedding (13.5 vs 4 days), greater likelihood of replication-competent virus at early stages of infection (6/8 [75%] vs 3/14 [23%]), and longer duration of culturable virus (median 7 vs 3 days) compared to non-Delta variants.[20] 																																			
Viral load	<p>Summary: Delta appears to have very high viral loads.</p> <ul style="list-style-type: none"> The magnitude of the increase in viral load is unclear. One pre-print reported 1000 times higher viral load on the first PCR positive test compared to the less transmissible ancestral variant.[14] Another paper estimated 4-fold increase in viral load compared to the more transmissible Alpha variant.[21] Higher viral load is also seen in national surveillance data from contact tracing in Public Health England data, and other preprints.[13, 14, 22] 	<p>Summary: Vaccinated cases may have a similar viral load to unvaccinated at the start of the infectious period.</p> <ul style="list-style-type: none"> Several studies have found that vaccinated and unvaccinated Delta cases have similar PCR cycle threshold (Ct) values (a proxy for viral load).[23-31] Some studies report that the viral load decreases more rapidly in vaccinated individuals.[24, 31] A study in vaccinated healthcare workers found that viral loads of breakthrough Delta cases were ~251 times higher than breakthrough cases infected with previous strains.[32] 																																			
Secondary attack rate (SAR)	<p>Summary: SAR varies widely depending on setting. Evidence is emerging showing that vaccinated index cases have lower secondary attack rates for Delta than unvaccinated index cases.</p> <ul style="list-style-type: none"> The household secondary attack rate from the New Zealand August 2021 outbreak was 45.6%; SAR for close-plus contacts was 11% (Ministry of Health internal preliminary analysis, extracted 11 October, see Table below). <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th>Secondary cases, n</th> <th>Contacts, N</th> <th>SAR, %</th> <th>SAR (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Total</td> <td>1,051</td> <td>40,089</td> <td>2.6</td> <td>(2.4-2.7)</td> </tr> <tr> <td>Contact risk type</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Casual plus</td> <td>0</td> <td>4052</td> <td>0.0</td> <td>(0.0-0.1)</td> </tr> <tr> <td>Close</td> <td>107</td> <td>34733</td> <td>0.3</td> <td>(0.3-0.4)</td> </tr> <tr> <td>Close plus</td> <td>42</td> <td>379</td> <td>11.1</td> <td>(8.0-15.0)</td> </tr> <tr> <td>Household</td> <td>902</td> <td>1976</td> <td>45.6</td> <td>(42.7-48.7)</td> </tr> </tbody> </table>			Secondary cases, n	Contacts, N	SAR, %	SAR (95% CI)	Total	1,051	40,089	2.6	(2.4-2.7)	Contact risk type					Casual plus	0	4052	0.0	(0.0-0.1)	Close	107	34733	0.3	(0.3-0.4)	Close plus	42	379	11.1	(8.0-15.0)	Household	902	1976	45.6	(42.7-48.7)
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COVID-19 Variants Update

	<ul style="list-style-type: none"> SAR varies widely, depending on setting. A US study in a gym found that among cohorts with identified cases, attack rates ranged from 8% to 60%, but the overall facility-associated attack rate among 194 exposed persons was reported as 24%. [33] A Korean contact tracing study on an outbreak of 405 cases reported a SAR of 63% in household contacts. [18] An outbreak report among unvaccinated soldiers on a single navy ship noted a 90% attack rate. [34] Currently, the SAR for household contacts based on contact tracing data in the UK is 11.2%. [35] noting that the relatively low SAR in the UK partly reflects the high vaccination coverage (approximately 80% aged 12+ are fully vaccinated). [36] Transmission study in Singapore found that household SAR among unvaccinated Delta-exposed contacts was 25.8% compared with 11.3% among vaccinated contacts. [37] A Dutch contact tracing study found that the crude SAR among unvaccinated household contacts for vaccinated index cases was lower compared to unvaccinated index cases (13% vs 22%). The corresponding adjusted vaccine effectiveness against transmission was 63% (95% CI: 46-75). [38] Results were not stratified by vaccine type. 									
Transmission	<p>Summary: Vaccination reduces transmission of Delta, but the vaccine's impact on transmission appears to reduce over time.</p> <ul style="list-style-type: none"> UK national surveillance data found 64% increase in household transmission with Delta compared with Alpha (aOR 1.64; 95% CI: 1.26-2.13, p <0.001). [39] Studies on Delta reported that 12-73.9% of the transmissions to close contacts occurred before symptom onset. [13, 18] Delta variant cases will infect 64% their 'close proximity' contacts. [40] An observational study in England found that two doses of the Pfizer vaccine reduced onwards transmission from breakthrough infections of the Delta variant by 50%, which was more than the AstraZeneca vaccine (Pfizer aRR=0.50 and AstraZeneca aRR=0.76). [41] A Dutch contact tracing study estimated that vaccine effectiveness against onwards transmission to fully vaccinated household contacts was 40% (95% CI: 20-54), which is in addition to the individual protection against infection. [38] <p>Effectiveness against onwards transmission to unvaccinated household contacts was 63% (95% CI: 46-75). Results were not stratified by vaccine type.</p>									
R ₀	<p>Summary: R₀ ~5.5-6.5, i.e., On average, each person transmits Delta to another 5-6 people.</p> <p>No data available</p> <ul style="list-style-type: none"> Highest range of estimate is 8-9, based on the upper limits of current ranges of increased transmission (e.g., starting from R=3 for wild type, then ~50% increase from wild type to Alpha, and ~90% from Alpha to Delta). A summary of 5 papers using differing methods to calculate an R₀ for Delta reported a mean R₀ of 5.08 (range, 3.2-8.0). [42] A Danish pre-print estimated that Delta increases R₀ by a factor of 2.17 (95% CI: 1.99-2.36) relative to Alpha and 3.28 (95% CI: 3.01-3.58) relative to the ancestral variant. [43] The UK REACT-1 study found an overall R of 1.03 (range: 0.94-1.14) among those aged 5 and above in September 2021. Those aged 17 years and under had an R of 1.18 (range: 1.03-1.34), and this was lower in those aged 18 to 54 years (R of 0.81, range: 0.68-0.97). [44] 									
Severity	<p>Summary: No clear evidence at this time that Delta symptoms differ from other VOCs or wild-type virus. The most common symptoms for COVID-19 caused by Delta are cough, fatigue, headache, sore throat, fever, loss of taste or smell, and myalgia.</p> <ul style="list-style-type: none"> A South Korean study found no significant difference between Delta-dominant and Delta-minor groups for COVID-19 symptoms in children and adolescents, except for the lower frequencies of rhinorrhea (25% vs. 10.5%, P = 0.003), nasal stuffiness (34.8% vs. 15.4%, P = 0.001) and sore throat (23.9% vs. 12.6%, P = 0.02). [45] Patients in the Delta-dominant group were more likely to be asymptomatic (29.3% vs. 43.4%, P = 0.03). Data from a retrospective cohort study in Singapore using national surveillance data showed that the most common Delta symptoms were similar to symptoms for Alpha, Beta and the wild-type virus. Among those with Delta infection (n=67), the most common symptoms were fever (72%), cough (46%), sore throat (34%), shortness of breath (19%), and nasal congestion/runny nose (16%). [19] The same study reported that 12% of Delta cases were asymptomatic. However, at the time the data was collected (1 January-22 May 2021) there was a very small number of Delta cases overall (n=67). An analysis of 159 hospitalised Delta cases in a local outbreak in Guangzhou, China reported that the most common symptoms within three days on admission was cough (65%), followed by fever (63%) and expectoration (53%). Gastrointestinal symptoms such as diarrhoea (5%) and vomiting (4%) were uncommon. [15] The UK COVID-19 Infection Survey collects data on characteristics of people testing positive for COVID-19, including data on symptoms for those who had strong positive tests - Ct value under 30 (see Table below). [46] These data are provisional, reflect infections reported in the community, and exclude infections reported in hospitals, care homes, or other institutional settings. These data can be used to infer common symptoms of the Delta variant, which has been predominant in the UK since June 2021. <table border="1" data-bbox="587 1402 1171 1570"> <thead> <tr> <th rowspan="2">Symptoms</th> <th>% of people with this symptom within 35 days of a positive PCR test, among those people with a Ct value under 30</th> </tr> <tr> <th>September 2021</th> </tr> </thead> <tbody> <tr> <td>Any symptoms</td> <td>61.9</td> </tr> <tr> <td>No symptoms (asymptomatic)</td> <td>38.1</td> </tr> <tr> <td>Classic symptoms (cough, fever, shortness of breath, loss of taste, loss of smell)</td> <td>54.2</td> </tr> </tbody> </table>	Symptoms	% of people with this symptom within 35 days of a positive PCR test, among those people with a Ct value under 30	September 2021	Any symptoms	61.9	No symptoms (asymptomatic)	38.1	Classic symptoms (cough, fever, shortness of breath, loss of taste, loss of smell)	54.2
Symptoms	% of people with this symptom within 35 days of a positive PCR test, among those people with a Ct value under 30									
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Any symptoms	61.9									
No symptoms (asymptomatic)	38.1									
Classic symptoms (cough, fever, shortness of breath, loss of taste, loss of smell)	54.2									

COVID-19 Variants Update

		Loss of taste or smell	28.4
		Gastrointestinal symptoms (abdominal pain, nausea or vomiting, diarrhoea)	17.9
		Cough	42.4
		Fatigue (weakness)	38.0
		Headache	38.7
		Sore throat	32.6
		Fever	27.9
		Loss of smell	23.7
		Muscle ache (myalgia)	25.0
		Loss of taste	23.7
		Shortness of breath	13.8
		Nausea or vomiting	10.3
		Abdominal pain	8.0
		Diarrhoea	7.3
Asymptomatic	<p>Summary: Data is emerging. Rate of asymptomatic cases depends on vaccination status, with vaccinated but infected people more likely to be asymptomatic. However, these data are not always reported. Breakthrough infections tend to be mild or asymptomatic.</p> <ul style="list-style-type: none"> Data from the UK COVID-19 infection survey indicated that during September, approximately 38% of positive cases did not report any symptoms. See Table above under 'Symptoms' for more details. This was during a period of relatively high vaccination coverage in the UK. A Korean study of 405 Delta cases reported that 20% were asymptomatic.[18] Proportion of vaccinated cases among asymptomatic was not reported. A Singaporean study using national surveillance data found 10% of Delta cases were asymptomatic.[19] However, at the time the data was collected (1 January-22 May 2021) there was a very small number of Delta cases (n=67) and proportion of vaccinated cases was not reported. One study in Singapore found the vaccinated group with Delta breakthrough infections (2 doses of mRNA vaccine; 71 of 218 Delta infections identified) were more likely to be asymptomatic (28.2% versus 9.2%, p<0.001) and had fewer symptoms than those unvaccinated. Higher proportion of pneumonia in unvaccinated group.[24] An outbreak report among unvaccinated soldiers on a single navy ship noted that 23% were asymptomatic.[34] 		
Hospitalisation	<p>Summary: Data indicates possible increased risk of hospitalisation. It is unclear whether the risk of ICU admission is higher for Delta once a patient is admitted to hospital.</p> <ul style="list-style-type: none"> Studies from England, Scotland, Denmark, and Canada have found that Delta was associated with approximately 2-3 times risk of hospitalisation compared to Alpha (hazard ratios ranging from 1.85-2.83).[47-50] In contrast, a Norwegian study found no difference in the risk of hospitalisation for Delta compared to Alpha.[51] A CDC study of data from 14 US states found no significant differences in the proportion of nonpregnant adults aged ≥18 hospitalised with severe outcomes between the pre-Delta and Delta periods. The proportion of hospitalised unvaccinated COVID-19 patients aged 18-49 years increased significantly during the Delta period.[52] The rate of new COVID-19 cases, emergency department visits, and hospital admissions increased for those aged 0-17 years after Delta became predominant in the US. Hospitalisation rates were highest among children aged 0-4 years (69.2 per 100,000) and adolescents aged 12-17 years (63.7 per 100,000), and lowest among children aged 5-11 years (24.0 per 100,000). Hospitalisation rates were 10 times higher among unvaccinated than among fully vaccinated adolescents. However, there was no difference in the severity of disease when compared with pre-Delta.[53, 54] 	<p>Summary: Unvaccinated people have higher case and hospitalisation rates for Delta than fully vaccinated people</p> <ul style="list-style-type: none"> Delta is currently the dominant variant in the US and the UK, making up more than 99% of recently sequenced cases in both countries.[55, 56] The US CDC COVID Data Tracker[55] reports that in September, unvaccinated people were 5.8 times more likely to test positive for COVID-19 and 9 times more likely to be hospitalised from COVID-19 than fully vaccinated people. The latest UKHSA COVID-19 vaccine surveillance report[57] indicates that the rate of a positive COVID-19 test varies by age and vaccination status. The rate of a positive COVID-19 test is substantially lower in vaccinated individuals compared to unvaccinated individuals up to the age of 29. In individuals aged greater than 30, the rate of a positive COVID-19 test is higher in vaccinated individuals compared to unvaccinated. This is likely to be due to a variety of reasons, including differences in the population of vaccinated and unvaccinated people as well as differences in testing patterns. The rate of hospitalisation within 28 days of a positive COVID-19 test increases with age and is substantially greater in unvaccinated people compared to vaccinated people. 	
Mortality/Case fatality rate	<p>Summary: Mortality/case fatality rate for Delta ~0.5-3%. It is important to note that the risk of mortality associated with COVID-19 is much higher for older age groups.</p> <ul style="list-style-type: none"> Our World in Data estimates the case fatality rate to be approximately 1-3% globally.[58] UKHSA reported that among 727,986 cases of Delta from 15 May 2021 to 24 October 2021, 3,813 had died within 28 days of testing positive, which is a case fatality rate of 0.53%.[35] 	<p>Summary: Unvaccinated people have higher mortality rates than fully vaccinated people</p> <ul style="list-style-type: none"> Delta is currently the dominant variant in the US and the UK, making up more than 99% of recently sequenced cases in both countries.[55, 56] The US CDC COVID Data Tracker[55] reports that in September, unvaccinated people were 14 times more likely to die from COVID-19 than fully vaccinated people. 	

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	<ul style="list-style-type: none"> A retrospective analysis of UK data found that Delta is associated with a lower case fatality rate than Alpha (all ages, 0.43% vs 1.07%), however, vaccination status of cases was not included in the analysis.[59] 	<ul style="list-style-type: none"> The latest UKHSA COVID-19 vaccine surveillance report[57] indicates that the rate of death within 28 days or within 60 days of a positive COVID-19 test increases with age and is substantially greater in unvaccinated people compared to fully vaccinated people.
Vaccine efficacy/effectiveness		
Against viral infection (positive PCR test)	<ul style="list-style-type: none"> Pfizer: 79% (95%CI: 75-82)[60]; 39% (95%CI: 9-59) in fully vaccinated (including those who received their second those several months earlier) in Israel[61]; 42% (95%CI: 13-62) in Minnesota in July when Delta became dominant compared to 76% (95%CI: 69-81) throughout January till July[62]; 52.4% (95%CI:48.0-56.4) in US nursing home residents during Delta prevalence compared to 74.2% (95%CI: 68.9-78.7) pre-Delta[63]; 53.5% (95%CI: 43.9-61.4) in those who received their second dose several months earlier in Qatar[64]; 93% (95%CI: 85-97) at <1 month to 53% (95%CI 39-65) at >4 months in US[65]; 85% (95%CI: 79-90) at 14 days post 2nd dose declining to 75% (95%CI: 70-80) at 90+ days in UK[66] AstraZeneca: 60% (95%CI: 53-66)[60]; 68% (95%CI: 61-73) at 14 days post 2nd dose declining to 61% (95%CI: 53-68) at 90+ days in UK[66] Janssen: 78% (95%CI: 73-82) during Delta prevalence in the US[67] 	
Against symptomatic disease	<ul style="list-style-type: none"> Pfizer: 87-88%[68, 69]; 40.5% (95%CI: 8.7-61.2) in fully vaccinated (including those who received their second those several months earlier) in Israel[61]; 56.1% (95%CI: 41.4-67.2) in those who received their second dose several months earlier in Qatar[64]; 92.4% (95%CI: 92.1-92.7) at 1 week after the second dose and then fell to 69.7% (95%CI: 68.7-70.5) by 20+ weeks[70]; 93% (95%CI: 89-96) at 14 days post 2nd dose declining to 78% (95%CI: 72-82) at 90+ days in UK[66] AstraZeneca: 67% (95%CI: 61.3-71.8)[68]; 62.7% (95%CI: 61.7-63.8) at 1 week after the second dose and then fell to 47.3% (95%CI: 45.0-49.6) by 20+ weeks[70]; 72% (95%CI: 64-78) at 14 days post 2nd dose declining to 63% (95%CI: 53-71) at 90+ days in UK[66] 	
Against hospitalisation	<ul style="list-style-type: none"> Pfizer: 96% (95%CI: 86-99)[71]; 80% (95%CI: 73-85) during Delta prevalence in the US[72]; 99.7% (95%CI: 97.6-100.0) at 1 week after the second dose and then fell to 92.7% (95%CI: 90.3-94.6) by 20+ weeks[70]; 96% (95%CI: 95-96) during Delta period in the Netherlands[73] AstraZeneca: 92% (95%CI: 75-97)[71]; 93.9% (95%CI: 91.3-95.7) at 1 week after the second dose and then fell to 77.0% (95%CI: 70.3-82.3) by 20+ weeks[70]; 94% (95%CI: 92-95) during Delta period in the Netherlands[73]; 88% (95%CI: 85-90) during Delta prevalence in Scotland[74] Janssen: 60-85% during Delta prevalence in the US[67, 72]; 91% (95%CI: 88-94) during Delta period in the Netherlands[73] 	
Against transmission	<ul style="list-style-type: none"> Pfizer: 50% (95%CI: 35-61) against onwards Delta transmission at 2 weeks after 2nd dose declining to 24% (95%CI: 20-28) through 3 months[75] AstraZeneca: 24% (95%CI: 18-30) against onwards Delta transmission at 2 weeks after 2nd dose declining to 2% (95%CI: -2-6) through 3 months[75] 	
Waning immunity	<ul style="list-style-type: none"> A study from Oxford University reported that during Delta prevalence, VE against infection for Pfizer declined by 22% (95%CI 6-41%) per month from second dose for 18-64 year olds, starting at 85% (95%CI 79-90) 14 days post-second dose.[66] A study from Southern California also reported waning of VE against infection, after adjusting for many confounders (demographics, comorbidities, social deprivation measures) and stratifying by age.[76] VE against Delta infections was high during the first month after full vaccination (93%) and declined to 53% at 24 months. The authors concluded that waning effectiveness was not due to the increasing prevalence of Delta, because waning effectiveness was also seen for non-Delta cases. Importantly, a high VE against hospitalisation (90-93%, stratified by age), associated with any variant, was maintained for the duration of the study. 	

Other Variants

Other Variants of Concern (VOC) - as listed by WHO	
Lineage: B.1.1.7 WHO label: Alpha	<ul style="list-style-type: none"> Number of cases in NZ: 178 (report date of last confirmed case: 06 August 2021) Prevalence: First identified in United Kingdom [77] Transmission/Secondary attack rate: ~40-80% more transmissible than Alpha (R₀ ~3.5-5.2) [77]. Severity: <ul style="list-style-type: none"> Mortality: 60-70% increased mortality compared to previous variants [77] Hospitalisation risk: 30-70% increased risk [77] Immune evasion: Minimal
Lineage: B.1.351 WHO label: Beta	<ul style="list-style-type: none"> Number of cases in NZ: 33 (report date of last confirmed case: 27 June 2021) Prevalence: First identified in South Africa [77] Transmission/Secondary attack rate: Not well established. Preliminary estimate ~50% more transmissible [77] Severity: <ul style="list-style-type: none"> Mortality: Not well established. One report of no increased risk of mortality [77] Hospitalisation: Not well established. Approximately 3-4 times risk of hospitalisation [78] Immune evasion: Moderate-Strong
Lineage: P.1 WHO label: Gamma	<ul style="list-style-type: none"> Number of cases in NZ: 8 (report date of last confirmed case: 01 June 2021) Prevalence: First identified in Brazil [77] Transmission/Secondary attack rate: Not established. Preliminary estimates 40%-160% more transmissible Severity: <ul style="list-style-type: none"> Mortality: Not established. One report of no increased risk of mortality. Hospitalisation: Not well established. Approximately 3 times risk of hospitalisation [78] Immune evasion: Moderate-Strong
Variants under Investigation (VUI) - as listed by UKHSA	
Lineage: AY.4.2 UKHSA label: VUI-21OCT-01	<ul style="list-style-type: none"> Number of cases in NZ: 5 (report date of last confirmed case: 04 November 2021) Prevalence: First identified in United Kingdom, October 2021. Increasing prevalence, particularly in the UK where cases of AY.4.2 have increased in proportion from 15.2% to 20.3% of all Delta cases, from the week of 07 November 2021 to the week of 21 November 2021, however the latest sequencing is incomplete. [56] Spike mutations: Contains spike mutations A222V and Y145H. [79] Transmission/Secondary attack rate: <ul style="list-style-type: none"> Experts suggest there may be an 'increase in transmissibility of 10-15% compared to the original Delta variant', however, evidence is yet to emerge, and AY.4.2 is unlikely to present significant risk at this stage. [80] Secondary attack rate slightly higher than Delta. [38] Severity: No evidence that AY.4.2 causes more severe disease than other Delta variants, according to recent analysis from the United Kingdom. [56] Immune evasion: Minimal effect on vaccine-induced neutralisation and vaccine efficacy compared to Delta. [81]
Lineage: B.1.621 WHO label: Mu UKHSA label: VUI-21JUL-01	<ul style="list-style-type: none"> Number of cases in NZ: 1 (report date of last confirmed case: 19 June 2021) Prevalence: First identified in Columbia. [82] Spike mutations: T95I, Y144-145TSN, R346K, E484K, N501Y, D614G, P681H, and D950N. Some of these are mutations shared present in other variants: E484K (shared with Beta, Gamma), N501Y (shared with Alpha), P681H (shared with Alpha) and D950N (shared with Delta). The E484K (shared with Beta, Gamma), which is associated with reduced sensitivity towards natural or vaccine induced antibodies. [83] Transmission/Secondary attack rate: Mu has not outcompeted Delta in any country to date. Immune evasion: Mu has more potential for immune escape than Beta (previous variant with most immune escape) based on one study of sera from Pfizer-vaccinated individuals. [83, 84]
Lineage: B.1.525 WHO label: Eta UKHSA label: VUI-21FEB-03	<ul style="list-style-type: none"> Number of cases in NZ: 8 (report date of last confirmed case: 08 June 2021) Prevalence: First identified in UK and Nigeria, December 2020. Spike mutations: Spike mutations A67V, E970 deletion, 144del, E484K, D614G, Q677H, and F888L. [85] Immune evasion: Potential reduction in neutralisation by some monoclonal antibody treatments, convalescent and post-vaccine sera. [86]
Lineage: B.1.1.318 UKHSA label: VUI-21FEB-04	<ul style="list-style-type: none"> Number of cases in NZ: No cases. Prevalence: First identified in United Kingdom, February 2021. Spike mutations: Contains spike mutations T95I, 144del, E484K, P681H, D796H. [87]

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<p>Lineage: P.3 WHO label: Theta UKHSA label: VUI-21MAR-02</p>	<ul style="list-style-type: none"> • Number of cases in NZ: 3 (report date of last confirmed case: 20 March 2021) • Prevalence: First identified in Philippines, January 2021 [88, 89] • Spike mutations: Contains spike mutations E484K, N501Y, P681H, 141-143del. [89, 90] <ul style="list-style-type: none"> ◦ From parent lineage B.1.1.28 (the same as Gamma and P.2 detected in Brazil) [91]
<p>Lineage: B.1.617.1 WHO label: Kappa UKHSA label: VUI-21APR-01</p>	<ul style="list-style-type: none"> • Number of cases in NZ: 5 (report date of last confirmed case: 09 April 2021) • Prevalence: First identified in India, October 2020. • Transmission/Secondary attack rate: Secondary attack rates similar to Delta. [92] • Immune evasion: Kappa was neutralised by Pfizer and Moderna, however 6.8-fold reduction observed. [93]
<p>Lineage: B.1.617.3 UKHSA label: VUI-21APR-03</p>	<ul style="list-style-type: none"> • Number of cases in NZ: 4 (report date of last confirmed case: 11 April 2021) • Prevalence: First identified India [77]
<p>Lineage: P.2 variant (descendent of B.1.1.28) WHO label: Zeta UKHSA label: VUI-21JAN-01</p>	<ul style="list-style-type: none"> • Number of cases in NZ: Last detected in a case reported New Zealand in on 05 March 2021. • Prevalence: First identified in Brazil, April 2020. • Spike mutations: Spike mutations E484K, D614K, and V1176F. [85] • Immune evasion: Possible reduced antibody neutralisation from studies on the spike protein mutation E484K. [94]

Glossary of Terms

The AstraZeneca vaccine	AZD1222 or ChAdOx1
The Pfizer/BioNTech vaccine	Comirnaty/BNT162b2
Global Initiative on Sharing Avian Influenza Data (GISAID)	This is a consortium that promotes and provides open access to SARS-CoV-2 genomic sequence data. Its original purpose was for sharing data on avian (bird) flu.
Immune escape	The ability of the virus to evade our body's immune response. See also Immune response.
Immune response	The response of our immune system to an infection. It includes development of specific antibodies to the virus and also cell-mediated responses (triggered by T cells).
Mutation	Small change made to the pattern of nucleotides that make up the virus. These occur as the virus spreads and replicates. Most do not confer a benefit to the virus.
Naming mutations	Mutation nomenclature (i.e., how they are named), describes what occurred at a specific location of the genome. For example, the 'E484K' mutation means that at the position 484, the amino acid changed from glutamic acid (E) to lysine (K). When a deletion occurs, the location is provided (e.g., deletion 144).
N-terminal domain	Part of the spike protein of the SARS-CoV-2 virus.
R₀, Reproductive number	The reproductive number R ₀ (R-naught), is a measure of how contagious a disease is. It is the average number of people who would catch a disease from one infected individual when there are no control measures in place, e.g., vaccination, lockdowns.
R_{eff}, Effective reproductive number	The 'effective R' (R _{eff}) is the R observed when control measures are in place. R _{eff} can therefore change depending on the control measures currently enacted in a particular population. In general, whenever R is less than 1, i.e., an infected person goes on to infect less than one person on average, then the prevalence of the disease would be expected to decrease.
Secondary attack rate	The probability that an infection occurs among persons within a reasonable incubation period after known contact with an infectious person in household or other close-contact environments.
Variant	Viruses with mutations are referred to as variants of the original virus. New variants of SARS-CoV-2 have been emerging as the virus has spread and evolved.
Variant of Concern (VOC)	<p>WHO definition: A SARS-CoV-2 variant that meets the definition of a VOI (see below) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:</p> <ul style="list-style-type: none"> • Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR • Increase in virulence or change in clinical disease presentation; OR

	<ul style="list-style-type: none"> Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.
Variant of Interest (VOI)	<p>WHO definition: A SARS-CoV-2 variant:</p> <ul style="list-style-type: none"> with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND Identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.
Variant under Investigation (VUI)	<p>UKHSA definition: SARS-CoV-2 variants, if considered to have concerning epidemiological, immunological or pathogenic properties, are raised for formal investigation. At this point they are designated Variant Under Investigation (VUI) with a year, month, and number. Following a risk assessment with the relevant expert committee, they may be designated Variant of Concern (VOC).</p>

Abbreviations

CDC: Centers for Disease Control and Prevention

GSAID: Global Initiative on Sharing Avian Influenza Data

RBD: Receptor binding domain (of the virus spike protein)

R_{eff}: 'Effective R', the effective reproductive number

R₀: 'R-naught', the baseline reproductive number

UKHSA: UK Health Security Agency

Useful Links

US CDC – SARS CoV-2 variant classifications and definitions	CDC classification of variants
Outbreak Info	Outbreak Info
WHO - Tracking SARS-CoV-2 variants	WHO Variant Tracking
UK Health Security Agency Technical Briefings (from October 2021 onwards)	Investigation of SARS-CoV-2 variants: technical briefings
Public Health England Technical Briefings	Investigation of SARS-CoV-2 variants: technical briefings

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COVID-19 Variants Update

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COVID-19 Variants Update

Date: 10 December 2021

About this update

During the COVID-19 pandemic, the Ministry of Health has seen high interest in all aspects of the virus from the scientific and healthcare community, and the general public. This update is currently produced weekly and is designed to provide new information on the variants of concern or that are of interest.

The format of this report has changed from earlier COVID-19 Variant Updates. The document now contains three sections: 1) Key Points; 2) Omicron variant summary table; 3) Delta variant summary table; 4) Other variants summary table.

The Omicron variant is the focus of this update. Information is emerging at pace. New information included since the previous update is provided in red text.

Key points

Omicron

- On 26 November 2021, the World Health Organisation (WHO) designated variant B.1.1.529 a variant of concern, named Omicron. This decision was made because the Omicron variant has several mutations in the spike protein that could influence how it behaves.
- **As at 08 December 2021, Omicron is present in at least 50 countries around the world.** Although there is limited evidence currently available for this variant, several countries globally have implemented stricter border measures to minimise risk of spread.
- **The UK Health Security Agency (UKHSA) now predicts that Omicron is likely to outcompete Delta in the UK based on analysis of increased household transmission risk, secondary attack rates and growth rates compared to Delta. The growth advantage observed could be due to increased transmissibility or increased immune evasion, or some combination of both.**
- PCR tests continue to detect Omicron infection. Studies are ongoing to determine whether there is any impact on other types of tests, including rapid antigen detection tests.
- Preliminary data from South Africa shows that the risk of reinfection has increased in the era of Omicron. This suggests that Omicron could have increased evasion of immunity following prior infection. However, this is not yet confirmed, and it is not yet clear if Omicron can evade vaccine-induced immunity.
- **The laboratory data on Omicron from antibody neutralisation studies to date is very limited and preliminary, and cannot be used to infer an impact on vaccine protection in real world settings at this stage. It is not known when data about effectiveness of vaccines against infection and disease caused by the Omicron variant will become available, but this is being investigated with urgency.**
- **UKHSA have stated that Omicron mutations appear likely to reduce the effectiveness of monoclonal antibodies. A preliminary German study reported as a pre-print on 8 December showed Omicron resistance to neutralisation by the monoclonal antibodies casirivimab and imdevimab, alone or in combination.**

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- Many characteristics of Omicron are still unclear. More robust data are required to determine:
 - if Omicron presents with different symptoms and if there are any changes to disease severity. Data reported over the next 1-2 months will be important.
 - **how transmissible Omicron is compared to Delta. The UKHSA risk assessment of 8 December states that Omicron is at least as transmissible as Delta.** Data reported over the next 2-4 weeks will be important.
 - if Omicron can escape vaccine-induced immunity. Laboratory data **is emerging**.

Delta

- Delta continues to be the most frequently detected variant of concern (VOC) globally, but the proportion of Delta cases is declining in some countries with the advent of Omicron. Delta is substantially more transmissible than previous variants, with a higher secondary attack rate.
- Two doses of Pfizer vaccine remain effective against infection, symptomatic disease and hospitalisation for cases associated with Delta. However, protection against infection wanes over time, indicating the need for a third (booster) dose after several months.
- Preliminary evidence indicates that COVID-19 vaccination reduces onwards transmission of Delta (i.e., both the chance of becoming infected and the likelihood of an infected person transmitting to another person), but this impact reduces over time.

Omicron (B.1.1.529) Variant of Concern

Characteristic	Data
Identification and global prevalence	<p>Summary: Omicron is increasing in prevalence globally and preliminary analysis suggests it may outcompete Delta.</p> <ul style="list-style-type: none"> The B.1.1.529 variant was first detected in samples collected on 11 November 2021 in Botswana and on 14 November 2021 in South Africa.[1] B.1.1.529 was first reported to WHO from South Africa on 24 November 2021. This variant was named 'Omicron' and designated a variant of concern on 26 November 2021 by WHO's Technical Advisory Group on Virus Evolution due to the high number of mutations in the spike protein.[2] Omicron is the most divergent variant detected so far, which raises concerns that it may be associated with increased transmissibility, significant reduction in vaccine effectiveness, and increased risk for reinfection. As at 08 December 2021, Omicron is present in at least 50 countries around the world, including Australia, the US, UK, Canada, Israel, and the Netherlands. Although there is limited evidence currently available for this variant, several countries globally have implemented stricter border measures to minimize risk of spread. The UK Health Security Agency (UKHSA) predicts that Omicron is likely to outcompete Delta in the UK based on analysis of increased household transmission risk, secondary attack rates and growth rates compared to Delta. [3]
Spike protein mutations	<p>Summary: Omicron contains many mutations in the spike protein, some of which have been associated with increased transmissibility and immune escape.</p> <ul style="list-style-type: none"> In comparison to the original strain, Omicron contains at least 30 mutations in the spike protein, including three deletions and one small insertion.[1, 2] Of these, 15 are located within the receptor binding domain (RBD). A particular cluster of mutations at the S1-S2 furin cleavage site (N655Y, N679K, P681H) are associated with more efficient cell entry, which may indicate an increase in transmissibility.[4] These mutations have been identified in other variants, but never reported together in one variant. [4] These mutations have been identified in other variants, but never reported together in one variant. For example, P681H is seen in Alpha and Mu; Delta contains P681R; and N679K is seen in C.1.2. The large number of mutations in the RBD, including K417N and E484A, may indicate an increased potential for immune escape.[4] There have been reports of a small number of cases of an Omicron sub-lineage that may not carry the Δ69-70 deletion.[5, 6] It has been proposed that this sub-lineage be named BA.2, with the original Omicron being BA.1. [5, 7]
Testing and detection	<p>Summary: PCR tests continue to detect Omicron infection. Studies are ongoing to determine whether there is any impact on other types of tests, including rapid antigen detection tests.</p> <ul style="list-style-type: none"> Omicron has a deletion Δ69-70 in the Spike protein (similar to Alpha, but different to Delta). One PCR test, ThermoFisher TaqPath, can detect the lack of this target gene (called S gene target failure or S gene dropout) [1, 2] and therefore this test can be used as an early marker to distinguish between Omicron and Delta, pending sequencing confirmation. However, reports of a small number of cases of an Omicron sub-lineage that may not carry the Δ69-70 deletion could affect this. Data from UKHSA as at 03 December 2021 shows that the [logistic] growth rate of S gene target failure has 'fluctuated between approximately -50% and +50% over the past 90 days but in the past week has climbed to +141%'. [8] UKHSA data as at 08 December 2021 also confirms that the number of cases with the S gene target failure has notably increased. [9] This signals the S gene target failure is growing faster, but UKHSA states this cannot be interpreted as a change in transmissibility or an increase in the absolute number of cases of the variant. [8] It has been suggested that reported cases of Omicron BA.2, which may not carry the Δ69-70 deletion, may be unable to be identified as Omicron via PCR by S gene target failure. PCR tests can still confirm this sub-lineage as a positive COVID-19 case but it is suggested that whole genome sequencing is required to confirm the infection as Omicron BA.2. [6, 7] It is unknown how rapid antigen tests will perform on Omicron. Since many tests in the market (but not all) target the nucleocapsid protein rather than the spike protein, they are expected to continue to work. Studies are ongoing to assess if rapid antigen tests may be impacted.[1, 2]
Symptoms and severity of disease	<p>Summary: More robust data is required to determine whether this variant presents with different symptoms. Data for severity and mortality is expected to become available in the next 1-2 months.</p> <ul style="list-style-type: none"> Preliminary information from South Africa indicates that there are currently no unusual symptoms associated with Omicron. As seen with other variants, some individuals are asymptomatic.[10] There have been some anecdotal reports from doctors in South Africa stating that Omicron causes milder symptoms and less severe illness.[11] However, these milder cases were in younger people. [11] It is too early to draw any conclusions on disease severity until more data for different age groups, especially the elderly, become available. Data for severity and mortality is expected to become available in the next 1-2 months, once outcomes for hospitalised cases are evaluated. As at 30 November 2021, hospitalisation or death had not been linked to any of the confirmed Omicron cases in England, however mortality in is a lagged indicator (deaths do not occur until some time after infection) so it is too early to draw conclusions about severity of Omicron disease. [8]
Transmission	<p>Summary: Omicron is at least as transmissible as Delta. Data reported over the next 2-4 weeks will continue to be important.</p> <ul style="list-style-type: none"> Early data shared on Twitter by Dr Tulio de Oliveira from the Center for Epidemic Response and Innovation in South Africa showed that prevalence of Omicron in genomically sequenced samples has increased to 75% in less than 2 weeks, indicating that this variant could potentially outcompete Delta.[12] The variant is now spreading quickly in South Africa, with over 360 confirmed cases, as at 08 December 2021. It should be noted that vaccine coverage is very low in South Africa, with only around 25% of people fully vaccinated.[13] More robust data are required to understand whether Omicron has increased transmissibility over other variants. If the variant has been seeded by several visitors to the country in different locations at the same time, then this could appear to be an increase in transmissibility initially, but then not be borne out by the data over time. International data on transmissibility in the coming weeks will therefore be very important to confirm these early observations. Nucleocapsid changes as well as mutations on the furin cleavage site and RBD suggest increased transmissibility compared to Delta is possible. [14] UKHSA has observed a growth advantage for Omicron noting that this could be due to increased transmissibility or increased immune evasion or a combination of both. [3] The UKHSA risk assessment of 8 December states that Omicron is at least as transmissible as Delta. [14]

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<p>Immune escape</p>	<p>Summary: Preliminary data from South Africa suggests that Omicron could have increased evasion of immunity following prior infection. It is unclear whether Omicron can escape vaccine-induced immunity. Laboratory data is emerging but is limited and preliminary.</p> <p>Prior infection</p> <ul style="list-style-type: none"> A pre-print from South Africa looking at infection trends in routine surveillance data found that Omicron is associated with a high risk of reinfection.[15] Reinfection was defined in the study as two positive tests (PCR or antigen detection), at least 90 days apart. [15] Reinfection was defined in the study as two positive tests (PCR or antigen detection), at least 90 days apart. The relative hazard ratio (reinfection versus primary infection) for the Omicron period versus the first wave of infection was 2.39 (95% CI: 1.88–3.11). These preliminary data suggest that Omicron has increased immune evasion to prior infection, but it is not yet clear if time since previous infection could have influenced these findings. <p>Vaccination</p> <ul style="list-style-type: none"> It is not yet clear if Omicron can evade vaccine induced immunity in real-world settings. Vaccine developers and scientists are expecting that the COVID-19 vaccines will still offer protection against severe disease and death.[16, 17]Vaccine developers and scientists are expecting that the COVID-19 vaccines will still offer protection against severe disease and death.[16, 17] Pfizer have begun the production of an upgraded vaccine to target the Omicron variant.[16] The Pfizer CEO has stated that if needed, an initial batch of 25-50 million doses would take about 100 days to produce, provided regulators are satisfied. Pfizer have begun the production of an upgraded vaccine to target the Omicron variant.[16] The Pfizer CEO has stated that if needed, an initial batch of 25-50 million doses would take about 100 days to produce, provided regulators are satisfied with the product. Risk assessments of the Omicron variant reported by the UKHSA on 3 December [14] and 8 December [3] state that changes in the RBD are likely to reduce antibody binding. The UKHSA are currently assessing the findings of new neutralisation studies. [3] Although these Omicron mutations suggest protection from vaccine derived immunity may be reduced, there is no body of epidemiological data yet available to confirm this prediction. [14] Structural modelling from the University of Oxford indicates that antibody binding (natural and therapeutic), is likely to be affected by Omicron's mutations. This modelling also suggested that compared with other variants, Omicron has enhanced ability to bind to human ACE2 receptors. [8] A few preliminary laboratory studies have evaluated antibody-mediated neutralisation of Omicron in vaccinated sera: <ul style="list-style-type: none"> A small South African study reported as a pre-print (non-peer reviewed) utilised samples taken from 12 participants vaccinated with the Pfizer vaccine, six of whom had a previous SARS-COV-2 infection with the ancestral D614G virus.[18] The study observed measurable neutralisation capacity but this was approximately 41-fold lower (across all 12 participants) against Omicron than the ancestral D614G variant. [18] Five of the six participants who had been infected (with the ancestral strain) and vaccinated (not stated, but likely 2 doses after infection) had "relatively high" neutralisation titres against Omicron. A German study reported as a pre-print (non-peer reviewed) on 8 December compared in vitro neutralisation of Omicron and Delta using sera from individuals vaccinated with the Pfizer vaccine (N=117). [19] An 11.4-fold reduction was observed for Omicron compared with Delta for sera from double vaccinated samples. [19] A Pfizer news article reported on the findings of laboratory studies investigating the effect of booster vaccine doses against Omicron. [20] The article reported that sera from individuals (number unclear) who received two Pfizer doses showed, on average, more than a 25-fold reduction in neutralisation titers against the Omicron variant compared to the wild-type Wuhan strain. However, sera from those who received a booster dose showed increased antibody titers (by 25-fold), at a level similar to those observed after two doses against wild-type, Beta and Delta variants. The article also stated: "As 80% of epitopes in the spike protein recognized by CD8+ T cells (cell-based immunity) are not affected by the mutations in the Omicron variant, two doses may still induce protection against severe disease." [20] Overall, there is insufficient data from laboratory studies to date to compare the <i>in vitro</i> neutralisation of Omicron with that of Delta by sera from vaccinated individuals. The laboratory data on Omicron from antibody neutralisation studies is very limited and preliminary, and cannot be used to infer an impact on vaccine protection in real world settings. It is not known when data about effectiveness of vaccines against infection and disease caused by the Omicron variant will become available, but this is being investigated with urgency. [21] <p>Therapeutics</p> <ul style="list-style-type: none"> UKHSA have stated, based on modelling, that Omicron mutations appear likely to reduce the effectiveness of therapeutic monoclonal antibodies, and seem unlikely to affect small molecule antivirals; but there was no laboratory or clinical evidence to support the modelling evidence at the time the statement was made. [14] A German study reported as a pre-print (non-peer reviewed) on 8 December showed Omicron resistance to neutralisation by the monoclonal antibodies casirivimab and imdevimab, either alone or in combination.[19]
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Delta (B.1.617.2) Variant of Concern

Characteristic	Data for unvaccinated	Data for vaccinated																																			
Viral dynamics (Note: It is difficult to estimate viral dynamics accurately due to differences in study methodologies. For example, results may vary depending on the contact tracing system of the country, on the timing that cases are isolated, or on the number of exposure events in a transmission study.)																																					
Latency period time from exposure to start of infectious period	<p>Summary: Evidence is limited. Delta may have the same or shorter latency period than other variants. Approximately 4 days.</p> <ul style="list-style-type: none"> One study reported the mean latency was 4 days.[22] Another study reported a time window of approximately 3.7 days.[23] 	No data available																																			
Incubation period time from exposure to symptom onset	<p>Summary: Evidence is limited. Delta may have a shorter incubation period than other variants. Range is approximately 4-6 days.</p> <ul style="list-style-type: none"> One study reported the mean incubation period was 5.8 days.[22] Another study reported a significantly shorter incubation period for Delta compared with the wild-type strain (4 versus 6 days).[24] 	No data available																																			
Serial interval time from onset of symptoms in the primary case to onset of symptoms in the secondary case	<p>Summary: The serial interval for Delta is approximately 2.5-3.3 days.[25-27]</p> <ul style="list-style-type: none"> One study reported that the serial interval was not different for Delta and non-Delta cases.[25] However, a study of an outbreak in South Korea found the mean serial interval declined from 4.0 days to 2.5 days as Delta became more prevalent (of note, Delta only accounted for ~40% of cases during this time).[26] A Korean contact tracing study reported a serial interval of 3.26 days.[27] 	No data available																																			
Duration of infectious period	<p>Summary: Evidence is limited on whether Delta has a longer infectious period.</p> <ul style="list-style-type: none"> Low cycle threshold (Ct) values correspond to high viral load. Ct values are used as a surrogate for infectiousness and may not correlate with risk of transmission. Ct values stay <30 for 18 days for severe/hospitalised cases.[28] However, some studies report similar values for non-Delta variants. This is likely an upper limit of infectious period given the data was based on hospitalised cases and total viral load (rather than total infectious virus). A Chinese study reported a longer duration of viral shedding in upper respiratory tract samples compared with the wild-type strain (14 versus 8 days).[24] 	<p>Summary: Evidence on duration of infection period in breakthrough infections is limited.</p> <ul style="list-style-type: none"> A US study of 8 Delta breakthrough infections found longer duration of viral shedding (13.5 vs 4 days), greater likelihood of replication-competent virus at early stages of infection (6/8 [75%] vs 3/14 [23%]), and longer duration of culturable virus (median 7 vs 3 days) compared to non-Delta variants.[29] 																																			
Viral load	<p>Summary: Delta appears to have very high viral loads.</p> <ul style="list-style-type: none"> The magnitude of the increase in viral load is unclear. One pre-print reported 1000 times higher viral load on the first PCR positive test compared to the less transmissible ancestral variant.[23] Another paper estimated 4-fold increase in viral load compared to the more transmissible Alpha variant.[30] Higher viral load is also seen in national surveillance data from contact tracing in Public Health England data, and other preprints.[22, 23, 31] 	<p>Summary: Vaccinated cases may have a similar viral load to unvaccinated at the start of the infectious period.</p> <ul style="list-style-type: none"> Several studies have found that vaccinated and unvaccinated Delta cases have similar PCR cycle threshold (Ct) values (a proxy for viral load).[32-40] Some studies report that the viral load decreases more rapidly in vaccinated individuals.[33, 40] A study in vaccinated healthcare workers found that viral loads of breakthrough Delta cases were ~251 times higher than breakthrough cases infected with previous strains.[41] 																																			
Secondary attack rate (SAR)	<p>Summary: SAR varies widely depending on setting. Evidence is emerging showing that vaccinated index cases have lower secondary attack rates for Delta than unvaccinated index cases.</p> <ul style="list-style-type: none"> The household secondary attack rate from the New Zealand August 2021 outbreak was 45.6%; SAR for close-plus contacts was 11% (Ministry of Health internal preliminary analysis, extracted 11 October, see Table below). <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th>Secondary cases, n</th> <th>Contacts, N</th> <th>SAR, %</th> <th>SAR (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Total</td> <td>1,051</td> <td>40,089</td> <td>2.6</td> <td>(2.4-2.7)</td> </tr> <tr> <td colspan="5">Contact risk type</td> </tr> <tr> <td>Casual plus</td> <td>0</td> <td>4052</td> <td>0.0</td> <td>(0.0-0.1)</td> </tr> <tr> <td>Close</td> <td>107</td> <td>34733</td> <td>0.3</td> <td>(0.3-0.4)</td> </tr> <tr> <td>Close plus</td> <td>42</td> <td>379</td> <td>11.1</td> <td>(8.0-15.0)</td> </tr> <tr> <td>Household</td> <td>902</td> <td>1976</td> <td>45.6</td> <td>(42.7-48.7)</td> </tr> </tbody> </table>			Secondary cases, n	Contacts, N	SAR, %	SAR (95% CI)	Total	1,051	40,089	2.6	(2.4-2.7)	Contact risk type					Casual plus	0	4052	0.0	(0.0-0.1)	Close	107	34733	0.3	(0.3-0.4)	Close plus	42	379	11.1	(8.0-15.0)	Household	902	1976	45.6	(42.7-48.7)
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	<ul style="list-style-type: none"> SAR varies widely, depending on setting. A US study in a gym found that among cohorts with identified cases, attack rates ranged from 8% to 60%, but the overall facility-associated attack rate among 194 exposed persons was reported as 24%. [42] A Korean contact tracing study on an outbreak of 405 cases reported a SAR of 63% in household contacts. [27] An outbreak report among unvaccinated soldiers on a single navy ship noted a 90% attack rate. [43] Currently, the SAR for household contacts based on contact tracing data in the UK is 11.2%. [44] noting that the relatively low SAR in the UK partly reflects the high vaccination coverage (approximately 80% aged 12+ are fully vaccinated) [45] Transmission study in Singapore found that household SAR among unvaccinated Delta-exposed contacts was 25.8% compared with 11.3% among vaccinated contacts. [46] A Dutch contact tracing study found that the crude SAR among unvaccinated household contacts for vaccinated index cases was lower compared to unvaccinated index cases (13% vs 22%). The corresponding adjusted vaccine effectiveness against transmission was 63% (95% CI: 46-75). [47] Results were not stratified by vaccine type. 									
Transmission	<p>Summary: Vaccination reduces transmission of Delta, but the vaccine's impact on transmission appears to reduce over time.</p> <ul style="list-style-type: none"> UK national surveillance data found 64% increase in household transmission with Delta compared with Alpha (aOR 1.64; 95% CI: 1.26-2.13, p < 0.001). [48] Studies on Delta reported that 12-73.9% of the transmissions to close contacts occurred before symptom onset. [22, 27] Delta variant cases will infect 64% their 'close proximity' contacts. [49] An observational study in England found that two doses of the Pfizer vaccine reduced onwards transmission from breakthrough infections of the Delta variant by 50%, which was more than the AstraZeneca vaccine (Pfizer aRR=0.50 and AstraZeneca aRR=0.76). [50] A Dutch contact tracing study estimated that vaccine effectiveness against onwards transmission to fully vaccinated household contacts was 40% (95% CI: 20-54), which is in addition to the individual protection against infection. [47] Effectiveness against onwards transmission to unvaccinated household contacts was 63% (95% CI: 46-75). Results were not stratified by vaccine type. 									
R ₀	<p>Summary: R₀ ~5.5-6.5, i.e. On average, each person transmits Delta to another 5-6 people.</p> <p>No data available</p> <ul style="list-style-type: none"> Highest range of estimate is 8-9, based on the upper limits of current ranges of increased transmission (e.g., starting from R=3 for wild type, then ~50% increase from wild type to Alpha, and ~90% from Alpha to Delta). A summary of 5 papers using differing methods to calculate an R₀ for Delta reported a mean R₀ of 5.08 (range, 3.2-8.0). [51] A Danish pre-print estimated that Delta increases R₀ by a factor of 2.17 (95% CI: 1.99-2.36) relative to Alpha and 3.28 (95% CI: 3.01-3.58) relative to the ancestral variant. [52] The UK REACT-1 study found an overall R of 1.03 (range: 0.94-1.14) among those aged 5 and above in September 2021. Those aged 17 years and under had an R of 1.18 (range: 1.03-1.34), and this was lower in those aged 18 to 54 years (R of 0.81, range: 0.68-0.97). [53] 									
Severity										
Symptoms	<p>Summary: No clear evidence at this time that Delta symptoms differ from other VOCs or wild-type virus. The most common symptoms for COVID-19 caused by Delta are cough, fatigue, headache, sore throat, fever, loss of taste or smell, and myalgia.</p> <ul style="list-style-type: none"> A South Korean study found no significant difference between Delta-dominant and Delta-minor groups for COVID-19 symptoms in children and adolescents, except for the lower frequencies of rhinorrhoea (25% vs. 10.5%, P = 0.003), nasal stuffiness (34.8% vs. 15.4%, P = 0.001) and sore throat (23.9% vs. 12.6%, P = 0.02). [54] Patients in the Delta-dominant group were more likely to be asymptomatic (29.3% vs. 43.4%, P = 0.03). Data from a retrospective cohort study in Singapore using national surveillance data showed that the most common Delta symptoms were similar to symptoms for Alpha, Beta and the wild-type virus. Among those with Delta infection (n=67), the most common symptoms were fever (72%), cough (46%), sore throat (34%), shortness of breath (19%), and nasal congestion/runny nose (16%). [28] The same study reported that 12% of Delta cases were asymptomatic. However, at the time the data was collected (1 January-22 May 2021) there was a very small number of Delta cases overall (n=67). An analysis of 159 hospitalised Delta cases in a local outbreak in Guangzhou, China reported that the most common symptoms within three days on admission was cough (65%), followed by fever (63%) and expectoration (53%). Gastrointestinal symptoms such as diarrhoea (5%) and vomiting (4%) were uncommon. [24] The UK COVID-19 Infection Survey collects data on characteristics of people testing positive for COVID-19, including data on symptoms for those who had strong positive tests - Ct value under 30 (see Table below). [55] These data are provisional, reflect infections reported in the community, and exclude infections reported in hospitals, care homes, or other institutional settings. These data can be used to infer common symptoms of the Delta variant, which has been predominant in the UK since June 2021. <table border="1" data-bbox="587 1406 1169 1572"> <thead> <tr> <th rowspan="2">Symptoms</th> <th>% of people with this symptom within 35 days of a positive PCR test, among those people with a Ct value under 30</th> </tr> <tr> <th>September 2021</th> </tr> </thead> <tbody> <tr> <td>Any symptoms</td> <td>61.9</td> </tr> <tr> <td>No symptoms (asymptomatic)</td> <td>38.1</td> </tr> <tr> <td>Classic symptoms (cough, fever, shortness of breath, loss of taste, loss of smell)</td> <td>54.2</td> </tr> </tbody> </table>	Symptoms	% of people with this symptom within 35 days of a positive PCR test, among those people with a Ct value under 30	September 2021	Any symptoms	61.9	No symptoms (asymptomatic)	38.1	Classic symptoms (cough, fever, shortness of breath, loss of taste, loss of smell)	54.2
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Any symptoms	61.9									
No symptoms (asymptomatic)	38.1									
Classic symptoms (cough, fever, shortness of breath, loss of taste, loss of smell)	54.2									

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		Loss of taste or smell	28.4	
		Gastrointestinal symptoms (abdominal pain, nausea or vomiting, diarrhoea)	17.9	
		Cough	42.4	
		Fatigue (weakness)	38.0	
		Headache	38.7	
		Sore throat	32.6	
		Fever	27.9	
		Loss of smell	23.7	
		Muscle ache (myalgia)	25.0	
		Loss of taste	23.7	
		Shortness of breath	13.8	
		Nausea or vomiting	10.3	
		Abdominal pain	8.0	
		Diarrhoea	7.3	
Asymptomatic	<p>Summary: Data is emerging. Rate of asymptomatic cases depends on vaccination status, with vaccinated but infected people more likely to be asymptomatic. However, these data are not always reported. Breakthrough infections tend to be mild or asymptomatic.</p> <ul style="list-style-type: none"> Data from the UK COVID-19 infection survey indicated that during September, approximately 38% of positive cases did not report any symptoms. See Table above under 'Symptoms' for more details. This was during a period of relatively high vaccination coverage in the UK. A Korean study of 405 Delta cases reported that 20% were asymptomatic.[27] Proportion of vaccinated cases among asymptomatic was not reported. A Singaporean study using national surveillance data found 10% of Delta cases were asymptomatic.[28] However, at the time the data was collected (1 January-22 May 2021) there was a very small number of Delta cases (n=67) and proportion of vaccinated cases was not reported. One study in Singapore found the vaccinated group with Delta breakthrough infections (2 doses of mRNA vaccine; 71 of 218 Delta infections identified) were more likely to be asymptomatic (28.2% versus 9.2%, p<0.001) and had fewer symptoms than those unvaccinated. Higher proportion of pneumonia in unvaccinated group.[33] An outbreak report among unvaccinated soldiers on a single navy ship noted that 23% were asymptomatic.[43] 			
Hospitalisation	<p>Summary: Data indicates possible increased risk of hospitalisation. It is unclear whether the risk of ICU admission is higher for Delta once a patient is admitted to hospital.</p> <ul style="list-style-type: none"> Studies from England, Scotland, Denmark, and Canada have found that Delta was associated with approximately 2-3 times risk of hospitalisation compared to Alpha (hazard ratios ranging from 1.85-2.83).[56-59] In contrast, a Norwegian study found no difference in the risk of hospitalisation for Delta compared to Alpha.[60] A CDC study of data from 14 US states found no significant differences in the proportion of nonpregnant adults aged ≥18 hospitalised with severe outcomes between the pre-Delta and Delta periods. The proportion of hospitalised unvaccinated COVID-19 patients aged 18-49 years increased significantly during the Delta period.[61] The rate of new COVID-19 cases, emergency department visits, and hospital admissions increased for those aged 0-17 years after Delta became predominant in the US. Hospitalisation rates were highest among children aged 0-4 years (69.2 per 100,000) and adolescents aged 12-17 years (63.7 per 100,000), and lowest among children aged 5-11 years (24.0 per 100,000). Hospitalisation rates were 10 times higher among unvaccinated than among fully vaccinated adolescents. However, there was no difference in the severity of disease when compared with pre-Delta.[62, 63] 	<p>Summary: Unvaccinated people have higher case and hospitalisation rates for Delta than fully vaccinated people</p> <ul style="list-style-type: none"> Delta is currently the dominant variant in the US and the UK, making up more than 99% of recently sequenced cases in both countries.[64, 65] The US CDC COVID Data Tracker[64] reports that in September, unvaccinated people were 5.8 times more likely to test positive for COVID-19 and 9 times more likely to be hospitalised from COVID-19 than fully vaccinated people. The latest UKHSA COVID-19 vaccine surveillance report[66] indicates that the rate of a positive COVID-19 test varies by age and vaccination status. The rate of a positive COVID-19 test is substantially lower in vaccinated individuals compared to unvaccinated individuals up to the age of 29. In individuals aged greater than 30, the rate of a positive COVID-19 test is higher in vaccinated individuals compared to unvaccinated. This is likely to be due to a variety of reasons, including differences in the population of vaccinated and unvaccinated people as well as differences in testing patterns. The rate of hospitalisation within 28 days of a positive COVID-19 test increases with age and is substantially greater in unvaccinated people compared to vaccinated people. 		
Mortality/Case fatality rate	<p>Summary: Mortality/case fatality rate for Delta ~0.5-3%. It is important to note that the risk of mortality associated with COVID-19 is much higher for older age groups.</p> <ul style="list-style-type: none"> Our World In Data estimates the case fatality rate to be approximately 1-3% globally.[67] UKHSA reported that among 727,986 cases of Delta from 15 May 2021 to 24 October 2021, 3,813 had died within 28 days of testing positive, which is a case fatality rate of 0.53%.[44] 	<p>Summary: Unvaccinated people have higher mortality rates than fully vaccinated people</p> <ul style="list-style-type: none"> Delta is currently the dominant variant in the US and the UK, making up more than 99% of recently sequenced cases in both countries.[64, 65] The US CDC COVID Data Tracker[64] reports that in September, unvaccinated people were 14 times more likely to die from COVID-19 than fully vaccinated people. 		

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	<ul style="list-style-type: none"> A retrospective analysis of UK data found that Delta is associated with a lower case fatality rate than Alpha (all ages, 0.43% vs 1.07%), however, vaccination status of cases was not included in the analysis.[68] 	<ul style="list-style-type: none"> The latest UKHSA COVID-19 vaccine surveillance report[66] indicates that the rate of death within 28 days or within 60 days of a positive COVID-19 test increases with age and is substantially greater in unvaccinated people compared to fully vaccinated people.
Vaccine efficacy/effectiveness		
Against viral infection (positive PCR test)	<ul style="list-style-type: none"> Pfizer: 79% (95%CI: 75-82)[69]; 39% (95%CI: 9-59) in fully vaccinated (including those who received their second dose several months earlier) in Israel[70]; 42% (95%CI: 13-62) in Minnesota in July when Delta became dominant compared to 76% (95%CI: 69-81) throughout January till July[71]; 52.4% (95%CI:48.0-56.4) in US nursing home residents during Delta prevalence compared to 74.2% (95%CI: 68.9-78.7) pre-Delta[72]; 53.5% (95%CI: 43.9-61.4) in those who received their second dose several months earlier in Qatar[73]; 93% (95%CI: 85-97) at <1 month to 53% (95%CI 39-65) at >4 months in US[74]; 85% (95%CI: 79-90) at 14 days post 2nd dose declining to 75% (95%CI: 70-80) at 90+ days in UK[75] AstraZeneca: 60% (95%CI: 53-66)[69]; 68% (95%CI: 61-73) at 14 days post 2nd dose declining to 61% (95%CI: 53-68) at 90+ days in UK[75] Janssen: 78% (95%CI: 73-82) during Delta prevalence in the US[76] 	
Against symptomatic disease	<ul style="list-style-type: none"> Pfizer: 87-88%[77, 78]; 40.5% (95%CI: 8.7-61.2) in fully vaccinated (including those who received their second dose several months earlier) in Israel[70]; 56.1% (95%CI: 41.4-67.2) in those who received their second dose several months earlier in Qatar[73]; 92.4% (95%CI: 92.1-92.7) at 1 week after the second dose and then fell to 69.7% (95%CI: 68.7-70.5) by 20+ weeks[79]; 93% (95%CI: 89-96) at 14 days post 2nd dose declining to 78% (95%CI: 72-82) at 90+ days in UK[75] AstraZeneca: 67% (95%CI: 61.3-71.8)[77]; 62.7% (95%CI: 61.7-63.8) at 1 week after the second dose and then fell to 47.3% (95%CI: 45.0-49.6) by 20+ weeks[79]; 72% (95%CI: 64-78) at 14 days post 2nd dose declining to 63% (95%CI: 53-71) at 90+ days in UK[75] 	
Against hospitalisation	<ul style="list-style-type: none"> Pfizer: 96% (95%CI: 86-99)[80]; 80% (95%CI: 73-85) during Delta prevalence in the US[81]; 99.7% (95%CI: 97.6-100.0) at 1 week after the second dose and then fell to 92.7% (95%CI: 90.3-94.6) by 20+ weeks[79]; 96% (95%CI: 95-96) during Delta period in the Netherlands[82] AstraZeneca: 92% (95%CI: 75-97)[80]; 93.9% (95%CI: 91.3-95.7) at 1 week after the second dose and then fell to 77.0% (95%CI: 70.3-82.3) by 20+ weeks[79]; 94% (95%CI: 92-95) during Delta period in the Netherlands[82]; 88% (95%CI: 85-90) during Delta prevalence in Scotland[83] Janssen: 60-85% during Delta prevalence in the US[76, 81]; 91% (95%CI: 88-94) during Delta period in the Netherlands[82] 	
Against transmission	<ul style="list-style-type: none"> Pfizer: 50% (95%CI: 35-61) against onwards Delta transmission at 2 weeks after 2nd dose declining to 24% (95%CI: 20-28) through 3 months[84] AstraZeneca: 24% (95%CI: 18-30) against onwards Delta transmission at 2 weeks after 2nd dose declining to 2% (95%CI: -2-6) through 3 months[84] 	
Waning immunity	<ul style="list-style-type: none"> A study from Oxford University reported that during Delta prevalence, VE against infection for Pfizer declined by 22% (95%CI 6-41%) per month from second dose for 18-64 year olds, starting at 85% (95%CI 79-90) 14 days post-second dose.[75] A study from Southern California also reported waning of VE against infection, after adjusting for many confounders (demographics, comorbidities, social deprivation measures) and stratifying by age.[85] VE against Delta infections was high during the first month after full vaccination (93%) and declined to 53% at 24 months. The authors concluded that waning effectiveness was not due to the increasing prevalence of Delta, because waning effectiveness was also seen for non-Delta cases. Importantly, a high VE against hospitalisation (90-93%, stratified by age), associated with any variant, was maintained for the duration of the study. 	

Other Variants

Other Variants of Concern (VOC) - as listed by WHO	
Lineage: B.1.1.7 WHO label: Alpha	<ul style="list-style-type: none"> Number of cases in NZ: 178 (report date of last confirmed case: 06 August 2021) First identified in United Kingdom Transmissibility: Increased transmissibility compared to previous variants[86] Disease severity: <ul style="list-style-type: none"> Mortality: Increased mortality compared to previous variants[86] Mortality: 60-70% increased mortality compared to previous variants [86] Hospitalisation risk: Increased risk of hospitalisation compared to previous variants[86] Impact on vaccine-induced immunity: Minimal; Pfizer and AstraZeneca vaccines remain effective and neutralisation capacity is largely maintained[86]
Lineage: B.1.351 WHO label: Beta	<ul style="list-style-type: none"> Number of cases in NZ: 33 (report date of last confirmed case: 27 June 2021) First identified in South Africa [86] Transmissibility: Increased transmissibility compared to previous variants [86] Disease severity: <ul style="list-style-type: none"> Mortality: Possible increased risk of mortality[86] Hospitalisation: Possible increased risk of hospitalisation Impact on vaccine-induced immunity: Moderate-Strong
Lineage: P.1 WHO label: Gamma	<ul style="list-style-type: none"> Number of cases in NZ: 8 (report date of last confirmed case: 01 June 2021) First identified in Brazil[86] Transmissibility: Increased transmissibility compared to previous variants Disease severity: <ul style="list-style-type: none"> Mortality: Possible increased risk of mortality[86] Hospitalisation: Possible increased risk of hospitalisation[86] Impact on vaccine-induced immunity: Moderate-Strong
Variants under Investigation (VUI) - as listed by UKHSA	
Lineage: AY.4.2 UKHSA label: VUI-21OCT-01	<ul style="list-style-type: none"> Number of cases in NZ: 5 (report date of last confirmed case: 04 November 2021) First identified in United Kingdom, October 2021. Increasing prevalence, particularly in the UK where cases of AY.4.2 have increased in proportion from 15.2-20.3% of all Delta cases, from the week of 07 November 2021 to the week of 21 November 2021, however the latest sequencing is incomplete [65] Spike mutations: Contains spike mutations A222V and Y145H [87] Transmissibility: Experts suggest there may be an 'increase in transmissibility of 10-15% compared to the original Delta variant', however, evidence is yet to emerge, and AY.4.2 is unlikely to present significant risk at this stage.[88] Secondary attack rate for AY.4.2 is slightly higher than Delta. [38] Disease severity: No evidence that AY.4.2 causes more severe disease than other Delta variants, according to recent analysis from the United Kingdom [65] Impact on vaccine-induced immunity: Minimal effect on vaccine-induced neutralisation and vaccine efficacy compared to Delta. [89]
Lineage: B.1.621 WHO label: Mu UKHSA label: VUI-21JUL-01	<ul style="list-style-type: none"> Number of cases in NZ: 1 (report date of last confirmed case: 19 June 2021) First identified in Columbia.[90] Spike mutations: T95I, YY144-145TSN, R346K, E484K, N501Y, D614G, P681H, and D950N. Some of these are mutations shared present in other variants: E484K (shared with Beta, Gamma), N501Y (shared with Alpha), P681H (shared with Alpha) and D950N (shared with Delta). The E484K (shared with Beta, Gamma), which is associated with reduced sensitivity towards natural or vaccine induced antibodies.[91] Transmission/Secondary attack rate: Mu has not outcompeted Delta in any country to date. Immune evasion: Mu has more potential for immune escape than Beta (previous variant with most immune escape) based on one study of sera from Pfizer-vaccinated individuals. [91, 92]
Lineage: B.1.525 WHO label: Eta UKHSA label: VUI-21FEB-03	<ul style="list-style-type: none"> Number of cases in NZ: 8 (report date of last confirmed case: 08 June 2021) First identified in UK and Nigeria, December 2020. Spike mutations: Spike mutations A67V, 69/70 deletion, 144del, E484K, D614G, Q677H, and F888L.[93] Immune evasion: Potential reduction in neutralisation by some monoclonal antibody treatments, convalescent and post-vaccine sera.[94]
Lineage: B.1.1.318 UKHSA label: VUI-21FEB-04	<ul style="list-style-type: none"> Number of cases in NZ: No cases. First identified in United Kingdom, February 2021. Spike mutations: Contains spike mutations T95I, 144del, E484K, P681H, D796H.[95]
Lineage: B.1.617.1 WHO label: Kappa	<ul style="list-style-type: none"> Number of cases in NZ: 5 (report date of last confirmed case: 09 April 2021) First identified in India, October 2020. Transmission/Secondary attack rate: Secondary attack rates similar to Delta.[96] Immune evasion: Kappa was neutralised by Pfizer and Moderna, however 6.8-fold reduction observed.[97]

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UKHSA label: VUI-21APR-01	
Lineage: B.1.617.3 UKHSA label: VUI-21APR-03	<ul style="list-style-type: none"> • Number of cases in NZ: 4 (report date of last confirmed case: 11 April 2021) • First identified India [86]
Lineage: P.2 variant (descendent of B.1.1.28) WHO label: Zeta UKHSA label: VUI-21JAN-01	<ul style="list-style-type: none"> • Number of cases in NZ: Last detected in a case reported New Zealand in on 05 March 2021. • First identified in Brazil, April 2020. • Spike mutations: Spike mutations E484K, D614K, and V1176F-[93] • Immune evasion: Possible reduced antibody neutralisation from studies on the spike protein mutation E484K.[98]

Glossary of Terms

The AstraZeneca vaccine	AZD1222 or ChAdOx1
The Pfizer/BioNTech vaccine	Comirnaty/BNT162b2
Global Initiative on Sharing Avian Influenza Data (GISAID)	This is a consortium that promotes and provides open access to SARS-CoV-2 genomic sequence data. Its original purpose was for sharing data on avian (bird) flu.
Immune escape	The ability of the virus to evade our body's immune response. See also Immune response.
Immune response	The response of our immune system to an infection. It includes development of specific antibodies to the virus and also cell-mediated responses (triggered by T cells).
Mutation	Small change made to the pattern of nucleotides that make up the virus. These occur as the virus spreads and replicates. Most do not confer a benefit to the virus.
Naming mutations	Mutation nomenclature (i.e., how they are named), describes what occurred at a specific location of the genome. For example, the 'E484K' mutation means that at the position 484, the amino acid changed from glutamic acid (E) to lysine (K). When a deletion occurs, the location is provided (e.g., deletion 144).
N-terminal domain	Part of the spike protein of the SARS-CoV-2 virus.
R₀, Reproductive number	The reproductive number R ₀ (R-naught), is a measure of how contagious a disease is. It is the average number of people who would catch a disease from one infected individual when there are no control measures in place, e.g., vaccination, lockdowns.
R_{eff}, Effective reproductive number	The 'effective R' (R _{eff}) is the R observed when control measures are in place. R _{eff} can therefore change depending on the control measures currently enacted in a particular population. In general, whenever R is less than 1, i.e., an infected person goes on to infect less than one person on average, then the prevalence of the disease would be expected to decrease.
Secondary attack rate	The probability that an infection occurs among persons within a reasonable incubation period after known contact with an infectious person in household or other close-contact environments.
Variant	Viruses with mutations are referred to as variants of the original virus. New variants of SARS-CoV-2 have been emerging as the virus has spread and evolved.
Variant of Concern (VOC)	<p>WHO definition: A SARS-CoV-2 variant that meets the definition of a VOI (see below) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:</p> <ul style="list-style-type: none"> • Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR • Increase in virulence or change in clinical disease presentation; OR

	<ul style="list-style-type: none"> Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.
Variant of Interest (VOI)	<p>WHO definition: A SARS-CoV-2 variant:</p> <ul style="list-style-type: none"> with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND Identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.
Variant under Investigation (VUI)	<p>UKHSA definition: SARS-CoV-2 variants, if considered to have concerning epidemiological, immunological or pathogenic properties, are raised for formal investigation. At this point they are designated Variant Under Investigation (VUI) with a year, month, and number. Following a risk assessment with the relevant expert committee, they may be designated Variant of Concern (VOC).</p>

Abbreviations

CDC: Centers for Disease Control and Prevention

GSAID: Global Initiative on Sharing Avian Influenza Data

RBD: Receptor binding domain (of the virus spike protein)

R_{eff}: 'Effective R', the effective reproductive number

R₀: 'R-naught', the baseline reproductive number

UKHSA: UK Health Security Agency

Useful Links

US CDC – SARS CoV-2 variant classifications and definitions	CDC classification of variants
Outbreak Info	Outbreak Info
WHO - Tracking SARS-CoV-2 variants	WHO Variant Tracking
UK Health Security Agency Technical Briefings (from October 2021 onwards)	Investigation of SARS-CoV-2 variants: technical briefings
Public Health England Technical Briefings	Investigation of SARS-CoV-2 variants: technical briefings

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COVID-19 Variants Update

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COVID-19 Variants Update

Date: 17 December 2021

About this update

During the COVID-19 pandemic, the Ministry of Health has seen high interest in all aspects of the virus from the scientific and healthcare community, and the general public. This update is designed to provide new information on the variants of concern or that are of interest.

This document contains three sections: 1) Key Points; 2) Omicron variant summary table; 3) Delta variant summary table; 4) Other variants summary table.

The Omicron variant is the focus of this update. Information is emerging at pace. New information included since the previous update is provided in red text.

Key points

Omicron

- On 26 November 2021, the World Health Organisation (WHO) designated variant B.1.1.529 a variant of concern, named Omicron. This decision was made because the Omicron variant has several mutations in the spike protein that could influence how it behaves.
- **As at 17 December 2021, Omicron is present in at least 70 countries around the world. Currently, countries with the highest detected Omicron case numbers are the United Kingdom, Denmark, Norway, and South Africa.** Although there is limited evidence currently available for this variant, several countries globally have implemented stricter border measures to minimise risk of spread.
- The UK Health Security Agency (UKHSA) now predicts that Omicron is likely to outcompete Delta in the UK based on analysis of increased household transmission risk, secondary attack rates and growth rates compared to Delta. The growth advantage observed could be due to increased transmissibility or increased immune evasion, or a combination of both.
- PCR tests continue to detect Omicron infection. **UKHSA reports that initial laboratory validation of rapid antigen tests has determined similar sensitivity to detect Omicron compared to Delta.**
- **Preliminary data suggests that Omicron could have an increased ability to evade immunity following vaccination or prior infection. The first estimate of vaccine effectiveness of the Pfizer vaccine against symptomatic Omicron infection (not peer-reviewed) from the UK is estimated to be high (approximately 88%) 2-9 weeks after the second dose, dropping to 35% after 4 months. The analysis was based on only 581 Omicron cases and all of the estimates for Omicron had wide confidence intervals. Therefore, these results are subject to significant uncertainty.**
- UKHSA have stated that Omicron mutations appear likely to reduce the effectiveness of monoclonal antibodies. **Preliminary reports from laboratory studies suggest that Omicron may be resistant to the majority of monoclonal antibody treatments, including the monoclonal antibody combination casirivimab and imdevimab (Ronapreve) but that sotrovimab retains some neutralising activity against Omicron.**

COVID-19 Variants Update

- Many characteristics of Omicron are still unclear. More robust data are required to determine:
 - if Omicron presents with different symptoms and if there are any changes to disease severity. **Data reported about disease severity over the next 2-8 weeks will be important, as data from “lagged outcomes” (e.g. ICU admission and death) become available.**
 - how transmissible Omicron is compared to Delta. The UKHSA risk assessment of 8 December states that Omicron is at least as transmissible as Delta. **Data are being reported now, but additional detailed analyses over the next 4 weeks will also be important.**
 - **the extent to which vaccine effectiveness is affected. Although it seems likely vaccine effectiveness against Omicron is reduced, it is not yet known to what extent vaccine effectiveness is affected. Laboratory and real-world data are emerging.**

Delta

- Delta continues to be the most frequently detected variant of concern (VOC) globally, but the proportion of Delta cases is declining in some countries with the advent of Omicron. Delta is substantially more transmissible than previous variants, with a higher secondary attack rate.
- Two doses of Pfizer vaccine remain effective against infection, symptomatic disease and hospitalisation for cases associated with Delta. However, protection against infection wanes over time, indicating the need for a third (booster) dose after several months.
- Preliminary evidence indicates that COVID-19 vaccination reduces onwards transmission of Delta (i.e., both the chance of becoming infected and the likelihood of an infected person transmitting to another person), but this impact reduces over time.

Omicron (B.1.1.529) Variant of Concern

Characteristic	Data
Identification and global prevalence	<p>Summary: Omicron is increasing in prevalence globally and preliminary analysis suggests it is likely to outcompete Delta.</p> <ul style="list-style-type: none"> The B.1.1.529 variant was first detected in samples collected on 11 November 2021 in Botswana and on 14 November 2021 in South Africa.[1] B.1.1.529 was first reported to WHO from South Africa on 24 November 2021. This variant was named 'Omicron' and designated a variant of concern on 26 November 2021 by WHO's Technical Advisory Group on Virus Evolution due to the high number of mutations in the spike protein.[2] Omicron is the most divergent variant detected so far, which raises concerns that it may be associated with increased transmissibility, significant reduction in vaccine effectiveness, and increased risk for reinfection. As at 17 December 2021, Omicron is present in at least 70 countries around the world. Currently, countries with the highest detected Omicron case numbers are the United Kingdom, Denmark, Norway, and South Africa. Although there is limited evidence currently available for this variant, several countries globally have implemented stricter border measures to minimise risk of spread. The UK Health Security Agency (UKHSA) predicts that Omicron is likely to outcompete Delta based on analysis of increased household transmission risk, secondary attack rates, and growth rates compared to Delta.[3]
Spike protein mutations	<p>Summary: Omicron contains many mutations in the spike protein, some of which have been associated with increased transmissibility and immune escape.</p> <ul style="list-style-type: none"> In comparison to the original strain, Omicron contains at least 30 mutations in the spike protein, including three deletions and one small insertion.[1, 2] Of these, 15 are located within the receptor binding domain (RBD). A particular cluster of mutations at the S1-S2 furin cleavage site (H655Y, N679K, P681H) are associated with more efficient cell entry, which may indicate an increase in transmissibility.[4] These mutations have been identified in other variants, but never reported together in one variant. For example, P681H is seen in Alpha and Mu; Delta contains P681R; and N679K is seen in C.1.2. The large number of mutations in the RBD, including K417N and E484A, may indicate an increased potential for immune escape.[4] The 10 December UKHSA briefing states that Omicron global phylogeny shows the presence of 2 clades, a large group (BA.1) with the typical Omicron mutations and a small outlying group (BA.2) with some shared mutations with Omicron and some differences, including an absence of the deletion in the spike protein at 69/70 which gives the SGTf result.[5] Structural modelling indicates that antibody binding (natural and therapeutic), is likely to be affected by Omicron's mutations.[6] Several modelling studies have suggested that compared with other variants, Omicron has an enhanced ability to bind to human ACE2 receptors.[6-9]
Testing and detection	<p>Summary: PCR tests continue to detect Omicron infection. Studies are ongoing to determine whether there is any impact on other types of tests, including rapid antigen detection tests (initial data suggest sensitivity preserved).</p> <ul style="list-style-type: none"> Omicron has a deletion Δ69-70 in the Spike protein (similar to Alpha, but different to Delta). One PCR test, ThermoFisher TaqPath, can detect the lack of this target gene (called S gene target failure or S gene dropout) [1, 2] and therefore this test can be used as an early marker to distinguish between Omicron and Delta, pending sequencing confirmation. However, reports of a small number of cases of an Omicron sub-lineage that may not carry the Δ69-70 deletion could affect this (see below). It has been suggested that reported cases of Omicron BA.2, which may not carry the Δ69-70 deletion, may be unable to be identified as Omicron via PCR by S gene target failure. PCR tests can still confirm this sub-lineage as a positive COVID-19 case but it is suggested that whole genome sequencing is required to confirm the infection as Omicron BA.2. [10, 11] It is unknown how rapid antigen tests will perform on Omicron. Since many tests in the market (but not all) target the nucleocapsid protein rather than the spike protein, they are expected to continue to work. Studies are ongoing to assess if rapid antigen tests may be impacted [1, 2] UKHSA reports that initial laboratory validation of rapid antigen tests in use by NHS Test and Trace has determined similar sensitivity to detect Omicron compared to Delta.[5]
Symptoms and severity of disease	<p>Summary: More robust data is required to determine whether this variant presents with different symptoms. Data for severity and mortality is expected to become available in the next 2 weeks to 2 months, as data from "lagged outcomes" accumulates.</p> <ul style="list-style-type: none"> There have been some anecdotal reports from doctors in South Africa stating that Omicron causes milder symptoms and less severe illness.[12] However, these milder cases were in younger people.[12] It is too early to draw any conclusions on disease severity until more data for different age groups, especially the elderly, become available. The WHO 10 December report highlights that: <ul style="list-style-type: none"> preliminary reports from South Africa have suggested the possibility of milder infection with Omicron than Delta, but there is insufficient data on the potential role of vaccination and previous infection on those case presentations.[13] All cases reported in the EU/EEA to 10th December 2021 were mild or asymptomatic.[13] A South African study reported on symptomatic breakthrough infections in seven tourists that had received three doses of COVID-19 vaccines.[14] The most common symptoms at the end of the 7-day observation period were dry cough (100%), rhinitis (71.4%), fatigue (57.1%), sore throat (57.1%), shortness of breath (42.9%) and headache (42.9%), with a general reduction of symptom severity as the infection progressed. Overall, all cases described their symptoms as mild or moderate and none required hospitalisation during the observation period. The CDC reported on 43 Omicron cases in the US, 34 (79%) of which occurred in fully vaccinated people.[15] 14 of these cases had received a third dose; five of whom had received the additional dose <14 days before symptom onset. Six (14%) persons had a documented previous SARS-CoV-2 infection. The most commonly reported symptoms were cough (89%), fatigue (65%), and congestion or runny nose (59%). One vaccinated patient was hospitalised for 2 days, and no deaths were reported. Recent data from Denmark does not indicate a difference in hospitalisation rates between those confirmed with Omicron compared to other variants.[16] There is insufficient information to determine disease severity and risk of hospitalisation with Omicron at this time.[5, 13] Data for severity and mortality is expected to become available in the next 2 weeks to 2 months, as data from "lagged outcomes" (e.g. ICU admission and death) become available.

COVID-19 Variants Update

<p>Transmission</p>	<p>Summary: Omicron is at least as transmissible and is likely to outcompete Delta. Data are being reported now, but additional detailed analyses over the next 4 weeks will also be important.</p> <ul style="list-style-type: none"> • Early data shared on Twitter by Dr Tulio de Oliveira from the Center for Epidemic Response and Innovation in South Africa showed that prevalence of Omicron in genomically sequenced samples has increased to 75% in less than 2 weeks, indicating that this variant could potentially outcompete Delta.[17] • More robust data are required to understand whether Omicron has increased transmissibility over other variants. If the variant has been seeded by several visitors to the country in different locations at the same time, then this could appear to be an increase in transmissibility initially, but then not be borne out by the data over time. International data on transmissibility in the coming weeks will therefore be very important to confirm these early observations. • UKHSA has observed a growth advantage for Omicron noting that this could be due to increased transmissibility or increased immune evasion or a combination of both.[3] • The UKHSA risk assessment of 8 December states that Omicron is at least as transmissible and is likely to outcompete Delta.[18] • UK studies of households and contacts show a higher risk of transmission to contacts from an Omicron index case, when compared to Delta index cases.[5] The studies did not adjust for vaccination status or prior infection, so this data should be viewed as evidence of growth advantage (which we use here to include both transmissibility, and the potential for immune evasion) rather than transmissibility alone. <ul style="list-style-type: none"> ◦ Risk of household transmission using routine testing data: adjusted odds ratio of transmission from an Omicron index case compared to a Delta index case was 3.2 (95% CI 2.0-5.0). ◦ Risk of a close contact becoming a secondary case: adjusted odds ratio was 2.09 (95% CI: 1.54-2.79). • Early lab-based and non-peer reviewed data shared by researchers from the LKS Faculty of Medicine at The University of Hong Kong (HKUMed) indicates that at 24 hours after infection, Omicron had replicated 70% faster in ex-vivo human bronchus tissue compared to the original strain and Delta.[19] Researchers suggested this may explain the observed increase in transmissibility compared to other variants. Omicron was also found to be less efficient (more than 10 times slower) at replicating in ex-vivo human lung tissue than the original strain. This could suggest lower severity of disease; however the researchers highlight that virus replication is not the sole determinant of severity of disease.[19]
<p>Immune escape</p>	<p>Summary: Preliminary data suggests that Omicron could have increased evasion of immunity following prior infection, vaccination, or administration of therapeutics. Although it seems likely vaccine effectiveness against Omicron is reduced, it is not yet known to what extent. Laboratory and real-world data are emerging.</p> <p>Prior infection and Vaccination</p> <ul style="list-style-type: none"> • A pre-print from South Africa looking at infection trends in routine surveillance data found that Omicron is associated with a high risk of reinfection.[20] Reinfection was defined in the study as two positive tests (PCR or antigen detection), at least 90 days apart. [20] Reinfection was defined in the study as two positive tests (PCR or antigen detection), at least 90 days apart. The relative hazard ratio (reinfection versus primary infection) for the Omicron period versus the first wave of infection was 2.39 (95% CI: 1.88-3.11). These preliminary data suggest that Omicron has increased immune evasion to prior infection, but it is not yet clear if time since previous infection could have influenced these findings. • Vaccine developers and scientists are expecting that the COVID-19 vaccines will still offer protection against severe disease and death.[21, 22] Pfizer have begun the production of an upgraded vaccine to target the Omicron variant.[21] The Pfizer CEO has stated that if needed, an initial batch of 25-50 million doses would take about 100 days to produce, provided regulators are satisfied. • Early data from the UK showed that vaccine effectiveness (VE) against symptomatic disease from a primary course of the Pfizer vaccine was lower against Omicron than Delta in the UK:[23] <ul style="list-style-type: none"> ◦ VE of two doses of Pfizer against Omicron was 88% (95%CI: 66 to 96%) at 2-9 weeks after dose two, declining to 48.5% (95%CI: 24.3-65.0) at 10-14 weeks and to 34.2% (95%CI: -5.8-7) at 25+ weeks. In comparison, VE against Delta was similar 2-9 weeks after dose two (VE 88%, 95%CI: 87 to 90%), but estimates did not drop as rapidly with time as for Omicron (VE for Delta 66%, 95%CI: 61 to 66%, 25+ weeks after dose two).[23] ◦ VE of a Pfizer booster after Pfizer primary course against Omicron increased to 76% (95%CI: 56 to 86%) at least 2 weeks after the booster dose, compared an increase against Delta to 93% (95%CI: 92 to 93%). ◦ For the AstraZeneca vaccine, there was no protection observed from 15 weeks after the second dose. However, VE increased to 71.4% (95%CI: 41.8-86.0) after a Pfizer booster in those who received a primary course of AstraZeneca. ◦ The analysis was based on only 581 Omicron cases and all of the VE estimates for Omicron had wide confidence intervals. These results are therefore subject to significant uncertainty. • A press release with data from South Africa during the Omicron wave states that two doses of Pfizer has a VE of 70% against hospitalisation, and 33% against COVID-19 infection, though the data does not mention time since vaccination.[24] • Preliminary laboratory studies have evaluated antibody neutralisation of Omicron: <ul style="list-style-type: none"> ◦ Those vaccinated with two doses of Pfizer had a 20-40 fold reduction in neutralising activity compared to previous strains.[5, 25-28] and at least a 10-fold reduction compared to the Delta variant.[5, 26, 27, 29] ◦ Those vaccinated with two doses of AstraZeneca had very low neutralising activity, sometimes negligible.[26, 27] ◦ Previously infected individuals who were vaccinated with two doses of Pfizer had higher neutralising activity than naïve vaccinated individuals.[25, 27, 29] ◦ A Pfizer booster dose in those vaccinated with a primary course of Pfizer or AstraZeneca substantially enhances neutralising activity against Omicron.[28, 29] • Cellular responses (T-cells) arising from previous infection or vaccination appear to be largely unaffected. This is likely because majority of the regions in the spike protein that are recognised by CD8+ T cells are unchanged in the Omicron variant.[28, 30] • Overall, there is limited antibody neutralisation and vaccine effectiveness data to understand the impact of Omicron on vaccine-induced protection. It is not known when more data about effectiveness of vaccines against infection and severe disease caused Omicron will become available, but this is being investigated with urgency.[31] <p>Therapeutics</p> <ul style="list-style-type: none"> • UKHSA have stated, based on modelling, that Omicron mutations appear likely to reduce the effectiveness of therapeutic monoclonal antibodies, and seem unlikely to affect small molecule antivirals; but there was no laboratory or clinical evidence to support the modelling evidence at the time the statement was made.[18] • Preliminary laboratory studies have evaluated antibody neutralisation of Omicron: <ul style="list-style-type: none"> ◦ A pre-print (non-peer reviewed) suggests that Omicron is resistant to neutralisation by a number of therapeutics, including REGEN-COV (casirivimab + imdevimab combination); sotrovimab was shown to have a reduced neutralisation effect against Omicron.[32] ◦ Another study also demonstrated in vitro neutralisation of pseudotyped virus encoding Omicron substitutions by VIR-7831 (sotrovimab).[33] ◦ A German study reported as a pre-print (non-peer reviewed) on 8 December showed Omicron resistance to neutralisation by the monoclonal antibodies casirivimab and imdevimab, either alone or in combination.[29]

Delta (B.1.617.2) Variant of Concern

Characteristic	Data for unvaccinated	Data for vaccinated																																			
Viral dynamics (Note: It is difficult to estimate viral dynamics accurately due to differences in study methodologies. For example, results may vary depending on the contact tracing system of the country, on the timing that cases are isolated, or on the number of exposure events in a transmission study.)																																					
Latency period time from exposure to start of infectious period	<p>Summary: Evidence is limited. Delta may have the same or shorter latency period than other variants. Approximately 4 days.</p> <ul style="list-style-type: none"> One study reported the mean latency was 4 days.[34] Another study reported a time window of approximately 3.7 days.[35] 	No data available																																			
Incubation period time from exposure to symptom onset	<p>Summary: Evidence is limited. Delta may have a shorter incubation period than other variants. Range is approximately 4-6 days.</p> <ul style="list-style-type: none"> One study reported the mean incubation period was 5.8 days.[34] Another study reported a significantly shorter incubation period for Delta compared with the wild-type strain (4 versus 6 days).[36] 	No data available																																			
Serial Interval time from onset of symptoms in the primary case to onset of symptoms in the secondary case	<p>Summary: The serial interval for Delta is approximately 2.5-3.3 days.[37-39]</p> <ul style="list-style-type: none"> One study reported that the serial interval was not different for Delta and non-Delta cases.[37] However, a study of an outbreak in South Korea found the mean serial interval declined from 4.0 days to 2.5 days as Delta became more prevalent (of note, Delta only accounted for ~40% of cases during this time).[38] A Korean contact tracing study reported a serial interval of 3.26 days.[39] 	No data available																																			
Duration of infectious period	<p>Summary: Evidence is limited on whether Delta has a longer infectious period.</p> <ul style="list-style-type: none"> Low cycle threshold (Ct) values correspond to high viral load. Ct values are used as a surrogate for infectiousness and may not correlate with risk of transmission. Ct values stay ≤ 30 for 18 days for severe/hospitalised cases.[40] However, some studies report similar values for non-Delta variants. This is likely an upper limit of infectious period given the data was based on hospitalised cases and total viral load (rather than total infectious virus). A Chinese study reported a longer duration of viral shedding in upper respiratory tract samples compared with the wild-type strain (14 versus 8 days).[36] 	<p>Summary: Evidence on duration of infection period in breakthrough infections is limited.</p> <ul style="list-style-type: none"> A US study of 8 Delta breakthrough infections found longer duration of viral shedding (13.5 vs 4 days), greater likelihood of replication-competent virus at early stages of infection (6/8 [75%] vs 3/14 [23%]), and longer duration of culturable virus (median 7 vs 3 days) compared to non-Delta variants.[41] 																																			
Viral load	<p>Summary: Delta appears to have very high viral loads.</p> <ul style="list-style-type: none"> The magnitude of the increase in viral load is unclear. One pre-print reported 1000 times higher viral load on the first PCR positive test compared to the less transmissible ancestral variant.[35] Another paper estimated 4-fold increase in viral load compared to the more transmissible Alpha variant.[42] Higher viral load is also seen in national surveillance data from contact tracing in Public Health England data, and other preprints.[34, 35, 43] 	<p>Summary: Vaccinated cases may have a similar viral load to unvaccinated at the start of the infectious period.</p> <ul style="list-style-type: none"> Several studies have found that vaccinated and unvaccinated Delta cases have similar PCR cycle threshold (Ct) values (a proxy for viral load).[44-52] Some studies report that the viral load decreases more rapidly in vaccinated individuals.[45, 52] A study in vaccinated healthcare workers found that viral loads of breakthrough Delta cases were ~251 times higher than breakthrough cases infected with previous strains.[53] 																																			
Secondary attack rate (SAR)	<p>Summary: SAR varies widely depending on setting. Evidence is emerging showing that vaccinated index cases have lower secondary attack rates for Delta than unvaccinated index cases.</p> <ul style="list-style-type: none"> The household secondary attack rate from the New Zealand August 2021 outbreak was 45.6%; SAR for close-plus contacts was 11% (Ministry of Health internal preliminary analysis, extracted 11 October, see Table below). <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th>Secondary cases, n</th> <th>Contacts, N</th> <th>SAR, %</th> <th>SAR (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Total</td> <td>1,051</td> <td>40,089</td> <td>2.6</td> <td>(2.4-2.7)</td> </tr> <tr> <td>Contact risk type</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Casual plus</td> <td>0</td> <td>4052</td> <td>0.0</td> <td>(0.0-0.1)</td> </tr> <tr> <td>Close</td> <td>107</td> <td>34733</td> <td>0.3</td> <td>(0.3-0.4)</td> </tr> <tr> <td>Close plus</td> <td>42</td> <td>379</td> <td>11.1</td> <td>(8.0-15.0)</td> </tr> <tr> <td>Household</td> <td>902</td> <td>1976</td> <td>45.6</td> <td>(42.7-48.7)</td> </tr> </tbody> </table> <ul style="list-style-type: none"> SAR varies widely, depending on setting. A US study in a gym found that among cohorts with identified cases, attack rates ranged from 8% to 60%, but the overall facility-associated attack rate among 194 exposed persons was reported as 24%.[54] A Korean contact tracing study on an outbreak of 405 cases reported a SAR of 63% in household contacts.[39] An outbreak report among unvaccinated soldiers on a single navy ship noted a 90% attack rate.[55] 			Secondary cases, n	Contacts, N	SAR, %	SAR (95% CI)	Total	1,051	40,089	2.6	(2.4-2.7)	Contact risk type					Casual plus	0	4052	0.0	(0.0-0.1)	Close	107	34733	0.3	(0.3-0.4)	Close plus	42	379	11.1	(8.0-15.0)	Household	902	1976	45.6	(42.7-48.7)
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COVID-19 Variants Update

	<ul style="list-style-type: none"> Currently, the SAR for household contacts based on contact tracing data in the UK is 11.2%,^[56] noting that the relatively low SAR in the UK partly reflects the high vaccination coverage (approximately 80% aged 12+ are fully vaccinated).^[57] Transmission study in Singapore found that household SAR among unvaccinated Delta-exposed contacts was 25.8% compared with 11.3% among vaccinated contacts.^[58] A Dutch contact tracing study found that the crude SAR among unvaccinated household contacts for vaccinated index cases was lower compared to unvaccinated index cases (13% vs 22%). The corresponding adjusted vaccine effectiveness against transmission was 63% (95% CI: 46-75).^[59] Results were not stratified by vaccine type. 																							
Transmission	<p>Summary: Vaccination reduces transmission of Delta, but the vaccine's impact on transmission appears to reduce over time.</p> <ul style="list-style-type: none"> UK national surveillance data found 64% increase in household transmission with Delta compared with Alpha (aOR 1.64; 95% CI: 1.26-2.13, p <0.001).^[60] Studies on Delta reported that 12-73.9% of the transmissions to close contacts occurred before symptom onset.^[34, 39] Delta variant cases will infect 64% their 'close proximity' contacts.^[61] An observational study in England found that two doses of the Pfizer vaccine reduced onwards transmission from breakthrough infections of the Delta variant by 50%, which was more than the AstraZeneca vaccine (Pfizer aRR=0.50 and AstraZeneca aRR=0.76).^[62] A Dutch contact tracing study estimated that vaccine effectiveness against onwards transmission to fully vaccinated household contacts was 40% (95% CI: 20-54), which is in addition to the individual protection against infection.^[59] Effectiveness against onwards transmission to unvaccinated household contacts was 63% (95% CI: 46-75). Results were not stratified by vaccine type. 																							
R₀	<p>Summary: R₀ ~5.5-6.5, i.e. On average, each person transmits Delta to another 5-6 people.</p> <ul style="list-style-type: none"> Highest range of estimate is 8-9, based on the upper limits of current ranges of increased transmission (e.g., starting from R=3 for wild type, then ~50% increase from wild type to Alpha, and ~90% from Alpha to Delta). A summary of 5 papers using differing methods to calculate an R₀ for Delta reported a mean R₀ of 5.08 (range, 3.2-8.0).^[63] A Danish pre-print estimated that Delta increases R₀ by a factor of 2.17 (95% CI: 1.99-2.36) relative to Alpha and 3.28 (95% CI: 3.01-3.58) relative to the ancestral variant.^[64] The UK REACT-1 study found an overall R of 1.03 (range: 0.94-1.14) among those aged 5 and above in September 2021. Those aged 17 years and under had an R of 1.18 (range: 1.03-1.34), and this was lower in those aged 18 to 54 years (R of 0.81, range: 0.68-0.97).^[65] <p>No data available</p>																							
Severity	<p>Summary: No clear evidence at this time that Delta symptoms differ from other VOCs or wild-type virus. The most common symptoms for COVID-19 caused by Delta are cough, fatigue, headache, sore throat, fever, loss of taste or smell, and myalgia.</p> <ul style="list-style-type: none"> A South Korean study found no significant difference between Delta-dominant and Delta-minor groups for COVID-19 symptoms in children and adolescents, except for the lower frequencies of rhinorrhoea (25% vs. 10.5%, P = 0.003), nasal stuffiness (34.8% vs. 15.4%, P = 0.001) and sore throat (23.9% vs. 12.6%, P = 0.02).^[66] Patients in the Delta-dominant group were more likely to be asymptomatic (29.3% vs. 43.4%, P = 0.03). Data from a retrospective cohort study in Singapore using national surveillance data showed that the most common Delta symptoms were similar to symptoms for Alpha, Beta and the wild-type virus. Among those with Delta infection (n=67), the most common symptoms were fever (72%), cough (46%), sore throat (34%), shortness of breath (19%), and nasal congestion/runny nose (18%).^[40] The same study reported that 12% of Delta cases were asymptomatic. However, at the time the data was collected (1 January-22 May 2021) there was a very small number of Delta cases overall (n=67). An analysis of 159 hospitalised Delta cases in a local outbreak in Guangzhou, China reported that the most common symptoms within three days on admission was cough (65%), followed by fever (63%) and expectoration (53%). Gastrointestinal symptoms such as diarrhoea (5%) and vomiting (4%) were uncommon.^[36] The UK COVID-19 Infection Survey collects data on characteristics of people testing positive for COVID-19, including data on symptoms for those who had strong positive tests - Ct value under 30 (see Table below).^[67] These data are provisional, reflect infections reported in the community, and exclude infections reported in hospitals, care homes, or other institutional settings. These data can be used to infer common symptoms of the Delta variant, which has been predominant in the UK since June 2021. <table border="1" data-bbox="582 1317 1166 1585"> <thead> <tr> <th rowspan="2">Symptoms</th> <th>% of people with this symptom within 35 days of a positive PCR test, among those people with a Ct value under 30</th> </tr> <tr> <th>September 2021</th> </tr> </thead> <tbody> <tr> <td>Any symptoms</td> <td>61.9</td> </tr> <tr> <td>No symptoms (asymptomatic)</td> <td>38.1</td> </tr> <tr> <td>Classic symptoms (cough, fever, shortness of breath, loss of taste, loss of smell)</td> <td>54.2</td> </tr> <tr> <td>Loss of taste or smell</td> <td>28.4</td> </tr> <tr> <td>Gastrointestinal symptoms (abdominal pain, nausea or vomiting, diarrhoea)</td> <td>17.9</td> </tr> <tr> <td>Cough</td> <td>42.4</td> </tr> <tr> <td>Fatigue (weakness)</td> <td>38.0</td> </tr> <tr> <td>Headache</td> <td>38.7</td> </tr> <tr> <td>Sore throat</td> <td>32.6</td> </tr> <tr> <td>Fever</td> <td>27.9</td> </tr> </tbody> </table>	Symptoms	% of people with this symptom within 35 days of a positive PCR test, among those people with a Ct value under 30	September 2021	Any symptoms	61.9	No symptoms (asymptomatic)	38.1	Classic symptoms (cough, fever, shortness of breath, loss of taste, loss of smell)	54.2	Loss of taste or smell	28.4	Gastrointestinal symptoms (abdominal pain, nausea or vomiting, diarrhoea)	17.9	Cough	42.4	Fatigue (weakness)	38.0	Headache	38.7	Sore throat	32.6	Fever	27.9
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COVID-19 Variants Update

		Loss of smell	23.7
		Muscle ache (myalgia)	25.0
		Loss of taste	23.7
		Shortness of breath	13.8
		Nausea or vomiting	10.3
		Abdominal pain	8.0
		Diarrhoea	7.3
Asymptomatic	<p>Summary: Data is emerging. Rate of asymptomatic cases depends on vaccination status, with vaccinated but infected people more likely to be asymptomatic. However, these data are not always reported. Breakthrough infections tend to be mild or asymptomatic.</p> <ul style="list-style-type: none"> Data from the UK COVID-19 Infection survey indicated that during September, approximately 38% of positive cases did not report any symptoms. See Table above under 'Symptoms' for more details. This was during a period of relatively high vaccination coverage in the UK. A Korean study of 405 Delta cases reported that 20% were asymptomatic.[39] Proportion of vaccinated cases among asymptomatic was not reported. A Singaporean study using national surveillance data found 10% of Delta cases were asymptomatic.[40] However, at the time the data was collected (1 January-22 May 2021) there was a very small number of Delta cases (n=67) and proportion of vaccinated cases was not reported. One study in Singapore found the vaccinated group with Delta breakthrough infections (2 doses of mRNA vaccine; 71 of 218 Delta infections identified) were more likely to be asymptomatic (28.2% versus 9.2%, p<0.001) and had fewer symptoms than those unvaccinated. Higher proportion of pneumonia in unvaccinated group.[45] An outbreak report among unvaccinated soldiers on a single navy ship noted that 23% were asymptomatic.[55] 		
Hospitalisation	<p>Summary: Data indicates possible increased risk of hospitalisation. It is unclear whether the risk of ICU admission is higher for Delta once a patient is admitted to hospital.</p> <ul style="list-style-type: none"> Studies from England, Scotland, Denmark, and Canada have found that Delta was associated with approximately 2-3 times risk of hospitalisation compared to Alpha (hazard ratios ranging from 1.85-2.83).[68-71] In contrast, a Norwegian study found no difference in the risk of hospitalisation for Delta compared to Alpha.[72] A CDC study of data from 14 US states found no significant differences in the proportion of nonpregnant adults aged ≥18 hospitalised with severe outcomes between the pre-Delta and Delta periods. The proportion of hospitalised unvaccinated COVID-19 patients aged 18-49 years increased significantly during the Delta period.[73] The rate of new COVID-19 cases, emergency department visits, and hospital admissions increased for those aged 0-17 years after Delta became predominant in the US. Hospitalisation rates were highest among children aged 0-4 years (69.2 per 100,000) and adolescents aged 12-17 years (63.7 per 100,000), and lowest among children aged 5-11 years (24.0 per 100,000). Hospitalisation rates were 10 times higher among unvaccinated than among fully vaccinated adolescents. However, there was no difference in the severity of disease when compared with pre-Delta.[74, 75] 	<p>Summary: Unvaccinated people have higher case and hospitalisation rates for Delta than fully vaccinated people</p> <ul style="list-style-type: none"> Delta is currently the dominant variant in the US and the UK, making up more than 99% of recently sequenced cases in both countries.[76, 77] The US CDC COVID Data Tracker[76] reports that in September, unvaccinated people were 5.8 times more likely to test positive for COVID-19 and 9 times more likely to be hospitalised from COVID-19 than fully vaccinated people. The latest UKHSA COVID-19 vaccine surveillance report[78] indicates that the rate of a positive COVID-19 test varies by age and vaccination status. The rate of a positive COVID-19 test is substantially lower in vaccinated individuals compared to unvaccinated individuals up to the age of 29. In individuals aged greater than 30, the rate of a positive COVID-19 test is higher in vaccinated individuals compared to unvaccinated. This is likely to be due to a variety of reasons, including differences in the population of vaccinated and unvaccinated people as well as differences in testing patterns. The rate of hospitalisation within 28 days of a positive COVID-19 test increases with age and is substantially greater in unvaccinated people compared to vaccinated people. 	
Mortality/Case fatality rate	<p>Summary: Mortality/case fatality rate for Delta ~0.5-3%. It is important to note that the risk of mortality associated with COVID-19 is much higher for older age groups.</p> <ul style="list-style-type: none"> Our World in Data estimates the case fatality rate to be approximately 1-3% globally.[79] UKHSA reported that among 727,986 cases of Delta from 15 May 2021 to 24 October 2021, 3,813 had died within 28 days of testing positive, which is a case fatality rate of 0.53%.[56] A retrospective analysis of UK data found that Delta is associated with a lower case fatality rate than Alpha (all ages, 0.43% vs 1.07%), however, vaccination status of cases was not included in the analysis.[80] 	<p>Summary: Unvaccinated people have higher mortality rates than fully vaccinated people</p> <ul style="list-style-type: none"> Delta is currently the dominant variant in the US and the UK, making up more than 99% of recently sequenced cases in both countries.[76, 77] The US CDC COVID Data Tracker[76] reports that in September, unvaccinated people were 14 times more likely to die from COVID-19 than fully vaccinated people. The latest UKHSA COVID-19 vaccine surveillance report[78] indicates that the rate of death within 28 days or within 60 days of a positive COVID-19 test increases with age and is substantially greater in unvaccinated people compared to fully vaccinated people. 	
Vaccine efficacy/effectiveness			
Against viral infection (positive PCR test)	<ul style="list-style-type: none"> Pfizer: 79% (95%CI: 75-82)[81]; 39% (95%CI: 9-59) in fully vaccinated (including those who received their second dose several months earlier) in Israel[82]; 42% (95%CI: 13-62) in Minnesota in July when Delta became dominant compared to 76% (95%CI: 69-81) throughout January till July[83]; 52.4% (95%CI:48.0-56.4) in US nursing home residents during Delta prevalence compared to 74.2% (95%CI: 68.9-78.7) pre-Delta[84]; 53.5% (95%CI: 43.9-61.4) in those who received their second dose several months earlier in Qatar[85]; 93% (95%CI: 85-97) at <1 month to 53% (95%CI 39-65) at >4 months in US[86]; 85% (95%CI: 79-90) at 14 days post 2nd dose declining to 75% (95%CI: 70-80) at 90+ days in UK[87] AstraZeneca: 60% (95%CI: 53-66)[81]; 68% (95%CI: 61-73) at 14 days post 2nd dose declining to 61% (95%CI: 53-68) at 90+ days in UK[87] Janssen: 78% (95%CI: 73-82) during Delta prevalence in the US[88] 		
Against symptomatic disease	<ul style="list-style-type: none"> Pfizer: 87-88%[89, 90]; 40.5% (95%CI: 8.7-61.2) in fully vaccinated (including those who received their second dose several months earlier) in Israel[82]; 56.1% (95%CI: 41.4-67.2) in those who received their second dose several months earlier in Qatar[85]; 92.4% (95%CI: 92.1-92.7) at 1 week after the second dose and then fell to 69.7% (95%CI: 68.7-70.5) by 20+ weeks[91]; 93% (95%CI: 89-96) at 14 days post 2nd dose declining to 78% (95%CI: 72-82) at 90+ days in UK[87] AstraZeneca: 67% (95%CI: 61.3-71.8)[89]; 62.7% (95%CI: 61.7-63.8) at 1 week after the second dose and then fell to 47.3% (95%CI: 45.0-49.6) by 20+ weeks[91]; 72% (95%CI: 64-78) at 14 days post 2nd dose declining to 63% (95%CI: 53-71) at 90+ days in UK[87] 		
Against hospitalisation	<ul style="list-style-type: none"> Pfizer: 96% (95%CI: 86-99)[92]; 80% (95%CI: 73-85) during Delta prevalence in the US[93]; 99.7% (95%CI: 97.6-100.0) at 1 week after the second dose and then fell to 92.7% (95%CI: 90.3-94.6) by 20+ weeks[91]; 96% (95%CI: 95-96) during Delta period in the Netherlands[94] 		

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	<ul style="list-style-type: none"> • AstraZeneca: 92% (95%CI: 75-97)[92]; 93.9% (95%CI: 91.3-95.7) at 1 week after the second dose and then fell to 77.0% (95%CI: 70.3-82.3) by 20+ weeks[91]; 94% (95%CI: 92-95) during Delta period in the Netherlands[94]; 88% (95%CI: 85-90) during Delta prevalence in Scotland[95] • Janssen: 60-85% during Delta prevalence in the US[88, 93]; 91% (95%CI: 88-94) during Delta period in the Netherlands[94]
Against transmission	<ul style="list-style-type: none"> • Pfizer: 50% (95%CI: 35-61) against onwards Delta transmission at 2 weeks after 2nd dose declining to 24% (95%CI: 20-28) through 3 months[96] • AstraZeneca: 24% (95%CI: 18-30) against onwards Delta transmission at 2 weeks after 2nd dose declining to 2% (95%CI: -2-6) through 3 months[96]
Waning immunity	<ul style="list-style-type: none"> • A study from Oxford University reported that during Delta prevalence, VE against infection for Pfizer declined by 22% (95%CI 6-41%) per month from second dose for 18-64 year olds, starting at 85% (95%CI 79-90) 14 days post-second dose.[87] • A study from Southern California also reported waning of VE against infection, after adjusting for many confounders (demographics, comorbidities, social deprivation measures) and stratifying by age.[97] VE against Delta infections was high during the first month after full vaccination (93%) and declined to 53% at 24 months. The authors concluded that waning effectiveness was not due to the increasing prevalence of Delta, because waning effectiveness was also seen for non-Delta cases. Importantly, a high VE against hospitalisation (90-93%, stratified by age), associated with any variant, was maintained for the duration of the study.

Other Variants

Other Variants of Concern (VOC) - as listed by WHO	
<p>Lineage: B.1.1.7 WHO label: Alpha</p>	<ul style="list-style-type: none"> • Number of cases in NZ: 178 (report date of last confirmed case: 06 August 2021) • First identified in United Kingdom • Transmissibility: Increased transmissibility compared to previous variants[98] • Disease severity: <ul style="list-style-type: none"> ◦ Mortality: Increased mortality compared to previous variants[98] ◦ Hospitalisation risk: Increased risk of hospitalisation compared to previous variants[98] • Impact on vaccine-induced immunity: Minimal; Pfizer and AstraZeneca vaccines remain effective and neutralisation capacity is largely maintained[98]
<p>Lineage: B.1.351 WHO label: Beta</p>	<ul style="list-style-type: none"> • Number of cases in NZ: 33 (report date of last confirmed case: 27 June 2021) • First identified in South Africa [98] • Transmissibility: Increased transmissibility compared to previous variants [98] • Disease severity: <ul style="list-style-type: none"> ◦ Mortality: Possible increased risk of mortality[98] ◦ Hospitalisation: Possible increased risk of hospitalisation • Impact on vaccine-induced immunity: Moderate-Strong
<p>Lineage: P.1 WHO label: Gamma</p>	<ul style="list-style-type: none"> • Number of cases in NZ: 8 (report date of last confirmed case: 01 June 2021) • First identified in Brazil[98] • Transmissibility: Increased transmissibility compared to previous variants • Disease severity: <ul style="list-style-type: none"> ◦ Mortality: Possible increased risk of mortality[98] ◦ Hospitalisation: Possible increased risk of hospitalisation[98] • Impact on vaccine-induced immunity: Moderate-Strong
Variants under Investigation (VUI) - as listed by UKHSA	
<p>Lineage: AY.4.2 UKHSA label: VUI-21OCT-01</p>	<ul style="list-style-type: none"> • Number of cases in NZ: 5 (report date of last confirmed case: 04 November 2021) • First identified in United Kingdom, October 2021. Increasing prevalence, particularly in the UK where cases of AY.4.2 have increased in proportion from 15.2-20.3% of all Delta cases, from the week of 07 November 2021 to the week of 21 November 2021, however the latest sequencing is incomplete.[77] • Spike mutations: Contains spike mutations A222V and Y145H.[99] • Transmissibility: Experts suggest there may be an "increase in transmissibility of 10-15% compared to the original Delta variant", however, evidence is yet to emerge, and AY.4.2 is unlikely to present significant risk at this stage.[100] Secondary attack rate for AY.4.2 is slightly higher than Delta.[38] • Disease severity: No evidence that AY.4.2 causes more severe disease than other Delta variants, according to recent analysis from the United Kingdom.[77] • Impact on vaccine-induced immunity: Minimal effect on vaccine-induced neutralisation and vaccine efficacy compared to Delta. [101]
<p>Lineage: B.1.621 WHO label: Mu UKHSA label: VUI-21JUL-01</p>	<ul style="list-style-type: none"> • Number of cases in NZ: 1 (report date of last confirmed case: 19 June 2021) • First identified in Columbia.[102] • Spike mutations: T95I, Y144-145TSN, R346K, E484K, N501Y, D614G, P681H, and D950N. Some of these are mutations shared present in other variants: E484K (shared with Beta, Gamma), N501Y (shared with Alpha), P681H (shared with Alpha) and D950N (shared with Delta). The E484K (shared with Beta, Gamma), which is associated with reduced sensitivity towards natural or vaccine induced antibodies.[103] • Transmissibility: Mu has not outcompeted Delta in any country to date. • Immune evasion: Mu has more potential for immune escape than Beta (previous variant with most immune escape) based on one study of sera from Pfizer-vaccinated individuals. [103, 104]
<p>Lineage: B.1.525 WHO label: Eta UKHSA label: VUI-21FEB-03</p>	<ul style="list-style-type: none"> • Number of cases in NZ: 8 (report date of last confirmed case: 08 June 2021) • First identified in UK and Nigeria, December 2020. • Spike mutations: Spike mutations A67V, 69/70 deletion, 144del, E484K, D614G, Q677H, and F888L [105] • Immune evasion: Potential reduction in neutralisation by some monoclonal antibody treatments, convalescent and post-vaccine sera.[106]
<p>Lineage: B.1.1.318 UKHSA label: VUI-21FEB-04</p>	<ul style="list-style-type: none"> • Number of cases in NZ: No cases. • First identified in United Kingdom, February 2021. • Spike mutations: Contains spike mutations T95I, 144del, E484K, P681H, D796H. [107]
<p>Lineage: B.1.617.1 WHO label: Kappa UKHSA label: VUI-21APR-01</p>	<ul style="list-style-type: none"> • Number of cases in NZ: 5 (report date of last confirmed case: 09 April 2021) • First identified in India, October 2020. • Transmissibility: Secondary attack rates similar to Delta.[108] • Immune evasion: Kappa was neutralised by Pfizer and Moderna, however 6.8-fold reduction observed.[109]

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<p>Lineage: B.1.617.3 UKHSA label: VUI-21APR-03</p>	<ul style="list-style-type: none"> • Number of cases in NZ: 4 (report date of last confirmed case: 11 April 2021) • First identified India [98]
<p>Lineage: P.2 variant (descendent of B.1.1.28) WHO label: Zeta UKHSA label: VUI-21JAN-01</p>	<ul style="list-style-type: none"> • Number of cases in NZ: Last detected in a case reported New Zealand in on 05 March 2021. • First identified in Brazil, April 2020. • Spike mutations: Spike mutations E484K, D614K, and V1176F. [105] • Immune evasion: Possible reduced antibody neutralisation from studies on the spike protein mutation E484K. [110]

Glossary of Terms

The AstraZeneca vaccine	AZD1222 or ChAdOx1
The Pfizer/BioNTech vaccine	Comirnaty/BNT162b2
Global Initiative on Sharing Avian Influenza Data (GISAID)	This is a consortium that promotes and provides open access to SARS-CoV-2 genomic sequence data. Its original purpose was for sharing data on avian (bird) flu.
Immune escape	The ability of the virus to evade our body's immune response. See also Immune response.
Immune response	The response of our immune system to an infection. It includes development of specific antibodies to the virus and also cell-mediated responses (triggered by T cells).
Mutation	Small change made to the pattern of nucleotides that make up the virus. These occur as the virus spreads and replicates. Most do not confer a benefit to the virus.
Naming mutations	Mutation nomenclature (i.e., how they are named), describes what occurred at a specific location of the genome. For example, the 'E484K' mutation means that at the position 484, the amino acid changed from glutamic acid (E) to lysine (K). When a deletion occurs, the location is provided (e.g., deletion 144).
N-terminal domain	Part of the spike protein of the SARS-CoV-2 virus.
R_0 , Reproductive number	The reproductive number R_0 (R-naught), is a measure of how contagious a disease is. It is the average number of people who would catch a disease from one infected individual when there are no control measures in place, e.g., vaccination, lockdowns.
R_{eff} , Effective reproductive number	The 'effective R' (R_{eff}) is the R observed when control measures are in place. R_{eff} can therefore change depending on the control measures currently enacted in a particular population. In general, whenever R is less than 1, i.e., an infected person goes on to infect less than one person on average, then the prevalence of the disease would be expected to decrease.
Secondary attack rate	The probability that an infection occurs among persons within a reasonable incubation period after known contact with an infectious person in household or other close-contact environments.
Variant	Viruses with mutations are referred to as variants of the original virus. New variants of SARS-CoV-2 have been emerging as the virus has spread and evolved.
Variant of Concern (VOC)	<p>WHO definition: A SARS-CoV-2 variant that meets the definition of a VOI (see below) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:</p> <ul style="list-style-type: none"> • Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR • Increase in virulence or change in clinical disease presentation; OR • Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.
Variant of Interest (VOI)	WHO definition: A SARS-CoV-2 variant:

	<ul style="list-style-type: none"> with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND Identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.
Variant under Investigation (VUI)	UKHSA definition: SARS-CoV-2 variants, if considered to have concerning epidemiological, immunological or pathogenic properties, are raised for formal investigation. At this point they are designated Variant Under Investigation (VUI) with a year, month, and number. Following a risk assessment with the relevant expert committee, they may be designated Variant of Concern (VOC).

Abbreviations

CDC: Centers for Disease Control and Prevention

GSAID: Global Initiative on Sharing Avian Influenza Data

RBD: Receptor binding domain (of the virus spike protein)

R_{eff}: 'Effective R', the effective reproductive number

R₀: 'R-naught', the baseline reproductive number

UKHSA: UK Health Security Agency

Useful Links

US CDC – SARS CoV-2 variant classifications and definitions	CDC classification of variants
Outbreak Info	Outbreak Info
WHO - Tracking SARS-CoV-2 variants	WHO Variant Tracking
UK Health Security Agency Technical Briefings (from October 2021 onwards)	Investigation of SARS-CoV-2 variants: technical briefings
Public Health England Technical Briefings	Investigation of SARS-CoV-2 variants: technical briefings

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Request for Advice (RfA)

This form contains the details relevant to the questions posed to the Science and Technical Advisory (STA). STA will respond to the request using this form which will also be stored in STA content management system for future reference.

This form, or parts of it, may also be forwarded to other relevant parties as appropriate.

Title	COVID-19 and Vaccination in 5-11-year-olds		
Subject	Supporting evidence to inform discussions of the risks and benefits of vaccination in 5-11-year-olds		
Reference No.	330	Date Received	12/11/2021
Requestor	Ian Town	Date Due	22/12/2021
Advisor	[REDACTED]	Date Completed	23/12/2021
Peer reviewed by	[REDACTED]	This is the exhibit marked "GT-6" referred to in the annexed Affidavit of GEORGE IAN TOWN affirmed at Christchurch this 10 th day of June 2022 before me:  Solicitor of the High Court of New Zealand	
Advice issued to	CV TAG		
Approved by	Ian Town		
Deliverables	Completed summary of evidence of COVID-19, transmission risk, and vaccination in 5-11-year-olds		
Request Outline	<p>Background/Context</p> <p>Pfizer will be applying for the use of vaccines in 5-11-year-olds to Medsafe, and advice is required from the COVID-19 Vaccine Technical Advisory Group on the risks and benefits of vaccinating this age group, alongside if and where there may be a need for prioritisation.</p> <p>Questions</p> <p><i>COVID-19 and children</i></p> <ul style="list-style-type: none"> • How does COVID-19 present in children? • What do we know about Delta's impact on children? • What is the risk of infection/severe disease/ hospitalisation? • What is the risk of long COVID? • Who is more at risk of severe outcomes among 5-11-year-olds? What are the individual level risk factors? What are broader social risk factors? <p><i>Vulnerable populations in the context of Aotearoa New Zealand</i></p> <ul style="list-style-type: none"> • Within the Aotearoa New Zealand context, what risk factors are more common and who would be most at risk within this age group? 		

Emma Louise Spratt
 Solicitor
 Christchurch

Request for Advice (RfA)

- What impact has the current Delta outbreak had on 5-11-year-olds? How many cases have there been? What severity and how many hospitalisations? Who is more at risk?

Transmission

- What is known about the role of children in transmission?
- What is known about transmission in education and household settings?

Non-pharmaceutical interventions for the prevention of COVID-19 in children

- What non-pharmaceutical interventions are available for children to prevent COVID-19?
- What evidence is there on the effectiveness of masks, distancing, cohorting, and school closures?

Vaccine

- What is the safety and reactogenicity profile of the Pfizer vaccine for 5-11-year-olds?
- What is known about the risk of myocarditis in 5-11-year-olds? Is there a risk profile/factors other than being male and young? What is there information on and what is there not?
- What is the efficacy of the vaccine in 5-11-year-olds against infection, severe disease and hospitalisation?
- Which countries have approved the vaccine for 5-11-year-olds, who has rolled it out, and what data is available from the real-world rollout?
- Do these countries have any specific guidance in relation to the dosing interval and co-administration?

Risks and Benefits of vaccinating 5–11-year-olds in Aotearoa New Zealand

- What are the relative risks and benefits of vaccinating 5–11-year-old in New Zealand?

Intended application of advice

To inform discussions at CV TAG and the Decision to Use.

Timeline

CV TAG to review this RfA on 30 November, 7 December, 14 December. Memo to be drafted by 7 December and finalised by 23 December.

What are the implications and considerations of this advice on Te Tiriti o Waitangi and equity?

Equity and Te Tiriti are relevant to assessing who is at greater risk of infection and more vulnerable to severe disease. It is important to examine the increased burden for Māori and Pacific People within New Zealand, particularly in the Delta outbreak.

Equity issues are relevant in relation to uptake of non-pharmaceutical public health measures and vaccines, and support options available to people with COVID-19. There may be disparities in who can access services.

Request for Advice (RfA)

In addition, the presence of pre-existing conditions or comorbidities increases individual risk factors and the likelihood of severe COVID-19 disease and hospitalisation. The higher prevalence of some conditions among Māori and Pacific People may further contribute to increased risk for these communities.

Equity is important to consider in relation to different physical and social environments. Māori and Pacific peoples are more likely to live in overcrowded and multigenerational housing, and more likely to face socioeconomic barriers with access to poor housing.[1] People living in rural communities (especially Māori) are more isolated and inaccessible to healthcare interventions including vaccination clinics. The impact of these broader social determinants of health on vulnerability to infection will need to be explored.

The risks of COVID-19 also need to be balanced against the risks of prolonged school closure on wellbeing and education for young people, the need for access to education, and how this could impact on equity by further increasing current social and economic inequities.

The principles of Te Tiriti o Waitangi provide the framework to guide the health and disability system towards health equity for Māori, and principles of tino rangatiratanga, equity, active protection, options and partnership will be forefront in the research. Tino rangatiratanga and self-determination are important in applying public health measures, and therefore it is essential that autonomy and options are given to communities to protect themselves, and in communicating public health measures. Partnership with diverse Māori communities in developing and communicating risk and public health measures are essential to ensure clear understandings of risk and develop appropriate public health measures tailored to the communities' needs.

Response to Request for Advice

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Key Points

- COVID-19 disease is rarely severe or fatal in previously well children between 5 and 11 years of age. However, COVID-19 is still a significant public health issue in this age group. The risk is not negligible, and incidence of the severe post-infection Multisystem Inflammatory Syndrome in Children (MIS-C) is highest among 5-11-year-olds. Current evidence is that children in this age group sometimes experience prolonged symptoms post recovery from SARS-CoV-2 infection (long COVID), but the frequency of this is not well established.
- Children living with pre-existing health conditions or comorbidities, disadvantage, low socioeconomic or minority ethnic status have a greater risk of severe disease from COVID-19.
- Māori and Pacific adults are at greater risk of COVID-19 hospitalisation and severe disease and more likely to live in multigenerational families housed in overcrowded conditions. Access to vaccines has been inequitable for Māori and Pacific adults and access issues for children aged 5-11 in these groups need close consideration.
- Children can transmit the virus, though they appear to play less of a role in transmission than teenagers and adults. Evidence to date has shown that transmission of SARS-CoV-2 in the school environment is more likely to occur between adults, followed by adult-to-child transmission, with lower risks of child-to-child or child-to-adult transmission. Transmission within households is common and this is where the greatest risk of transmission is due to the ongoing and close nature of exposure.
- The phase 3 trial of the lower-dose formulation of the Pfizer vaccine in 5-11-year-olds showed local and systemic side effects generally in the same range as those observed with the full dose in 12-15-year-olds. Importantly, fever (7% vs 20%) and antipyretic use (20% vs 51%) after the second dose was less common. No cases of myocarditis were observed, but there was an excess of lymphadenopathy cases (10 (0.9%) vs 1 (0.1%) with the placebo).
- In the same phase 3 trial, vaccine efficacy against symptomatic COVID-19 7 days post-second dose was 90.7%. This was based on 3 cases in the vaccine group and 16 in the placebo group during the follow-up of 2.3 months. No cases were severe, but the number of participants was relatively small, with a total of 1,518 vaccine and 751 placebo participants.
- While there is some urgency for vaccination in order to protect New Zealand's population, the only available safety and efficacy data are from this phase 3 trial with 2268 participants, and therefore there has been a very limited ability to study rare, but serious, side effects. More data on potential side effects from the vaccine rollout in this age group in other countries would be beneficial in determining the risk-benefit ratio in New Zealand.
- The decision to vaccinate children requires careful weighing of the known and potential risks and benefits. The balance of risks and benefits of COVID-19 vaccination in children is more complex than in adults. In addition to potential direct effects (both positive and negative) from vaccination for this group, there are also potential indirect effects e.g., avoidance of school closures and other indirect harms of lockdowns, including the risk that a COVID-19 vaccination rollout in this group may negatively impact the national immunisation schedule for children etc.
- If vaccination is offered to this age group, to mitigate against unintended consequences such as stigmatisation and exclusion, children aged 5-11 should not be subject to vaccine mandates and should not have to be vaccinated in order to participate in any of their usual activities, including education, childcare, and recreational activities.

Introduction

Vaccination of 5-11-year-olds has begun internationally. Planning is underway for a New Zealand rollout in this age group if it is approved by Medsafe and Cabinet decides to use it. The COVID-19 Vaccine Technical Advisory Group (CV TAG) also has an important role in the Decision to Use. Their advice is required on the risks and benefits of vaccinating this age group, alongside if and where there may be a need for prioritisation. This RfA collates a wide range of information related to children, COVID-19 and the Pfizer vaccine to inform discussions at CV TAG and the Decision to Use.

COVID-19 and Children

COVID-19 presentation and severity

Children and adolescents who have COVID-19 will commonly have no or only mild respiratory symptoms, similar to a cold. Those who are symptomatic generally have a short duration of illness and a low symptom burden. A systematic review of COVID-19 in children conducted early in the pandemic found typical symptoms included fever, cough, a sore throat, blocked or runny nose, sneezing, muscle aches, and fatigue. Changes in smell or taste, diarrhoea and vomiting were less common.[2]

COVID-19 disease in children is rarely severe and significantly less likely to cause death than in adults. On 24 November 2021, the WHO published an interim statement on COVID-19 vaccination for children and adolescents,[3] where they note that overall, there are proportionally fewer symptomatic infections and cases with severe disease and deaths from COVID-19 in children and adolescents. However, it is important to bear in mind that COVID-19 in children is still a major public health problem,[4] and that the impact of COVID-19 on children should not be minimised by comparison to the impact experienced in adult populations. Even though the direct effects of infection are generally less severe in children, this does not diminish the significance for those who do experience worse outcomes. Age-disaggregated cases reported to WHO from 30 December 2019 to 25 October 2021 show that older children and younger adolescents (5 to 14 years) account for 7% (7,058,748) of reported global cases and 0.1% (1,328) of reported global deaths. However, milder symptoms and asymptomatic presentations may mean less testing in these groups, and cases may go unreported.[3]

A systematic review and meta-analysis including over 350 studies from between January 2020 and April 2021 estimated that the overall percentage of cases that never developed clinical symptoms (i.e., truly asymptomatic, rather than pre-symptomatic), was 35.1% (95% CI:: 30.7 to 39.9%). Asymptomatic infection was higher among children at 46.7% (95% CI:: 32.0 to 62.0%).[5] A study of 2,143 clinically diagnosed or laboratory confirmed cases among children found that more than 90% were asymptomatic or had mild or moderate disease.[6] The prevalence of severe and critical disease was 10.6% in children aged <1 at diagnosis, 7.3% in those aged 1-5 years, 4.2% in those aged 6-10 years, 4.1% in those aged 11-15 years, and 3% in those aged 16-17 years.[6] When severe COVID-19 occurs in children, it is usually characterised by pneumonia and respiratory distress, and may lead to admission to hospital or intensive care.[7]

Two longer term risks or consequences of SARS-CoV-2 infection might be more of a concern in this age group: Multisystem Inflammatory Syndrome in children (MIS-C, also known as Paediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2, or PIMS-TS) and long COVID (discussed below).

The Delta variant does not appear to cause more severe disease than previous variants, but because it spreads faster, the number of children who will develop severe disease and go to hospital will be greater.[7] In addition, in areas where an increasing percentage of adults are fully vaccinated but where children are not vaccinated, there are likely to be relatively more infections among children.[7, 8]

Initial reports through the media from South Africa indicate that the Omicron variant is resulting in a disproportionately large number of children being admitted to hospital with COVID-19, particularly in the under 5 age group, however evidence on this is still emerging.[9]

Multisystem Inflammatory Syndrome in Children (MIS-C)

MIS-C is a very rare but serious condition that can occur approximately one month after COVID-19, causing inflammation in different parts of the body.[10] Children and adolescents with MIS-C usually have a fever, rash and abdominal pain. Severe MIS-C may cause inflammation of the heart muscle, and this may result in low blood pressure. Some MIS-C patients do not require treatment, but patients with more severe disease often need admission to an intensive care unit. MIS-C can occur even in those with no symptoms from initial COVID-19 infection.

MIS-C has caused deaths among a small proportion of children overseas, mainly early in the pandemic. However, increased awareness of MIS-C has allowed for earlier diagnosis, more appropriate treatments and improved outcomes. In 2021, almost all children with MIS-C have recovered fully, and the long-term outcomes appear good, with resolution of the inflammation of the heart.[7, 10] In the US, evidence has shown that MIS-C occurs more frequently among marginalised Black, non-Black Hispanic, Pacific and indigenous children,[11, 12] and similar inequities may occur for Māori and Pacific children. As of 4 October 2021, the CDC had received reports of 5,217 cases of MIS-C; 44% of MIS-C cases were in children aged 5–11 years.[4]

Long COVID in children

For some people COVID-19 can lead to persistent illness, with ongoing and often debilitating symptoms.[13-15] Long COVID is a generic term used to describe signs and symptoms that continue or develop after acute COVID-19. Symptoms of long COVID are wide ranging, and the World Health Organization (WHO) has recently developed a clinical case definition of post COVID-19 conditions by a Delphi consensus:[16]

Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.

The WHO notes that a separate definition may be applicable for children. Long COVID in children is not well described, and the studies to date have generally been of poor quality, with some major limitations (such as a lack of a clear case definition, arbitrary follow up time points, subjective assessment, lack of control groups, and low response rates).[7, 17] Evidence is predominantly limited to select populations without control groups.[18] Relatively few studies have focused on SARS-CoV-2 infection sequelae in children and adolescents, and large, harmonised longitudinal studies are needed.[19] Persistent illness in children has

been noted in some studies and in patient support groups, but its prevalence, characteristics and duration are unclear.[20, 21]

Estimates of the prevalence of long COVID in children vary widely.[17] The variability in prevalence estimates could be due to a range of factors, such as initial SARS-CoV-2 infection severity, different methodological approaches (clinical assessment vs self-report), definition of cases (diagnosed vs suspected), variable follow-up times, and prevalence of pre-existing clinical conditions.[18] In the US, a large long-term study of the impacts of COVID-19 on children has recently begun. It will track up to 1,000 children and young adults and evaluate the impacts on their physical and mental health over three years.[14] Some studies suggest that long COVID in children is less common and tends to be less protracted than in adults. [22]

Some of the studies of long COVID in children include:

- A review of studies of long COVID in children and adolescents identified 14 heterogeneous studies (4 cross-sectional, 9 prospective cohort, 1 prospective cohort) investigating long COVID symptoms in a total of 19,426 children and adolescents. The prevalence of long COVID symptoms varied from 4% to 66%, and there was also large variation in the reported frequency of different symptoms. Zimmerman et al (2021) note that all the studies in their review were likely to have been conducted before the Delta variant became dominant, which may have a different risk of long COVID.[17]
- A recent pre-print describes a German study of 157,134 individuals (11,950 children/adolescents and 145,184 adults) with confirmed COVID-19.[23] The COVID-19 and control cohorts were well-balanced regarding covariates. For all adverse health outcomes combined, incidence rates (IRs) in the COVID-19 cohort were significantly higher than those in the control cohort in both children/adolescents. Incidence rate ratio (IRR) estimates were similar for the age groups 0-11 and 12-17. Incidence rates in children/adolescents were consistently lower than those in adults. Among the specific outcomes with the highest IRR and an incidence rate of at least 1/100 person-years in the COVID-19 cohort in children and adolescents were malaise/fatigue/exhaustion, cough, and throat/chest pain.
- The UK Office of National Statistics found that 9.8% of children aged 2-11 years and 13% aged 12-16 years reported at least one ongoing symptom five weeks after a positive diagnosis, whereas 25% of adults aged 35-69-years had symptoms five weeks after a positive diagnosis.[24, 25]
- A paper describing data from the UK COVID Symptom Study (a citizen science project with data collected via an app, which has some associated limitations) found that of 1,734 children aged 5-17 years who were symptomatic at the time of their positive test and reported symptoms regularly for at least 28 days, 4.4% had an illness duration of at least 28 days.[20] Ongoing symptoms for at least 28 days was less common in younger children aged 5-11 years (3.1%, $p=0.046$). Over 98% of 1,379 children had recovered by 56 days.[20] However, there may be some bias as using apps is likely to select participants from higher socio-economic background, who have a lower risk of poor outcomes.[17]
- One of the earliest studies on long COVID in children (a cross-sectional study of 129 children in Italy who were diagnosed with COVID-19 between March and November 2020) reported that 42.6% of children surveyed had one or more symptoms >60 days post infection.[26] This included children with mild or asymptomatic initial infection.
- A cohort study of 136 children (most of whom had mild or asymptomatic COVID-19) in Melbourne in 2020 observed that 8% of children had post-acute symptoms. They found that full recovery

occurred within weeks of acute symptom onset and reported symptoms were mild in severity but noted this was a young cohort (median age three years).[22]

Long-term SARS-CoV-2 infection–associated symptoms can be difficult to distinguish from pandemic-associated symptoms.[7, 17] Some studies have found that children who tested negative for COVID-19 have had similar symptoms, which are common after other viral infections, and could also be due to the experience of lockdown and other social restrictions.[27, 28] Given that acute COVID-19 generally poses a low risk to children, an accurate determination of the risk of long COVID is important in the debate about the risks and benefits of vaccination in this age group.[17] Similar to adults, it is likely that long COVID in children may have a greater impact on those from socioeconomically disadvantaged areas and ethnic minority groups.[19]

In summary, “the relative scarcity of studies of long COVID and the limitations of those reported to date mean the true incidence of this syndrome in children and adolescents remains uncertain. The impact of age, disease severity and duration, virus strain, and other factors on the risk of long COVID in this age group also remains to be determined.”[17] However, even if the proportion of children experiencing post acute impacts is relatively low, if transmission is widespread then the impact of persisting symptoms will be considerable.

At-risk and vulnerable children

Children living with pre-existing health conditions or comorbidities, disadvantage, low socioeconomic or minority ethnic status have a greater risk of severe disease from COVID-19.[7] Paediatric studies have found comorbidities that increase the risk of severe COVID-19 include but are not limited to: cancer, obesity, chronic respiratory disease, chronic kidney disease, cardiovascular disease, neurological disorders, immune disorders, metabolic disease and hematologic disorders.[29-31] A systematic review of children and adolescents (analysing 42 studies that included 275,661 without comorbidities and 9,353 with comorbidities) found that severe COVID-19 occurred in 5.1% of those with comorbidities, and in 0.2% of those without comorbidities. There was also a higher risk of COVID-19 associated mortality in those with comorbidities (relative risk ratio 2.81, 95% CI: 1.31 - 6.02; $I^2 = 82\%$).[29]

One meta-analysis found comorbidities in children with the highest risk (in terms of relative risk) include obesity, asthma or chronic respiratory disease, cardiovascular disease, neurologic or neuromuscular disorders, immune disorders, or metabolic disease.[32] Another systematic review identifying predictors of unfavourable prognosis of COVID-19 in children and adolescents found an association with congenital heart disease, chronic pulmonary disease, neurological diseases, obesity, MIS-C, shortness of breath, acute respiratory distress syndrome, acute kidney injury, gastrointestinal symptoms, and elevated C-reactive protein and D-dimer.[32] Another study found children with obesity had a relative risk ratio of 2.87 (95% CI: 1.16 - 7.07; $I^2 = 36\%$).[29] A Scottish study of over 750,000 school-aged children found that 5-17 year olds with poorly controlled asthma (who have been hospitalised with asthma or prescribed two or more courses of oral steroids for asthma within the past two years) are between three to six times more likely to be hospitalised with COVID-19 compared to those without asthma.[33] A recent multinational cohort study (pre-print) of 403 COVID admissions found that in age-stratified adjusted analyses, neurological disorder was associated with disease severity in children under 12 years of age.[34] There is also a strong argument for vaccinating children and adolescents who live with immunosuppressed or other high-risk household members, not only for the protection of the latter but also to benefit the mental health of the former.[35]

The ECDC notes that the presence of an underlying condition among children aged 5-11 years is associated with about 12 times higher odds of hospitalisation and 19 times higher odds of ICU admission.[36] However, the majority (78%) of hospitalised children of this age had no reported underlying medical condition.

Indirect impacts of COVID-19 on children

Given the knowledge of the often-mild nature of COVID-19 in children, the Murdoch Children's Research Institute has argued that the main risks to children and adolescents' health in this pandemic continues to be due to indirect effects on mental health, wellbeing and education, which are worsened by continued lockdowns and school closures.[7, 37] Negative impacts of the pandemic, including effects of school closures, have implications for communities, families and children.

Studies are continuing to emerge that highlight the negative effects of the pandemic on the mental health of children and adolescents. The pandemic limits opportunities for social connection and physical activity while increasing loneliness, uncertainty, fear, and boredom.[19] The WHO has also identified that children have been disproportionately affected by COVID-19 control measures, particularly due to school closures.[3]

Closure of day-cares and schools may not only have affected educational outcomes, but also influenced social and emotional wellbeing of children through physically being disconnected to schools, with these impacts even more severe for children living with disadvantage.[38, 39] A New Zealand study found that hospital avoidance and reduced access to primary and secondary care were associated with significant potential harm for children in New Zealand during the first lockdown.[40]

Adverse childhood experiences, including family violence, nonaccidental trauma and mental illness are expected to increase during lockdowns and worsen during the anticipated economic recession. Employment and financial instability as a result of service closures or economic recession also has flow-on effects to children.[41, 42]

Aside from an educational setting, children are also impacted by COVID-19 if a parent or caregiver is hospitalised or dies due to COVID-19. These outcomes result in psychological and socioeconomic harms. It is estimated that more than 1.1 million children worldwide would have experienced the death of a primary parent or caregiver grandparent after the first year of the COVID-19 pandemic.[43] Importantly, indigenous and ethnic minority children are up to 4.5 times more likely to lose a parent or caregiver due to COVID-19 compared to white children.[44] In the United States, 140,000 children are estimated to have lost a parent or grandparent caregiver, with an estimated 1/753 white children, 1/412 Hispanic children, 1/310 Black children, and 1/168 indigenous children experiencing this loss.[44] These losses are likely to be similarly inequitable in Aotearoa New Zealand.

Aotearoa New Zealand context

COVID-19 infections, hospitalisations and deaths in children aged 5-11 years in New Zealand Delta outbreak

To 19 November 2021, children under 12 made up 22.9% of cases in the current Delta outbreak (1,538/6,714), and there had been 1,003 5-11-year-old children who tested positive for SARS-CoV-2 (14.9% of cases, 1,003/6,714). Data about these cases are shown in Table 1.

Currently, the Ministry of Health's Public Intelligence team cannot specify why the COVID-19 positive cases among 5-11-year-olds were hospitalised, and it is possible that some were in hospital for a reason other than COVID-19. As an estimate of the severity of the hospitalisation event, it is possible to look at length of stay, if they were ever admitted to ICU, and to look at the list of symptoms and comorbidities for each case. All but one case had pre-existing conditions, which included a respiratory disorder (asthma). However, this and the other cases were never admitted to ICU. Four cases had unknown lengths of stay, while three stayed in hospital between 4 and 6 hours. Of note, one case is recorded staying in hospital for 14 days -- but once again this cannot be attributed to COVID-19. No cases showed symptoms at the time of diagnosis apart from one, and none showed serious respiratory symptoms such as dyspnoea (shortness of breath). If needed, any further medical and hospitalisation details should be obtained from local DHB and PHU authorities.

Table 1: SARS-CoV-2 infection in children aged 5-11 years in New Zealand (Delta outbreak, data from August 17th - November 19th 2021)

Characteristic	Number of cases (n =1,003)	% of total ¹
Number of Symptoms²		
0 symptoms	832	83.0
1 symptom	62	6.2
2 symptoms	59	5.9
3 symptoms	31	3.1
4 symptoms	14	1.4
5 symptoms	5	0.5
Hospitalised³		
Yes	8	0.8
No	995	99.2
Number of co-morbidities⁴		
0 comorbidities	982	97.9
1 comorbidity	18	1.8
2 comorbidities	2	0.2
3 comorbidities	1	0.1
Ethnicity⁵		
Māori	521	51.9
Pacific Peoples	304	30.3
European or Other	130	13.0
Asian	33	3.3
Unknown	15	1.5
Socioeconomic deprivation		
1 (least deprived)	26	2.6

Characteristic	Number of cases (n =1,003)	% of total ¹
2	22	2.2
3	26	2.6
4	35	3.5
5	39	3.9
6	54	5.4
7	81	8.1
8	102	10.2
9	238	23.7
10 (most deprived)	367	36.5
Unknown	13	1.3

¹ Due to rounding, percentages may not add to 100.0%

² Symptoms at time of diagnosis

³ Includes hospitalisation of any duration (hours to days)

⁴ Includes cardiovascular disease, chronic lung disease, diabetes, immunodeficiency, malignancy, liver disease and renal failure

⁵ This is prioritised ethnicity (prioritised order Māori, Pacific, Asian and European/Other) This data shows that the burden of COVID-19 has disproportionately affected Māori and Pacific peoples aged 5-11, which intersects with socioeconomic deprivation reported for these cases. This mirrors the wider shift in the ethnic groups affected by COVID-19 in Aotearoa, with the outbreak now dominated by those of Māori descent, with 43% of cases identifying as Māori, and 32% of hospitalised cases identifying as Māori.

As a comparison, between 16 June and 13 November 2021 in Sydney, 14,154 cases (19.4%) were aged 0-11 years and not eligible for vaccination. Of these cases, 632 were hospitalised, 9 were in ICU, and 0 patients died. It was not mentioned whether any of these cases had pre-existing conditions or comorbidities. The Sydney data further demonstrates that COVID-19 is relatively mild in most young children. Despite children aged 0-11 years accounting for 19.4% of cases in Sydney since 16 June, they accounted for only 5.9% of hospitalisations, 0.6% of ICU admissions, and no deaths.[45]

At-risk groups and vulnerable children in Aotearoa New Zealand

There is limited data on the prevalence of serious health conditions in children in Aotearoa New Zealand. In the 2020 New Zealand Health Survey, 2.1% of under 14-year-olds (estimated 20,000 children) were rated as having poor or fair health by their parents. The percentage rating varied considerably between regions and socioeconomic area. Northland (3%), Tairāwhiti (3.1%), Lakes (3.4%), Hawkes Bay (4.9%), Hutt Valley (4.2%) and the West Coast (5.2%) had the highest rates of children and young people experiencing poor health.[46] Of note, there is considerable overlap between areas with poor child health and areas with lower vaccination rates.

In adults, risk factors for poor outcomes associated with COVID-19 include respiratory disease and obesity. According to data from the 2020/2021 New Zealand Health Survey, New Zealand has a high prevalence of childhood asthma, with 11.9% (101,000) of children aged 2-14 years reporting taking current asthma medication (though this number is lower than previous years which ranged from 13-15%, and recruitment for the study was impacted by COVID-19 lockdowns).[47] OECD statistics indicate New Zealand has one of the highest hospital admission rates for asthma of OECD countries, and these rates are higher among Māori, Pacific peoples, and in more deprived areas.[48] New Zealand also has a high prevalence of obesity,

with 12.7% (107,000) children aged 2-14 years classified as obese in the 2020/2021 New Zealand Health Survey (with a BMI equivalent to an adult BMI of 30 or greater).[47] Prevalence of obesity also increases in the most deprived living areas, with quintile five prevalence at 18.7%. Pacific children are nearly three times as likely to be obese (reported prevalence of 28.8%).[46]

Another high-risk factor for poor outcomes in the adult population is being disabled, particularly for learning or intellectual disabilities. Ministry of Education enrolment data indicates that at 1 July 2020, there were 10,160 students receiving Ongoing Resourcing Support (ORS) for high or very high educational support needs, with the regions of Auckland (3,359), Waikato (1,019) Wellington (1,050), and Canterbury (1,091) providing education for the bulk of these students.[49] Māori and Pacific students were significantly overrepresented in these enrolments.[49] Higher Māori enrolment rates are possibly due to a notable increase in tamariki Māori starting school with serious disability in the last 10 years.[50] Child poverty statistics show that 1 in 5 disabled children live in material hardship, two and a half times more often than children who are not disabled.[51]

Māori and Pacific adults are also at greater risk of hospitalisation due to COVID-19 and severe COVID-19. An 80-year-old patient with COVID-19 who is NZ European/Other without reported comorbidities has the same predicted risk of hospitalisation as a 59.3-year-old (95% CI: 46.9–73.7) patient who is Māori without reported comorbidities.[52] Similar differences are seen across all ages and for cases with at least one reported comorbidity, and therefore it is likely to also be represented in children. Māori have 2.5 times (95% CI: 1.39-4.51) higher odds of being hospitalised than non-Māori and are likely to spend around 4.9 days longer in hospital than other ethnicities, even after controlling for age and pre-existing conditions. Pacific peoples have three times (95% CI: 1.75-5.33) greater odds of being hospitalised.[52] There are an estimated 115,562 tamariki Māori aged 5 to 11 years in Aotearoa, and an estimated 49,398 Pacific children.[53] This amounts to over 160,000 children that are likely at higher risk.

In New Zealand, factors which would increase the risk of transmission include social deprivation, quality of housing, fuel and heating, poverty and household crowding, and each of these are also more likely to affect Māori and Pacific People.[1] One in five Māori live in overcrowded housing compared to one in 25 New Zealand Europeans.[54]

If and when vaccination does rollout, the risk of infection and severe disease will be higher among areas with low uptake among 5-11-year-olds. Examining the uptake of other childhood vaccinations may indicate where there is greater risk of this occurring. Over the last decade there has been increasing concern about falling rates of immunisation for many infectious diseases, and the widening inequities and gaps in immunisation coverage rates in Aotearoa New Zealand.[55] In a 10-year immunisation coverage analysis, Marek et al. showed that although the least deprived regions have the highest immunisation coverage, there was a declining trend in coverage rates over 2006-2017 in high decile regions. Immunisation coverage was lowest in the most deprived areas with the northern part of the South Island, the central-southern part of the North Island, around Auckland, and Northland most negatively impacted by this. Additionally, Māori tamariki were more likely to not be fully immunised.[55] The younger age demographic of the Māori population also means that a relatively larger proportion of Māori compared to the wider population are children who are unable to be vaccinated at present and remain susceptible to infection, with a risk of onwards spread to their whānau and communities. Not only does the Māori population have a younger age structure, but Māori whānau often have more tamariki and live in intergenerational households, alongside experiencing disproportionate levels of socioeconomic inequality.[1, 54] According to a Horizon Research

survey, 72% of those who care for 5-11-year-olds would allow their child to receive the COVID-19 vaccine, however this was lower among Māori caregivers at 51%.[56]

Transmission

During the early pandemic, children were rarely identified as index cases of transmission clusters,[57] though this was likely influenced by the closure of schools and lockdowns. Meta-analyses from 2020 gave some support to the hypothesis that children are less susceptible to SARS-CoV-2 infection, though their infectivity and overall role in transmission was less clear.[57, 58] However, with schools reopening and extracurricular activities resuming, outbreaks have demonstrated that children do play a role in transmission, though likely less of a role than adults. Children and young people have become more prevalent in positive case numbers in many countries as the pandemic has progressed and older age groups have had increased access to vaccination,[59] and this population group is also being recognised as a growing community 'reservoir' for the virus.[60] Since the Delta variant emerged, the USA recorded cumulative increases of childhood cases in most states each week.[61]

In July 2021 the ECDC updated its assessment of the susceptibility of children to SARS-CoV-2 infection, now noting that children appear to be equally susceptible to SARS-CoV-2 infection compared to other age groups (low confidence), although severe disease is much less common in children than in adults.[8] They note that while multiple studies have suggested that children may be less susceptible to SARS-CoV-2 infection than adults, potential reporting biases due to lower-case ascertainment in children may contribute to this interpretation, particularly for studies published during 2020. Recent prevalence and seroprevalence studies have tended to conclude that there are no significant differences across age groups. However, they note that cases of SARS-CoV-2 in younger children appear to lead to onward transmission less frequently than cases in older children and adults.[8] ATAGI also notes that available evidence suggests that the transmissibility of infection in younger children is lower than in older age groups.[62]

Transmission in education settings

Within education settings, transmission of SARS-CoV-2 occurs but appears to be limited. Transmission of SARS-CoV-2 in schools appears to be affected by how widespread the virus is in the broader community.[63-65] The CDC notes that although outbreaks in schools can occur, multiple studies have shown that transmission in school settings is typically lower than – or at least similar to – levels of community transmission, when prevention strategies are in place in schools.[66]

Overall, in the school environment, transmission is more likely to occur between adults, followed by adult-to-child transmission, with the risks of child-to-child or child-to-adult transmission being considerably less.

- An investigation of SARS-CoV-2 transmission in a Georgia school district during 1 December 2020 to 22 January 2021 identified nine clusters of COVID-19 cases involving 13 educators and 32 students at six elementary schools. Two clusters involved probable educator-to-educator transmission that was followed by educator-to-student transmission in classrooms and resulted in approximately one half (15 of 31) of school-associated cases. The paper concluded that educators might play a central role in in-school transmission networks.[64]
- Data from a prospective, cross-sectional analysis from the UK's national surveillance also found most cases were in staff. Following the reopening of educational settings during the summer mini-term from 1 June-21 July 2020, staff were found to have an increased risk of infection. Staff had

higher incidence than students (27 cases [95% CI: 23-32] per 100,000 per day among staff compared with 18 cases [14-24] in early years students, 6.0 cases [4.3-8.2] in primary school students, and 6.8 cases [2.7-14] in secondary school students), and most cases linked to outbreaks were among staff members (154 [73%] staff vs 56 [27%] children of 210 total cases). The probable transmission direction for the 55 confirmed outbreaks was: staff-to-staff (n=26), staff-to-student (n=8), student-to-staff (n=16) and student-to-student (n=5).[65, 67]

- Data from New South Wales shows that the largest risk to children in schools is from adults. There were 59 individuals (34 students [57.6%] and 25 staff members [42.3%]) from 51 educational settings (19 schools and 32 ECEC services) confirmed as primary COVID-19 cases who had an opportunity to transmit SARS-CoV-2 to others in their school or early childhood centres. 2,347 individuals (1,830 students [77.9%] and 517 staff members [22.0%]) were identified as close contacts of these 59 primary cases. 106 secondary cases (69 students and 37 staff members) occurred in 19 of the 51 educational settings resulting in a secondary attack rate (SAR) of 4.7%. The highest transmission rate occurred between staff members (16.9%). The rate was low in primary schools (1.7%); however, this would have been affected by school holidays and subsequent limited attendance. Early childhood education centres remained fully open during the report period, and there was an overall SAR of 6.4%. When transmission did occur to children, the household tertiary attack rates following exposure to a secondary case from a school was 70.7%.[68] Figure 1 provides a breakdown of transmission routes and the associated risks.

Primary case type	Close contact type	n positive NAT/N tested	Attack rate (%)
Overall			
Any	All	106/2253	4.7%
Adult	All	88/1027	8.6%
Adult	Adult	33/294	11.2%
Adult	Child	51/733	7.0%
Child	All	21/1316	1.6%
Child	Adult	4/274	1.5%
Child	Child	17/1042	1.6%
High schools			
Any	All	0/202	0.0%
Primary schools			
Any	All	9/526	1.7%
Adult	All	3/162	1.9%
Adult	Adult	0/60	0.0%
Adult	Child	3/102	2.9%
Child	All	9/454	2.0%
Child	Adult	2/86	2.3%
Child	Child	7/368	1.9%
ECEC services			
Any	All	97/1515	6.4%
Adult	All	85/823	10.3%
Adult	Adult	33/195	16.9%
Adult	Child	51/628	8.1%
Child	All	12/692	1.7%
Child	Adult	2/151	1.3%
Child	Child	10/541	1.8%

Note: For one primary school where both a staff member and student were co-primary cases, the close contacts have been counted in attack rate calculations for both categories of primary cases.

Figure 1: Secondary attack rates in NSW educational settings, by primary and secondary case type and educational setting type, between 16 June and 31 July 2021 [68]

Transmission in household settings

Transmission within households is common. This is where the greatest risk of transmission is due to the ongoing and close nature of exposure.

Pre-Delta, the risk of transmission to a household contact was approximately 30%, however the risk ranged in studies between 10% and 60%.[69-72] This will be higher with the Delta variant. Transmission to other household members has occurred with most cases in the current New Zealand Delta outbreak. Pre-Delta, children under the age of 10 appeared to be about half as susceptible to infection.[73-76] In a household cohort study, Li et al. found the secondary attack rate was even lower for children, at 4% compared with 17.1% for adults.[77] However, there are some limitations associated with studies conducted in 2020, and as mentioned above, the ECDC updated its assessment of the susceptibility of children to SARS-CoV-2 infection in July 2021, now noting that children appear to be equally susceptible to SARS-CoV-2 infection compared to other age groups (low confidence).[8]

Children were also at a lower risk of transmission or being the index case in households.[75, 78] However, one study suggests that children and adolescents are more likely to infect others.[79] Another study reported that household transmission was more common from children aged 0-3 years than from children aged 14-17 years.[80]

Data from the Imperial-led REACT coronavirus monitoring programme found the highest prevalence was in children aged 5-12 years at 5.85% (1 in 17), followed by secondary school-aged children aged 13-17 years at 5.75%. Prevalence was also more than four times higher in households with one or more children (3.09%), compared to those without children (0.75%).[81]

Modelling the impact of vaccination of 5-11-year-olds on case numbers in New Zealand

The Ministry is undertaking ongoing internal modelling studies. The modelling considers vaccination of 5-11-year-olds in a subset of the scenarios. Assuming roughly 50% uptake in this group and the same vaccine effectiveness as in older age groups, preliminary analysis suggests that vaccination of 5-11-year-olds could substantially decrease transmission, resulting in half as many cases, hospitalisations and deaths across all age groups.

Non-pharmaceutical interventions for the prevention of COVID-19 in children

Given that aerosol transmission is a key mechanism for spread of SARS-CoV-2, there is increasing focus on the need for strategies such as optimising ventilation, air quality and mask wearing. OzSAGE (a multidisciplinary group of experts in Australia) recommends the following strategies to help protect children from SARS-CoV-2 infection:[82]

- Vaccinating eligible children, their parents and teachers as soon as possible
- Ensuring access to safe indoor air through ventilation and filtration
- Using high quality masks for children and teachers in schools
- Providing families with flexible learning options so they can make their own decisions about their children attending school in-person.

The ECDC recommends the following measures to prevent the spread of infection in schools (adapted to levels of community SARS-CoV-2 transmission as well as to the education setting and age group):[63]

- Physical distancing (by cohorting, ensuring physical distance in the classroom, reducing class sizes, staggering arrival and break times, and holding classes outdoors)

- Improved ventilation
- Promotion of 'stay-at-home' when sick policies
- Promotion of respiratory etiquette
- Regular handwashing
- Use of masks when feasible.

In addition, testing strategies for educational settings aiming at timely testing of symptomatic cases are recommended to ensure isolation of cases and tracing and quarantine of their contacts.[8] The ECDC notes that the decision to close schools to control the COVID-19 pandemic should be used as a last resort, given the negative physical, mental and educational impacts on children and the economic impact on society more broadly[36]: "While a measure of last resort, school closures can contribute to a reduction in SARS-CoV-2 transmission, but are by themselves insufficient to prevent community transmission of COVID-19 in the absence of other non-pharmaceutical interventions and the expansion of vaccination coverage. The effectiveness of school closures appears to have declined in the second wave as compared to the first wave of the COVID-19 pandemic, possibly in part due to better hygiene measures in school settings."

Evidence from the United States shows wearing masks in classrooms may reduce the chance of transmission. After adjusting for potential described confounders, the odds of a school-associated COVID-19 outbreak in schools without a mask requirement were 3.5 times higher than those in schools with an early mask requirement (OR: 3.5; 95% CI: 1.8–6.9).[83] Another MMWR analysis indicated that increases in paediatric COVID-19 case rates during the start of the 2021-22 school year were smaller in US counties with school mask requirements than in those without school mask requirements.[84]

A recent systematic review has investigated the effectiveness of public health measures in reducing the incidence of COVID-19, SARS-CoV-2 transmission, and COVID-19 mortality, focussing only on empirical studies.[85] They noted two studies [86, 87] that assessed the effectiveness of school closures on incidence of COVID-19 or COVID-19 mortality. Both were rated at moderate risk of bias.[85] One of these studies was a US population-based time series analysis conducted in 2020, and it found that school closure was temporally associated with decreased COVID-19 incidence (adjusted relative change per week, -62%) and mortality (adjusted relative change per week, -58%).[87] States that closed schools earlier, when the cumulative incidence of COVID-19 was low, had the largest relative reduction in incidence and mortality. However, some of the reduction could have been related to other concurrent pharmaceutical interventions.[88] On the other hand, time series analyses to evaluate the effectiveness of school closure in Japan found no effect on the incidence of COVID-19.[86]

The systematic review identified three studies investigating the impact of school closures on transmission, all rated at moderate risk of bias.[85] The review notes that two natural experiments from the US reported a reduction in transmission (i.e., reproductive number); one study reported a reduction of 13% (relative risk 0.87, 95% CI: 0.86 - 0.89) and another reported a 10% reduction (0.90, 95% CI: 0.86 - 0.93). It also cites a Swedish study that reported an association between school closures and a small increase in confirmed SARS-CoV-2 infections in parents (odds ratio 1.17, 95% CI: 1.03 - 1.32), but observed that teachers in lower secondary schools were twice as likely to become infected than teachers in upper secondary schools (odds ratio 2.01, 95% CI: 1.52 - 2.67).

Another study experimentally evaluated the impact of ventilation on aerosol dynamics and distribution, along with the effective filtration efficiency (EFE) of four different mask types, with and without mask fitters, in a classroom setting.[89] Infection probability estimates indicated that ventilation alone is not able

to achieve probabilities of <0.01 (1%). The use of moderate to high EFE masks reduces infection probability, by >5× in some cases. Reductions provided by ventilation and masks are synergistic and multiplicative.

A retrospective cohort study from the US investigated the effectiveness of 3 versus 6 ft of physical distancing for controlling spread among primary and secondary students and staff.[90] Student case rates were similar in the 242 districts with ≥3 versus ≥6 ft of physical distancing between students (IRR, 0.891; 95% CI: 0.594-1.335); results were similar after adjustment for community incidence (adjusted IRR, 0.904; 95% CI: .616-1.325). Cases among school staff in districts with ≥3 versus ≥6 ft of physical distancing were also similar (IRR, 1.015, 95% CI: 0.754-1.365).

A recent study used epidemiological models to simulate the spread of SARS-CoV-2 among students, teachers, and staff in both primary and secondary schools and applied these to better understand the risks of reopening schools and to explore the effectiveness of different mitigation strategies.[91] The models indicate that several measures can help substantially: dividing students into multiple cohorts who attend school on an alternating basis, frequently testing teachers and students, and vaccinating teachers and staff. The authors emphasise that basic transmission control strategies such as mask use, social distancing, and ventilation remain essential.[91]

Prior to COVID-19 vaccines being available for children, UNICEF and WHO developed guidance on how to minimise transmission in schools and keep schools open.[3] These recommendations are still applicable, even with vaccines now being available. The CDC recommends layering multiple prevention strategies, including: promoting vaccination, consistent and correct use of masks, physical distancing, screening for prompt identification of cases, improved ventilation, handwashing and respiratory etiquette, staying home when sick and getting tested, contact tracing in combination with isolation and quarantine, and routine cleaning with disinfection under certain conditions.[66] Studies of SARS-CoV-2 transmission in schools that consistently implemented layered prevention strategies have shown success in limiting transmission in schools, even when testing of close contacts has been incomplete.[66] In June 2020 the Harvard School of Public Health published “Healthy Schools Risk Reduction Strategies for Reopening Schools” which outlined a range of mitigation strategies under the themes of healthy classrooms, healthy buildings, healthy policies, healthy schedules and healthy activities.[92]

The Pfizer COVID-19 vaccine for 5–11-year-olds

A phase 3 randomised control trial was conducted to assess the safety, immunogenicity and efficacy of two doses of the Pfizer Comirnaty (BNT162b2) vaccine (‘the Pfizer vaccine’) administered 21 days apart in children aged 6 months to 11 years, with findings thus far published for 5-11-year-olds.[93]

During the phase 1 study from 24 March through 14 April 2021, a total of 48 children 5-11 years of age received 10 µg, 20 µg, or 30 µg of the Pfizer vaccine (16 children at each dose level). For the phase 1 trial, a total of 50 5-11-year-olds were screened for inclusion at four US sites, and 48 received escalating doses of the Pfizer vaccine. Half the children were male, 79% were White, 6% were Black, 10% were Asian, and 8% were Hispanic or Latinx. The mean age was 7.9 years. Based on reactogenicity and immunogenicity, a dose level of 10 µg was selected for further study.[93]

In the phase 2/3 trial, a total of 2268 children were randomly assigned in a 2:1 ratio to receive two doses of either the Pfizer vaccine at 10 µg (1517 children) or placebo (751 children). At data cut-off, the median follow-up was 2.3 months.[93] The trial was run across 81 sites in the US, Spain, Finland and Poland. Overall, 52% were male, 79% were White, 6% were Black, 6% were Asian, and 21% were Hispanic or Latinx.

The mean age was 8.2 years; 20% of children had coexisting conditions (including 12% with obesity and approximately 8% with asthma), and 9% were SARS-CoV-2–positive at baseline. Apart from younger age and a lower percentage of Black and Hispanic or Latinx 5-11-year-olds (6% and 18%, respectively) than 16-25-year-olds (12% and 36%, respectively), demographic characteristics were similar among the 5-11-year-old and 16-25-year-old Pfizer recipients who were included in the immunobridging subset.[93]

Children with no or stable pre-existing conditions were eligible to participate, except those with an immunocompromising or immunodeficiency disorder, those with a history of MIS-C, or those receiving immunosuppressive therapy (including cytotoxic agents and systemic glucocorticoids). In addition, in the phase 1 study, children with a previous clinical or virologic COVID-19 diagnosis were excluded.[93]

Safety and reactogenicity

Safety evaluations included assessment of reactogenicity events reported by a parent or guardian using an electronic diary for 7 days after each dose. Data on unsolicited adverse events, including confirmed diagnoses of myocarditis or pericarditis, were collected from the first dose through 1 month after the second dose. Data on serious adverse events will be collected from the first dose through 6 months after the second dose.[93]

In the 5-11-year-olds, as in other age groups, the Pfizer vaccine had a favourable safety profile. Side effects were generally comparable to those observed in 16-25-year-olds who received standard 30 µg doses.[94] Most local reactions were mild to moderate, lasting 1-2 days. Injection-site pain was the most common local reaction, occurring in 71-74% of Pfizer recipients. Fatigue and headache were the most frequently reported systemic events. In general, systemic events were reported more after the second dose than first dose (see Figure 2). As compared with adults and adolescents in the pivotal trial, 5-11-year-olds reported a higher incidence of injection-site redness (15 to 19%, vs. 5 to 7%) and swelling (10 to 15%, vs. 5 to 8%), but a generally lower incidence of systemic events, including fever (3 to 7%, vs. 1 to 20%) and chills (5 to 10%, vs. 6 to 42%).[93, 95, 96]

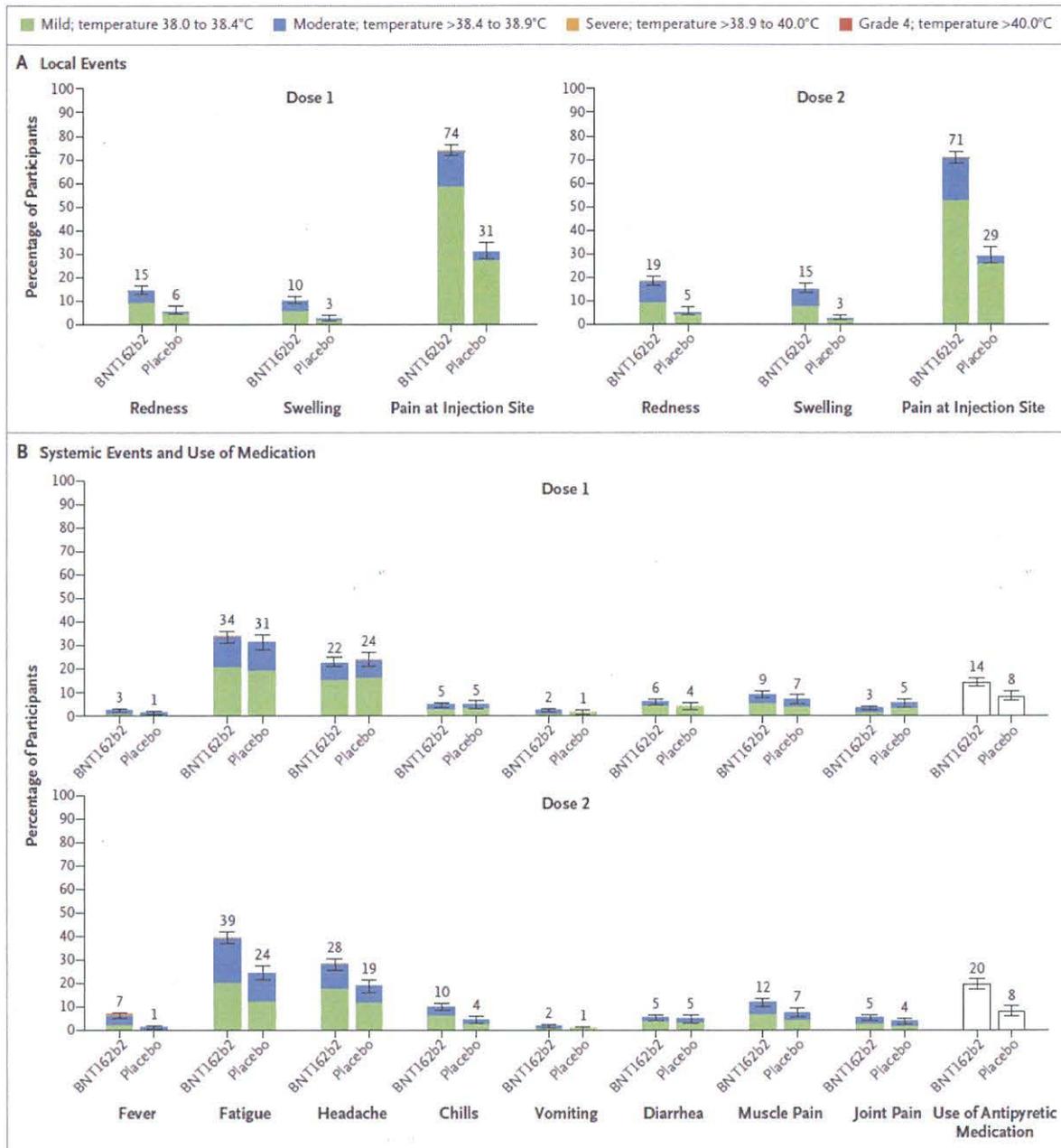


Figure 2: Local Reactions and Systemic Events Reported in the Phase 2-3 Trial (5-11-year-olds) within 7 Days of Injection of Pfizer or Placebo.[93]

No vaccine-related serious adverse events were noted in the clinical trial; however, the trial was too small and therefore not powered to detect rare side effects such as myocarditis or thrombosis with thrombocytopenia.[62] No myocarditis, pericarditis, hypersensitivity, or anaphylaxis in Pfizer recipients was reported. From the first dose through one month after the second dose, adverse events were reported by 10.9% of Pfizer recipients and 9.2% of placebo recipients. Slightly more Pfizer recipients (3.0%) than placebo recipients (2.1%) reported adverse events that were considered by the investigators to be related to the vaccine or placebo. Severe adverse events were reported in 0.1% of Pfizer recipients and 0.1% of placebo recipients. Three serious adverse events in two participants were reported by the cut-off date; all three (postinjury abdominal pain and pancreatitis in a placebo recipient and arm fracture in a Pfizer

recipient) were considered to be unrelated to the vaccine or placebo. No deaths or adverse events leading to withdrawal were reported. Lymphadenopathy was reported in 10 Pfizer recipients (0.9%) and 1 placebo recipient (0.1%). Four rashes in Pfizer recipients (observed on the arm, torso, face, or body, with no consistent pattern) were considered to be related to vaccination; the rashes were mild and self-limiting, and onset was typically 7 days or more after vaccination.[93]

Immunogenicity and Efficacy

For all participants in the phase 1 and for a subset of participants in phase 2/3, blood samples were collected for immunogenicity assessments, which included determination of SARS-CoV-2 neutralisation titres. Serum samples collected from 5-11-year-olds and 16-25-year-olds were assayed to ensure comparability of titres.[93]

Immune responses one month after the second dose of the Pfizer vaccine were immunologically bridged to those in 16-25-year-olds from the pivotal trial of two 30 µg doses of Pfizer. Children aged 5-11 receiving two 10 µg doses had similar, statistically non-inferior, neutralising antibody responses with a geometric mean titre (GMT) of 1,197.6 (95% CI: 1,106.1-1,296.6) vs 1,146.5 (95% CI: 1,045.5-1,257.2) for ages 16-25.[94] One month after the second dose, the geometric mean ratio (GMR) of SARS-CoV-2 neutralising titres in 5-11-year-olds to those in 16-to-25-year-olds was 1.04 (95% CI: 0.93- 1.18). This ratio met the prespecified immunogenicity success criterion (lower bound of two-sided 95% CI: >0.67; GMR point estimate, ≥0.8).[93, 94]

Vaccine efficacy against symptomatic NAAT-confirmed COVID-19 at 7 days or more after the second dose was assessed. COVID-19 with onset 7 days or more after the second dose was reported in three recipients of the Pfizer vaccine and in 16 placebo recipients, producing a vaccine efficacy of 90.7% (95% CI: 67.7 to 98.3).[93] No cases of severe COVID-19 or MIS-C were reported.

Data are not yet available on the real-world effectiveness of the vaccine to protect against hospitalisation or infection in this age group but are expected in coming months.[62]

Real-world rollout

In October 2021, the Global Advisory Committee on Vaccine Safety (GACVS) concluded that in all age groups the benefits of mRNA COVID-19 vaccines in reducing hospitalisations and deaths due to COVID-19 outweigh the risks. The Advisory Committee on Immunization Practices (ACIP) made an interim recommendation for use of the Pfizer vaccine in children aged 5-11 years in the United States for prevention of COVID-19.[4, 97] This was unanimously supported by the Committee. In making this recommendation, ACIP considered the importance of COVID-19 as a public health problem, as well as benefits and harms, parents' values and preferences, acceptability, feasibility, resource use, and equity for use of the vaccine among children.[4, 97]

The US FDA approved a modified formulation of the Pfizer vaccine (10 µg each dose, administered 3 weeks apart) for children aged 5-11 on 29 October 2021.[98] On 2 November, the CDC recommended the use of the vaccine in this age group.[99] The White House announced on 18 November that 2.6 million children had received the vaccine.[100] From December 14, children aged 5-11 will need to show proof of at least one dose of COVID-19 vaccine to participate in indoor activities in New York City. As of 12 December, almost 5.4 million children aged 5-11 in the US had received at least one dose and almost 2.5 million children had received their second dose.[101] Other countries including Canada, Israel, UAE, Costa Rica,

Singapore, Malaysia, Bahrain, Slovakia, Saudi Arabia, Australia and Kuwait have authorised use of the Pfizer vaccine in children aged 5-11 years. Data are yet to be reported from any of these countries.

On 25 November, the European Medicines Agency recommended granting approval for children aged 5-11. On 1 December 2021 the European Centre for Disease Prevention and Control published interim public health considerations for COVID-19 vaccination of children aged 5-11 years.[36]

In Australia, on 5 December the Therapeutic Goods Administration (TGA) provisionally approved the Pfizer vaccine as safe and effective for use among this age group.[102] On 10 December, the Australian Technical Advisory Group on Immunisation (ATAGI) recommended use of this vaccine in 5-11-year-olds.[62] The Australian Government will start rolling out the Pfizer vaccine to 5- 11-year-olds from early January 2022.

The UK's Medicines and Healthcare products Regulatory Agency approved the use of the paediatric formulation on 22 December 2021.[103] The UK's JCVI has recommended vaccination for clinically vulnerable 5-11-year-olds or children living with someone who is immunosuppressed.[104]

Dosing intervals

The US has recommended a 3-week interval between doses as in the clinical trials. There are no data available about extending the interval of the paediatric formulation of the Pfizer vaccine, however Canada and the UK is recommending a minimum 8 week interval.[104, 105] Similarly, in Australia, the schedule recommended by ATAGI for this age group is 2 doses, 8 weeks apart. In special circumstances the interval may be shortened to a minimum of 3 weeks.[62] Data from older age groups has showed that an extended dosing interval may improve immunogenicity and the effectiveness after the second vaccine, and may also reduce the risk of myocarditis and pericarditis after vaccination.[62]

Data are also very limited on extended dosing intervals for the Pfizer vaccine in adults and the impact on vaccine efficacy and safety. However, emerging data suggests that the immune response is likely improved somewhat by extending the dosing interval. This is consistent with basic principles of vaccinology and immunology, that suggests that immune responses are generally better with longer intervals.

Several countries have been using extended intervals, ranging from approximately 6-16 weeks for the Pfizer vaccine for their general populations, including England, Canada, and several countries in Europe. A study of 750 participants aged 50-89 years in the UK found higher protection following extended schedules. GMTs at 14-34 days were 6703 (95% CI: 5887-7633), higher than those receiving Pfizer 19-29 days apart (694; 95% CI: 540-893). Higher two-dose vaccine efficacy was also observed with >6 week intervals between Pfizer doses compared to the authorised 3-week schedule, including ≥80 year-olds.[106] Another study from Canada found efficacy was significantly higher against both infection and hospitalisation with the longer 7-8 week interval vs. manufacturer-specified 3-4 week interval between doses.[107] With both studies however it's unclear whether this results in more durable protection, as waning protection, at least against infection, seems to be similar across different interval periods used. The studies have also had small sample sizes.

There may also be a connection between shorter intervals and increased reactogenicity or adverse events. One study found reactogenicity after a late second dose (given at 44-45 weeks post-first dose) or a third dose was lower than reactogenicity after a first dose.[108] Considering the increased risk of serious adverse events such as myocarditis in younger age groups, there could be an argument for an extended dosing interval. A pre-print paper has shown a statistically significant increase in myocarditis occurrence following

the second dose of the Pfizer vaccine if the second dose was given at a shorter interval of less than 30 days between doses.[109] However, the study was limited to those aged 12 and over.

Coadministration

There are limited clinical trial, observational, or laboratory data on the safety and immunogenicity associated with the coadministration of the Pfizer COVID-19 vaccine and other vaccines in all populations. Based on first principles, there is the potential for a reduced immune response when two different types of vaccine are administered together or within several days of each other. However, there are no additional safety concerns associated with coadministration, over and above each vaccine's individual safety profile. Given that the catch-up campaigns for MMR, HPV, and Boostrix are largely among younger age groups, and that these individuals are likely to have a robust immune response, younger age groups are less likely to be adversely impacted by coadministration of vaccines. Younger age groups have lower vaccination rates compared to others. Any obstacles to accessing and completing vaccinations should be removed and steps should be taken to encourage completion of the recommended vaccine schedules. In general, the risk of reduced immune protection from coadministration of the Pfizer COVID-19 vaccine and other vaccines is low in younger age groups, while the public health benefit gained from higher vaccine coverage is substantial.

In New Zealand adults, CV TAG earlier recommended either dose of the Pfizer vaccine can be administered at any time before, after or simultaneously with other Schedule vaccines (in separate syringes, at separate sites), including MMR, influenza, HPV, Tdap and meningococcal vaccines, and this has been included within the Immunisation Handbook. The only exception is the live herpes zoster vaccine for which spacing of at least 7 days is recommended before or after the Pfizer vaccine.[110]

The CDC has stated that COVID-19 vaccines 'may be administered without regard to timing of other vaccines, which includes simultaneous administration of COVID-19 vaccine and other vaccines on the same day'.[111] The American Medical Association states it is considered best practice to administer all the vaccines someone is eligible for in the same visit as it helps ensure that people are up to date with their vaccinations, though there are some exceptions, such as children with asplenia, complement component deficiency or HIV infection.[112] They also state that for those children who need two doses of the influenza vaccine, they should receive their first dose early as the second dose cannot be given until four weeks later but the circulation of influenza can fluctuate at different times.

In Australia, ATAGI has said that the paediatric Pfizer COVID-19 vaccine can be co-administered with other vaccines, though parents and guardians should be aware that this may be associated with an increase in mild-moderate adverse events.[62] Health Canada recommends that if possible, children shouldn't receive the Pfizer vaccine within 14 days of other vaccines, such as the flu vaccine, as a precaution to monitor any side effects from the COVID-19 vaccine or another vaccine.[105]

Number needed to treat

The number needed to treat (NNT) for a vaccine is interpreted as the average number of people who need to be vaccinated to prevent one additional adverse outcome from the disease. It is calculated as $1/(\text{incidence in unvaccinated} - \text{incidence in vaccinated})$.

It is important to note that the NNT is not a fixed value for any one vaccine, outcome or population. It will vary with baseline risk (incidence in unvaccinated), which for infectious diseases can fluctuate with factors such as control measures in place (e.g., border controls, lockdowns, masks) and season. Although the simplest calculations of NNT can be performed using trial data, it should be noted that trial data are likely

to overestimate the NNT. This is because trials are often “completed” relatively early which may appear to reduce the background risk (and increase the NNT). The NNTs for Pfizer vaccine trials are shown in **Table 2**.

Table 2: Numbers Needed to Treat, Pfizer COVID-19 vaccine trials

Trial	NNT confirmed COVID-19	NNT severe disease/hospitalisation	NNT death	Notes
Pfizer phase 3 COVID-19 vaccine trial, adults (16 years and over)	141 Vaccine: 8/21,720 Placebo: 162/21,728	2716 Vaccine: 1/21,720 Placebo: 9/21,728	Not calculable (no cases in either group)	To October 9 th 2020[95]
	30 Vaccine: 77/23,153* Placebo: 850/23,153*	723 Vaccine: 0/23,153* Placebo: 32/23,153*	N/A (not reported)	To March 13 th 2021[113]
Pfizer phase 3 COVID-19 vaccine trial, adolescents (12-15 years)	71 Vaccine: 0/1131 Placebo: 16/1129	N/A (not reported)	Not calculable (no cases in either group)	58% had at least 2 months of follow-up after their second vaccine dose[96]
Pfizer phase 3 COVID-19 vaccine trial, children (5-11 years)	51 Vaccine: 3/1517 Placebo: 16/751	Not calculable (no cases in either group)	Not calculable (no cases in either group)	Median 2.3 months follow up. All recruited early to mid-June 2021[93]

* Denominators per group not reported but groups previously very closely balanced

It is challenging to present a fair comparison of NNTs across childhood vaccines. This is because baseline incidence of these infectious disease can vary substantially over time period, and the length of time that the population is observed for. **Table 3** presents NNTs for a range of scenarios, with worked examples for measles vaccine and COVID-19 in children. To make these comparisons as fair as possible, it is assumed that in a hypothetical, completely unvaccinated population of children, each virus is allowed to circulate freely until the herd immunity threshold is reached. Because of this, the baseline risk for COVID-19 outcomes is substantially higher than in the Phase 3 trials reported in **Table 2**, and the NNTs therefore lower. Additionally, for the calculations around NNTs for COVID-19 in children, there are many uncertainties around numbers used to calculate these estimates, including R_0 in children, and the proportion of infected children who go on to die. However, in these examples, the NNTs for COVID-19 vaccine for each outcome are generally around 5 times that for measles vaccine.

Table 3: Number needed to treat with different percentage of population with outcome with no vaccination, and vaccines of different efficacy

	Number Needed to Treat to Prevent One Occurrence of the Outcome									
	Percentage of population with outcome of interest in absence of vaccine									
	100%	75%	50%	10%	5%	1%	.75%	.5%	.1%	.01%
95% effective vaccine	1.1	1.4	2.1	11	21	105	140	211	1053	10526
80% effective vaccine	1.3	1.7	2.5	13	25	125	167	250	1250	12500
50% effective vaccine	2	2.7	4	20	40	200	267	400	2000	20000

Worked examples:

Measles in children: With no vaccination, around 92-94% of the population will become infected (usually in childhood), based on R_0 of 12-15. With vaccine efficacy of 95%, NNT would be **just over 1 to prevent 1 case of measles**. The NNT to prevent 1 hospitalisation would be **just over 4** (based on around 1 in 4 cases needing hospitalisation), and just over **1000 to prevent one measles death** (based on around 1 per thousand).

COVID-19 in children: It should be noted there are many uncertainties around these estimates. With no vaccination, and assuming R_0 of 6, around 83% of the population would become infected at some point (possibly fewer if R_0 lower in children resulting in higher NNTs, possibly higher if natural infection doesn't prevent re-infection, allowing ongoing circulation). With vaccine efficacy of 95%, NNT would be around **2.5 to prevent 1 symptomatic case** (based on around 50% of cases in children being symptomatic [5]). The NNT would be around **30 to prevent 1 hospitalisation** (based on 1 in 25 of cases in 6-11 year olds being severe [6]). The NNT would range from **5,000 to 25,000 to prevent 1 death** depending on the mortality rate used in the calculation. The NNT of 5,000 is based on 1 in 4,000 cases dying (4% of cases being severe and 0.6% of severe cases dying[114]) and the NNT of **25,000** is based on 1 in 20,000 cases dying.[115]

Risks and benefits of vaccinating 5–11-year-olds in Aotearoa New Zealand

The decision to vaccinate children requires very careful weighing of the known and potential risks and benefits. The balance of risks and benefits of COVID-19 vaccination in children is more complex than in adults as the relative harms from vaccination and disease are less well established in this age group.[35, 62]

Below is a **summary of possible arguments that could favour vaccination for 5-11-year-olds and arguments for caution around vaccination of this age group, divided into various themes.**

Burden of COVID-19 in children

Favouring vaccination: While children under 18 years of age infected with SARS-CoV-2 are less likely to develop severe illness compared with adults, children are still at risk of developing severe illness and complications from COVID-19 and contribute to transmission in households and communities.[97] The risk of hospitalisation and death from COVID-19 is similar or even higher than the pre-vaccine-era of other diseases for which vaccines are routinely given.[97] In addition, if a high proportion of children are infected, even a very low rate of severe illness might translate to a high absolute number of cases.[35] Although severe or fatal COVID-19 is rare in the 5-11 age group, some children (e.g. those with certain co-morbidities) are substantially more vulnerable. To expand COVID-19 vaccine access, additional considerations should be given to demographic groups that have experienced disproportionate COVID-19 morbidity and mortality, as well as those with barriers to routine health care.[4]

Favouring caution: The direct health benefit of vaccinating children and adolescents is lower compared with adults, due to the lower incidence of severe COVID-19 and deaths in these age groups.

Longer term impacts in children following COVID-19 (MIS-C and long COVID)

Favouring vaccination: Protecting as many children as possible through vaccination would reduce the numbers of children who go on to have complications from COVID-19 infection. MIS-C is most frequent among children 5-11 years of age and other post-COVID conditions have been reported in children.[97] Long COVID can occur after mild COVID-19 illness.

Favouring caution: The efficacy of vaccines against MIS-C and long COVID are still unknown, and therefore vaccines may not protect children against these conditions. (However, reducing the number of children infected would theoretically reduce the absolute case numbers of long COVID).

Vaccine efficacy

Favouring vaccination: Vaccine efficacy against symptomatic COVID-19 7 days post-second dose was 90.7%, based on 3 cases in the vaccine group and 16 in the placebo group between 21 and 126 days. From the ACIP GRADE evidence assessment, the level of certainty for the benefits of Pfizer vaccination among children aged 5-11 years was type 1 (high certainty) for the prevention of symptomatic laboratory-confirmed COVID-19. [97] Data are not yet available on the real world effectiveness of the vaccine to protect against hospitalisation or infection in this age group, but are expected in the coming months.[62]

Risk of adverse events/ long-term safety of the vaccine

Favouring vaccination: Several scientific bodies have established that the risks are outweighed by the benefits of vaccination. In the trials in this age group, serious adverse events were uncommon and occurred with similar frequency among vaccine (0.07%) and placebo (0.10%) recipients, with no statistically significant difference in frequency observed between the two groups.[4] An expanded safety cohort of 2,379 children (including 1,591 vaccine recipients) was added to monitor for serious adverse events, which had a median follow-up of 2.4 weeks after receipt of the second dose. No serious adverse events related to the vaccination were identified in either group, and no specific safety concerns were identified among vaccine recipients aged 5-11 years.[4] ATAGI states that the risk of myocarditis or pericarditis after mRNA COVID-19 vaccination in children aged 5-11 years is not yet known but appears to be rare based on preliminary data from US surveillance networks.[62] Paediatric cardiologists have noted that myocarditis after the vaccine is rarer and usually milder than the cardiac complications from COVID-19, including those

from multisystem inflammatory syndrome (MIS-C).[116] In a US CDC report, myocarditis was reported up to 37 times more often in unvaccinated children less than 16 years old with COVID-19.[36]

Favouring caution: Careful consideration must be given to the incidence of severe adverse events in this age group. The risk of myocarditis (or other rare, serious adverse events) in children has not yet been fully determined, nor has the long-term safety of the vaccine. This is a new class of vaccine and it cannot be assumed that the responses of younger children will be the same as older children or adults. Some adverse events in other age groups have only become apparent following widespread rollout. However, the WHO noted in November that available data suggested that the cases of myocarditis and pericarditis following vaccination are generally mild and respond to conservative treatment, and are less severe with better outcomes than classical myocarditis or COVID-19.[3] They also noted that the risk of myocarditis/pericarditis associated with SARS-CoV-2 infection is higher than the risk after vaccination.[3] Regarding potential harms after vaccination, ACIP rated evidence as type 4 (very low certainty) for serious adverse events because of small sample size and short follow-up time and type 2 (moderate certainty) for reactogenicity for imprecision.[97] Vaccination may have mild side effects in children, including fatigue resulting in absences from school. Given COVID-19 is generally mild and rarely severe, this risk of adverse events must be balanced. Within several months, millions of children in the US will have been vaccinated, which will provide much more information about safety as well as potential impact on community transmission. An option could be to wait for further real-world data before making a final decision.

Role of children in transmission

Favouring vaccination: Vaccinating this age group could help protect those who are immunocompromised, those who are very young or otherwise unable to be vaccinated and provide protection for the vulnerable in multi-generational households. While the role of children in transmission may be smaller, given the vaccine reduces the risk of infection, it will reduce the risk of children introducing COVID-19 into the home and exposing family members, who might then need to stand down from education and work. This is particularly important in households with several children. Having ongoing exposures and consecutive isolation periods may result in children having to isolate for a significant period.

US scenario modelling looking at implementation of vaccination of children 5-11 years with and without new and more transmissible variants has been undertaken.[97] In the absence of a new and more transmissible variant, childhood vaccination among 5-11-year-olds is expected to accelerate the decline in cases, reducing cumulative incidence nationally by an expected 8% (approximately 600,000 cases) from November 1, 2021 to March 12, 2022. In scenarios where a variant that is 50% more transmissible than Delta arises in mid-November 2021 (as may be the case with Omicron), childhood vaccination reduces cases by about 13% (nearly 1.2 million cases) over the same period. Altogether, vaccination of 5-11-year-olds would dampen, but not eliminate a new variant emergence.[97]

Favouring caution: The role of children in transmission still requires further investigation. It is possible that a national rollout in the 5-11-year-old age group would not significantly reduce overall levels of infection. Most children who get COVID-19 do so from a household exposure, so high coverage in adults and older children is a good strategy for protecting children. Given that vaccinated and unvaccinated people can have similar peak viral loads during infection and transmission of the Delta variant in households occurs equally as often from vaccinated and unvaccinated individuals,[117] vaccination of this age group may have little impact on transmission in households in the context of high community transmission. However, there have

been few studies that have specifically looked at the ability of children with breakthrough infections to transmit.

Global equity

Favouring caution: The WHO states that before considering implementing primary vaccination series in adolescents and children, it is important to attain high coverage of primary vaccination in highest risk subgroups, such as older adults or people with comorbidities (taking into account booster doses as needed based on evidence of waning and optimising vaccination impact).[3] As a matter of global equity, as long as many parts of the world are facing extreme vaccine shortages, countries that have achieved high vaccine coverage in their high-risk populations should prioritise global sharing of COVID-19 vaccines through the COVAX facility before proceeding to vaccination of children and adolescents who are at low risk for severe disease.[3]

National equity

Favouring vaccination: Vaccinating this age group will be very important for equity, as currently many of New Zealand's COVID-19 cases are in children and in disadvantaged communities. In high-income countries, children from deprived and ethnic minority groups are more frequently infected with SARS-CoV-2 which might be due to a greater likelihood of living with unvaccinated adults or in multigenerational and overcrowded households.[35] They may also have more severe outcomes associated with infection.[35]

Favouring caution: There is the risk that rolling out the Pfizer vaccine in this age group will further negatively impact the national immunisation schedule for children, where vaccination rates for MMR, HPV and Boostrix are falling, and campaigns have been impacted by COVID-19 and lockdowns. There is a danger that rolling out an additional vaccine will further derail catch-up campaigns that are currently underway through the diverting of public health resources, increasing the public health risk of outbreaks. Vaccination rates are lowest among Māori and Pacific, and therefore there are equity concerns that there will be greater risk in these populations. If unanticipated safety issues were to emerge with wider use of the Pfizer vaccine, this could also impact trust in the national immunisation programme generally.

Indirect child and community impacts

Favouring vaccination: Vaccination also brings wider benefits through the avoidance of isolation, quarantine, school closures and other indirect harms of lockdowns. School attendance is critical to the wellbeing and life prospects of children and to parental participation in the economy.[3] Vaccinating school-aged children may help minimise school disruptions by reducing the number of infections at school and the number of children required to miss school because of quarantine requirements.[3] In addition, some children are reliant on meals provided at schools, as food insecurity is increasingly common, particularly in low decile schools. Allowing schools to remain open will allow these programmes to continue. In an educational setting, vaccination may mean that other measures which have been challenging to implement can be reduced, such as social distancing and the wearing of masks. Vaccination will also help protect teaching staff and their whānau at home who may not be eligible to be vaccinated. From a wellbeing perspective, vaccination will help maintain normality in the education system and keep learning in a structured classroom environment. This will help contribute to normal routines and a sense of stability for children after nearly two years of disruption, will mean a reduced need to subject children to testing which can be quite invasive, and will help make children feel more involved in the 'team of five million' messaging that has underpinned New Zealand's response to the pandemic.

Concerns around possible stigmatisation and exclusions could be addressed in other ways, and not necessarily influence the decision to use. For example, there could be a policy decision that children cannot be denied access to locations/events on the basis of vaccination status, which could be operationalised by not issuing vaccine certificates for this age group.

Favouring caution: Vaccination status and the potential for mandates also has inherent risk as it may be that this is a cause for exclusion (whether vaccinated or unvaccinated), and those who are unvaccinated may not be able to fully participate in some environments (even if not required by law). This is likely to inequitably impact communities who are already experiencing disadvantage and where current vaccine coverage is poor. Given parental consent is required for vaccination in this group, there may be some reluctance by some parents to vaccinate children who would like to be vaccinated.

Another advantage of vaccinating children is the possibility of decreasing transmission and thus reducing severe cases in adults and the risk of new virus variants emerging.[35] If vaccinating 5-11-year-olds also reduces cases in other age groups, this might also lower the likelihood of increased restriction settings and lockdowns and minimise disruption to young peoples' lives.

Impact on other vaccination programmes

Favouring vaccination: Whilst there may be some concerns about the effect of extending the vaccination programme to 5-11-year-olds on other vaccination programmes, this operational consideration could be better seen as an opportunity to improve the system going forward, rather than a reason to recommend against vaccinating 5-11-year-olds for SARS-CoV-2. There is potential for a COVID-19 vaccination rollout in 5-11-year-olds to be used to also catch children up on other childhood immunisations, assuming that coadministration of vaccines can occur.

Further rollout equity considerations

Key conclusions from ACIP included:

“ACIP determined that use of the Pfizer-BioNTech COVID-19 vaccine among children is a reasonable and efficient allocation of resources. To expand COVID-19 vaccine access, additional considerations should be given to demographic groups that have experienced disproportionate COVID-19 morbidity and mortality, as well as those with barriers to routine health care (e.g., members of certain racial/ethnic groups and those living in a rural or frontier area, experiencing homelessness, with a disability, or lacking health insurance). Children from racial and ethnic minority groups have experienced a disproportionately high incidence of COVID-19 as well as secondary impacts of the COVID-19 pandemic such as reduced in-person learning (12). Providing rapid and equitable access to COVID-19 vaccines for children will necessitate increasing the enrollment of pediatric health care providers into the COVID-19 vaccination program, using the broad geographic accessibility of pharmacies, and expanding school-focused strategies to ensure vaccination opportunities for a diverse population, as well as engagement with community leaders, pediatric health care providers, and parents or guardians.”[4]

These comments have high relevance for New Zealand in terms of the need to give additional consideration to certain groups in planning for the rollout of the paediatric vaccine if it goes ahead.

It is also important to note the te ao Māori view of tamariki is not just as individual entities, as they have very strong links to whānau and communities and consider them inextricably interlinked. This has important implications if vaccination was to be offered to this age group. Older family members may be

more likely to take up the opportunity to get vaccinated as a whānau, in settings familiar to them, such as those offered by Māori health providers or iwi/hapu-led vaccine initiatives. It is likely that the lower rates of vaccination in Māori are not due to hesitancy so much as inadequate access to the vaccine and culturally appropriate care and messaging.

In addition, it is possible that without introducing vaccines to this age group, there may be a series of rolling outbreaks in Māori and Pacific tamariki, resulting in significant impacts on their whānau and communities with isolations required for multiple children within families in succession, which could continue for an extended period. However, it is worth noting that isolation period length does not vary depending on vaccination status.

Importantly, the mode of delivery for vaccination in this age group will need to be equitable, noting that in-school models of vaccine delivery have been used in the past and been a success. This will not reach some children in this age group, and consideration will need to be given to those in isolated communities, undertaking distance learning, or home-schooled.

Next Steps

A memo based on this RfA and CV-TAG discussions will be written and shared with CV TAG for approval.

In the development of this work, the following parties have been consulted with:

Intelligence and Surveillance team, Science and Insights CV-TAG and invited guests, including Māori paediatricians

Resources used:

Ministry of Health Policies and Procedures	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
External Health Scientific organisations	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Existing database of RFAs	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Internal Ministry of Health Advice	<input type="checkbox"/> Yes <input type="checkbox"/> No
External Expert Advice	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Request for Advice (RfA)

Literature Review

Yes

No

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This is the exhibit marked "GT-7" referred to in the annexed Affidavit of **GEORGE IAN TOWN** affirmed at **Christchurch** this **10th** day of **June 2022** before me:



Memo


Solicitor of the High Court of New Zealand

Emma Louise Spratt
Solicitor
Christchurch

Use of the paediatric Pfizer COVID-19 vaccine in 5-11 year-olds – second dose and dosing interval: COVID-19 Vaccine Technical Advisory Group (CV TAG) recommendations

Date: 16 February 2022

To: Dr Ashley Bloomfield, Director-General of Health

Copy to:

██
██
██

From: Dr Ian Town, Chief Science Advisor

For your: Consideration

Purpose of report

1. To outline the COVID-19 Vaccine Technical Advisory Group's (CV TAG) advice about the administration of a second dose of the paediatric Pfizer vaccine and the interval between the first and second doses of the COVID-19 vaccine for 5–11 year-olds.
2. This report also provides an update on international and local safety data.

Background and context

3. Vaccination of 5–11-year-olds in New Zealand is now underway. The approved COVID-19 paediatric Pfizer vaccine being used has a lower dose (10 µg) and a smaller volume (0.2 mL) than the adult vaccine and is administered using a smaller needle. As at 13 February 2022, 214,857 (45%) of 5–11-year-olds had received their first dose in New Zealand. [1] Only 26% of Māori 5-11 year-olds and 36% of Pacific 5-11 year-olds have received their first dose. To be fully immunised against COVID-19, a child needs to receive two doses of the paediatric vaccine.
4. In December 2021, CV TAG recommended that two doses of the paediatric Pfizer vaccine be offered to all 5-11 year-olds in Aotearoa New Zealand, with an 8-week interval between doses (Appendix 1, *Decision to Use the Pfizer mRNA COVID-19 vaccine for children aged 5-11 years: COVID-19 Vaccine Technical Advisory Group (CV TAG) recommendations*). It was also indicated that in February 2022, CV TAG would assess the latest data and provide updated recommendations prior to any second doses being given to this age group in New Zealand.

Safety data for the Pfizer vaccine in 5–11-year-olds

5. A randomised clinical trial to assess the safety, immunogenicity, and efficacy of the Pfizer vaccine in 5-11 year-olds of two doses administered three weeks apart reported more local reactions and systemic events than placebo recipients. [2] The reactions and events reported were generally mild to moderate, lasting 1 to 2 days. Injection-site pain was the most common local reaction, occurring in 71 to 74% of Pfizer recipients. Severe injection-site pain after the first or second dose was reported in 0.6% of Pfizer recipients and in no placebo recipients.
6. In the clinical trial, fatigue and headache were the most frequently reported systemic events (0.9%), headache (0.3%), chills (0.1%), and muscle pain (0.1%) were also reported after the first or second dose of Pfizer. [2] Frequencies of fatigue, headache, and chills were similar among Pfizer and placebo recipients after the first dose and were more frequent among Pfizer recipients than among placebo recipients after the second dose.
7. No vaccine-related serious adverse events were noted in the clinical trial; however, the trial was too small to detect rare side effects such as myocarditis. [2] Three serious adverse events were reported from two participants (postinjury abdominal pain and pancreatitis in a placebo recipient and arm fracture in a Pfizer recipient), however, none of these were related to the vaccine or placebo. No deaths or adverse events leading to withdrawal were reported. There were no cases of severe COVID-19 or Multisystem Inflammatory Syndrome in Children (MIS-C)—a condition associated with COVID-19 where body parts can become inflamed. Lymphadenopathy was reported in ten Pfizer recipients (0.9%) and one placebo recipient (0.1%). No myocarditis, pericarditis, hypersensitivity, or anaphylaxis in Pfizer recipients was reported. Rashes in four Pfizer recipients (observed on the arm, torso, face, or body, with no consistent pattern) were related to vaccination; the rashes were mild and self-limiting, and onset was typically 7 days or more after vaccination.
8. Real-world safety data has been collected from over 8 million doses of the Pfizer vaccine administered to children aged 5–11 years in the United States. These data have been collected in the Vaccine Adverse Event Reporting System (VAERS), a national passive vaccine safety surveillance system, and through V-safe, a voluntary smartphone-based safety surveillance system for adverse events after COVID-19 vaccination. [3] From November 3 to December 19, 2021, VAERS received and processed 4,249 reports of adverse events for children aged 5–11 years who received Pfizer COVID-19 vaccine. Overall, among VAERS reports for children aged 5–11 years who received the Pfizer vaccine, approximately 97% were non-serious. The most commonly reported conditions among the 100 reports of serious events were fever (29.0%), vomiting (21.0%), and increased troponin-(15.0%). Among 12 serious reports of seizure, five children experienced new-onset seizures. Among 15 preliminary reports of myocarditis identified during the analytic period, 11 met the case definition for myocarditis. VAERS received two reports of death both of whom had complicated medical histories and were in fragile health before vaccination. None of the data suggested a causal association between death and vaccination. In V-safe, fever was found to be more frequently reported in 5-11 year-olds after dose 2 (4,001: 13.4%) than dose 1 (3,350; 7.9%) among 42,504 recipients of dose 1 and 29,899 recipients of dose 2. Overall, systemic reactions after dose 2 among registrants aged 5-11 years were less frequent than among children aged 12-15 years. Fourteen registrants aged 5–11 years received hospital care after vaccination. Information regarding reason for hospitalisation was available for five children

and included appendicitis (two), vomiting and dehydration (one), respiratory infection (one), and retropharyngeal cellulitis (one).

Reporting of Adverse Events following Vaccination in New Zealand

9. In New Zealand, preliminary unpublished data from Medsafe indicates that there have been 352 adverse events following immunisation (AEFIs) reported from 17 January to 30 January 2022 in children aged 5-11 who received the approved COVID-19 paediatric Pfizer vaccine. Of these, 96.9% (341) reports were classified as non-serious. A small number of individuals (10) reported that an AEFI required emergency care and one AEFI case was admitted to hospital for observation (no evidence of myocarditis despite reporting chest discomfort). Of these 11 cases, six were reported as recovered or recovering, one was ongoing, and four had an unknown outcome. Chest discomfort was the most frequently reported reaction (6), followed by vasovagal reaction (4), and there was one case of anaphylaxis (Brighton criteria level 4).
10. Medsafe is in regular contact with other regulators and have noted that to date nothing of concern has been drawn to their attention regarding the safety profile of the paediatric Pfizer vaccine.

Rationale for an 8-week interval

11. The manufacturer's recommended schedule for the paediatric Pfizer vaccine is 2 doses, 3 weeks apart.
12. Research conducted in adults into extending the dosing interval (e.g., to 8 weeks or longer) has shown that longer intervals between the first and second Pfizer dose can lead to higher humoral and cellular immune responses, improved vaccine effectiveness, and potentially a longer duration of protection compared with the standard interval. [4-7] In addition, data from adults show that an extended dosing interval may also reduce the risk of myocarditis and pericarditis after vaccination. [8]
13. Extended dosing intervals has not yet been studied in children, but it is expected that similar effects would be observed to those after extended dosing intervals in adults, such as improved immunogenicity and the potential for a lower risk of serious side effects. The recommendation for an 8-week interval between doses is consistent with other international advisory groups, such as in the UK, Canada, and Australia. [9-11] In addition, a longer interval between doses would allow more time to continue monitoring international safety data as it emerges.

Priority groups for children aged 5-11 years

14. Māori and Pacific children have been disproportionately affected in this pandemic. For community-acquired cases up to 11 February 2022, Māori made up 45.7% of total cases in 5- to 11-year-olds, and Pacific children have made up 28.7% of cases among 5- to 11-year-olds. Of these cases, a total of ten have been hospitalised, with Māori and Pacific children combined making up 90% of these cases. As noted above, in the vaccine rollout for 5-11-year-olds, fewer Māori and Pacific children have been vaccinated than other ethnicities. Prioritisation of Māori and Pacific children remains important, and the emphasis should be to get the first dose administered to as many as children as possible.

15. Children living with pre-existing conditions or comorbidities, from disadvantaged backgrounds, or those living within a lower socioeconomic status have a greater risk of severe disease from COVID-19. [12-16]
16. Starship Child Health has listed risk factors for COVID-19 disease [17] that may be used as guidance for prioritising children with high-risk pre-existing conditions. The current list of risk factors includes children with:
 - Chronic lung disease including bronchiectasis, cystic fibrosis, BiPAP for OSA
 - Non-repaired congenital heart disease, acquired heart disease or congestive heart failure
 - Poorly controlled asthma (regular symptoms occurring in a usual week that affect the patient's quality of life and includes anyone with an admission in the last 2 years or anyone with 2 or more courses of steroids in the last two years)
 - Obesity (BMI \geq 95th centile for age)
 - Diabetes (insulin-dependent)
 - Chronic kidney disease (GFR $<$ 15 ml/min/1.73m²)
 - Severe cerebral palsy (or neurodevelopmental disorder)
 - Complex genetic, metabolic disease or multiple congenital anomalies.
17. Children in other recognised clinical risk groups who are at higher risk of severe COVID-19 should also include those who are a household contact of someone who is immunosuppressed (defined as those who expect to share living accommodation on most days (and therefore for whom continuing close contact is unavoidable) with individuals of any age who are immunosuppressed).

Recommendations

18. CV TAG met on 1, 8, and 15 February 2022 to consider guidance on administering a second dose of the vaccine and the interval between doses for 5–11-year-olds.
19. CV TAG noted:
 - a. **The direct and indirect impacts on children.** Children who have COVID-19 will commonly have few or only mild respiratory symptoms. COVID-19 in this age group is rarely severe or fatal, [18, 19] and the rate of severe COVID-19 disease in this age group is the lowest of any age group. However, there is a very small but real risk of MIS-C (described above) at this age which has occurred more frequently among ethnic minorities in the US. [12, 20] A very small proportion of children also experience persistent illness and ongoing symptoms, though evidence about its incidence is limited.
 - b. Children living with pre-existing conditions or comorbidities, from disadvantaged backgrounds, or those living within a lower socioeconomic status have a greater risk of severe disease from COVID-19. [12-15]
 - c. Even though the direct effects of infection are generally less severe in children, this should not diminish the significance for those who have experienced worse outcomes. [19] Alongside the direct risks and impacts to health and individuals, COVID-19 also has indirect impacts for children on mental health, wellbeing, education and social development, and these are worsened by lockdowns and school closures. [12, 21-23]
 - d. **Children do play a role in transmission however it is significantly smaller than for adults.** Transmission within education settings has occurred but is limited and is more

likely to occur between adults. [24-26] Transmission in households is much more common. [27, 28] The benefit of vaccination on onward transmission in households could be lower than in other settings due to the ongoing and close nature of exposure. [29, 30] but this is not confirmed. The effect of vaccination of children on household transmission is unknown.

- e. **There are a number of equity considerations which are important to consider:**
- i. Māori and Pacific children have been disproportionately affected in the current outbreak. To 11 February 2022, Māori made up 45.7% of cases in 5-11 year-olds, and Pacific children have made up 28.7% of cases among 5-11 year-olds.
 - ii. Māori and Pacific adults are at greater risk of COVID-19 hospitalisation and severe disease. Māori and Pacific adults have respectively 2.5-fold and 3-fold higher odds of being hospitalised compared to non-Māori, and Māori are likely to spend 4.9 days longer in hospital. [31, 32]
 - iii. Māori and Pacific children are more likely to live in multigenerational families housed in overcrowded conditions, increasing the risk of transmission. The younger age structure of the Māori population also means that a larger proportion are currently unable to be vaccinated and remain susceptible to infection and transmission, with a risk of onwards transmission to whānau and communities, [33, 34] though the risk of transmission from children is lower than from adults.
- f. **The paediatric formulation of the vaccine has been approved for emergency use and rolled out in the USA, Canada, and Israel.** The Advisory Committee on Immunization Practices (ACIP) made an interim recommendation for the emergency use of the Pfizer vaccine in children aged 5-11 years in the United States for prevention of COVID-19. [19, 35] This was unanimously supported by the Committee. In making this recommendation, ACIP considered the importance of COVID-19 as a public health problem, as well as benefits and harms, parents' values and preferences, acceptability, feasibility, resource use, and equity for use of the vaccine among children. [19, 35] ACIP additionally stated: "children from racial and ethnic minority groups have experienced a disproportionately high incidence of COVID-19 as well as secondary impacts of the COVID-19 pandemic such as reduced in-person learning". [19] These comments have high relevance for New Zealand given the similar effects of the pandemic on Māori and Pacific Peoples as described above.
- g. **In Australia, the Therapeutic Goods Administration (TGA)** provisionally approved the Pfizer vaccine as safe and effective for use among this age group on 5 December 2021. [36] ATAGI recommends all 5–11-year-olds be vaccinated with an 8-week interval between doses, and that those at risk of severe disease, Aboriginal and Torres Strait Islanders, and children in crowded conditions or outbreak areas be prioritised. [37]
- h. **On dosing intervals,** there are no data available about extending the interval between doses of the paediatric formulation of the Pfizer vaccine, however, emerging data in adults suggests that the immune response is likely improved by extending the dosing interval. [4-7] This is consistent with basic principles of vaccinology and immunology which suggests that immune responses are generally better with longer intervals. There may also be a connection between shorter intervals and increased reactogenicity or adverse events, and one pre-print paper on individuals aged 12 and over has shown

a statistically significant increase in myocarditis if the second dose was given at a shorter interval of less than 30 days. [8] Australia, Canada, and the UK have recommended an 8-week interval between doses for 5-11 year-olds, noting this may improve immunogenicity and reduce side effects. Having a longer interval would also allow more time to monitor international safety data.

- i. **On vaccine requirements**, there is a significant risk that use of vaccination mandates or certificates in this age group will result in exclusion and an inability to fully participate in schooling and extracurricular activities. This is likely to inequitably impact communities who are already experiencing disadvantage and where current vaccine coverage is poor. Concerns regarding possible stigmatisation and exclusions could be addressed in ways that do not necessarily influence the decision to use. For example, there could be a policy decision that children cannot be denied access to locations/events on the basis of vaccination status, which could be operationalised by not issuing vaccine certificates for this age group.
- j. **On safety of the paediatric vaccine**, real-world data on the rollout of the vaccine to 5-11-year-olds have reported nothing of concern to date.

20. **CV TAG recommended that:**

- a. A second dose of the paediatric Pfizer vaccine be offered to all 5-11 year-olds in Aotearoa New Zealand, with a minimum 8-week interval between doses.
- b. Māori and Pacific children, children with high-risk pre-existing conditions, and children living with vulnerable people should continue to be prioritised for vaccination.

21. CV TAG will continue to monitor all relevant information (including safety data) and will update their recommendations as information becomes available.

Ian G Town

Dr Ian Town
**Chief Science Advisor and
Chair of the COVID-19 Vaccine Technical Advisory Group**

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**Appendix 1 – Decision to Use the Pfizer mRNA COVID-19 vaccine for children aged 5-11 years:
COVID-19 Vaccine Technical Advisory Group (CV TAG) recommendations**

Memo

Decision to use the Pfizer mRNA COVID-19 vaccine for children aged 5-11 years: COVID-19 Vaccine Technical Advisory Group (CV TAG) recommendations

Date:	15 December 2021
To:	Dr Ashley Bloomfield, Director-General of Health
Copy to:	Astrid Koornneef, Director of National Operations, COVID Vaccine Immunisation Programme Allison Bennett, Manager, System Enablers, System Strategy and Policy Dr Caroline McElnay, Director of Public Health
From:	Dr Ian Town, Chief Science Advisor and Chair of CV TAG
For your:	Information

Purpose of report

1. To summarise the CV TAG recommendations on the decision to use the paediatric formulation of the Pfizer mRNA COVID-19 vaccine ('the Pfizer vaccine') for children who are 5 to 11 years of age.

Background and context

2. In February 2021, CV TAG advice was sought for use of the Pfizer COVID-19 vaccine in people who were 16 years and over, following Medsafe approval. Cabinet agreed that the COVID-19 Immunisation Programme proceed with the roll out of the Pfizer vaccine, and this has been underway since February.
3. In August 2021, CV TAG confirmed support to extend the age of people who can receive the Pfizer vaccine to 12- to 15-year-olds, noting that this would likely lead to a reduction in school closures and disruption to education, and contribute to equitable vaccination coverage in Māori and Pacific peoples.
4. Medsafe is assessing an application submitted by Pfizer for the use of a paediatric formulation of the vaccine in 5- to 11-year-olds within New Zealand. The CV TAG recommendations presented here are subject to Medsafe approval and any listed clinical conditions.

5. The Ministry's Policy team has sought clinical and scientific advice from CV TAG on the use of the Pfizer vaccine for children who are 5- to 11-years of age. This advice will be considered as part of the Decision to Use Framework, and alongside policy considerations for the sequencing of the COVID-19 Immunisation Programme.

The COVID-19 vaccine in 5- to 11-year-olds

Phase 2/3 trial findings

6. One phase 2/3 randomised control trial was conducted to assess the safety, immunogenicity, and efficacy of two doses of the Pfizer vaccine administered 21 days apart in children aged 6 months to 11 years, with findings published for 5- to 11-year-olds to date [2].
7. In the phase 2/3 trial, participants were randomly assigned in a 2:1 ratio to receive two doses of either the Pfizer vaccine at 10 µg (a lower dose than the 30 µg used in older age groups), or a placebo. A total of 2268 children were assigned to receive the Pfizer vaccine (1517 children) or placebo (751 children) [2].
8. The trial was run across 81 sites in the US, Spain, Finland and Poland. Overall, 52% were male, 79% were White, 6% were Black, 6% were Asian, and 21% were Hispanic or Latinx. The mean age was 8.2 years; 20% of children had coexisting conditions (including 12% with obesity and approximately 8% with asthma), and 9% were SARS-CoV-2-positive at baseline. Demographic characteristics were similar between the 5- to 11-year-old and 16- to 25-year-old Pfizer recipients who were included in the immuno-bridging subset, apart from younger age and the percentage of Black and Hispanic or Latinx in the 5- to 11-year-old group (6% and 18%, respectively) being lower than in the 16- to 25-year-old group (12% and 36%, respectively) [2].

Safety and reactogenicity

9. In the 5- to 11-year-olds, as in other age groups, the Pfizer vaccine had a favourable safety profile, with side effects generally comparable to those observed in 16- to 25-year-olds who received the standard 30 µg doses [2].
10. Safety evaluations included assessment of reactogenicity events reported by a parent or guardian using an electronic diary for 7 days after each dose. Data on unsolicited adverse events, including confirmed diagnoses of myocarditis or pericarditis, were collected from the first dose through 1 month after the second dose. Data on serious adverse events will be collected from the first dose through 6 months after the second dose [2]. At data cut-off, the median follow-up was 2.3 months [2].
11. Most local reactions were mild to moderate, lasting 1-2 days. Injection-site pain was the most common local reaction, occurring in 71-74% of Pfizer recipients. Fatigue and headache were the most frequently reported systemic events. In general, systemic events were reported more frequently after the second dose than first dose. As compared with adults and adolescents in the pivotal trial, 5- to 11-year-olds reported a higher incidence of injection-site redness (15 to 19%, vs. 5 to 7%) and swelling (10 to 15%, vs. 5 to 8%), but a generally lower incidence of systemic events, including fever (3 to 7%, vs. 1 to 20%) and chills (5 to 10%, vs. 6 to 42%) [2, 38, 39].

12. From the first dose through to one month after the second dose, adverse events were reported by 10.9% of Pfizer recipients and 9.2% of placebo recipients. Slightly more Pfizer recipients (3.0%) than placebo recipients (2.1%) reported adverse events that were considered by the investigators to be related to the vaccine or placebo [2].
13. No vaccine-related serious adverse events were noted in the clinical trial; however, the trial was too small to detect rare side effects such as myocarditis. Three serious adverse events were reported from two participants (postinjury abdominal pain and pancreatitis in a placebo recipient and arm fracture in a Pfizer recipient). None of these were considered to be related to the vaccine or placebo. No deaths or adverse events leading to withdrawal were reported [2]. No cases of severe COVID-19 or Multisystem Inflammatory Syndrome in Children (MIS-C) were reported—a condition associated with COVID-19 where body parts can become inflamed [2, 20]. Lymphadenopathy was reported in 10 Pfizer recipients (0.9%) and 1 placebo recipient (0.1%). No myocarditis, pericarditis, hypersensitivity, or anaphylaxis in Pfizer recipients was reported. Four rashes in Pfizer recipients (observed on the arm, torso, face, or body, with no consistent pattern) were considered to be related to vaccination; the rashes were mild and self-limiting, and onset was typically 7 days or more after vaccination [2].
14. No safety data are yet available from the large-scale roll out of the Pfizer vaccine to 5- to 11-year-olds in the USA, though will likely be available by late December 2021 or early January 2022.

Immunogenicity and efficacy

15. Immune responses in the single clinical trial conducted were assessed one month after the second dose of the Pfizer vaccine were equivalent to those in 16- to 25-year-olds. Children aged 5-11 receiving two 10 µg doses had a similar, statistically non-inferior, neutralising antibody responses with a geometric mean titre (GMT) of 1,197.6 (95% CI: 1,106.1, 1,296.6) vs 1,146.5 (95% CI: 1,045.5, 1,257.2) for ages 16-25 [2].
16. Vaccine efficacy against symptomatic NAAT-confirmed COVID-19 at 7 days or more after the second dose (to a median follow up of 2.3 months at data cut-off) was assessed. Among participants without evidence of previous SARS-CoV-2 infection, symptomatic COVID-19 was reported in three recipients of the Pfizer vaccine and in 16 placebo recipients, producing a vaccine efficacy of 90.7% (95% CI, 67.7 to 98.3) [2].

CV TAG Recommendations

17. CV TAG discussed the use of the Pfizer COVID-19 vaccine in children aged 5-11 years at meetings between October and December 2021 and consulted with Māori paediatricians and Māori general practitioners at two meetings in December 2021.¹
18. CV TAG noted:

¹ CV TAG discussed use of the Pfizer vaccine in the 5-11 age group on: 19 October, 2 November, 9 November, 23 November, 30 November, 7 December, and 14 December.

- a. **The direct and indirect impacts on children.** Children who have COVID-19 will commonly have few or only mild respiratory symptoms. COVID-19 in this age group is rarely severe or fatal [18, 19], and the rate of severe COVID-19 disease in this age group is the lowest of any age group. However, there is a very small but real risk of MIS-C (described above) at this age which has occurred more frequently among ethnic minorities in the US [12, 20]. A very small proportion of children also experience persistent illness and ongoing symptoms, though evidence about its incidence is limited.
- b. In the current Delta outbreak in New Zealand (data to 19 November 2021), children aged 5-11 made up 14.9% of cases (1,003/6,714). Eight of these children were hospitalised but none were admitted to ICU. Of those who were hospitalised, all but one had a pre-existing condition and three were in hospital for less than six hours. As a comparison, between 16 June and 13 November 2021 in Sydney, 14,154 cases (19.4%) were aged 0-11 years and not eligible for vaccination. Of these cases, 632 were hospitalised, 9 were in ICU, and 0 patients died. It was not mentioned whether any of these cases had pre-existing conditions or comorbidities. The Sydney data further demonstrates that COVID-19 is relatively mild in most young children as despite accounting for 19.4% of cases in Sydney since 16 June, they account for only 5.9% of hospitalisations, 0.6% of ICU admissions, and no deaths [40].
- c. Children living with pre-existing conditions or comorbidities, from disadvantaged backgrounds, or those living within a lower socioeconomic status have a greater risk of severe disease from COVID-19 [12-15].
- d. Even though the direct effects of infection are generally less severe in children, this should not diminish the significance for those who have experienced worse outcomes [19]. Alongside the direct risks and impacts to health and individuals, COVID-19 also has indirect impacts for children on mental health, wellbeing, education and social development, and these are worsened by lockdowns and school closures [12, 21-23].
- e. **Children do play a role in transmission however it is significantly smaller than for adults.** Transmission within education settings has occurred but is limited and is more likely to occur between adults [24-26]. Transmission in households is much more common [27, 28]. The benefit of vaccination on onward transmission in households could be lower than in other settings due to the ongoing and close nature of exposure [29, 30], but this is not confirmed. The effect of vaccination of children on household transmission is unknown.
- f. **There are a number of equity considerations which are important to consider:**
 - i. Māori and Pacific children have been disproportionately affected in the current outbreak. To 19 November 2021, Māori made up 52% of cases in 5- to 11-year-olds, and Pacific children have made up 30% of cases among 5- to 11-year-olds.
 - ii. Māori and Pacific adults are at greater risk of COVID-19 hospitalisation and severe disease. Māori and Pacific adults have respectively 2.5-fold and 3-fold higher odds of being hospitalised compared to non-Māori, and Māori are likely to spend 4.9 days longer in hospital [31, 32].

- iii. Māori and Pacific children are more likely to live in multigenerational families housed in overcrowded conditions, increasing the risk of transmission. The younger age structure of the Māori population also means that a larger proportion are currently unable to be vaccinated and remain susceptible to infection and transmission, with a risk of onwards transmission to whānau and communities [33, 34], though the risk of transmission from children is lower than from adults.
 - iv. The vaccine rollout in adults resulted in inequities for Māori and Pacific adults, and the rollout for Māori and Pacific children aged 5-11 will need close consideration and more tailored implementation. This emphasises the need for culturally appropriate messaging and Māori-led initiatives. Whānau-based approaches to the 5-11 rollout may also improve uptake among Māori adults.
 - v. According to a Horizon Research survey, 72% of those who care for 5- to 11-year-olds would allow their child to receive the COVID-19 vaccine, however this was lower among Māori caregivers at 51% [41]. However, we note that the Māori adult rate of uptake and the Māori childhood immunisation rates are much higher than 51%. Given this we believe with a correctly tailored programme, high rates of immunisation in tamariki Māori are achievable.
- g. **The paediatric formulation of the vaccine has been approved for emergency use and rolled out in the USA, Canada, and Israel.** The Advisory Committee on Immunization Practices (ACIP) made an interim recommendation for the emergency use of the Pfizer vaccine in children aged 5-11 years in the United States for prevention of COVID-19 [19, 35]. This was unanimously supported by the Committee. In making this recommendation, ACIP considered the importance of COVID-19 as a public health problem, as well as benefits and harms, parents' values and preferences, acceptability, feasibility, resource use, and equity for use of the vaccine among children [19, 35]. ACIP additionally stated: "children from racial and ethnic minority groups have experienced a disproportionately high incidence of COVID-19 as well as secondary impacts of the COVID-19 pandemic such as reduced in-person learning"[19]. These comments have high relevance for New Zealand given the similar effects of the pandemic on Māori and Pacific peoples as described above.
- h. **In Australia, the Therapeutic Goods Administration (TGA)** provisionally approved the Pfizer vaccine as safe and effective for use among this age group on 5 December [36]. ATAGI recommends all 5–11-year-olds be vaccinated with an 8-week interval between doses, and that those at risk of severe disease, Aboriginal and Torres Strait Islanders, and children in crowded conditions or outbreak areas be prioritised [37].
- i. **Data are still accumulating from the real-world rollout of vaccines in 5- to 11-year-olds, and there is currently limited safety data available post-second dose.** Some adverse events in other age groups (e.g. myocarditis) have only become apparent following widespread rollout, and as noted above the trials in young children are too small to be able to detect rare side effects. Further data on potential side effects from the vaccine rollout in this age group in other countries will become progressively available.

- j. **On coadministration and other vaccines**, there is limited evidence on the safety and immunogenicity of coadministration of the Pfizer vaccine with other vaccines in all populations, however based on first principles of vaccinology it is likely to be safe and effective, particularly in younger age groups.
- k. **The wider National Immunisation Schedule** has been facing challenges for some time with declining vaccination rates since before COVID-19, and are particularly marked for Māori and Pacific infants and children. Catch-up campaigns for the MMR, HPV and Tdap vaccines were further delayed by COVID-19 and lockdowns. There is a risk that rolling out the Pfizer vaccine in this age group could further adversely impact the wider immunisation programme through diverting public health resources. This could increase the risk of outbreaks of other infectious diseases. The risk of a significant measles outbreak is of particular concern once the international borders re-open. Vaccination rates are lowest among Māori, and therefore there are equity concerns that there will be greater risk in this population. However, there is also the opportunity to increase coverage with other vaccines with a thoughtfully implemented COVID-19 vaccination programme in this age group.
- l. **On dosing intervals**, there are no data available about extending the interval between doses of the paediatric formulation of the Pfizer vaccine, however, emerging data in adults suggests that the immune response is likely improved by extending the dosing interval [42, 43]. This is consistent with basic principles of vaccinology and immunology which suggests that immune responses are generally better with longer intervals. There may also be a connection between shorter intervals and increased reactogenicity or adverse events, and one pre-print paper on individuals aged 12 and over has shown a statistically significant increase in myocarditis if the second dose was given at a shorter interval of less than 30 days [44]. Australia and Canada have recommended an 8-week interval between doses for 5-11-year-olds, noting this may improve immunogenicity and reduce side effects. Having a longer interval would also allow greater time to monitor international safety data.
- m. **On vaccine requirements**, there is a significant risk that use of vaccination mandates or certificates in this age group will result in exclusion and an inability to fully participate in schooling and extracurricular activities. This is likely to inequitably impact communities who are already experiencing disadvantage and where current vaccine coverage is poor. Concerns regarding possible stigmatisation and exclusions could be addressed in ways that do not necessarily influence the decision to use. For example, there could be a policy decision that children cannot be denied access to locations/events on the basis of vaccination status, which could be operationalised by not issuing vaccine certificates for this age group.

19. **CV TAG recommended:**

- a. **Two doses of the paediatric Pfizer vaccine be offered to all 5-11-year-olds in Aotearoa New Zealand, with an 8-week interval between doses.**

- b. Māori and Pacific children, children with high-risk pre-existing conditions, and children living with vulnerable people should be prioritised for vaccination and tailored programmes developed.
- c. On the schedule between doses:
 - i. The interval between doses can be shortened in limited circumstances to a minimum of 3 weeks, such as prior to the initiation of significant immunosuppression or international travel.
 - ii. Children who turn 12 after their first dose should follow the authorised schedule which uses the paediatric primary formulation (10 µg). They should not be offered the adolescent/adult formulation (30 µg) of the Pfizer COVID-19 vaccine.
 - iii. Children in this age group who experience a clinically significant adverse event after their first dose should be carefully reviewed by a specialist clinician. An individual risk:benefit assessment should be made on whether to administer the second dose. Children in this age group are not obliged to receive a second dose if not clinically appropriate.
- d. The paediatric Pfizer vaccine can be administered before, after, or at the same time as other vaccines in this age group.
- e. The adolescent/adult Pfizer vaccine formulation (30 µg) should not be used in children aged 5-11 years.
- f. Mandates, vaccine certificates or vaccine targets **must not** be used or required for this age group, and children in this age group should not be denied access to locations or events based on their vaccination status. There should be no unintended consequences in terms of participation if children in this age group are not vaccinated, and any use of mandates, certificates or targets that may formally or informally encourage inappropriate exclusion from activities. Exemptions from vaccination should therefore also not be required for this age group. We recommend specific public education campaigns about why children should not be excluded from activities, in order to reduce the risk of informal exclusions.
- g. Specific consideration must be given to promoting and improving vaccine access to groups that have experienced disproportionate COVID-19 morbidity and mortality, as well as those with barriers to routine health care, especially for Māori and Pacific peoples. This could be achieved through using the broad geographic accessibility of pharmacies and expanding school-focused strategies. Whānau centred approaches should be considered within these environments to improve primary vaccination and booster rates in the adult population.
- h. Emphasis must be given to using the rollout of the COVID-19 vaccine as an opportunity to improve delivery and uptake of the wider National Immunisation Schedule, and large-scale events with whānau-based approaches should be organised to aid catch-up campaigns for other vaccines. The coverage of the childhood National Immunisation Schedule should be closely monitored to ensure that the COVID-19 vaccination rollout for this age group does not adversely impact on the uptake of other important childhood vaccines.

- i. In making vaccination available, it should not be solely relied upon and other public health measures in schools and other educational settings should be strengthened, including ensuring good ventilation and filtration of air indoors, use of masks, physical distancing, and promotion of children staying at home if sick.
20. CV TAG will continue to monitor all relevant information (including vaccine efficacy data against emerging variants of concern and emerging evidence on the duration of immunity) and will update their recommendations as further evidence becomes available.
- a. New Zealand and international safety data will be carefully monitored, and the recommendations here will be reassessed by CV TAG in February 2022 prior to second doses being given to any 5–11-year-olds in Aotearoa New Zealand.
 - b. Advice for severely immunocompromised children who may need a third primary dose will be reconsidered once further evidence emerges on the need, safety, and efficacy.

Recommendations

It is recommended that you:

2.	Note this advice has been received.	Yes/No
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Ian G Town

Dr Ian Town
**Chief Science Advisor and
 Chair of the COVID-19 Vaccine Technical Advisory Group**

Signature _____
 Dr Ashley Bloomfield
Director-General of Health

Date:

"GT-8"

SCIENCE &
TECHNICAL
ADVISORY

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HANGARAU

Request for Advice (RfA)



This form contains the details relevant to the questions posed to the Science and Technical Advisory (STA). STA will respond to the request using this form which will also be stored in STA content management system for future reference.

This form, or parts of it, may also be forwarded to other relevant parties as appropriate.

Title	Use of a third primary dose of paediatric Pfizer mRNA COVID-19 vaccine for severely immunocompromised 5–11-year-olds		
Subject	Information on the use of a 3 rd primary dose for 5–11-year-olds following a 2-dose series of the COVID-19 vaccine for severely immunocompromised 5–11-year-olds		
Reference No.	463	Date Received	22/02/2022
Requestor	COVID-19 Vaccine Technical Advisory Group (CV TAG)	Date Due	8/03/2022
Advisor		Date Completed	4/03/2022
Peer reviewed by			
Advice issued to	CV TAG		
Approved by	Dr Ian Town		
Deliverables	Review of evidence and international guidance		
Request Outline	<p>Background/Context</p> <p>To date, New Zealand has implemented a predominantly Pfizer-based COVID-19 immunisation programme. Cabinet approved use of the Pfizer vaccine to protect 5–11-year-olds in New Zealand on 21 December 2021. This followed advice from the COVID-19 Technical Advisory Group, and Medsafe approval.</p> <p>Individuals who are severely immunocompromised might not produce a sufficiently strong immune response after two doses of the Pfizer COVID-19 vaccine. Currently a third primary dose of the Pfizer COVID-19 vaccine is recommended for people aged 12 and over who are severely immunocompromised. Based on an evaluation of available data to support the use of the Pfizer vaccine and its safety and efficacy amongst children aged 5 to 11 years who are immunocompromised and vaccine first principles, some jurisdictions are now recommending that severely immunocompromised children aged 5 to 11 years receive a third primary dose.</p> <p>CV TAG is seeking advice about the administration of a 3rd dose of the paediatric Pfizer vaccine following a 2-dose series of the COVID-19 vaccine for severely immunocompromised 5–11-year-olds.</p> <p>Questions</p>		

This is the exhibit marked "GT-8" referred to in the annexed Affidavit of **GEORGE IAN TOWN** affirmed at **Christchurch** this 10th day of **June 2022** before me:

Solicitor of the High Court of New Zealand

Emma Louise Spratt
Solicitor
Christchurch

10/06/2022

What safety and efficacy data are available for introducing a third dose of the paediatric vaccine following a 2-dose series of the COVID-19 vaccine for severely immunocompromised 5–11-year-olds?

Which countries have recommended a third dose of the COVID vaccine be administered to eligible severely immunocompromised 5–11-year-olds?

What is the recommended interval for between a second and third dose of the vaccine for immunocompromised children aged 5 to 11 years?

Intended application of advice

To inform recommendations for a third dose following a 2-dose series of the COVID-19 vaccine for eligible severely immunocompromised 5–11-year-olds.

Timeline

Due 8 March 2022

The current objective of the COVID-19 vaccine immunisation programme is to protect individuals from severe disease outcomes and to reduce the impact of the virus on the healthcare system. Equity and Te Tiriti are relevant to assessing who is impacted by a recommendation for a third dose in 5–11-year-olds who are severely immunocompromised. Given these groups are more likely to have severe outcomes as a consequence of SARS-CoV-2 infection, it is important they are prioritised. Māori and Pacific peoples are more vulnerable to severe disease and hospitalisation due to COVID-19 ([link](#)), and therefore a pathway for immunocompromised Māori and Pacific children is of significant importance.

What are the implications and considerations of this advice on Te Tiriti o Waitangi and equity?

Response to Request for Advice

Key points

- Children 5 to 11 years of age who are severely immunocompromised might not produce a sufficiently strong immune response after two doses of the Pfizer COVID-19 vaccine and therefore may be at increased risk of severe outcomes from COVID-19.
- There is not currently safety data for third doses in the 5-11 age group. However, safety data for primary series in this age group and for older children, can be used to gain an impression of this, alongside vaccine first principles.
- Australia, the US, the UK and Canada have all recommended severely immunocompromised 5-11-year-olds receive a third primary dose of the COVID-19 vaccine. Most peak bodies suggest an interval of 4-8 weeks; however, ATAGI suggest a 2–6-month interval. Special attention must also be paid to current or planned immunosuppressive therapies.

Background

Vaccination of 5–11-year-olds in New Zealand has been underway since 17 January 2022. The approved COVID-19 paediatric Pfizer vaccine being used has a lower dose (10 µg) and smaller volume (0.2 mL) than the adult vaccine and is administered using a smaller needle. As at 2 March 2022, 244,626 (51%) of 5–11-year-olds had received their first dose in New Zealand.

In September 2021, the COVID-19 Vaccine Technical Advisory Group (CV TAG) issued recommendations for a third primary Pfizer mRNA COVID-19 vaccine dose in the immunocompromised. CV TAG recommended that those with severe immunocompromise disease be offered an additional dose of the Pfizer vaccine. The list of eligible individuals was informed by guidance created by the Australian Technical Advisory Group on Immunisation (ATAGI). [1]

These recommendations were updated on 17 November 2021 to include all individuals aged 12 years and over who are severely immunocompromised to offer them a third primary dose of the Pfizer vaccine.

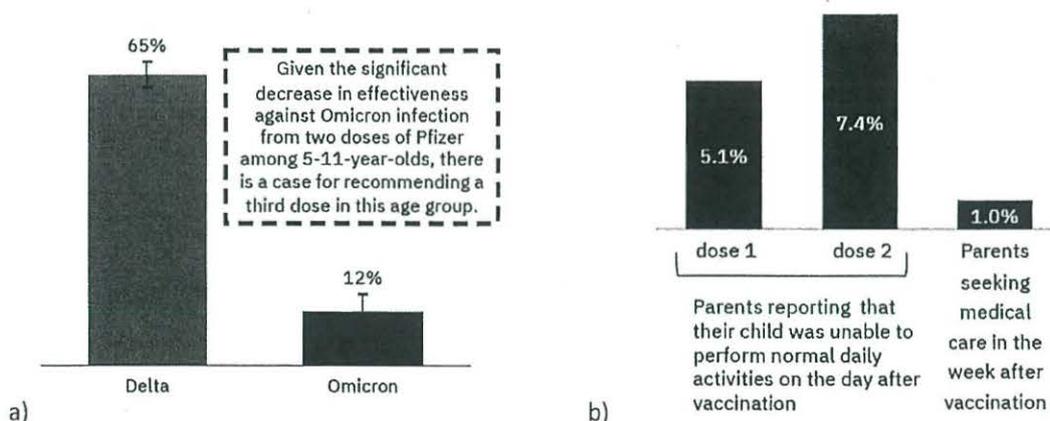
In New Zealand, some children aged 5 to 11 years who are severely immunocompromised will soon have completed their 2-dose series and will be seeking guidance on whether a third dose is required. Current available data suggests that Omicron has significantly reduced the effectiveness of two doses against infection, giving a case for a need for extra protection in those vulnerable to severe disease. Available safety data suggests that this would be safe.

Globally, some jurisdictions are now recommending that severely immunocompromised children aged 5 to 11 years receive a third primary dose of COVID-19 vaccine, in line with other severely immunocompromised age cohorts. This document presents an analysis of the evidence to support a third dose of the vaccine to immunocompromised 5-11-year-olds.

Immunogenicity and safety of a 3-dose COVID-19 vaccine post 2-dose series in paediatric populations who are immunocompromised

There is not currently safety data for third doses in the 5-11 age group. However, safety data for primary series in this age group (Figure 1a and b) and for older children, can be used to gain an impression of this.

Figures 1a and b. Effectiveness of two doses of Pfizer against infection among 5–11-year-olds [2]; primary series safety among 5–11-year-olds from a US study (% of parents reporting different outcomes after vaccination) [3] (Visualisation: Airfinity)



Immunogenicity: Canadian researchers highlighted four studies (n=105 persons) which reported on the immunogenicity after the second dose in paediatric populations [4-7] who were immunocompromised. Overall, the seroconversion rate after the second dose of the Pfizer-BioNTech vaccine was moderately reduced compared to paediatric populations who were not immunocompromised. Specific adolescent

populations had reduced seroconversion rates (patients with solid tumours, solid organ transplant recipients [5-7] and these conditions were also associated with a lower risk of seroconversion in an analogous review in the adult population [8].

Safety: Only two studies (n=38 persons) reported safety outcomes [6] [9]. The safety profile was similar to that observed in adult populations [3] who were immunocompromised; overall the vaccine was well tolerated. There were no cases of myocarditis observed in any study, although sample sizes were small.

Overall, there is limited data from adolescent populations who are immunocompromised, however the current data indicates a similar seroconversion rate after a second dose to adult populations who are immunocompromised, as well as a similar safety profile. [10]

A rapid review of the evidence was undertaken by Canadian researchers to study the effectiveness, immunogenicity and safety of a two- or three-dose primary series of a COVID-19 mRNA vaccine in pediatric populations who are severely immunocompromised (≤ 18 years of age). This review identified five observational studies from four countries (Canada, France, United Kingdom, US [n=2]) [4-6] [9]. A total of 179 persons who were moderately to severely immunocompromised were included (solid tumor [n=13], solid organ transplant [n=45], inflammatory bowel disease (IBD) patients receiving anti-TNF [n=68], heart transplant [n=26], and children with severe neurodisabilities [n=27]). There were no children under the age of 12 years included in any of the identified studies. All studies used the Pfizer-BioNTech mRNA COVID-19 vaccine; however, none of the studies reported VE. However, of importance to note, there were no children under the age of 12 years included in any of the identified studies.

Status of other jurisdictions – 3rd dose for severely immunocompromised 5-11-year-olds post a 2-dose primary series

Currently, Australia, the United States, Canada and the United Kingdom recommend a third dose of Pfizer for severely immunocompromised 5-11-year-olds post a 2-dose primary series.

- On 11 January 2022, the Australian Technical Advisory Group on Immunisation (ATAGI) advised that a third vaccine dose be offered to individuals aged 5-11 years who had severe immunosuppression. The recommended interval for a third primary dose for all age groups, is 2-6 months after the second dose. Conditions listed are covered in Appendix 1. [11].
- The US CDC [12] recommend that severely immunocompromised children aged 5 to 11 years receive a third primary dose of COVID-19 vaccine, to be given at least 4 weeks after the second dose.
- In Canada the recommendation is that children aged 5-11 year should be offered a third dose post a 2-dose primary series, and that this be given 4 to 8 weeks after the second dose. [10]
- The UK JCVI recommend a third primary dose be given to 5-11-year-olds at least 8 weeks after their second dose, however with special attention paid to current or planned immunosuppressive therapies. Where possible the third dose should be delayed until two weeks after the period of immunosuppression, in addition to the time period for clearance of the therapeutic agent. If not possible, consideration should be given to vaccination during a treatment 'holiday' or when the degree of immunosuppression is at a minimum. [13]

Appendix 1 - Updated ATAGI guidance on individuals who should be offered a third primary dose of the Pfizer COVID-19 vaccine as of February 2022 [11]

N.B. This list is not exhaustive. Clinicians may use their judgement for conditions or medications that are not listed, and which are associated with severe immunocompromise.

- Active haematological malignancy
- Non-haematological malignancy with current active treatment (e.g. chemotherapy, whole body irradiation)
- Solid organ transplant with immunosuppressive therapy
- Haematopoietic stem cell transplant (HSCT) recipients or chimeric antigen receptor T-cell (CAR-T) therapy within 2 years of transplantation.
 - These patients require *revaccination with 3 additional doses* of COVID-19 vaccine, irrespective of doses given prior to transplantation, commencing generally ≥ 3 -6 months after their transplant after discussion with their treating specialist.
 - Those beyond 2 years from transplant should discuss with their treating specialist about the need for a 3rd dose.
- Immunosuppressive therapies including:
 - High dose corticosteroid treatment equivalent to >20 mg/day of prednisone for ≥ 14 days in a month, or pulse corticosteroid therapy.
 - Multiple immunosuppressants where the cumulative effect is considered to be severely immunosuppressive.
 - Selected conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs):
 - including mycophenolate, methotrexate (≥ 10 mg/week), leflunomide, azathioprine (≥ 1 mg/kg day), 6-mercaptopurine (≥ 0.5 mg/kg/day), alkylating agents (e.g. cyclophosphamide, chlorambucil), and systemic calcineurin inhibitors (e.g. cyclosporin, tacrolimus).
 - excluding hydroxychloroquine or sulfasalazine when used as monotherapy.
 - Biologic and targeted therapies anticipated to reduce the immune response to COVID-19 vaccine. Refer to **Table 1** below for examples. However, clinicians may use their judgement for medications which are not listed.
- Primary immunodeficiency including combined immunodeficiency and syndromes, major antibody deficiency (e.g. common variable immune deficiency (CVID) or agammaglobulinemia), defects of innate immunity (including phagocytic cells), defects of immune regulation, complement deficiencies and phenocopies of primary immunodeficiencies.
- Advanced or untreated HIV with CD4 counts $<250/\mu\text{L}$ or those with a higher CD4 count unable to be established on effective anti-retroviral therapy.
 - a 3rd primary dose is not required for people living with HIV, receiving ART with CD4 counts $\geq 250/\mu\text{L}$.
- Long term haemodialysis or peritoneal dialysis.

Request for Advice (RfA)

Table 1(a): A 3rd dose is recommended for people taking the following biologics

Class	Examples
Anti-CD20 antibodies	rituximab, obinutuzumab, ocrelizumab, ofatumumab
BTK inhibitors	ibrutinib, acalabrutinib, zanubrutinib
JAK inhibitors	tofacitinib, baricitinib, ruxolitinib
Sphingosine 1-phosphate receptor modulators	fingolimod, siponimod
Anti-CD52 antibodies	alemtuzumab
Anti-complement antibodies	eculizumab
Anti-thymocyte globulin	anti-thymocyte globulin

Table 1(b): A 3rd primary dose is not recommended for people taking the following biologics*

Class	Examples
Anti-integrins	natalizumab, vedolizumab
Anti-TNF- α antibodies	infliximab, adalimumab, etanercept, golimumab, certolizumab
Anti-IL1 antibodies	anakinra
Anti-IL6 antibodies	Tocilizumab
Anti-IL17 antibodies	secukinumab, ixekizumab
Anti-IL4 antibodies	dupilumab
Anti-IL23 antibodies	ustekinumab
Immune checkpoint inhibitors	nivolumab, pembrolizumab, ipilimumab, atezolizumab

*A 3rd primary dose is recommended for people taking multiple immunosuppressants where the cumulative effect is considered to be severely immunosuppressive.

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Next Steps	Share with CV TAG
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In the development of this work, the following parties have been consulted with:	Airfinity
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Resources used:	
Ministry of Health Policies and Procedures	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
External Health Scientific organisations	<input type="checkbox"/> Yes <input type="checkbox"/> No
Existing database of RFAs	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Internal Ministry of Health Advice	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
External Expert Advice	<input type="checkbox"/> Yes <input type="checkbox"/> No
Literature Review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

This is the exhibit marked "GT-9" referred to in the annexed Affidavit of **GEORGE IAN TOWN** affirmed at **Christchurch** this 10th day of **June 2022** before me:



Memo

Solicitor of the High Court of New Zealand

Emma Louise Spratt
Solicitor
Christchurch

Third Primary Pfizer mRNA COVID-19 vaccine dose in the immunocompromised: COVID-19 Vaccine Technical Advisory Group (CV TAG) Updated recommendations

Date:	17 November 2021
To:	Joanne Gibbs, Director of National Operations, COVID Vaccine Immunisation Programme
From:	Dr Ian Town, Chief Science Advisor
For your:	Consideration

Purpose of report

1. To summarise the COVID-19 Vaccine Technical Advisory Group's (CV TAG) updated recommendations on the use of a third primary Pfizer mRNA COVID-19 vaccine dose in those who are severely immunocompromised.

Background and context

2. On 21 September 2021, CV TAG issued recommendations for a third primary Pfizer mRNA COVID-19 vaccine dose in the immunocompromised. CV TAG recommended that:
 - a. Those with severe immunocompromise be offered an additional dose of the Pfizer vaccine. The list of eligible individuals is taken from the one developed by the UK's Joint Committee on Vaccination and Immunisation (JCVI).[1]
 - b. The additional dose should be administered more than 8 weeks after the second dose, with special attention paid to current or planned immunosuppressive therapies. Where possible, the third primary dose should be delayed until 2 weeks after the period of immunosuppression, in addition to the time period for clearance of the therapeutic agent. If not possible, consideration should be given to vaccination during a treatment 'holiday' or at a nadir of immunosuppression between doses of treatment.
 - c. The administration of an additional dose is covered by s25 of The Medicines Act 1981, and as such, should only be offered by an authorised prescriber with informed consent from the consumer.
 - d. The standard two-dose course of vaccine should be offered to any eligible unvaccinated household contacts aged 12 and over, of immunocompromised individuals.
3. Since then, the Australian Technical Advisory Group on Immunisation (ATAGI) issued updated guidance on the use of a third primary dose of COVID-19 vaccine in individuals who are severely immunocompromised.[2]

4. The Ministry has also received requests for a revised list of individuals from rheumatologists, haematologists, and gastroenterologists.
5. Accordingly, CV TAG met on 9 November 2021 to update recommendations for the use of a third primary Pfizer COVID-19 vaccine dose in the immunocompromised, based on the recently released ATAGI guidance.

Recommendations

6. CV TAG recommend that:
 - a. All individuals aged 12 years and over who are severely immunocompromised should be offered a third primary dose of the Pfizer vaccine.
 - i. The updated guidance on individuals who should be offered a third primary dose of the Pfizer COVID-19 vaccine is provided in Appendix 1. The list is not exhaustive but provides guidance on scenarios where a consumer should receive a third primary dose. The list may expand or be modified over time as more evidence emerges. Advice for clinicians on the guidance is available through the Immunisation Advisory Centre, and this information will be updated periodically through the Immunisation Handbook.
 - ii. Clinical judgement should be applied by the prescriber to determine whether a third primary dose is required for conditions or medicines that are not listed that are associated with severe immunocompromise.
 - b. The third primary dose should be administered from 8 weeks after the second dose but can be administered from 4 weeks after the second dose after consideration of current or planned immunosuppressive therapies.
 - i. For time limited immunosuppressive treatment, where possible the dose should be delayed until 2 weeks after the period of immunosuppression, in addition to the time period for clearance of the therapeutic agent.
 - ii. For long term immunosuppressive treatment, consideration should be given to vaccination during a treatment 'holiday'.
 - c. Pfizer is the preferred vaccine in New Zealand for the third primary dose. AstraZeneca can be used for the third dose if a significant adverse reaction has occurred after a previous mRNA vaccine dose which contraindicates further doses of mRNA vaccine (e.g. anaphylaxis, myocarditis).
 - d. The administration of a third primary dose is covered by s25 of The Medicines Act 1981, and as such, should only be offered by an authorised prescriber with informed consent from the consumer.
 - e. The third primary dose should be distinguished from the booster dose. Those aged over 18 who are immunocompromised and have received a third primary dose of a COVID-19 vaccine should only receive a booster dose 6 months after completion of their primary course (i.e., 6 months after their third dose). The booster dose can be spaced strategically to allow for optimal dosing in the immunocompromised.
 - f. The standard two-dose course of vaccine should be offered to any eligible unvaccinated household contacts (aged 12 and over) of immunocompromised individuals.

7. CV TAG will continue to monitor all relevant information and will update their recommendations as further evidence becomes available.

Ian G Town

Dr Ian Town

Chief Science Advisor and

Chair of the COVID-19 Vaccine Technical Advisory Group

Appendix 1

Updated guidance on individuals who should be offered a third primary dose of the Pfizer COVID-19 vaccine

Note: This list has been updated based on the recent ATAGI guidance. It is not exhaustive but provides guidance on scenarios where a consumer should receive a third primary dose. Drug dose, disease activity, and co-morbidity can affect the severity of immunocompromise. The list may expand or be modified over time as more evidence emerges. Advice for clinicians on the guidance is available through the Immunisation Advisory Centre, and this information will be updated periodically through the Immunisation Handbook.

- Clinical judgement should be applied by the prescriber to determine whether a third primary dose is required for conditions or medicines that are not listed below that are associated with severe immunocompromise.
 - Conversely, clinicians may decide that individual patients with conditions or medicines listed below are at low risk of being severely immunocompromised and do not require a third primary vaccine dose.
1. Individuals with primary or acquired immunodeficiency states at the time of vaccination due to conditions including but not limited to (see note above):
 - a. acute and chronic leukaemias, and clinically aggressive lymphomas (including Hodgkin's lymphoma) who were under treatment or within 12 months of achieving cure.
 - b. individuals under follow up for chronic lymphoproliferative disorders including haematological malignancies such as indolent lymphoma, chronic lymphoid leukaemia, myeloma, Waldenstrom's macroglobulinemia and other plasma cell dyscrasias.
 - c. immunosuppression due to HIV/AIDS with a current CD4 count of <200 cells/ μ l for adults or children 12 years of age and over.
 - d. primary or acquired cellular and combined immune deficiencies – those with lymphopaenia (<10⁹ lymphocytes/L) or with a functional lymphocyte disorder.
 - e. those who had received an allogeneic (cells from a donor) or an autologous (using their own cells) stem cell transplant in the previous 24 months.
 - f. those who had received a stem cell transplant more than 24 months ago but had ongoing immunosuppression or graft versus host disease (GVHD).
 - g. persistent agammaglobulinaemia (IgG <3g/L) due to primary immunodeficiency (for example, common variable immunodeficiency) or secondary to disease/therapy.
 2. Individuals on, or recently on, immunosuppressive therapy at the time of vaccination including but not limited to (see note above):
 - a. receiving immunosuppressive therapy for a solid organ transplant.
 - b. received within the previous 6 months rituximab or other B cell-depleting biologic therapy for autoimmune or autoinflammatory disease.
 - c. received within the previous 3 months other biologics or targeted therapy for autoimmune or autoinflammatory disease. Examples are provided in **Table 1** and are

- based on the ATAGI list. Clinicians may use their judgement for medicines which are not listed.
- d. received within the previous 6 months cytotoxic chemotherapy or immunosuppressive radiotherapy for any indication.
3. Individuals with chronic immune-mediated inflammatory disease who were receiving or had received immunosuppressive therapy prior to vaccination including but not limited to (see note above):
 - a. high dose or long-term moderate dose corticosteroids. Indicative dosage thresholds are provided in **Table 2**.
 - b. immunosuppressants:
 - i. including mycophenolate, methotrexate, leflunomide, thiopurines (e.g., azathioprine), 6-mercaptopurine, alkylating agents (e.g., cyclophosphamide, chlorambucil), and systemic calcineurin inhibitors (e.g., cyclosporin, tacrolimus). Clinical judgement should be applied by the prescriber to determine whether a third primary dose is required.
 - ii. excluding hydroxychloroquine, sulfasalazine, or mesalazine, when used as monotherapy
 - c. combinations of immunosuppressive therapy where the cumulative effect is considered to be severely immunosuppressive, as determined by clinical judgement.
 4. Individuals receiving long term haemodialysis or peritoneal dialysis should be offered a third primary dose of the Pfizer COVID-19 vaccine.

Table 1: Examples for biologics

A third primary dose **is recommended** for people taking the following biologics

Class	Examples
Anti CD 20 antibodies	rituximab, obinutuzumab, ocrelizumab
BTK inhibitors	ibrutinib,
JAK inhibitors	ruxolitinib
Sphingosine 1-phosphate receptor modulators	fingolimod
Anti-CD52 antibodies	alemtuzumab
Anti-complement antibodies	eculizumab
Anti-thymocyte globulin	anti-thymocyte globulin
A third primary dose is not routinely recommended for people taking the following biologics*	
Anti-integrins	natalizumab
Anti-TNF-α antibodies	infliximab, adalimumab, etanercept
Anti-IL1 antibodies	anakinra
Anti-IL6 antibodies	tocilizumab
Anti-IL17 antibodies	secukinumab
Anti-IL4 antibodies	dupilumab
Anti-IL23 antibodies	ustekinumab
Immune checkpoint inhibitors	nivolumab, pembrolizumab, ipilimumab, atezolizumab

*A third primary dose is recommended for people taking multiple immunosuppressants where the cumulative effect is considered to be severely immunosuppressive.

Table 2: Indicative dosage thresholds for corticosteroids

A third primary dose **is recommended** for:

- a. Individuals with chronic immune-mediated inflammatory disease:
 - i. on high dose corticosteroids (equivalent to ≥ 20 mg prednisone per day for more than 10 days, in the previous month)
 - ii. on long-term moderate dose corticosteroids (equivalent to ≥ 10 mg prednisone per day for more than 4 weeks, in the previous 3 months)
- b. Individuals who had received high-dose steroids (equivalent to >40 mg prednisone per day for more than a week) for any reason, in the previous month

A third primary dose **is not routinely recommended** for:

- a. Individuals who had received brief immunosuppression (equivalent to ≤ 40 mg prednisone per day), for example, asthma / chronic obstructive pulmonary disease / COVID-19)
- b. Individuals receiving low dose locally acting steroids (inhaled or topical)
- c. Individuals on replacement corticosteroids for adrenal insufficiency

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Interim report 2021

COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB)

This is the exhibit marked "GT-10" referred to in the annexed Affidavit of **GEORGE IAN TOWN** affirmed at **Christchurch** this 10th day of **June 2022** before me:


Solicitor of the High Court of New Zealand

Emma Louise Sprott
Solicitor
Christchurch

Published April 2022

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Definitions

Adverse Event Following Immunisation (AEFI)

An AEFI is an untoward medical event which follows immunisation and does not necessarily have a causal relationship with the administration of the vaccine. The adverse event may be an unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

Adverse events of special interest (AESI)

An AESI is a pre-specified medically significant event that has the potential to be causally associated with the vaccine product based on past experience, the technology used to make the vaccine or the infection the vaccine is used to protect against. AESIs need to be carefully monitored and any potential association to vaccination confirmed by further analysis and studies.

Safety signal

Information on a new or known adverse event that may be caused by the vaccine and requires further investigation. Safety signals can be detected from a wide range of sources such as AEFI reports, clinical studies and scientific literature.

Serious adverse event following immunisation

An AEFI is considered serious if it:

- is a medically important event or reaction
- requires hospitalisation or prolongs an existing hospitalisation
- causes persistent or significant disability or incapacity
- is life threatening
- causes a congenital anomaly/birth defect
- results in death.

It is possible for different people to have experienced the same event but for the report to be serious for one person and non-serious for another person, depending on the impact or outcome of the event in each person.

Causality assessment

Systematic review and evaluation of available data about the AEFI to determine the likelihood of a causal association between the event(s) and the vaccine received.

1 Overview

Cases investigated (up to 28 November 2021)

The AstraZeneca COVID-19 vaccine is not included in this overview because the data thus far is extremely limited, and an update will be provided in the new year (see Section 7).

Number of AEFIs reported in the COVID CARM database: **39,973**

Number of Pfizer/BioNTech doses administered: **7,498,139**

Total number of serious cases reported to COVID CARM	Serious cases presented to CV-ISMB	Safety signals investigated
1,593	508	18

Type of incidents reported

AEFI type	Number reported	Cases presented to CV-ISMB*
Hospitalisation	662	187
Medically Significant	543	123
Died	123	123
Life Threatening	91	45
Persisting Disability	149	27
Congenital effect	3	3
Non-serious	38,379	227

*Cases presented to CV-ISMB have been primarily for signal review. Individual events have not been evaluated by the Board for causality.

CV-ISMB meetings

Members recruited

16

Meetings held

16

Number of recommendations

28

NOTE: Given that more than 3.7 million people in New Zealand have been vaccinated, a number of medical events will occur coincidentally in the period following vaccination and this should be taken into consideration when reading this report.

1.1 Introduction

In 2020, the New Zealand government secured advanced purchase agreements for a portfolio of four different COVID-19 vaccines (Pfizer/BioNTech, AstraZeneca, Janssen and Novavax), with a view for delivery to the population in 2021.

The COVID-19 Vaccine and Immunisation Programme (CVIP) is delivering New Zealand's largest ever immunisation programme, to vaccinate as many eligible people as possible throughout 2021. The COVID-19 vaccine rollout commenced in New Zealand in February 2021 with the Pfizer/BioNTech vaccine.

The CVIP's purpose is to make the best use of any vaccines, to support the immediate health response and to help achieve the COVID-19 vaccine strategy longer-term outcomes which include:

- sufficient supply of a safe and effective vaccine to achieve population immunity to COVID-19, affordably
- protection for Māori, Pacific peoples, and population groups at particular risk from COVID-19
- full cultural, social and economic recovery from the impacts of COVID-19
- recognition of New Zealand as a valued contributor to global wellbeing and the COVID-19 response
- New Zealand, Pacific and global preparedness for response to future disease outbreaks.

The COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB) was established in February 2021. The purpose and function of the Board is to provide expert advice on the safety of the COVID-19 vaccine(s) to the Centre for Adverse Reactions Monitoring (CARM), Medsafe, the CVIP and the Ministry of Health during the rollout across Aotearoa New Zealand.

Seven Pacific countries have been offered access to New Zealand's vaccine portfolio: Fiji, the three Realm countries (Cook Islands, Niue and Tokelau), and Samoa, Tonga and Tuvalu. The Board is also providing support to these countries if requested.

Key areas of focus for the Board include:

- support with assessment of potential causal links between reported adverse events following immunisation (AEFI) and COVID-19 vaccines
- review of all serious and significant AEFI for the COVID-19 vaccines that are presented for expert opinion (this includes all fatal reports)
- advice to Medsafe and the CVIP in relation to the balance of benefits and risks for potential safety signals under investigation and whether further action is needed
- ensuring that equity is a key consideration for the collection, monitoring and reporting of AEFI for the COVID-19 vaccines.

Further detailed information about the role/function, composition, workplan, reporting and duties/responsibilities of the Board and its members is available within the Terms of Reference (Appendix 1).

1.2 Members

The Chair and other members of the Board are drawn from experts in various fields of clinical medicine, biostatistics, microbiology and immunology. The Board also holds a position for a lay member (non-healthcare professional) to represent the interests of the consumer. The composition of the CV-ISMB is as follows:

- a neurologist
- two general practitioners (one in urban practice, one in rural practice)
- a cardiologist
- a clinical pharmacologist
- two biostatisticians
- a haematologist
- a paediatrician
- a consumer
- a general medicine specialist
- two immunologists
- a clinical microbiologist
- an obstetrician and gynaecologist
- a rheumatologist.

The Chairperson of the COVID-19 Vaccine Technical Advisory Group (CV-TAG) is an ex-officio (non-voting) member of the Board and attends meetings to provide a link between CV-TAG and the CV-ISMB. The Director of the New Zealand Pharmacovigilance Centre (NZPhvC) attends meetings to present case details to the Board. Technical experts from Medsafe and the CVIP also attend to present information on safety signals under investigation and other safety surveillance work for the COVID-19 vaccines.

1.2.1 Chair and Deputy Chair

Mr John Tait (Chair) (MB, MS, FRCOG, FRANZCOG)

Mr Tait is an obstetrician and gynaecologist who has worked in Wellington since 1986. He is the current Chief Medical Officer at Capital & Coast and Hutt Valley District Health Boards. Prior to this role he was the Executive Director Clinical, Surgery, Women's and Children's. Mr Tait is the Chair of the Perinatal & Maternal Mortality Review Committee (PMMRC), Vice President of the Asia and Oceania Federation of Obstetricians and Gynaecologists (AOFOG) and an ex-officio member of the National Maternity Monitoring Group. Mr Tait provides expertise in the field of obstetrics.

Honorary Associate Professor Hilary Longhurst (Deputy Chair) (MA, FRCP(UK), PhD, FRCPATH)

Dr Longhurst is a clinical immunologist at Auckland District Health Board. She has extensive experience in treating allergic and immunological problems, with particular interests in immune deficiency, rare angioedemas and telomere biology disorders. Throughout her career, she has worked closely with patient groups on research aimed at developing better treatments and improving health for those with rare immunological disorders. Dr Longhurst provides expertise in the field of immunology, including those with immune deficiency and allergy.

1.2.2 Current members

Dr Nick Cutfield (MBChB, FRACP, MD(RES))

Dr Cutfield is the Clinical Director of Neurology and Clinical Neurophysiology at Southern District Health Board. He is a Clinical Senior Lecturer at the Dunedin School of Medicine, University of Otago. Dr Cutfield is the Director of the New Zealand Creutzfeldt-Jakob Disease surveillance registry and the Director of the Brain Research New Zealand Dementia Prevention Research Clinic (Dunedin). He was previously the Clinical Deputy Director of the University of Otago Brain Health Research Centre and Member of the Neurological Foundation of New Zealand Scientific Advisory Committee. Dr Cutfield provides expertise in the field of neurology.

Associate Professor Matt Doogue (BSc, MBChB, DipPaeds, FRACP)

Associate Professor Doogue is a clinical pharmacologist, Clinical Director of the Department of Clinical Pharmacology at the Canterbury District Health Board (CDHB) and a physician on general medicine at CDHB. He is a clinical academic at the University of Otago, Christchurch, with interests including adverse drug reactions, clinical decision support, therapeutic drug monitoring and medical education. He is vice-chair of the International Union of Basic and Clinical Pharmacology (IUPHAR) clinical division. Dr Doogue provides expertise in the field of clinical pharmacology.

Dr Kyle Eggleton (BHB, MBChB, MMedSci, MPH, PhD, DipObstMedGyn, DipPaeds, DIH, FRNZCGP(Dist))

Dr Eggleton is a rural general practitioner at Hauora Hokianga in Northland. He is also Associate Dean of Rural Health at the University of Auckland. Dr Eggleton has worked as a general practitioner in rural Whangārei, Ruakākā and Rawene, mostly working for Māori health providers. He sits on a number of governance boards including the Northland District Health Board. Dr Eggleton provides expertise in the field of rural general practice and equity.

Professor Chris Frampton (BSc Hons, PhD)

Professor Frampton is a part time biostatistician within the departments of Psychological medicine and Medicine at the University of Otago, Christchurch. He is a member of the Standing Committee on Therapeutic Trials (SCOTT), the PHARMAC Cancer Treatments Subcommittee (CaTSoP) and the Medicines Assessment Advisory Committee (MAAC). Professor Frampton is a member of the invited faculty for the Australasian Clinical Oncology Research Development (ACORD) and the international Collaboration for Research Development in Oncology (CREDO) workshops, run biennially in Australia and annually in India. His specific research focus is on the design, conduct and analysis of randomised controlled trials (RCTs) and he serves on many international data safety monitoring committees overseeing multi-national RCTs. Professor Frampton provides expertise in the field of biostatistics.

Dr Maryann Heather (BHB, MBChB, MAvMed, DipOccMed, PGCertTravMed, PGCertHsC(SportsMed), FRNZCGP)

Dr Heather is a general practitioner working at Etu Pasifika Auckland. She has worked in Australia, Samoa, American Samoa, and China. She is also an emerging Pacific Health researcher and Senior Lecturer in Pacific Health at the School of Population Health, Faculty of

Medical and Health Sciences, University of Auckland, and a GP teacher and student supervisor in Pacific Health, Public Health and General Practice. She is a member of the Pacific GP network, Pacific Chapter Royal New Zealand College of General Practitioners (RNZCGP), executive committee member Auckland Faculty RNZCGP, Goodfellow Unit Advisory Board Member (Pacific), Pasifika Medical Association Governance Membership Board (Director), Influenza Working Group (Pacific and Primary Care), RUAG Pharmac (Medicines Equity in Primary Care - Pacific), COVID-19 Pacific Response media team, Science Media Centre advisory team (Pacific), NZ Breast Cancer Foundation Medical Advisory Committee (Primary Care and Pacific), Health Research Council (HRC) Co-opted panel assessment committee (Primary Care and Pacific). Dr Heather brings expertise in Primary Care, Pacific Health and Health Equity.

Dr Tom Hills (MBChB, MSc, DPhil, FRACP)

Dr Tom Hills is a University of Otago-trained clinical immunologist, with a doctorate in rapid response vaccine design from the University of Oxford. His clinical work is in Auckland, with a research appointment at the Medical Research Institute of New Zealand in Wellington. Dr Hills provides expertise in the fields of immunology and clinical trials.

Professor Thomas Lumley (PhD, FRSNZ)

Professor Lumley is the Chair in Biostatistics in the Department of Statistics at the University of Auckland and an Affiliate Professor in the Department of Biostatistics at the University of Washington. He has a wide range of research interests in theoretical and applied biostatistics. Professor Lumley also chairs the HRC Data Monitoring Core Committee, which provides data monitoring to publicly funded clinical trials in New Zealand. He is a Fellow of the Royal Society of New Zealand and of the American Statistical Association. Professor Lumley provides expertise in biostatistics.

Ms Saskia Schuitemaker (MSocSc, PGDipPsych(Comm))

Ms Schuitemaker is the Coordinator of the Child and Mortality Review Group (CYMRG) under the Māori, Equity and Health Improvement Directorate at the Waikato District Health Board. She was previously employed as a Health Consumer Service Facilitator of health consumer complaints. Ms Schuitemaker served as a lay member representing consumer interests on the Waikato Medical Ethics Committee for six years. She is also informed by her work as a Community Magistrate and Community Development Advisor. Ms Schuitemaker is a lay member (non-health professional) who provides a consumer lens.

Dr Owen Sinclair (MBChB, MPH, FRACP)

Dr Sinclair is a consultant General Paediatrician and Paediatric Emergency Medicine specialist working at Waitakere District Health Board. He is of Māori descent (Te Rarawa). He lectures in Māori health at the University of Auckland and is the lead for the Māori support network of Te Kāhui Mātai Arotamariki o Aotearoa, the Paediatric Society of New Zealand. He has completed research looking into ethnic inequalities in health, including vaccine preventable disease in children, and Māori attitudes to immunisation. He has given multiple presentations on the causes of ethnic inequalities in health in New Zealand and overseas. Dr Sinclair provides expertise in the fields of paediatrics and Māori health.

Professor Lisa Stamp (MBChB, PhD, DipMus, FRACP)

Professor Stamp is a consultant rheumatologist at Christchurch Hospital and an academic rheumatologist and Associate Dean of Research at the University of Otago, Christchurch. She is Director of the Canterbury Rheumatology and Immunology Research Group. Professor Stamp provides a rural clinic in Kaikōura and is a member of PHARMAC's Pharmacology and Therapeutics Advisory Committee (PTAC). Her research interests include gout and rheumatoid arthritis, and she has published over 170 papers in these areas. Professor Stamp received the Value of Medicines NZ prize in 2017 for her world leading work in the use of allopurinol. Professor Stamp provides expertise in the field of rheumatology.

Honorary Professor Ralph Stewart (MD, FRACP, FCSANZ, FESC)

Dr Stewart is a cardiologist at Auckland City Hospital and the Auckland Heart Group, and an Honorary Professor of Medicine at the University of Auckland. He is past Chairman of the New Zealand Division of the Cardiac Society of Australia and New Zealand, and of the National Cardiac Network, and is a member of a number of national and international cardiology and research organisations. Dr Stewart provides expertise in the field of cardiology.

Dr Anja Werno (MD, PhD, MBA, FRCPA, FFSc)

Dr Werno was born and raised in Germany where she graduated in medicine in 1993. She was granted her Microbiology Fellowship (Royal College of Pathologists of Australasia, RCPA) in 2004. Dr Werno's longstanding research interest is reflected in an MD in the field of HIV (University of the Saarland, Germany), her PhD in the field of invasive pneumococcal disease (University of Otago), and her recent admission as a Fellow of the Faculty of Science (RCPA) on the grounds of scientific achievement. Since the start of the SARS-CoV-2 pandemic, Dr Werno has been a member of the Ministry of Health's Science and Technical Advisory Expert Network. From 2017 to 2020 she chaired the NZ Microbiology Network and was a nominated representative on Australia's Public Health Laboratory Network (PHLN). She is currently employed as a clinical microbiologist, the Acting Clinical Director of Microbiology and Chief of Pathology & Laboratories at Canterbury Health Laboratories and as a Clinical Senior Lecturer at the Christchurch School of Medicine, University of Otago. Dr Werno provides expertise in the fields of microbiology and pathology.

Dr Laura Young (MBChB, PhD, FRACP, FRCPA)

Dr Young is a clinical haematologist at Auckland District Health Board (ADHB) with an honorary lecturer appointment at the University of Auckland. She works predominantly in the Thrombosis Unit and Haemophilia Centre in Cancer and Blood at ADHB. She has a PhD and has clinical and translational research interests in this area. Dr Young provides expertise in the field of haematology.

Dr Enver Yousuf (BSc, MB BS, Dip Pharm Med, FFPM)

Dr Yousuf obtained his medical degree in the United Kingdom (UK) in 1994 and has worked in New Zealand (NZ) since 2008. He is an expert in pharmaceutical medicine and is a Fellow of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians UK. He has experience working on medicine and vaccine safety in NZ and internationally. Dr Yousuf provides expertise in the field of general medicine and pharmaceutical medicine.

1.2.3 Conflicts of interest

The European Medicines Agency (EMA) policy on the handling of competing interests of scientific committees' members and experts was used to determine conflicts of interest prior to a member's appointment to the Board, and for participation in subsequent meetings (where required).

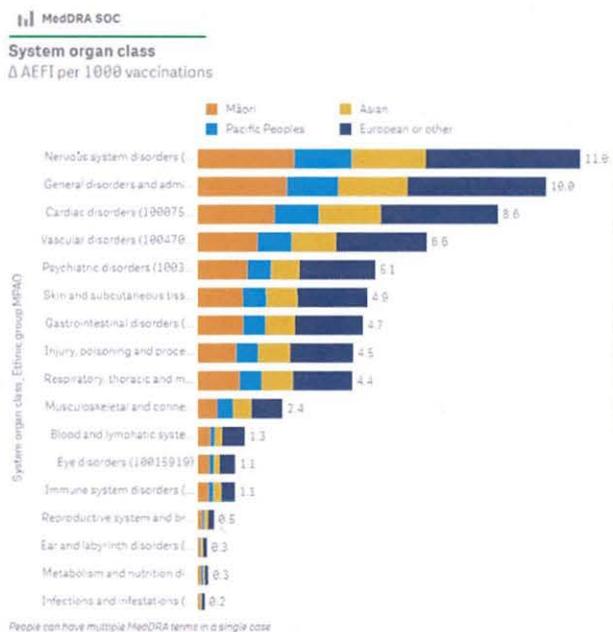
1.3 Equity

A primary focus of the Board is to ensure that equity is a key consideration in the collection, monitoring and reporting of AEFI to uphold the Crown's commitment to Te Tiriti o Waitangi and achieving equitable health outcomes for all people in Aotearoa New Zealand.

The Board includes expertise to represent the interests of Māori and Pasifika. The Board also includes two general practitioners (one in urban practice and one in rural practice), along with a lay member (non-healthcare professional) to represent the interests of the consumer.

An overview of AEFI reporting is regularly provided to the Board, with consideration given to reporting by ethnicity, age, gender and geographic location. Qlik Applications are being utilised to allow visualisation of safety data for the COVID-19 vaccines. Following feedback from the Board, the Qlik application for AEFI reporting was updated to allow standardisation of reported AEFI by ethnicity for events reported. An example of this is provided in Figure 1 below.

Figure 1: Visualisation from Qlik app of reported AEFIs per 1000 vaccinations by systemic organ class and ethnicity.



Source: Ministry of Health Qlik app. Data extracted 28 November 2021.

2 Safety signals investigated

A safety signal is information on a new or known adverse event that may be caused by the vaccine and requires further investigation. Safety signals can be detected from a wide range of sources such as CARM reports, clinical studies and scientific literature.

The assessment of safety signals establishes if there is a causal relationship between the vaccine and the reported adverse event.

As part of the assessment and evaluation of a safety signal, Medsafe considers:

- cases reported to CARM
- relevant information in the literature
- observed versus expected analysis if background rate is available
- Safety Reports the sponsor
- information from other international regulatory authorities.

Safety signals for the COVID-19 vaccines are presented and discussed with the CV-ISMB. Recommendations from the Board can include:

- continuing to monitor through routine pharmacovigilance
- Monitoring communication from Medsafe
- Alert communication from Medsafe
- updating the label (data sheet and consumer medicine information)
- holding or stopping the immunisation programme.

To date, Medsafe has evaluated 18 safety signals for the Pfizer/BioNTech vaccine. Once recommendation(s) have been made and implemented, safety signal investigations are considered closed. An investigation can be re-opened if needed, for example, if there is an increase in the number of reported cases (ie, menstrual disorders or unexpected vaginal bleeding) or further information is obtained from other regulatory agencies and the sponsor (ie, myocarditis). Table 1 provides a summary of these investigations, including information on the number of times a safety signal has been discussed by the Board, the outcome of the investigation, the most recent date it was presented to the Board, and any resulting recommendations/actions.

Table 1. Summary of investigations into possible safety signals

Safety signal (no. of times presented to board)	Outcome	most recent time considered	Cases reviewed	Explanation	Regulator action
Thrombosis with thrombocytopenia syndrome (TTS) (1)	Unlikely association. Continue to monitor. See also the Monitoring communication.	22/04/21	0	The Board was reassured by the international experience with the Pfizer/BioNTech vaccine which has been widely used in several countries, and the local experience in New Zealand to date, which did not identify a risk with the Pfizer/BioNTech vaccine. A Monitoring communication was recommended to reassure people that Medsafe is aware of the association between TTS and the Janssen and AstraZeneca COVID-19 vaccines. The safety of the Pfizer/BioNTech vaccine is being monitored closely for this issue.	Y
Appendicitis (1)	Unlikely association. Continue to monitor.	27/05/21	1	The Board agreed that current evidence does not suggest a safety signal for appendicitis, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Anaphylaxis (6)	Associated with any vaccine. Continue to monitor. Implement anaphylaxis checklist.	24/06/21	41	The Board agreed that if the numbers continue to track similarly (around 10 cases per million doses) that there is no need to continue to review in this forum.	Y
Pancreatitis (1)	Possible association. Continue to monitor.	24/06/21	1	The Board noted the individual had a previous history of pancreatitis, which is a known risk factor for future episodes. The Board acknowledged that it is not always going to be possible to determine the underlying cause of some events.	N
AEFIs in the elderly (1)	Unlikely association. Continue to monitor. Data sheet updated.	21/07/21	N/A*	The Board noted that even if elderly have limited life expectancy, vaccination can still help protect both the individual and those around them. It was also noted that most elderly who are competent to consent are willing to be vaccinated. Given there is no clear signal indicating that death is a consequence of vaccination, it is important to ensure they have the opportunity to be vaccinated. The Board recommended wording be included in the data sheet around consideration of the risk/benefit profile for vaccination of frail elderly consumers.	Y

Safety signal (no. of times presented to board)	Outcome	most recent time considered	Cases reviewed	Explanation	Regulator action
Seizure (1)	Unlikely association. Continue to monitor.	21/07/21	31	The Board agreed that the current data does not suggest a safety signal for seizures, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Tinnitus (1)	Unlikely association. Continue to monitor.	25/08/21	34	The Board noted that tinnitus occurs commonly in the general population, with the underlying cause in most cases remaining unknown. The description of tinnitus can vary between people and may be observed more frequently in individuals with anxiety due to heightened awareness. It was agreed that the current evidence did not present a concern at this stage, but that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Glomerular diseases (1)	Unlikely association. Continue to monitor.	25/08/21	15	The Board agreed that there was no particular concern at this stage regarding glomerular disease, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Guillain-Barré Syndrome (GBS) (1)	Possible association. Continue to monitor.	25/08/21	3	The Board agreed that current evidence does not suggest a safety signal for GBS. Some cases are expected to occur in the weeks following vaccination due to the background incidence of GBS. Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Thrombocytopenia (1)	Possible association. Continue to monitor.	25/08/21	5	The Board agreed that the data at this stage is reassuring, with low case numbers, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Thrombosis (blood clots) (2)	Unlikely association. Continue to monitor.	04/10/21	121	The Board agreed that current evidence does not suggest a safety signal for thrombosis, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	Y
Myocarditis/pericarditis (7)	Associated with the vaccine. Information has been added to Comirnaty data sheet. See also the Alert communication	27/10/21	10	Myocarditis has been shown nationally and internationally to be a rare side effect of the Pfizer/BioNTech vaccine, with current evidence suggesting most cases are mild and self-limiting. Given that COVID-19 induces myocarditis at a higher rate than the vaccine, the risk/benefit consideration is still in favour of vaccination. Medsafe and the Board continue to monitor this issue closely.	Y

Safety signal (no. of times presented to board)	Outcome	most recent time considered	Cases reviewed	Explanation	Regulator action
Menstrual disorder (2)	Unlikely association. Continue to monitor. See also the Monitoring communication.	27/10/21	9	The Board noted that due to how commonly menstrual disorders occur in the population generally, the most convincing data comes from the clinical trials where there is a control group. The Board discussed the merits of providing communications to the public to give reassurance that menstrual disorders have not been found to be linked to vaccination and any changes that occur after vaccination are likely to be temporary, with no evidence to suggest these temporary changes will impact on fertility.	Y
Pregnancy related outcomes (1)	Unlikely association. Continue to monitor. See the Monitoring communication.	27/10/21	2	The Board noted the concerning data emerging from the UK relating to COVID-19 infection (Delta variant) in unvaccinated pregnant woman, with several cases resulting in stillbirth. In contrast, the current data does not suggest any association between the vaccine and miscarriage or congenital abnormalities. The Board recommended a communication be issued advising that the available information for the use of the Pfizer/BioNTech vaccine in pregnancy had been reviewed with no safety concerns identified.	Y
Stroke (2)	Unlikely association. Continue to monitor.	17/11/21	80	The Board agreed that current evidence does not suggest a safety signal for stroke, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Erythema multiforme (1)	Unlikely association. Continue to monitor.	17/11/21	10	The Board agreed that current evidence does not suggest a safety signal for erythema multiforme, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Herpes zoster (2)	Probable association. Continue to monitor.	15/12/21	46	The Board agreed that current evidence does not suggest a safety signal for herpes zoster, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
AEFIs in children (12+) (2)	Unlikely association. Continue to monitor	15/12/21	N/A*	The Board agreed that the current data does not suggest a safety concern for AEFIs in children (12+), and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N

*Rather than looking at individual cases, these presentations focussed on overall trends within these groups. Cases are included in reviews for other safety signal investigations where applicable.

2.1 Anaphylaxis

Hypersensitivity to the active ingredient or to any of the excipients is the only contraindication for the Pfizer/BioNTech vaccine (Comirnaty). In addition, the [data sheet](#) includes the following warning and precaution for hypersensitivity and anaphylaxis, as below.

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of COMIRNATY.

The individual should be kept under close observation for at least 15 minutes following vaccination. A second dose of COMIRNATY should not be given to those who have experienced anaphylaxis to the first dose of COMIRNATY.

The Board considered anaphylaxis in their first few meetings. Early in the vaccine rollout, when only a small number of people had been vaccinated, CARM had received three potential reports of anaphylaxis. This gave a reporting rate of 3 reports per 20,000 doses given. From a clinical perspective, these events had been managed appropriately. However, anaphylaxis is a rare post-vaccination event for other vaccines, with a reporting rate of 3 to 5 cases per million doses given.

On 11 March 2021, the Board recommended that all potential anaphylaxis reports be assessed against the Brighton Collaboration Criteria for anaphylaxis to determine whether a reaction constitutes anaphylaxis. The Anaphylaxis Tabular Checklist (Appendix 2) was presented to the Board by CARM as a proposed mechanism to evaluate reported cases of anaphylaxis for the CVIP. The checklist incorporates the Brighton criteria and allows for the collection of detailed information at the time of the event to support medical assessment. The checklist was endorsed by the Board as a useful document, and this was implemented by CARM. In a memo to the CVIP Steering Group on 7 May 2021, the Board recommended that consideration be given to the checklist being made available at vaccination sites. This was agreed and implemented by the CVIP.

In subsequent meetings (April to June), CARM provided an overview of the anaphylaxis reports received to date, including Brighton level, dose number, and time to onset. On 24 June 2021, the Board considered the rate of anaphylaxis according to the case definition (Brighton level 1-3). They noted that this data was reassuring, with a similar rate as that reported by the Centers for Disease Control (CDC) in the United States (US). The Board recommended that CARM should continue to monitor reports of anaphylaxis and only bring this safety issue back to the Board if there is a spike in reporting, or unusual cases reported.

2.2 Myocarditis

Myocarditis was first presented and discussed with the Board on 27 May 2021, at which point CARM had received two case reports of potential myocarditis in association with the Pfizer/BioNTech vaccine. At this time there was limited overseas data, with other regulatory agencies continuing to investigate. The sponsor's evaluation had not identified myocarditis as a potential safety signal, and they were continuing to monitor the concern. The Board recommended that Medsafe continue to monitor this closely. Medsafe published a [Monitoring Communication](#) issued on 9 June 2021, to provide reassurance and encourage reporting of any suspected myocarditis cases following the Pfizer/BioNTech vaccine.

A further update was provided to the Board on 24 June 2021, based on data from the CDC. The data showed young males in the US were experiencing higher rates of myocarditis than expected for the 12 to 24 years (significantly higher) and 25 to 39 years (slightly higher) age groups, with more reactions occurring after the second dose. There was also a higher rate of myocarditis for females following the second dose in the 12 to 24 years age group, however this wasn't as pronounced as the difference observed in males. The CDC had conducted rapid cycle analyses for myocarditis/pericarditis following administration of mRNA COVID-19 vaccines (Moderna and Pfizer/BioNTech) and concluded that the benefits clearly outweighed the risks.

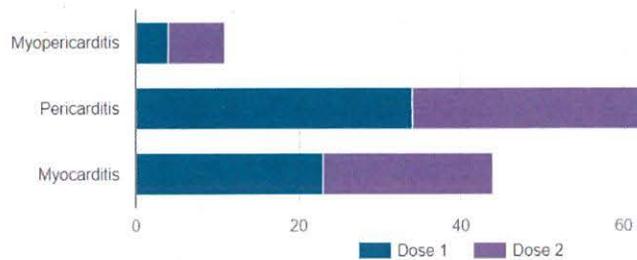
On 21 July 2021, Medsafe published an [Alert communication](#) for myocarditis and pericarditis as rare adverse reactions of the Pfizer/BioNTech vaccine. Based on international evidence and cases of myocarditis and pericarditis reported in New Zealand following the Pfizer/BioNTech vaccine, the [data sheet](#) and [consumer medicine information](#) were updated on 28 July 2021 to include myocarditis and pericarditis as rare adverse events, as below.

Very rare cases of myocarditis and pericarditis have been observed following vaccination with COMIRNATY. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The Board continues to receive regular updates from Medsafe on the number of myocarditis and pericarditis cases (including myopericarditis) reported in New Zealand, with analysis of trends by dose, age range of individuals, and time to onset. As reported in Medsafe's [COVID-19 Vaccine Safety Report #33](#), up to 14 October 2021, CARM had received 61 reports of clinically confirmed myocarditis or pericarditis after dose one and 57 reports after dose two. The number of reports is shown in Figure 2 below.

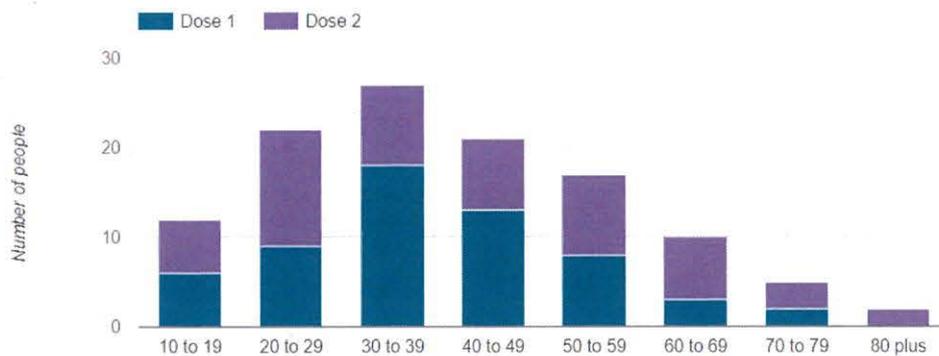
Figure 2. Number of reports of myocarditis and pericarditis after dose 1 and dose 2 of the Pfizer/BioNTech vaccine, up to 14 October 2021



Source: Medsafe. 2021. *Adverse events following immunisation with COVID-19 vaccines: Safety Report #33 – 16 October 2021*. URL: <https://www.medsafe.govt.nz/COVID-19/safety-report-33.asp>.

In 61 reports the sex was noted as female, and male in 57 reports. Ethnicity, when reported, was 84% European or other, 10.5% Asian, 4.5% Māori and 1% Pacific Peoples. The age of those reported to have experienced myocarditis or pericarditis after dose 1 or dose 2 is shown in Figure 3.

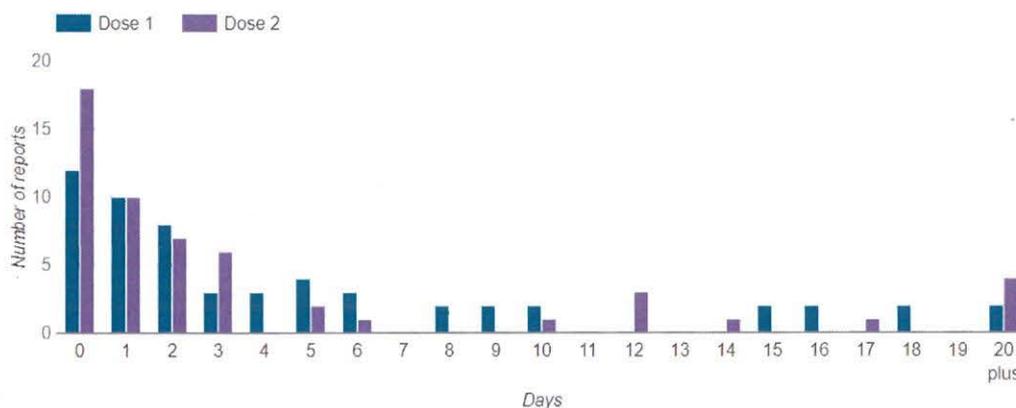
Figure 3. Age range of people reported to have experienced myocarditis or pericarditis after vaccination, up to 14 October 2021



Source: Medsafe. 2021. *Adverse events following immunisation with COVID-19 vaccines: Safety Report #33 – 16 October 2021*. URL: <https://www.medsafe.govt.nz/COVID-19/safety-report-33.asp>.

The time between vaccination and the first symptoms was generally within the first five days after vaccination (Figure 4).

Figure 4. Time between vaccination and first symptoms, up to 14 October 2021



Source: Medsafe. 2021. *Adverse events following immunisation with COVID-19 vaccines: Safety Report #33 – 16 October 2021*. URL: <https://www.medsafe.govt.nz/COVID-19/safety-report-33.asp>.

There have been two reports of likely vaccine-mediated myocarditis with a fatal outcome. The coroner is investigating these reports. See Section 3.2 for further details about these reports.

2.3 Menstrual bleeding or unexpected vaginal bleeding

In June 2021, the Board considered menstrual disorders or unexpected vaginal bleeding as a potential safety signal for the Pfizer/BioNTech vaccine. At this time, CARM had received 22 reports of menstrual disorders or unexpected vaginal bleeding. The Board considered that the available evidence does not suggest an increased risk of these disorders following vaccination with the Pfizer/BioNTech vaccine. Medsafe will continue to monitor reports of menstrual disorders and unexpected vaginal bleeding.

Due to public interest and an increase in the number of reported cases (503 reports of menstrual disorders or unexpected vaginal bleeding up to 7 October 2021), this topic was brought back to the Board in October 2021 for review. The Board concluded that there was insufficient information to confirm a safety signal for menstrual disorders or unexpected vaginal bleeding with the Pfizer/BioNTech vaccine. Pfizer had also recently performed an in-depth analysis of heavy menstrual bleeding and postmenopausal bleeding and did not find a signal.

The Board recommended a communication from Medsafe on this topic to highlight that these disorders are common and can have many causes; and that any changes after COVID-19 vaccination are likely to be temporary, with no evidence that these temporary changes will impact future fertility. Medsafe published a [Monitoring communication](#) on 17 November 2021.

2.4 Use of the Pfizer/BioNTech vaccine in pregnancy

In May 2021 the COVID-19 Vaccine Technical Advisory Group (CV-TAG) recommended that pregnant people should be routinely offered COVID-19 vaccination at any stage of pregnancy.

There is a high level of public interest for the use of the COVID-19 vaccines in pregnancy, along with misinformation around this topic and the vaccine's effect on fertility. Therefore, it was important that the Board review the available information for use of the Pfizer/BioNTech vaccine in pregnancy, specific to the New Zealand context.

Medsafe presented the available data to the Board on 27 October 2021. The Board noted that there did not appear to be any concerns from the reported events to date for the use of the Pfizer/BioNTech in pregnant women. The Board also noted that pregnant women with symptomatic COVID-19 infection appear to have an increased risk of a more severe outcome (eg, ICU admission) in comparison with non-pregnant women of reproductive age and may also be at increased risk of preterm birth.

Medsafe will continue to closely monitor the use of the Pfizer/BioNTech vaccine in pregnancy through routine pharmacovigilance activities. The Board recommended that the CVIP send a communication to vaccinators around the risk/benefit considerations for the use of the Pfizer-BioNTech vaccine in pregnancy. Medsafe also published a [Monitoring communication](#) on 17 November 2021, stating that there are no safety concerns for the use of the Pfizer/BioNTech vaccine in pregnancy.

2.5 AEFIs in the elderly

In May 2020 a [Norwegian study](#) investigated reports of death in frail and elderly individuals residing in care home facilities after receiving the Pfizer/BioNTech vaccine. The review concluded that a causal link between the Pfizer/BioNTech vaccine and death was considered "likely" in 10 of the 100 cases, "possible" in 26 cases, and "unlikely" in 59 cases. The remaining five were deemed "unclassifiable." While emphasising considerable uncertainty around its conclusions, the authors acknowledged that adverse reactions from the vaccine in very frail elderly patients could initiate a cascade of complications, which in the worst-case scenario could lead to earlier death.

Based on this study, Medsafe conducted a review of the New Zealand data on AEFIs in the elderly to understand if these differed from other age groups, both in terms of the type of AEFIs reported and the severity. Medsafe presented a summary of the data to the Board on 21 July 2021. The Board concluded there was insufficient evidence to suggest that the vaccine had a disproportionate negative impact in the elderly compared to other age groups. However, the Board recommended an update to the [data sheet](#) around consideration of the risk/benefit profile for this age group, as below.

The data for use in the frail elderly (>85 years) is limited. The potential benefits of vaccination versus the potential risk and clinical impact of even relatively mild systemic adverse events in the frail elderly should be carefully assessed on a case-by-case basis.

3 Ad-hoc meetings

In addition to regular meetings every 3 to 4 weeks, the Board has the provision to hold ad-hoc meetings to discuss any urgent safety concerns that arise. An ad-hoc meeting of the Board would be triggered in the following circumstances:

- An urgent issue arising internationally that could threaten the stability of the CVIP
- A report of a serious unexpected event where further expert advice is urgently required by CARM, Medsafe or the CVIP.

The Board has held three ad-hoc meetings. The first was to discuss the concern developing overseas in relation to reports of thrombosis with thrombocytopenia syndrome (TTS) with the Janssen and AstraZeneca vaccines. The other two meetings have been following reports of potential vaccine-mediated myocarditis that resulted in death.

3.1 Thrombosis with thrombocytopenia syndrome safety concern

An ad-hoc meeting to discuss TTS was held on 22 April 2021. The purpose of the meeting was to discuss:

- if a similar risk has been identified in New Zealand
- whether the Pfizer/BioNTech vaccine is associated with this concern
- if it would be beneficial to provide information on this clotting/bleeding syndrome for the public, and if so, what communication would be needed.

At the time, a haematologist was not appointed to the Board and so Dr Laura Young was engaged to provide expert advice in this capacity. Dr Young was formally appointed as a Board member in August 2021, following an increase in the number of thrombotic and bleeding events reported for the Pfizer/BioNTech vaccine and the potential for New Zealand to start using the Janssen or AstraZeneca COVID-19 vaccines.

The Board considered the available information for TTS and was reassured by the extensive international experience with the Pfizer/BioNTech vaccine and the local experience to date in New Zealand. No risk was identified with the Pfizer/BioNTech vaccine. The Board recommended a [Monitoring communication](#) to reassure people that Medsafe is aware of the association between TTS and the Janssen and AstraZeneca COVID-19 vaccines, and that the safety of the Pfizer/BioNTech vaccine is being monitored closely for this issue but no such link has been identified.

3.2 Vaccine-mediated myocarditis death

The Board held an ad-hoc meeting on 9 August 2021 to discuss a fatal report of concern in an individual following COVID-19 vaccination.

On 2 August 2021, CARM received a report from a forensic pathologist for a woman who had passed away approximately four days after their first dose of the Pfizer/BioNTech vaccine. Myocarditis was a finding of the post-mortem examination that had not been recognised prior, with follow-up investigations indicating that the myocarditis could have been temporally associated with the individual's vaccination event.

At the 9 August 2021 meeting, the Director of CARM provided an overview of the case followed by a presentation from the forensic pathologist of their findings to date. The Board had also received an expert opinion from Dr Ralph Stewart, a cardiologist recently appointed to the Board.

The Board considered the potential causes of the individual's myocarditis, including the Pfizer/BioNTech vaccine, and noted the following.

- The Pfizer/BioNTech vaccine and some other COVID-19 vaccines increase the risk of myocarditis; Medsafe issued an [Alert communication](#) on 21 July 2021.
- COVID-19 infection increases the risk of myocarditis substantially more than COVID-19 vaccination.
- There are many possible causes of myocarditis, the most common being viral infection. Over 100 people are discharged from hospital with a principal diagnosis of myocarditis in New Zealand every year.
- In this case, other factors have been identified that may have potentially caused the myocarditis or led to a more severe myocarditis.
- The individual had no symptoms prior to the vaccine and the symptoms of myocarditis developed in the days immediately following the first vaccine dose.

The Board concluded that based on the currently available information, the vaccination event was the likely cause of the myocarditis. The Board considered that the circumstances of this case do not impact or change the known information on myocarditis, and the benefits of vaccination with the Pfizer/BioNTech vaccine for COVID-19 continue to greatly outweigh the risks of this rare side effect.

The forensic pathologist sent histology slides to cardiac pathologists in the United Kingdom (UK) and United States (US) for review to confirm the myocarditis type. Feedback received from the UK cardiac pathologist agreed with the findings of the case. Review from the US was still pending at the time the Board issued their statement; however, it was considered that this would not change the viewpoint taken by the Board.

The Board recommended that the Ministry of Health advise clinicians to be aware of myocarditis and pericarditis symptoms. The Ministry of Health issued a [media release](#) on 30 August 2021.

3.3 Potential vaccine-mediated myocarditis deaths

The Board met on 8 December 2021 to discuss three fatal reports of concern in individuals following COVID-19 vaccination.

In the week commencing 29 November 2021, CARM received three fatal reports for individuals who passed away in the period following vaccination, where vaccine-mediated myocarditis was proposed as the cause of death.

Two of the reported cases are under investigation by the coroner and were reported to CARM by the pathologists. The third case was reported to CARM by the district health board (DHB), following a review by their Adverse Reactions Committee.

High level details of the cases are presented below.

- A 26-year-old man who passed away 12 days after their first dose of the vaccine. He was reported to be experiencing symptoms that could be indicative of myocarditis in the days preceding death, however, medical attention was not sought.
- A young person who passed away 11 days after their second dose of the vaccine.
- A man in his 60s who passed away approximately one month after the second dose of the vaccine. The individual's death was not considered to be linked to the vaccine. However, following a review by the DHB, the death was reported due to the temporality of the vaccination event.

At the 8 December meeting, the Director of CARM provided an overview of the cases to the Board. The pathologist investigating the case of the 26-year-old and the forensic pathologist investigating the case of the young person both attended the meeting and presented their findings to date.

The death of the young person was discussed at length, however the Board considered that further information from pending investigations was needed before a determination on the role of the Pfizer/BioNTech vaccine could be made. A further ad-hoc meeting to discuss this case will be held once this information becomes available.

On review of the case of the man in his 60s, the Board considered the myocarditis was unlikely related to the vaccination event. The time from vaccination to the onset of symptoms and clinical factors point to other causes and is not consistent with a causal link.

The Board considered the death of the 26-year-old man and noted the following.

- There were no reported symptoms prior to the administration of the Pfizer/BioNTech vaccine, and the symptoms of myocarditis developed in the days following the first dose.
- The individual was reported to not have sought medical advice or treatment for their symptoms.
- Myocarditis is a treatable condition, if identified, and outcomes are better the earlier that treatment is started.

Based on the available information, the Board concluded that the vaccination event was the likely cause of the myocarditis in the 26-year-old man. The Board made the following recommendations to the CVIP around communications.

- Updating communications to the public on symptoms of potential myocarditis and pericarditis (eg, is chest pain sufficient or is this better reflected as chest pain, tightness and/or chest discomfort?).
- Ensuring that information on side effects is detailed at the time of vaccination; individuals need to be provided with verbal and written information about what to expect after their COVID-19 vaccine. This should include discussion of common and rare side effects and when/where/how an individual can seek medical advice.
- An update to the healthcare sector, in particular vaccinators, Whakarongorau, general practitioners and emergency departments, about the risk of myocarditis with the Pfizer/BioNTech vaccine and myocarditis signs/symptoms.

The Board considered that the circumstances of these cases did not impact or change the known information on myocarditis, and the benefits of vaccination with the Pfizer/BioNTech vaccine for COVID-19 continue to greatly outweigh the risks of this rare side effect.

The Board also noted that Medsafe was actively engaging with other international regulators to understand whether they have received similar reports.

On 20 December 2021, the Board [issued a statement](#) outlining the findings of the 8 December meeting.

4 CV-ISMB working group

The Ministry allocated resources to create a monitoring tool that allows for near real-time investigation of AESIs following immunisation. The monitoring tool compares cases observed at a particular point in time to what would be expected based on background rates. The CV-ISMB working group was set up to refine the logic used in these analyses and to provide guidance on any follow-up safety signal investigations. Based on the advice of the working group, the hospital discharge records were further interrogated to do specific signal investigations based on international concerns.

4.1 Members

The CV-ISMB working group consists of volunteers from the Board and a representative from Medsafe (Table 2).

Table 2: CV-ISMB working group members and expertise

Name	Expertise
Honorary Associate Professor Hilary Longhurst (ISMB Deputy Chair)	Clinical immunologist
Associate Professor Matt Doogue	Clinical pharmacologist
Professor Thomas Lumley	Biostatistics
Honorary Professor Ralph Stewart	Cardiologist
Dr Enver Yousuf	General medicine and pharmaceutical medicine
Dr Susan Kenyon (Manager Clinical Risk, Medsafe)	Medsafe representative

4.2 Observed vs expected analysis (rapid cycle analysis)

Rapid Cycle Analysis (RCA) allows for near real time detection of AESIs by calculating the relative risk (RR) at a specific point in time from observed and expected rates within specific risk windows. To do this effectively, criteria used to measure these AESIs must be individualised. For example, the onset time of a particular disease could influence the risk window, or a subset of the population might be at higher risk. The CV-ISMB working group has agreed to help refine the criteria used to detect a select amount of AESIs for COVID-19 vaccines. The Board provided further feedback on publishing mortality rates following vaccination with the Pfizer/BioNTech vaccine in Medsafe's [COVID-19 Vaccine Safety Report #36](#).

4.3 Specific safety questions

Based on reports of vaccine-mediated myocarditis, the CV-ISMB working group requested further interrogation of the hospital discharge records to investigate whether people with a pre-existing heart condition were at a higher risk of death following immunisation. The working group was engaged to provide further insight and technical expertise to approach this problem.

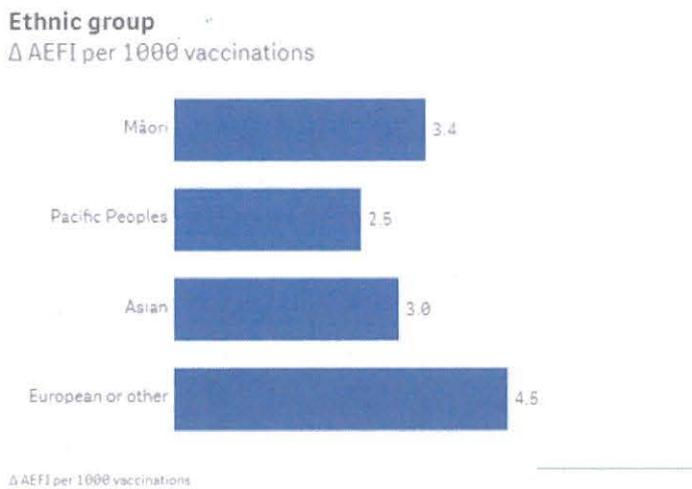
Several approaches were used to assess the risk following vaccination with the Pfizer/BioNTech vaccine. The preliminary data suggests that people with a pre-existing heart condition are not at increased risk of mortality following vaccination.

5 Under-reporting of AEFIs

Vaccine uptake significantly increased through August and early September 2021. On 15 September 2021, Medsafe provided an overview of reported adverse events by ethnicity to the Board.

Underreporting for Pacific Peoples was noted, with a reporting rate of 0.25%, while the reporting rates for Māori (0.34%) and Asian (0.3%) were also lower than the overall reporting rate (see Figure 5). There was no clear difference in the types of AEFI reported by ethnicity. However, a lack of engagement with consumer reporting for Pacific Peoples was evident, based on the significantly lower proportion of consumer reports for Pacific Peoples (16.7%) compared to all groups combined (31.0%) (see Figure 6 and Figure 7; consumer reports are labelled as Public:Patient).

Figure 5. Reporting rate by ethnic group, up to 14 September 2021



Source: Ministry of Health Qlik app.

Figure 6. Overall reporter type, up to 14 September 2021

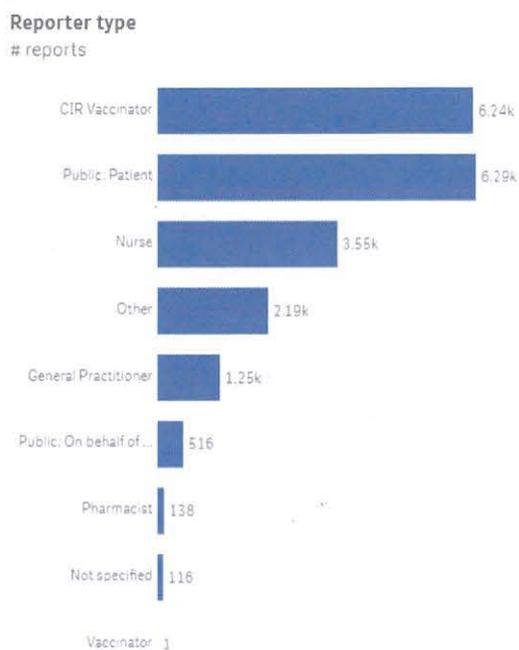
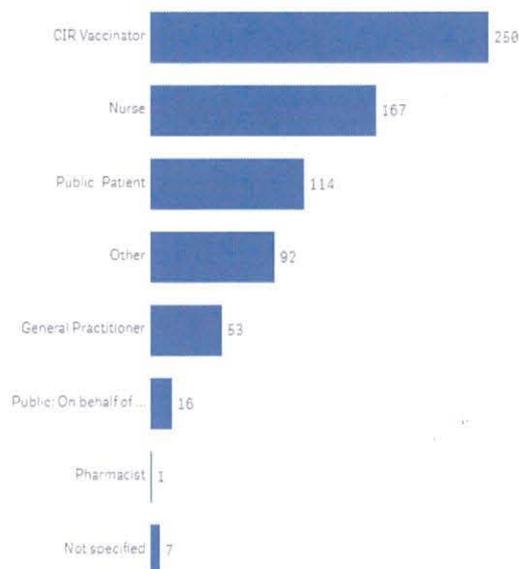


Figure 7. Pacific Peoples* reporter type, up to 14 September 2021



* Refers to the ethnicity of the patient, not the reporter.

Source: Ministry of Health Qlik app.

The Board recommended communicating to the public around underreporting of AEFIs in Pacific Peoples, along with guidance around the AEFI reporting process. If reporting is emphasised for Pacific Peoples, this would likely have a positive impact on reporting rates across in ethnicities. Consideration should also be given to translation of any communication, to enable better access to information.

The National Director, CVIP agreed to this recommendation, and it is being actively worked on in the Programme by Post Event, Equity, and Communications. Ideas being explored include:

- increased messaging at vaccination sites around the 'why' for adverse event reporting
- capturing AEFIs through alternative approaches other than consumers completing the CARM webform (eg, healthcare professionals and vaccinators reporting on behalf of consumer)
- general communications targeted to consumers and healthcare professionals explaining the importance of reporting for COVID-19 vaccines and how to make a report.

6 ISMB support to Pacific countries

6.1 Participating countries

The Realm countries (Cook Islands, Niue and Tokelau) have used Pfizer/BioNTech vaccine doses donated by New Zealand for their respective vaccine rollouts. Vaccinations commenced on 18 May 2021 in the Cook Islands for their 16+ year-old population, with Niue and Tokelau following two months later. The requirement from Pfizer for donating the vaccine to these countries was dependent on the New Zealand Ministry of Health providing adequate pharmacovigilance support. This included receiving, documenting, anonymising, and assessing all AEFIs, and reporting these back to Pfizer.

Conversely, Samoa, Tonga and Fiji had received other vaccines for their general populations and received support from New Zealand related to training, cold storage and consumables. These countries later received donations of the Pfizer/BioNTech vaccine for their younger population (ranging from 12 to 17 years, see Table 3). These countries already had adequate pharmacovigilance capabilities, and only required support with reporting AEFIs back to Pfizer and accessing medical advice for treatment and management of serious AEFIs. A secure Microsoft Teams channel has been created to facilitate direct reporting of AEFIs to Pfizer, and the Immunisation Advisory Centre (IMAC) medical advisors are providing medical advice to Samoa, Tonga and Fiji as needed.

6.2 Role of the CV-ISMB

The Director-General of Health (DG) established the Board for the purposes of providing technical advice on the safety of COVID-19 vaccines during the rollout across Aotearoa New Zealand. The Board also provides support to the Pacific countries that were offered access to Aotearoa New Zealand's vaccine portfolio. The Board's expertise, specifically their knowledge around adverse events following the Pfizer/BioNTech vaccine, is invaluable for a successful vaccine rollout in these countries.

The Board's support was crucial for the three Realm countries, because these countries have limited domestic capacity and capability to meet the Pfizer pharmacovigilance system requirements for vaccine dose donation. Support was also extended to Samoa, Tonga, and Fiji, even though their pharmacovigilance systems were more advanced.

Table 3 provides a summary of the vaccine rollout in these countries, and AEFI reporting to date.

Table 3. Countries receiving CV-ISMB support, and summary of the Pfizer/BioNTech vaccines donated, data to 21 December 2021

Country	Date vaccine rollout started (Pfizer only)	Doses administered	Population receiving Pfizer (years)	AEFIs	CV-ISMB advice requested
Cook Islands^a	18 May 2021	23,049	12+	91	None
Niue^a	10 Jun 2021	2,352	12+	8	None
Tokelau^a	19 Jul 2021	1,936	12+	21	None
Samoa^{a,b}	25 Oct 2021	41,669	12–17	15	None
Tonga^{a,b}	22 Oct 2021	24,375	12–17	31	None
Fiji^b	15 Nov 2021	25,049	12–14	0	None

a. Includes pregnant women who are eligible

b. Samoa, Tonga and Fiji used different vaccines for their adult populations.

7 AstraZeneca COVID-19 vaccine use in New Zealand

Medsafe provisionally approved the AstraZeneca COVID-19 vaccine on 22 July 2021. In October/November 2021, the Programme recognised that a second vaccine was needed for people who:

- had experienced a serious adverse event after their first dose of the Pfizer/BioNTech vaccine and were advised not receive the second dose of this vaccine
- preferred a different type of vaccine technology (viral vector rather than mRNA).

Following a recommendation by CV-TAG, Cabinet approved the use of the AstraZeneca vaccine in New Zealand. The vaccine became available for use on 29 November 2021.

Medsafe will bring an overview of the New Zealand safety data for the AstraZeneca vaccine to the Board in late January 2022.

8 Conclusion

In 2021, the CV-ISMB has held 16 meetings (including three ad-hoc meetings) to review and discuss safety data for the COVID-19 vaccines.

The data cut-off for this report is 28 November 2021, at which point only the Pfizer/BioNTech vaccine was available in New Zealand. More than 7 million doses of the Pfizer/BioNTech vaccine had been administered and almost 90 percent of the eligible population (12 years and older) had received two doses of the Pfizer/BioNTech vaccine. The Programme also recommended a third dose for immunocompromised (primary course) people and Medsafe approved a booster dose for adults.

The Board has considered 18 safety signals for the Pfizer/BioNTech vaccine, which has led to 28 recommendations to either Medsafe or the Programme. To date, only one safety signal has been confirmed, with myocarditis and pericarditis identified as very rare adverse reactions to the Pfizer/BioNTech vaccine. Information about myocarditis and pericarditis was added to the vaccine data sheet in July 2021.

Sadly, there have been two deaths likely associated with the Pfizer/BioNTech vaccine. The coroner is still investigating, but vaccine-mediated myocarditis was implicated as the cause of death in both cases. Following review of both cases, the Board issued statements in August and December 2021 advising the public and healthcare professionals to be aware of the signs and symptoms of myocarditis. Based on the information presented for the second case in December 2021, the Board also made recommendations to the Programme around the importance of communications for myocarditis.

The Board continues to closely monitor myocarditis cases reported in New Zealand along with the international evidence. The Board considers that the benefits of vaccination with the Pfizer/BioNTech vaccine continue to greatly outweigh the risks of this rare adverse reaction. In early 2022, Medsafe along with the Programme will commence a study to follow up reported cases of myocarditis and pericarditis in New Zealand, which will further enhance our understanding of this adverse reaction and its impact.

Other safety signals reviewed throughout 2021 for the Pfizer/BioNTech vaccine have included anaphylaxis, thrombosis, stroke, menstrual disorder, herpes zoster and tinnitus. For all of the safety signals, the Board recommended that Medsafe should continue monitoring these respective events through routine pharmacovigilance activities. The Board also reviewed the available safety data around the use of the Pfizer/BioNTech in pregnancy, with no concerns identified. Vaccine use in pregnancy will continue to be a key focus for the Board, Medsafe and the Programme as this data continues to mature in 2022. The Board continues to closely monitor the safety data of the Pfizer/BioNTech vaccine in children. Available data for children aged 12 years and older was reviewed in September and December 2021 and no concerns were identified. Vaccine use in children will be another key focus area for 2022.

Given the large proportion of the population being vaccinated in a relatively short period of time, there is an expected background level of adverse events occurring in close temporality to

the vaccination event. However, the Board has been reassured by both the international and New Zealand data presented, that the Pfizer/BioNTech vaccine is a very safe vaccine.

Looking ahead to 2022 will see safety data available for the AstraZeneca COVID-19 vaccine, along with the administration of booster doses for most of the population, 18 years and older and the rollout of the Pfizer/BioNTech vaccine in younger children (aged 5–11 years).

Appendix 1

Terms of Reference of the COVID-19 Vaccine Independent Safety Monitoring Board

1. Introduction

Given the desire to clearly indicate the independence of this group from the rest of the COVID-19 Vaccine & Immunisation Programme (CVIP), Medsafe and the Ministry of Health, the group is to be named the COVID-19 Vaccine Independent Safety Monitoring Board.

These Terms of Reference establish the Independent Safety Monitoring Board (the Board) to support the COVID-19 Vaccine and Immunisation Programme and set out the:

- role and functions of the Board
- composition of the Board
- term and workplan requirements
- reporting requirements
- terms and conditions of appointment
- duties and responsibilities of Board members.

2. Functions of the Board

The purpose and function of the Board is to provide expert advice on the safety of COVID-19 vaccine(s) during the rollout across Aotearoa New Zealand and in support of Fiji and the six Polynesian countries: the three Realm countries (Cook Islands, Niue, Tokelau) and Samoa, Tonga and Tuvalu offered access to Aotearoa New Zealand's vaccine portfolio. The Board does not have powers of veto, direction, or instruction actual or implied.

The Board is to be a pool of experts convened to:

- assess potential causal links between adverse events following immunisation (AEFI) and adverse events of special interest (AESI) and COVID-19 vaccines;
- review all serious or significant AEFIs presented for expert opinion;
- provide expert advice to Medsafe, the CVIP, Ministry of Health and if requested the Health Authorities within the six Polynesian countries and Fiji in relation to the balance of benefits and risks (ie, safety or efficacy) of COVID-19 vaccines;
- consider information about the safety of COVID-19 vaccines that is referred to the Board by the Centre for Adverse Reactions Monitoring (CARM) and/or Medsafe and provide expert advice to Medsafe, the CVIP, Ministry of Health and, if requested, the Health Authorities within the six Polynesian countries and Fiji, on:
 - the interpretation of the information
 - the significance of the information in relation to the risk-benefit profile of the vaccine
 - whether an issue needs referral to the Medicines Adverse Reactions Committee (MARC) for advice or Medsafe should consider regulatory intervention
 - if a potential hold or stop to the CVIP is required

- confirming CVIP process and procedures;
- ensure that equity is a key consideration in the collection, monitoring and reporting of AEFI to uphold the Crown’s commitment to Te Tiriti o Waitangi and achieving equitable health outcomes for all people in Aotearoa New Zealand.

The ultimate decision(s) about regulatory intervention and the programme rollout within Aotearoa New Zealand will be made by Medsafe and the Ministry of Health respectively. The six Polynesian countries and Fiji will have their own government processes regarding their COVID-19 vaccination programmes.

3. Composition of the Board

The Chair and other members of the Board are drawn from experts in various fields of clinical medicine, microbiology, epidemiology and biostatistics.

The Board also holds a position for a lay person (non-healthcare professional) to represent consumer interests.

The term of membership will be determined by the CVIP. In making themselves available for appointment, members should ensure that:

- there is no conflict of interest which would preclude their appointment; and
- they are available to serve for the full term of their appointment.

Co-opted non-voting members

Not limited to the Director of the New Zealand Pharmacovigilance Centre (NZPhvC), a representative from the Immunisation Advisory Centre (IMAC), technical experts from Medsafe, the CVIP and from within the Ministry and representatives from Fiji and the six Polynesian countries can also have membership of the Board as needed.

Ex-Officio (non-voting)

Chairperson of COVID-19 Vaccine Technical Advisory Group.

4. Workplan development

The Board will not be asked to develop a work plan. Information will be presented to the Board for consideration and advice by CARM, Medsafe, the CVIP and the Ministry.

5. Reporting Requirements

The Board will make recommendations to the COVID-19 Vaccine and Immunisation Programme (CVIP) Steering Group, copied to Medsafe. Recommendations may also be made directly to Global Health, Ministry of Health regarding the six Polynesian countries and Fiji. Medsafe, the CVIP Steering Group and Global Health can discuss findings with the Chair of the Board.

When ad hoc meetings of the Board are held, summaries will be produced by the secretariat but not published. Summaries are subject to the Official Information Act 1982 (OIA), but any confidential information will be withheld.

The Chair of the Board will not be a direct media contact but will be available for public comment at the request and arrangement of the Ministry.

A report to the CVIP Steering Group and Medsafe will be provided at the Board's end date.

6. Establishment, Review process and End Date

The Board will be established by the Director General for the purposes of providing technical advice on the safety of COVID-19 vaccines during the rollout across Aotearoa New Zealand and in support of Fiji and the six Polynesian countries: the three Realm countries (Cook Islands, Niue, Tokelau) and Samoa, Tonga and Tuvalu offered access to Aotearoa New Zealand's vaccine portfolio.

The Board's Terms of Reference will be reviewed at 12 monthly intervals alongside the Ministry's annual stocktake of Ministerial and Ministry Groups.

7. Meetings

It is intended that the Board will do most of its work virtually via email and teleconferencing. If necessary, meetings will be held on an ad hoc basis. Meetings may be held face-to-face if necessary and appropriate. There may be a preliminary face to face meeting of the Board (COVID alert levels permitting) to consider data requirements and to be provided with an overview of the CVIP and strategy.

The Board will determine its own meeting frequency around the key milestones which may include but not limited to sequencing, change points and data report publications. The Board will be on call for any serious or significant adverse events during the rollout.

There may be, at the discretion of the chair, both open and closed sessions for the Board, the sequence of which will be determined by the Board. Open sessions will enable the attendance of co-opted non-voting members.

At any meeting of the Board most of the appointed members must be present to form a quorum (the ISMB membership is established at 14 members, so eight members form a quorum). All members forming the quorum must be eligible to vote, for example not abstaining from discussion due to a conflict of interest.

The dossier will be transmitted and accessed via a secure electronic file transfer system (EFT) made available to members where practical at least one week before each meeting to allow time for preparation. Information on urgent medicine safety issues will be sent to members where practical two days prior to the meeting.

The Secretariat of the Board is provided by the CVIP. The Secretariat will:

- process travel and expense claims
- process preparation and attendance fees
- prepare the agenda and dossier for each meeting
- prepare the minutes of each meeting
- report back to the Committee on action(s) taken since the previous meeting.

8. Duties and Responsibilities of a Member

Members have a commitment to work for the public of Aotearoa New Zealand. Members are accountable to the Ministry of Health. Board members ensure familiarity with and provide advice that is congruent with the principles of Te Tiriti o Waitangi to prioritise equitable health outcomes for Māori.

Board members attend meetings and undertake Board activities as independent persons responsible to the Board as a whole and are not representatives of professional organisations or communities. This issue is particularly important when Board members may, at times, be required to be party to decisions which conflict with the views of other organisations with which they are involved.

There is an expectation that members will attend all meetings and devote sufficient time to become familiar with the affairs of the Board and the wider environment within which it operates.

Members of the Board are asked to:

- ensure all activity and advice is undertaken with consideration of and respect for equity of outcomes across all people in Aotearoa New Zealand, including but not limited to; ethnicity, disability, geographic location, age, health, gender and socioeconomic position, living and working conditions;
- provide guidance for AEFI investigations so that the cause can be determined correctly;
- assess potential causal links between AEFIs and vaccines, using standard procedures;
- develop standard protocols for management of review of adverse events (ie, serious allergic reactions);
- members may nominate additional expertise if required, but these must be agreed by the chair and Ministry;
- provide guidance on potential signals of previously unrecognized vaccine-related adverse events and support further investigations to establish if causality exists;
- make recommendations to action any issues which may arise, communicate with national stakeholders and other national and international experts, when required.

9. Removal from the Board

The Ministry may, at any time and entirely at the Ministry's discretion, remove any member from the Board.

The Ministry may, at any time, exclude a member from discussions of the Board in the case of a conflict of interest.

10. Conflicts of Interest

Members should perform their functions in good faith, honestly and impartially and avoid situations that might compromise their integrity or otherwise lead to conflicts of interest. Proper observation of these principles will enable public confidence in the work of the Board to be maintained.

When members believe they have a conflict of interest on a subject which will prevent them from reaching an impartial decision or undertaking an activity consistent with the Board's functions, then they must declare a conflict of interest and absent themselves from the discussion and/or activity. This must be done at the earliest possible opportunity, in the regular agenda item around conflicts of interest, and at the point the relevant item of business comes up in the meeting.

The European Medicines Agency (EMA) policy on the handling of competing interests of scientific committees' members and experts will be used to determine conflicts of interest and participation in meetings.

11. Liability

Members are not liable for any act or omission done or omitted in their capacity as a member, if they acted in good faith, and with reasonable care, in pursuance of the functions of the Board.

12. Confidentiality

Meetings, including agenda material and minutes, are confidential. Members must ensure that the confidentiality of Board business is maintained.

Members are free to, and are expected to, express their own views within the context of meetings, or the general business of the Board. Members must publicly support a course of action decided by the Board, or if unable to do that, must not publicly comment on decisions.

At no time shall members divulge details of Board matters or decisions to people who are not members, or Ministry employees. Disclosure of Board business to anyone outside the Ministry must be the decision of the Ministry.

Board members must ensure that documents are kept securely to ensure that confidentiality is maintained. Release of correspondence or papers can only be made with the approval of the Ministry. At the end of a member's term, all Board information must be returned to the Ministry.

13. Remuneration and expenses

Members of the Board are paid fees for attendance at meetings, in accordance with the Cabinet Office Circular CO (12) 6 *Fees framework for members appointed to bodies in which the Crown has an interest* (or its successor circular).

The fee for Board members is currently \$865 per day and \$108 per hour for any part day (before tax) and this is reviewed annually.

Members who are employees of the wider State sector are not entitled to be paid fees for Board business if this is conducted during regular paid work time (ie, members cannot be paid twice by the Crown for the same hours).

Members are entitled to be reimbursed for actual and reasonable travelling and other expenses incurred in carrying out their duties. The expectation is that the standards of travel, accommodation, meals and other expenses are modest and appropriate to reflect public sector norms.

Appendix 2

Anaphylaxis Checklist for: Vaccinator

STEP 1. Record Patient Details:

Patient Name	NHI	CIR Adverse Event Code	Patient Phone No.

Adrenaline Given Time	Adrenaline Dose	Transfer to ED (Name)	Transfer Time

STEP 2. Record course of illness:

Must be able to check both 2.1 and 2.2 to meet any level of certainty for anaphylaxis.

- 2.1 SUDDEN ONSET of signs & symptoms** *"An event that occurred unexpectedly and without warning leading to a marked change in a subject's previously stable condition"*
AND
 2.2 RAPID PROGRESSION of signs & symptoms

STEP 3. Tick Symptoms and Signs:

Check all symptoms/signs present by ticking appropriate boxes in rows below.
 Anaphylaxis requires two or more body systems involved.

Body System	B. Major Criteria	C. Minor Criteria	
Skin <i>*Excluding hereditary angioedema</i>	<input type="checkbox"/> Generalized urticaria (hives) <input type="checkbox"/> Generalized erythema <input type="checkbox"/> Angioedema* (general or localized including lip) <input type="checkbox"/> Generalized pruritus WITH skin rash	<input type="checkbox"/> Localized injection site urticaria <input type="checkbox"/> Red AND itchy eyes <input type="checkbox"/> Generalized prickle sensation <input type="checkbox"/> Generalized pruritus WITHOUT skin rash	
Respiratory	<input type="checkbox"/> Bilateral wheeze (bronchospasm; by stethoscope) <input type="checkbox"/> Stridor <input type="checkbox"/> Upper airway swelling (tongue, throat, uvula, larynx) <input type="checkbox"/> ≥ 2 indicators of respiratory distress: <input type="checkbox"/> Tachypnea <input type="checkbox"/> Cyanosis <input type="checkbox"/> Grunting <input type="checkbox"/> Chest wall retractions <input type="checkbox"/> Increased use of accessory respiratory muscles	<input type="checkbox"/> Persistent dry cough <input type="checkbox"/> Hoarse voice <input type="checkbox"/> Sensation of throat closure <input type="checkbox"/> Sneezing OR rhinorrhea <input type="checkbox"/> Difficulty breathing WITHOUT wheeze or stridor	
Cardiovascular (CVS)	<input type="checkbox"/> Measured hypotension <input type="checkbox"/> ≥ 3 signs of uncompensated shock: <input type="checkbox"/> Tachycardia <input type="checkbox"/> Capillary refill >3 seconds <input type="checkbox"/> Reduced central pulse volume <input type="checkbox"/> Decreased level or loss of consciousness	<input type="checkbox"/> ≥ 2 signs of reduced peripheral circulation <input type="checkbox"/> Tachycardia <input type="checkbox"/> Capillary refill >3 seconds <input type="checkbox"/> Decreased level of consciousness	
Gastro-intestinal (GI)	None	<input type="checkbox"/> Nausea <input type="checkbox"/> Abdominal pain	<input type="checkbox"/> Vomiting <input type="checkbox"/> Diarrhea
Laboratory	None	<input type="checkbox"/> Elevated mast cell tryptase (> upper normal limit for laboratory doing test)	

STEP 4. Upload this form to the Centre for Adverse Reactions Monitoring (CARM) Dropbox:

<https://www.dropbox.com/request/tvmefV4XPpGdKfAyr07L>

GLOSSARY OF TERMS

Accessory muscles	Muscles, primarily in the neck (sternocleidomastoid which elevates sternum; scalene group which elevates upper ribs) which assist but don't play a primary role in breathing. When used at rest they indicate a level of respiratory distress or increased work of breathing.
Angioedema	Areas of deeper swelling of the skin and/or mucosal tissues in either single or multiple sites which may not be well circumscribed and usually not itchy. (Reported symptoms of "swelling of the tongue" or "throat swelling" should not be documented as angioedema unless there is visible skin or mucosal swelling). NOTE: hereditary angioedema, usually with a history of recurrent episodes of swelling, should be excluded (affects 1 in 50,000).
Capillary refill time	The time required for normal skin colour to reappear after a blanching pressure is applied for 5 seconds. Usually assessed by pressing on the nail bed to cause blanching and then counting the time it takes for the blood to return to the tissue indicated by a pink colour returning to the nail. It normally takes < 3 seconds.
Cyanosis	A dark bluish or purplish discolouration of the skin and/or mucous membranes due to lack of oxygen in the blood
Dry cough	Rapid expulsion of air from the lungs and not accompanied by expectoration/sputum (a non-productive cough)
Erythema	Abnormal redness of the skin without any raised skin lesions
Generalized	Involving >1 body site – that is each limb is counted separately as is the abdomen, back, head and neck
Grunting	A sudden and short noise with each breath when breathing out
Hoarse voice	An unnaturally harsh cry in an infant or vocalisation in an adult or child
Hypotension	An abnormally low blood pressure (BP) documented by appropriate measurement. For infants and children: age specific systolic BP <3-5th percentile OR >30% decrease from that person's baseline; For adults: Systolic BP of <90mm Hg or >30% decrease from that person's baseline.
In-drawing or retractions	Inward movement of the muscles between the ribs (inter-costal), in the lower part of the neck (supra-clavicular or tracheal tug) or below the chest (sub-costal). The movements are usually a sign of difficulty with breathing which results in increased use of 'accessory respiratory muscles' (sternocleidomastoid and intercostal).
Injection site urticaria	Urticaria which is continuous with the injection site or involves other aspects of the injected limb
Localised	Involving one body site only
Loss of consciousness	Total suspension of conscious relationship with the outside world as demonstrated by an inability to perceive and respond to verbal, visual or painful stimulus
Mast cell tryptase	Inflammatory mediator released by mast cells during acute anaphylaxis. Typically levels peak between 15 and 120 minutes after onset; samples for measurement should be taken within 6 hours of onset of signs/symptoms.
Prickle sensation	An unpleasant skin sensation that provokes the desire to run and/or scratch to obtain relief
Pruritus	Itchiness
Red and itchy eyes	Redness of the whites of the eyes (sclera) with sensation that provokes the desire to rub and/or scratch to obtain relief.
Retractions	Indrawing of skin while breathing in (implies an obstruction to breathing); may be supraclavicular (above the collarbone), suprasternal (above the sternum), intercostal (between the ribs), substernal (below the sternum) or subcostal (abdomen just below the rib cage)
Rhinorrhea	Discharge of thin nasal mucus
Sensation of throat closure	Feeling or perception of throat closing with a sensation of difficulty breathing
Sneezing	An involuntary (reflex), sudden, violent, and audible expulsion of air through the mouth and nose.
Stridor	A harsh and continuous sound made on breathing in
Tachycardia	Faster than normal heart rate which varies by age – Adult >100 bpm
Tachypnoea	Faster than normal respiratory rate which varies by age – Adult >16 bpm
Urticaria	Localized redness of superficial layers of skin that is itchy, raised, sharply demarcated and transient (that is skin changes at any location are usually present for less than 12 hours)
Wheezing	A whistling, squeaking, musical or puffing sound made on breathing out



"GT-11"

Emma Louise Spratt
Solicitor
Christchurch

This is the exhibit marked GT-11 referred to in the Sworn affidavit of GEORGE IANTOWN sworn at CHRISTCHURCH on 10 June 2022 before me:

Weekly / April 22, 2022 / 71(16);574-581

On April 19, 2022, this report was posted online as an MMWR Early Release.

[Signature]
Solicitor of the High Court of New Zealand

Dallas S. Shi, MD, PhD^{1,2}; Michael Whitaker, MPH¹; Kristin J. Marks, PhD^{1,2}; Onika Anglin, MPH^{1,3}; Jennifer Milucky, MSPH¹; Kadam Patel, MPH^{1,3}; Huong Pham, MPH¹; Shua J. Chai, MD^{4,5}; Breanna Kawasaki, MPH⁶; James Meek, MPH⁷; Evan J. Anderson, MD^{8,9,10}; Andy Weigel, MSW¹¹; Justin Henderson, MPH¹²; Ruth Lynfield, MD¹³; Susan L. Ropp, PhD¹⁴; Alison Muse, MPH¹⁵; Sophrena Bushey, MHS¹⁶; Laurie M. Billing, MPH¹⁷; Melissa Sutton, MD¹⁸; H. Keipp Talbot, MD¹⁹; Andrea Price²⁰; Christopher A. Taylor, PhD¹; Fiona P. Havers, MD¹; COVID-NET Surveillance Team (View author affiliations)

View suggested citation

Summary

What is already known about this topic?

COVID-19 can cause severe illness in children. Children aged 5–11 years became eligible for COVID-19 vaccination on November 2, 2021.

What is added by this report?

During the period of Omicron predominance (December 19, 2021–February 28, 2022), COVID-19–associated hospitalization rates in children aged 5–11 years were approximately twice as high among unvaccinated as among vaccinated children. Non-Hispanic Black children represented the largest group of unvaccinated children. Thirty percent of hospitalized children had no underlying medical conditions, and 19% were admitted to an intensive care unit. Children with diabetes and obesity were more likely to experience severe COVID-19.

What are the implications for public health practice?

Increasing COVID-19 vaccination coverage among children aged 5–11 years, particularly among racial and ethnic minority groups disproportionately affected by COVID-19, can prevent COVID-19–associated hospitalization and severe outcomes.

Article Metrics

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- News (168)
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- Figure
- Tables
 - Table 1
 - Table 2
- References

Related Materials

PDF [402K]

COVID-19 can make some children very sick

Among nearly 400 children ages 5–11 years hospitalized with COVID-19 during the first few months of Omicron:*

- 3 in 10 had NO underlying conditions
- 9 in 10 were unvaccinated
- 2 in 10 required ICU care

Protect all eligible children by keeping their vaccinations up to date

[bit.ly/MMWR7116](https://www.cdc.gov/mmwr/volumes/71/wr/mm7116e1.htm)

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On October 29, 2021, the Food and Drug Administration expanded the Emergency Use Authorization for Pfizer-BioNTech COVID-19 vaccine to children aged 5–11 years; CDC's Advisory Committee on Immunization Practices' recommendation followed on November 2, 2021.* In late December 2021, the B.1.1.529 (Omicron) variant of SARS-CoV-2 (the virus that causes COVID-19) became the predominant strain in the United States,[†] coinciding with a rapid increase in COVID-19-associated hospitalizations among all age groups, including children aged 5–11 years (7). COVID-19-Associated Hospitalization Surveillance Network (COVID-NET)[‡] data were analyzed to describe characteristics of COVID-19-associated hospitalizations among 1,475 U.S. children aged 5–11 years throughout the pandemic, focusing on the period of early Omicron predominance (December 19, 2021–February 28, 2022). Among 397 children hospitalized during the Omicron-predominant period, 87% were unvaccinated, 30% had no underlying medical conditions, and 19% were admitted to an intensive care unit (ICU). The cumulative hospitalization rate during the Omicron-predominant period was 2.1 times as high among unvaccinated children (19.1 per 100,000 population) as among vaccinated[¶] children (9.2).** Non-Hispanic Black (Black) children accounted for the largest proportion of unvaccinated children (34%) and represented approximately one third of COVID-19-associated hospitalizations in this age group. Children with diabetes and obesity were more likely to experience severe COVID-19. The potential for serious illness among children aged 5–11 years, including those with no underlying health conditions, highlights the importance of vaccination among this age group. Increasing vaccination coverage among children, particularly among racial and ethnic minority groups disproportionately affected by COVID-19, is critical to preventing COVID-19-associated hospitalization and severe outcomes.

COVID-NET conducts population-based surveillance for laboratory-confirmed COVID-19-associated hospitalizations in 99 counties across 14 U.S. states.^{‡‡} COVID-19-associated hospitalizations are defined as receipt of a positive SARS-CoV-2 nucleic acid amplification tests or rapid antigen detection test result during hospitalization or during the 14 days preceding admission. This analysis describes hospitalization rates among children aged 5–11 years during March 1, 2020–February 28, 2022. Clinical data from the Omicron-predominant period were compared with those from the Delta-predominant (June 27–December 18, 2021) and pre-Delta (March 1, 2020–June 26, 2021) periods; a variant that accounted for >50% of sequenced isolates was considered predominant. Unadjusted weekly COVID-19-associated hospitalization rates (COVID-19-related hospitalizations per 100,000 children) were calculated by dividing the total number of COVID-19-associated hospitalizations by the population estimates for the counties included in the surveillance area.^{§§} ICU admission rates were calculated using 2-week periods. Population-based hospitalization rates and data for hospitalized children were compared by COVID-19 vaccination status for the Omicron-predominant period using linkage to state immunization information systems data.^{¶¶}

Trained surveillance officers abstracted medical charts for hospitalized pediatric patients using standardized case report forms through November 2021. Because of the surge in hospitalizations during December 2021–February 2022, some sites examined clinical data on a representative sample of hospitalized children during this period.*** The representative sample included 1,252 of 1,475 (84.9%) children with positive SARS-CoV-2 test results; complete clinical data were available for 595 of 596 (99.8%), 438 of 468 (93.6%), and 219 of 225 (97.3%) sampled children aged 5–11 years during the pre-Delta period, Delta-predominant period, and Omicron-predominant period.

Data regarding likely primary reason for hospital admission,^{†††} symptoms at admission,^{§§§} underlying medical conditions,^{¶¶¶} vaccination status (complete versus incomplete), and indicators of severe disease (e.g., length of stay, ICU admission, receipt of invasive mechanical ventilation [IMV],^{****} and in-hospital death) were collected (2). Children who completed their primary COVID-19 vaccination series were defined as those who had received the second dose of a 2-dose series ≥ 14 days before receipt of a positive SARS-CoV-2 test result associated with their hospitalization. Wilcoxon rank-sum tests and chi-square tests were used to compare medians and proportions, respectively; $p < 0.05$ was considered statistically significant. Percentages were weighted to account for probability of selection for sampled cases and adjusted to account for nonresponse. Association of underlying medical conditions with severe COVID-19 (defined as requiring ICU admission or IMV, or in-hospital death) was modeled using multivariable generalized estimating equations (2). Multivariable models were limited to children whose primary reason for admission was likely COVID-19-related. Unadjusted risk ratios (RRs), adjusted RRs (aRRs), and 95% CIs were calculated for the association of demographic characteristics, underlying medical conditions, and variant periods with severe COVID-19. Data were analyzed using SAS (version 9.4; SAS Institute). This activity was reviewed by CDC and conducted consistent with applicable federal law and CDC policy.^{††††}

During the Delta- and Omicron-predominant periods, weekly hospitalization rates of children aged 5–11 years peaked during the weeks ending September 25, 2021 and January 22, 2022, respectively; the Omicron-predominant peak (2.8 per 100,000 children) was 2.3 times the Delta-predominant peak (1.2).^{§§§§} Peak ICU admission rates were 1.7 times as high during Omicron predominance (2-week period ending January 25, 2022 [1.2]) than during Delta predominance (2-week period ending October 2, 2021 [0.7]).

During the Omicron-predominant period, cumulative hospitalization rates among unvaccinated children aged 5–11 years were 2.1 times as high (19.1) as those among vaccinated children (9.2) (Figure). Most (87%) children aged 5–11 years hospitalized during the Omicron-predominant period were unvaccinated (Supplemental Table, <https://stacks.cdc.gov/view/cdc/116353>). Among unvaccinated children, the largest proportion were Black (34%), followed by White (31%), and Hispanic (19%). There were no significant differences for severe outcomes by vaccination status. However, the number of vaccinated children was small. No vaccinated children required higher level O₂ support (e.g., bilevel positive airway pressure/continuous positive airway pressure [BiPAP/CPAP], high flow nasal canula, or IMV).

COVID-19-related illness was the primary reason for admission among a lower proportion of hospitalized children aged 5–11 years during the Omicron period (73%) compared with the Delta period (84%) ($p < 0.01$); across all periods, a majority (78%) of children were hospitalized with COVID-19 as the likely primary reason for admission (Table 1). Of the hospitalized children, 67% had one or more underlying medical conditions. During the period of Omicron predominance, a larger proportion of children hospitalized with COVID-19 had neurologic disorders (33%) compared with those hospitalized during the pre-Delta period (21%) ($p < 0.01$), and a lower proportion had obesity (33% and 21%, respectively; $p = 0.01$). Similar trends were observed when comparing the Omicron- and Delta-predominant periods. Among children hospitalized during the Omicron-predominant period, 19% required ICU admission, including 15% with no underlying medical conditions; 5% received IMV; none died.

Across periods, 32% of hospitalized children aged 5–11 years had severe COVID-19; 44% of Black children and 26% of Hispanic children experienced severe disease, compared with 22% of White children, but the association between severe COVID-19 and race or Hispanic ethnicity was not statistically significant (Table 2). The risk for severe COVID-19 among hospitalized children was significantly higher among those with diabetes (aRR = 2.5) and obesity (aRR = 1.2). Risk for severe disease was lower among children with asthma (aRR = 0.8), immunocompromising conditions (aRR = 0.7), and those hospitalized during the Delta-predominant (aRR = 0.8) and Omicron-predominant periods (aRR = 0.6). Other conditions were not significantly associated with severe COVID-19 among hospitalized children.

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Discussion

Peak weekly COVID-19-associated hospitalization rates among children aged 5–11 years were higher during the Omicron-predominant period than during the Delta-predominant period. During Omicron predominance, shortly after the Food and Drug Administration authorized COVID-19 vaccination for this age group, population-based hospitalization rates among unvaccinated children were twice as high as were those among vaccinated children. Most hospitalized children were unvaccinated, and nearly one in three were Black. Approximately one third had no underlying medical conditions, and nearly one fifth required ICU admission. The potential for serious illness among children aged 5–11 years, including those with no underlying health conditions, highlights the importance of vaccination among this age group.

Vaccination eligibility was expanded to include children aged 5–11 years on November 2, 2021. As of March 5, 2022, 32% of children in this age group had completed a COVID-19 primary vaccination series.^{11,12} In this study, approximately one half (53%) of unvaccinated hospitalized children were Black or Hispanic, two groups known to have lower vaccination rates (3). Implementing strategies that result in equitable receipt of COVID-19 vaccine among children is a public health priority.

The finding that hospitalization rates in unvaccinated children were double those of vaccinated children suggests that vaccines are effective in preventing COVID-19-associated morbidities. This is consistent with recent studies, which suggest that vaccination reduces the risk for Omicron infection, protects against COVID-19-associated illness among children aged 5–11 years and prevents multisystem inflammatory syndrome in children, a severe postinfectious hyperinflammatory condition with a higher incidence in this age group than in other age groups (4–7).

Consistent with other studies, this analysis demonstrated that the Omicron-predominant period was associated with less severe disease among hospitalized children (8). However, both population-based peak hospitalization and ICU admission rates were higher during the Omicron-predominant period compared with those during the Delta-predominant period, likely because of the high transmissibility of the Omicron variant and greater number of persons infected. Although a higher proportion of children hospitalized with laboratory-confirmed SARS-CoV-2 infection were admitted for reasons that were not likely primarily COVID-19-related during the Omicron period compared with the Delta period, most children admitted during both periods were hospitalized primarily for COVID-19. These findings suggest that incidental admissions do not account for the increase in hospitalization rates observed during the Omicron period and reinforce that children continued to experience serious COVID-19 illness.

As in previous investigations, diabetes and obesity were associated with increased risk for severe COVID-19 in children (2). One third of hospitalized children aged 5–11 years had underlying neurologic disorders during the Omicron-predominant period, an increase from previous periods. Neurologic disorders have been shown to increase risk for severe illness in other respiratory diseases such as influenza (9). Consistent with findings from influenza-associated hospitalizations, this study found that some underlying medical conditions, including asthma and immunocompromising conditions, were not associated with increased risk for severe COVID-19, which might be explained by a lower threshold for hospital admission in children with these conditions (10).

The findings in this report are subject to at least five limitations. First, COVID-19-associated hospitalizations might have been missed because of testing practices and availability. Second, stratification of hospitalization rate by vaccination status is subject to error if misclassification of vaccination status occurred. Third, analyses based on vaccination status are biased toward the null because partially vaccinated children were grouped with unvaccinated children. Fourth, primary reason for admission was not always clear, and medical charts might not completely capture underlying conditions, potentially resulting in misclassification. Finally, COVID-NET catchment areas include approximately 10% of the U.S. population; thus, these findings might not be generalizable to the rest of the United States.

Potential for serious disease requiring hospitalization, ICU admission, or IMV among children aged 5–11 years reinforces the importance of increasing vaccination coverage among this population. Black children accounted for the highest percentage of unvaccinated children in this analysis and represented one third of COVID-19-associated hospitalizations in this age group. Increasing COVID-19 vaccination coverage among children aged 5–11 years, with particular attention to racial and ethnic minority groups disproportionately affected by COVID-19, is critical to reducing COVID-19-associated morbidity.*****

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* <https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age> ; <https://www.cdc.gov/media/releases/2021/s1102-PediatricCOVID-19Vaccine.html>

† Omicron became the predominant variant during the week ending December 25, 2021 at 74% of sequenced isolates. <https://covid.cdc.gov/covid-data-tracker/#variant-proportions>

‡ <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html>

¶ Vaccinated children aged 5–11 years were defined as those who had received the final dose in their primary series ≥ 14 days before receiving a positive SARS-CoV-2 test result associated with their hospitalization. Children who had received only 1 vaccine dose ≥ 14 days before the SARS-CoV-2 test date or had received a single dose of vaccine < 14 days before the positive SARS-CoV-2 test results were considered partially vaccinated; these children were not included in rates and were grouped with unvaccinated children in other analyses.

** <https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination>

†† California, Colorado, Connecticut, Georgia, Iowa, Maryland, Michigan, Minnesota, New Mexico, New York, Ohio, Oregon, Tennessee, and Utah.

‡‡ Rates are calculated using the National Center for Health Statistics' vintage 2020 bridged-race postcensal population estimates for the counties included in surveillance. https://www.cdc.gov/nchs/nvss/bridged_race.htm

¶¶ COVID-NET sites, through agreements with state health departments and other partners, collect COVID-19 vaccination information on COVID-19-associated hospitalizations through state-based vaccination registries. When possible, sites collect COVID-19 vaccination status on all persons with COVID-19 cases who are hospitalized, including the number of vaccine doses received, the vaccine product, and dates of vaccine administration. Vaccination information was not available for Iowa, Maryland, and Michigan and only available for sampled cases in Minnesota.

*** During December 2021–February 2022, sites sampled pediatric patients at rates of 12%–100%. Random numbers (1–100) were automatically generated and assigned to each patient on entry into the surveillance database to produce random samples of hospitalized patients for medical record abstraction. Percentages were weighted to account for the probability of

selection for sampled patients.

^{†††} Among sampled cases, COVID-NET collects data on the primary reason for admission to differentiate hospitalizations of patients with laboratory-confirmed SARS-CoV-2 infection who are likely admitted primarily for COVID-19 illness from those admitted for other reasons, including inpatient surgery or trauma. During chart review, if the surveillance officer finds that the chief complaint or history of present illness mentions fever/respiratory illness, COVID-19–like illness, or a suspicion for COVID-19, then the case is categorized with COVID-19–related illness as the primary reason for admission.

^{§§§} COVID-19–related symptoms included respiratory symptoms (congestion/runny nose, cough, hemoptysis/bloody sputum, shortness of breath/respiratory distress, sore throat, upper respiratory infection, influenza-like illness, and wheezing) and nonrespiratory symptoms (abdominal pain, altered mental status/confusion, anosmia/decreased smell, chest pain, conjunctivitis, diarrhea, dysgeusia/decreased taste, fatigue, fever/chills, headache, muscle aches/myalgias, nausea/vomiting, rash, and seizures). Symptoms were abstracted from the medical chart and might be incomplete.

^{¶¶¶} Thirteen underlying conditions were considered, including airway abnormality, asthma, blood disorders, cardiovascular disease, developmental delay, diabetes mellitus (type 1 or 2), feeding tube dependence, immunocompromising conditions, obesity (body mass index [kg/m²] ≥95th percentile for age and sex based on CDC growth charts; *International Classification of Diseases, Tenth Revision, Clinical Modification* codes for obesity; or obesity selected on the case report form), nonasthma chronic lung disease, nondiabetes chronic metabolic disease, nondevelopmental delay neurologic disorders, or other conditions (gastrointestinal or liver disease; renal disease; or rheumatologic, autoimmune, or inflammatory disease).

**** ICU admission and need for mechanical ventilation are not mutually exclusive categories, and patients could have received both.

^{††††} 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

^{§§§§} <https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network>

^{¶¶¶¶} <https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends>

***** <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html>

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	Total	Pre-Delta Mar 1, 2020– Jun 26, 2021	Delta predominant Jun 27, 2021–Dec 18, 2021	Omicron predominant Dec 19, 2021–Feb 28, 2022		
Total no. of hospitalized children	1,475 [¶]	596 [¶]	482 [¶]	397 [¶]	NA	NA
Age, yrs, median (IQR)	8 (6–10)	8 (6–10)	9 (6–10)	8 (6–10)	0.03	0.01
Sex						
Male	829 (56.2)	353 (59.2)	258 (53.6)	218 (54.9)	0.18	0.71
Female	645 (43.8)	243 (40.8)	223 (46.4)	179 (45.1)		
Race/Ethnicity**						
White, non-Hispanic	430 (29.2)	129 (21.6)	163 (33.9)	138 (34.8)	<0.01	0.42
Black, non-Hispanic	484 (32.8)	197 (33.1)	167 (34.7)	120 (30.2)		
Asian or Pacific Islander, non-Hispanic	64 (4.3)	24 (4.0)	19 (4.0)	21 (5.3)		
Hispanic	420 (28.5)	212 (35.6)	114 (23.7)	94 (23.7)		
Persons of all other races ^{††}	26 (1.8)	14 (2.3)	6 (1.2)	6 (1.5)		
Unknown race/ethnicity	50 (3.4)	20 (3.4)	12 (2.5)	18 (4.5)		
Primary reason for admission^{§§}						
Likely COVID-19–related	944 (78.2)	420 (76.7)	364 (84.2)	160 (72.9)	0.31	<0.01
Underlying medical conditions						
One or more underlying medical condition ^{¶¶}	824 (66.7)	383 (64.9)	288 (66.6)	153 (69.6)	0.25	0.48
Obesity	302 (29.0)	152 (33.0)	111 (30.6)	39 (21.3)	0.01	0.03
Neurologic disorder ^{***}	306 (25.3)	124 (21.0)	106 (24.5)	76 (33.4)	<0.01	0.02

Asthma	282 (22.4)	133 (22.6)	100 (23.1)	49 (21.4)	0.73	0.63
Chronic lung disease, not including asthma ^{†††}	130 (10.5)	62 (10.6)	41 (9.5)	27 (11.4)	0.74	0.46
Cardiovascular disease ^{§§§}	141 (11.8)	53 (9.1)	55 (13.0)	33 (14.9)	0.02	0.50
Blood disorder ^{¶¶¶}	111 (9.1)	47 (8.0)	42 (9.9)	22 (9.9)	0.43	0.99
Immunocompromising conditions ^{****}	117 (10.0)	49 (8.4)	38 (9.1)	30 (13.8)	0.03	0.09
Feeding tube dependence	78 (6.5)	32 (5.4)	25 (6.0)	21 (9.0)	0.07	0.18
Diabetes mellitus	58 (5.0)	24 (4.1)	18 (4.1)	16 (7.7)	0.06	0.07
Chronic metabolic disease, not including diabetes mellitus ^{†††}	40 (3.3)	11 (1.9)	19 (4.6)	10 (3.9)	0.09	0.69
Rheumatologic/Autoimmune/Inflammatory disorders ^{§§§§}	44 (3.6)	19 (3.2)	16 (3.7)	9 (4.2)	0.54	0.79
GI/Liver disease ^{¶¶¶¶}	35 (2.9)	17 (3.0)	15 (3.5)	3 (2.1)	0.59	0.42
Renal disease ^{*****}	29 (2.4)	11 (1.8)	11 (2.7)	7 (3.2)	0.25	0.77
Genetic disease ^{††††}	27 (2.2)	11 (1.9)	7 (1.6)	9 (3.7)	0.13	0.09
Viral codetections^{§§§§§}						
Positive test results	85 (12.3)	33 (12.3)	37 (14.6)	15 (9.7)	0.43	0.17
Hospitalization outcomes^{¶¶¶¶¶}						
Length of hospital stay, days, median (IQR)	3 (2–5)	3 (2–6)	3 (1–5)	3 (1–5)	0.01	0.54
ICU admission	349 (27.0)	191 (32.6)	114 (26.1)	44 (18.9)	<0.01	0.05

Invasive mechanical ventilation	79 (6.2)	40 (6.7)	29 (6.8)	10 (4.6)	0.28	0.28
In-hospital death	4 (0.3)	4 (0.7)	0 (—)	0 (—)	—	—

Abbreviations: COVID-NET = COVID-19–Associated Hospitalization Surveillance Network; GI = gastrointestinal; ICU = intensive care unit; NA = not applicable.

* Includes persons admitted to a hospital during March 1, 2020–February 28, 2022. Maryland contributed data through November 26, 2021. Counties included in COVID-NET surveillance during this period: California (Alameda, Contra Costa, and San Francisco counties); Colorado (Adams, Arapahoe, Denver, Douglas, and Jefferson counties); Connecticut (Middlesex and New Haven counties); Georgia (Clayton, Cobb, DeKalb, Douglas, Fulton, Gwinnett, Newton, and Rockdale counties); Iowa (one county represented); Maryland (Allegany, Anne Arundel, Baltimore, Baltimore City, Calvert, Caroline, Carroll, Cecil, Charles, Dorchester, Frederick, Garrett, Harford, Howard, Kent, Montgomery, Prince George's, Queen Anne's, St. Mary's, Somerset, Talbot, Washington, Wicomico, and Worcester counties); Michigan (Clinton, Eaton, Genesee, Ingham, and Washtenaw counties); Minnesota (Anoka, Carver, Dakota, Hennepin, Ramsey, Scott, and Washington counties); New Mexico (Bernalillo, Chaves, Doña Ana, Grant, Luna, San Juan, and Santa Fe counties); New York (Albany, Columbia, Genesee, Greene, Livingston, Monroe, Montgomery, Ontario, Orleans, Rensselaer, Saratoga, Schenectady, Schoharie, Wayne, and Yates counties); Ohio (Delaware, Fairfield, Franklin, Hocking, Licking, Madison, Morrow, Perry, Pickaway and Union counties); Oregon (Clackamas, Multnomah, and Washington counties); Tennessee (Cheatham, Davidson, Dickson, Robertson, Rutherford, Sumner, Williamson, and Wilson counties); and Utah (Salt Lake County).

† Data are from a weighted sample of hospitalized children with completed medical record abstractions. Sample sizes presented are unweighted with weighted percentages.

‡ Proportions between the Omicron and Delta- and Omicron-predominant and pre-Delta periods were compared using chi-square tests, and medians were compared using Wilcoxon rank-sum tests; $p < 0.05$ was considered statistically significant.

§ Data are missing for <3% of observations for all variables.

** If ethnicity was unknown, non-Hispanic ethnicity was assumed.

†† Includes non-Hispanic persons reported as other or multiple races.

‡‡ Primary reason for admission was collected beginning June 1, 2020; hospitalizations before June 1, 2020 (42) are excluded. Among sampled patients, COVID-NET collects data on the primary reason for admission to differentiate hospitalizations of patients with laboratory-confirmed SARS-CoV-2 infection who are likely admitted primarily for COVID-19 illness rather than for other reasons. During chart review, if the surveillance officer finds that the chief complaint or history of present illness mentions fever or respiratory illness, COVID-19–like illness, or suspected COVID-19, then the case is categorized with COVID-19–related illness as the primary reason for admission. Reasons for admission that are likely primarily not related to COVID-19 include the following categories: inpatient surgery or procedures, psychiatric admission requiring acute medical care, trauma, other, or unknown. Reasons categorized as “other” are reviewed by two physicians to determine whether the admission is likely COVID-19–related.

‡‡‡ Defined as one or more of the following: chronic lung disease, chronic metabolic disease, blood disorder/hemoglobinopathy, cardiovascular disease, neurologic disorder, immunocompromising condition, renal disease, gastrointestinal/liver disease, rheumatologic/autoimmune/inflammatory condition, obesity, feeding tube dependency, and wheelchair dependency.

‡‡‡‡ Includes children with development delay (211), seizure disorders (139), cerebral palsy (62), and other neurologic disorders such as Down Syndrome, neural tube defect, neuropathy, paralysis, and mitochondrial disorders.

‡‡‡‡‡ Includes children with obstructive sleep apnea (74), oxygen dependency (18), bronchopulmonary dysplasia (22), and other chronic lung conditions such as airway abnormality, tracheostomy dependency, restrictive lung disease, pulmonary fibrosis, chronic obstructive pulmonary disease, idiopathic lung disease, chronic bronchitis, bronchiolitis obliterans, and bronchiectasis.

‡‡‡‡‡‡ Includes children with congenital heart disease (55), aortic regurgitation (45), aortic stenosis (30) and other cardiological disorders such as cardiomyopathy and dysrhythmias.

^{¶¶¶} Includes children with sickle cell anemia (81), asplenia (20), thrombocytopenia (11), and other blood disorders such as thalassemia, coagulopathy, and myelodysplastic syndromes.

^{****} Includes children with immunosuppressive therapy (70), leukemia (40), immunoglobulin deficiency (13), and other immunocompromising conditions including lymphoma and solid organ malignancies.

^{†††} Includes children with thyroid dysfunction (20), adrenal disorders (13), and other metabolic conditions such as pituitary dysfunction, inborn errors of metabolism, parathyroid dysfunction, and glycogen or other storage diseases.

^{§§§§} Includes children with rheumatoid arthritis (32), lupus erythematosus (four), systemic sclerosis (four), and other autoimmune or inflammatory disorders such as Kawasaki disease and juvenile idiopathic arthritis.

^{¶¶¶¶} Includes children with ulcerative colitis (six), Crohn’s disease (two), chronic liver disease (two), and other GI/liver diseases such as nonalcoholic fatty liver disease, hepatitis B, and esophageal strictures.

^{*****} Includes children with renal insufficiency (13), nephrotic syndrome (five), and other renal diseases, such as glomerulonephritis, polycystic kidney disease, and end stage renal disease.

^{††††} Excludes genetic diseases listed above.

^{§§§§§} Across periods, the number of children aged 5–11 years tested for additional viral pathogens was 654 (55%); 85 (12%) had received a positive test result. Positive test results include those for respiratory syncytial virus (13), influenza (four), rhinovirus/enterovirus (52), and other viruses (19).

^{¶¶¶¶¶} Hospitalization outcomes are not mutually exclusive; patients can be included in more than one category.

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TABLE 2. Demographic characteristics, underlying conditions, and variant periods associated with severe COVID-19* among children aged 5–11 years hospitalized with COVID-19 as the primary reason for admission† — COVID-NET, March 1, 2020–February 28, 2022

Return

Characteristic	No. (%) of hospitalized children [§]				Bivariate models	Multivariable models
	Severe disease		No severe disease		RR (95% CI)	aRR (95% CI)
Age, yrs, median (IQR)	304	8 (6–10) [¶]	639	8 (6–10) [¶]	1.02 (1.00–1.04)	1.02 (0.99–1.05)
Sex						
Male	165	53.5	345	52.9	1.02 (0.86–1.21)	1.03 (0.87–1.21)
Female	139	46.5	294	47.1	Ref	Ref
Race/Ethnicity						
White, non-Hispanic	67	22.4	180	28.0	Ref	Ref
Black, non-Hispanic	134	43.6	224	34.9	1.36 (0.85–2.18)	1.38 (0.95–2.00)
Asian or Pacific Islander, non-Hispanic	13	4.4	28	4.6	1.15 (0.44–3.01)	1.13 (0.47–2.76)
Hispanic	78	25.9	172	27.2	1.13 (0.79–1.63)	1.15 (0.70–1.88)
Unknown/Other races ^{**}	12	3.7	35	5.2	0.91 (0.35–2.36)	0.97 (0.41–2.27)
Underlying medical conditions [†]						
Diabetes mellitus ^{††}	34	12.2	18	3.3	2.16 (1.46–3.20)	2.47 (2.12–2.87)
Chronic lung disease ^{§§}	45	15.2	69	10.8	1.29 (0.89–1.88)	1.35 (0.81–2.24)

Characteristic	No. (%) of hospitalized children [§]				Bivariate models	Multivariable models
	Severe disease		No severe disease		RR (95% CI)	aRR (95% CI)
Feeding tube dependence	31	10.3	35	5.9	1.46 (1.29–1.66)	1.28 (0.97–1.69)
Neurologic disorder	91	31.3	159	24.9	1.24 (1.03–1.50)	1.23 (0.92–1.63)
Chronic metabolic disease ^{§§}	14	4.6	22	3.5	1.22 (0.81–1.85)	1.20 (0.85–1.70)
Obesity	87	27.1	151	23.7	1.13 (1.00–1.28)	1.19 (1.06–1.34)
Cardiovascular disease	42	14.4	84	13.5	1.05 (0.91–1.21)	0.99 (0.82–1.19)
Asthma	64	21.0	177	26.7	0.80 (0.66–0.97)	0.75 (0.65–0.86)
Immunocompromising condition	18	6.1	71	11.7	0.59 (0.50–0.70)	0.68 (0.60–0.78)
Blood disorder	18	6.2	81	12.6	0.55 (0.28–1.12)	0.56 (0.29–1.07)
Other ^{¶¶}	39	13.3	80	12.9	1.02 (0.90–1.16)	0.91 (0.71–1.17)
Variant periods						
Pre-Delta	154	47.7	266	36.4	Ref	Ref
Delta-predominant	112	34.8	251	35.7	0.82 (0.72–0.93)	0.83 (0.69–0.99)
Omicron-predominant	38	17.5	122	28.0	0.59 (0.47–0.74)	0.57 (0.43–0.76)

Abbreviations: aRR = adjusted risk ratio; COVID-NET = COVID-19–Associated Hospitalization Surveillance Network; ICU = intensive care unit; Ref = referent group; RR = risk ratio.

* Defined as requiring ICU admission or invasive mechanical ventilation, or in-hospital death.

† Among sampled patients, COVID-NET collects data on the primary reason for admission to differentiate hospitalizations of patients with laboratory-confirmed SARS-CoV-2 infection who are likely admitted primarily for COVID-19 illness rather than for other reasons. During chart review, if the surveillance officer finds that the chief complaint or history of present illness mentions fever or respiratory illness, COVID-19–like illness, or suspected COVID-19, then the case is categorized with COVID-19–related illness as the primary reason for admission. Reasons for admission that are likely primarily not related to COVID-19 include the following categories: inpatient surgery or procedures, psychiatric admission requiring acute medical care, trauma, other, or unknown. Reasons categorized as “other” are reviewed by two physicians to determine whether the admission is likely COVID-19–related.

§ Data are from a weighted sample of hospitalized children with completed medical record abstractions. Sample sizes presented are unweighted with weighted percentages.

¶ Age was modeled as a continuous variable and presented as the median and IQR.

** Includes non-Hispanic persons reported as other, multiple races, and unknown race or ethnicity.

†† Includes type 1 and type 2 diabetes mellitus.

§§ Chronic lung disease excludes asthma and chronic metabolic disease excludes diabetes mellitus.

¶¶ Includes liver disease; renal disease; rheumatologic, autoimmune, and inflammatory conditions; and other conditions specified on the case report form.

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Suggested citation for this article: Shi DS, Whitaker M, Marks KJ, et al. Hospitalizations of Children Aged 5–11 Years with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 2020–February 2022. MMWR Morb Mortal Wkly Rep 2022;71:574–581. DOI: <http://dx.doi.org/10.15585/mmwr.mm7116e1> .

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Page last reviewed: May 4, 2022

"GT-12"

COVID-19 vaccine effectiveness during Omicron for children and adolescents

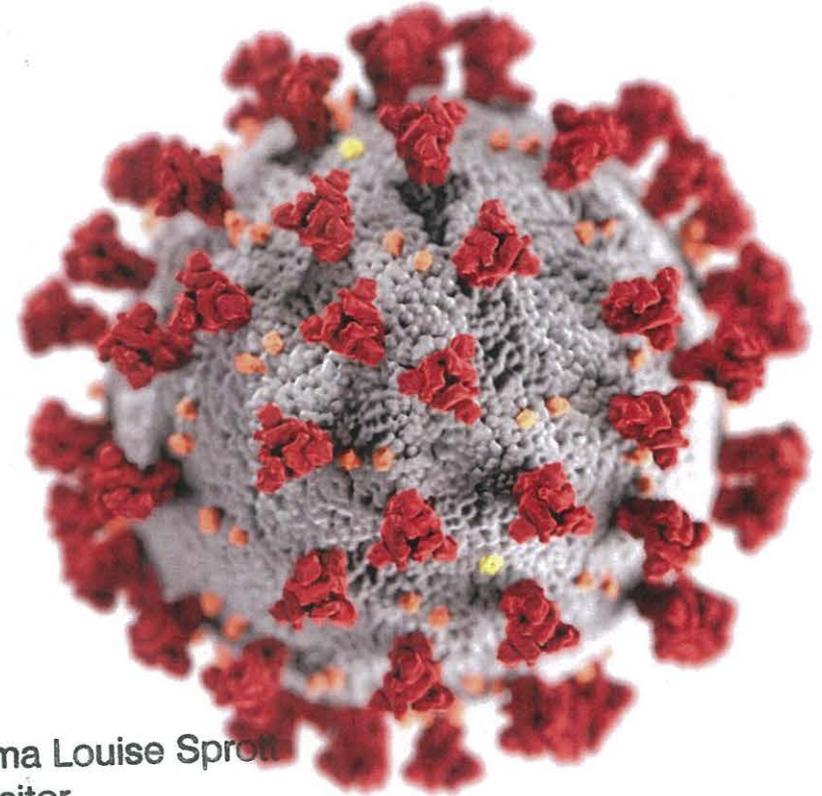
Ruth Link-Gelles, PhD, MPH
LCDR, US Public Health Service
Program Lead, COVID-19 Vaccine Effectiveness
Epidemiology Task Force, CDC

ACIP
May 19, 2022



This is the exhibit marked "GT-12" referred to in the annexed Affidavit of **GEORGE IAN TOWN** affirmed at **Christchurch** this 10th day of **June 2022** before me:

Solicitor of the High Court of New Zealand



Emma Louise Spronk
Solicitor
Christchurch

cdc.gov/coronavirus

Pediatric Research Observing Trends and Exposures in COVID-19 Timelines (PROTECT)

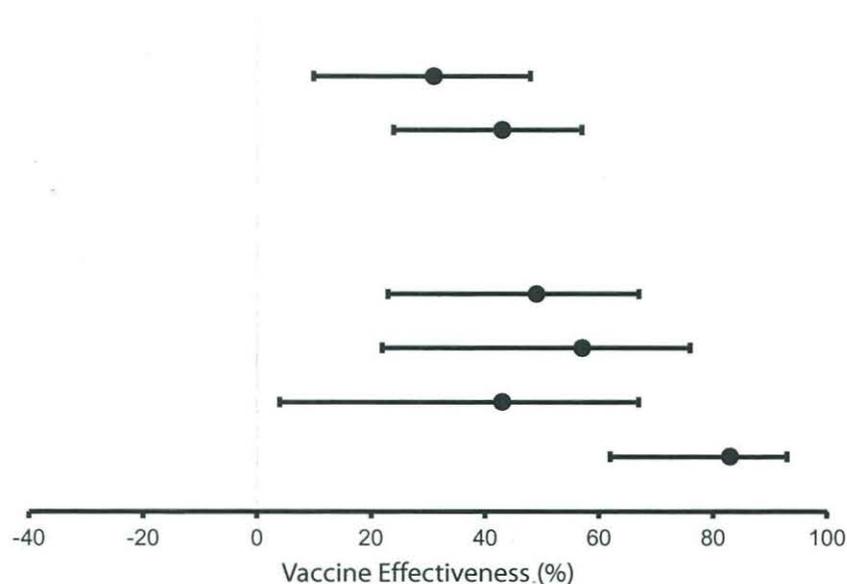
- **Design:** Prospective cohort study
- **Population:** Children ages 4 months - 17 years
- **Methods:** Weekly surveillance and self-swab
 - SARS-CoV-2 testing by RT-PCR and whole genome sequencing
 - Electronic surveys during and after SARS-CoV-2 infection
 - Multi-method vaccination documentation
- **Analysis:** Cox proportional hazards model adjusted by propensity to be vaccinated, site, SARS-CoV-2 circulation, and community mask use
 - Timeframe for analysis during local Omicron predominance
 - December 14, 2021 - April 23, 2022



Recruitment includes children of adult participants in a similar study (HEROES-RECOVER) of frontline workers and from the local community

PROTECT: VE against SARS-CoV-2 infection by age group during Omicron variant predominance, Dec 2021-Apr 2022

	Person-days	SARS-CoV-2 positive	Adjusted VE % (95% CI)
5 - 11 years			
2 doses (≥ 14 days)	60,290	212	31 (10-48)
2 doses (14-59 days)	26,411	156	43 (24-57)
12 - 17 years			
2 doses (≥ 14 days)	14,501	59	49 (23-67)
2 doses (14-59 days)	785	20	57 (22-76)
2 doses (≥ 60 days)	13,716	39	43 (4-67)
3 doses (≥ 7 days)*	8,340	8	83 (62-93)

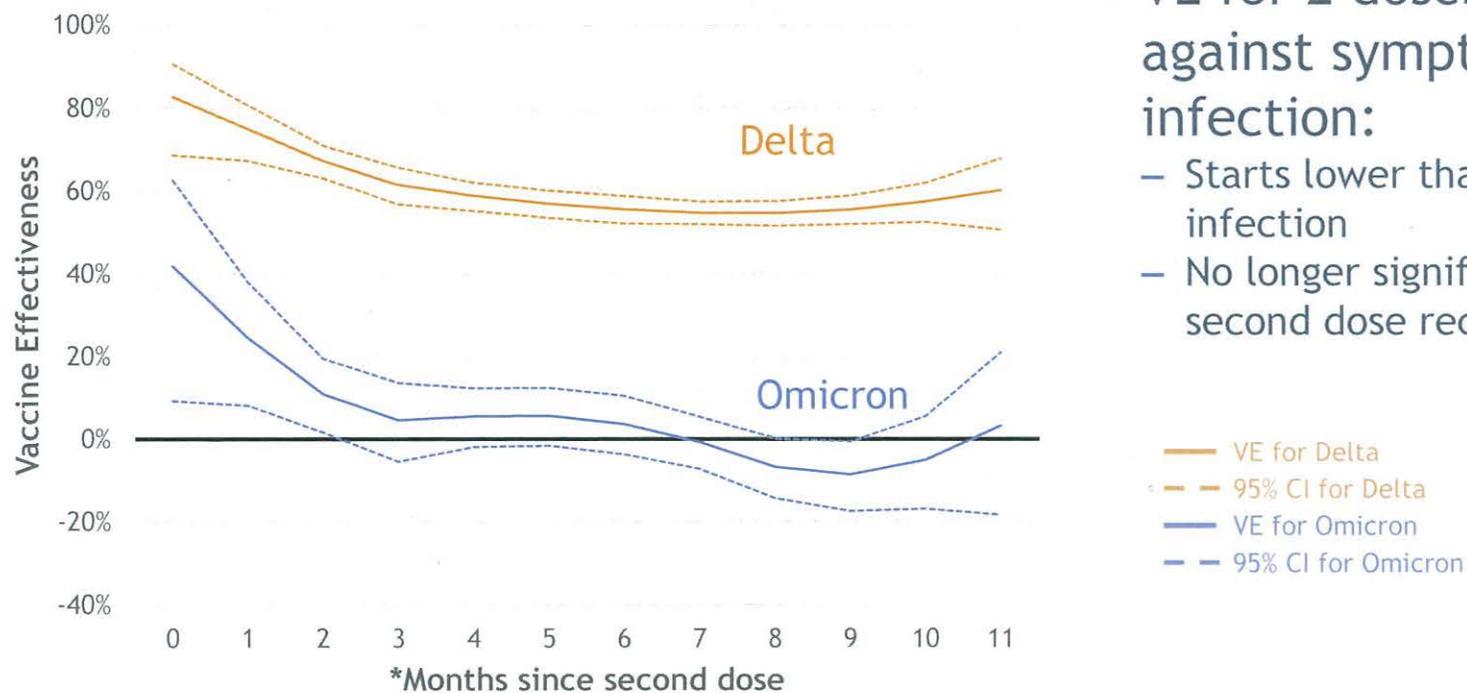


* Median time from vaccination to test was 95 days

Increasing Community Access to Testing (ICATT) Partnership: VE analysis for symptomatic infection

- Nationwide community-based drive-through COVID-19 testing via pharmacies
 - Self-reported vaccine history at time of registration for COVID-19 testing; excluded those who did not report vaccination status
 - **Design:** Test-negative, case-control analysis
 - **Population:** Persons with ≥ 1 COVID-like symptom and nucleic acid amplification testing (NAAT)
 - **Adjusted for:**
 - Calendar day, race, ethnicity, gender, site's HHS region, site census tract's social vulnerability index (SVI)
 - **Not** adjusted for prior infection
 - **Period:**
 - **Adults:** Tested December 10, 2021 – January 1, 2022, also adjusted for number of underlying conditions and tests, excluded if prior positive test within 90 days (Omicron defined by s-gene target failure)
 - **Children:** Tested December 26, 2021 – February 21, 2022 (Omicron variant increased from 74 to >99% weekly in nationally sequenced specimens)
- 

ICATT: Pfizer-BioNTech 2-dose VE against symptomatic infection by variant and time since 2nd dose receipt, adults ages ≥18 years, Dec 10, 2021-Jan 1, 2022



- VE for 2 doses of Pfizer-BioNTech against symptomatic Omicron infection:

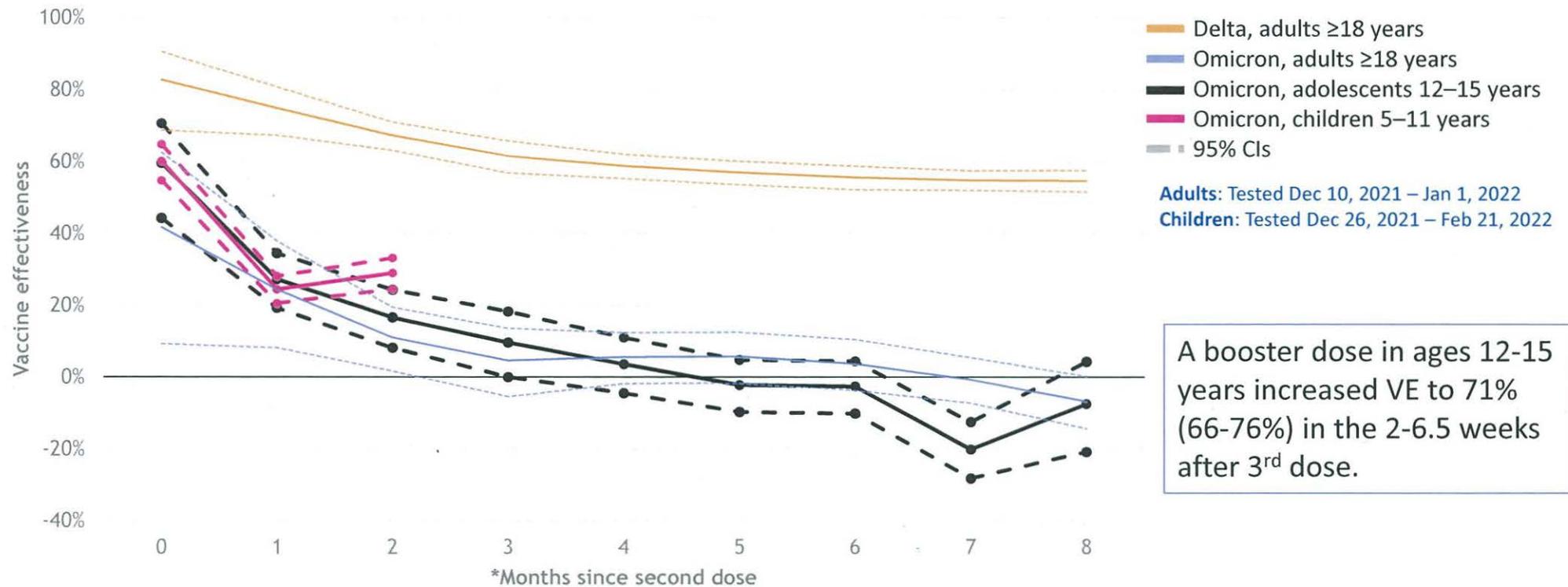
- Starts lower than 2-dose VE against Delta infection
- No longer significant by 3 months after second dose receipt

— VE for Delta
- - 95% CI for Delta
— VE for Omicron
- - 95% CI for Omicron

*Vaccination dose dates are collected as month and year. Month 0 represents tests in the same month as 2nd dose (at least 2 weeks after 2nd dose). For all months greater than or equal to 1 the value represents the difference between calendar month of test and calendar month of 2nd dose receipt (at least 2 weeks after 2nd dose).

Accorsi EK, Britton A, Fleming-Dutra KE, et al. Association Between 3 Doses of mRNA COVID-19 Vaccine and Symptomatic Infection Caused by the SARS-CoV-2 Omicron and Delta Variants. JAMA. 2022;327(7):639-651. doi:10.1001/jama.2022.0470

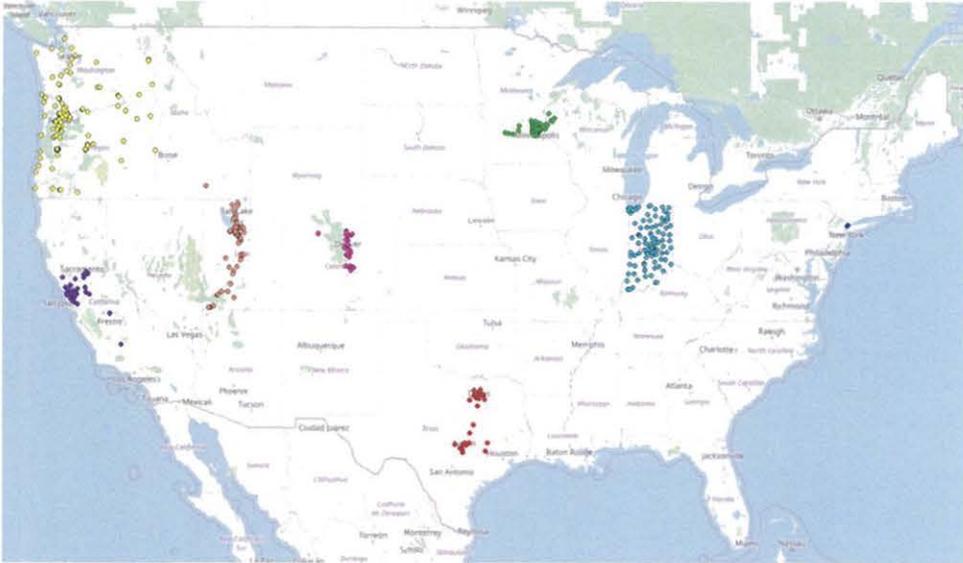
ICATT: Pfizer-BioNTech 2-dose VE against symptomatic infection, by age group and variant



A booster dose in ages 12-15 years increased VE to 71% (66-76%) in the 2-6.5 weeks after 3rd dose.

*Vaccination dose dates are collected as month and year. Month 0 represents tests in the same month as 2nd dose (at least 2 weeks after 2nd dose). For all months greater than or equal to 1 the value represents the difference between calendar month of test and calendar month of 2nd dose receipt (at least 2 weeks after 2nd dose).

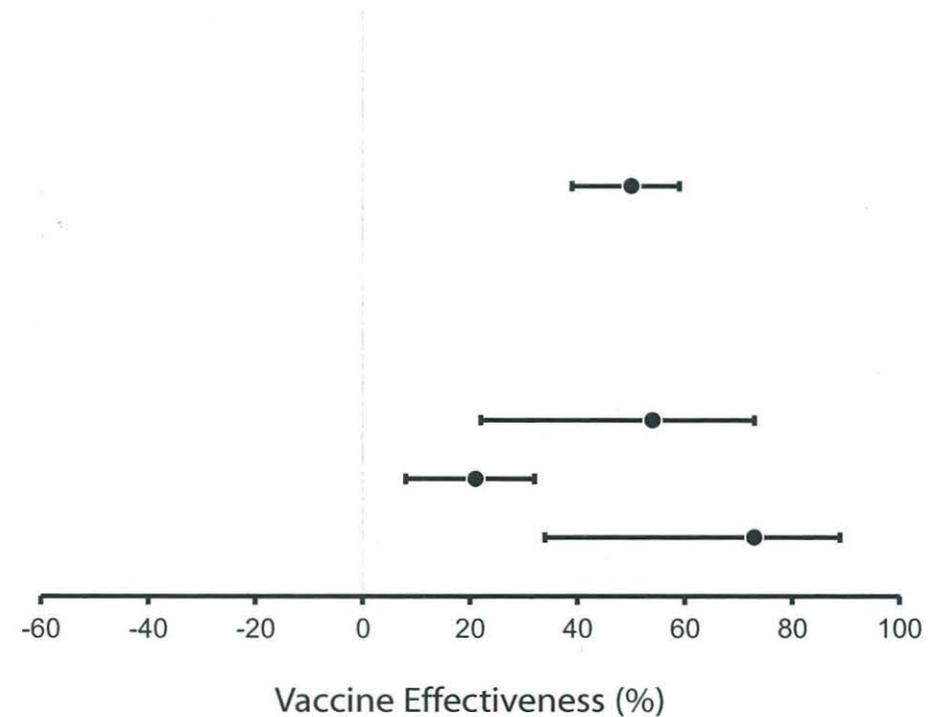
VISION Multi-State Network of Electronic Health Records



- **Cases:** COVID-like illness (CLI) with positive PCR for SARS-CoV-2 within 14 days before or 72 hours after the admission or encounter
- **Controls:** CLI with negative PCR for SARS-CoV-2
- Delta vs. Omicron determined by time when Omicron predominated in study site (mid-December 2021)
- VE adjusted by propensity to be vaccinated weights, calendar time, region, local virus circulation, and age
- Vaccination documented by electronic health records and state and city registries

VISION: mRNA VE for ED/UC visits by number of doses and time since last dose receipt for children and adolescents during Omicron, Dec 2021–Mar 2022

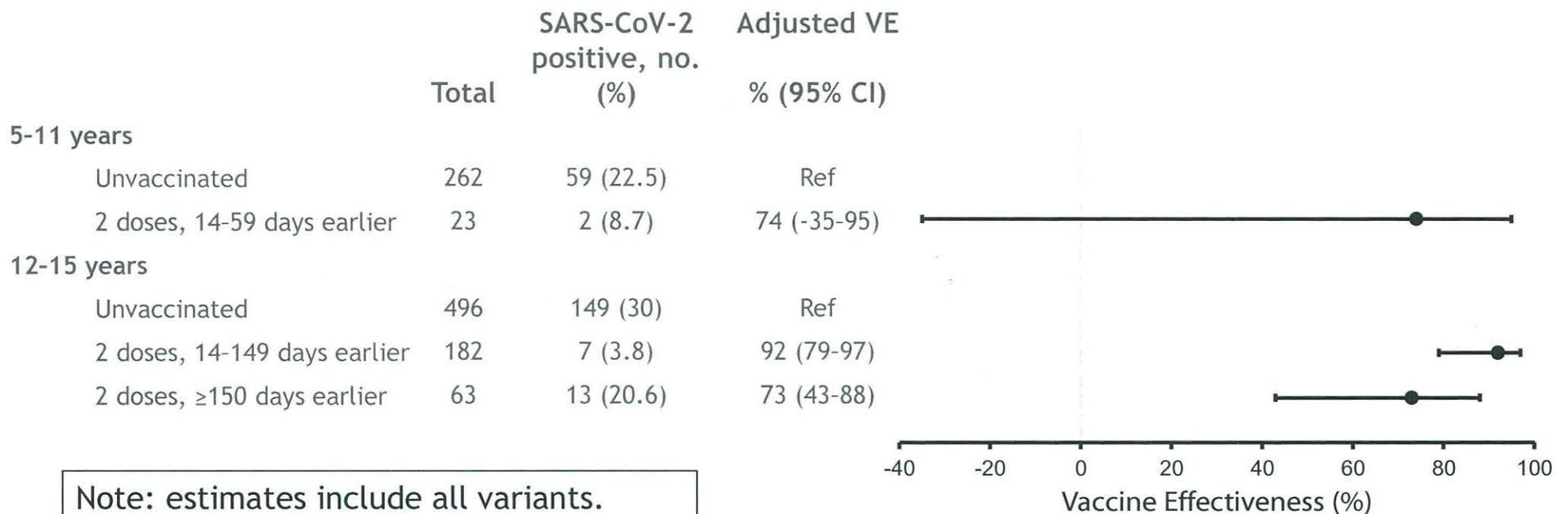
	Total	SARS-CoV-2 positive, N (%)	VE (95% CI)
5-11 years			
Unvaccinated	13611	2736 (20)	Ref.
2 doses 14-59 days	1297	205 (16)	50 (39-59)
12-15 years			
Unvaccinated	4034	1192 (30)	Ref.
2 doses 14-59 days	151	22 (15)	54 (22-73)
2 doses ≥60 days	2219	573 (26)	21 (8-32)
3 doses ≥7 days*	236	8 (3)	73 (34-89)



* Median days from 3rd dose to ED/UC encounter: 45 (IQR 27-64)

CDC, preliminary unpublished data. Individuals with prior infections excluded. Logistic regression conditioned on calendar week and geographic area, and adjusted for age, sex, race, ethnicity, local virus circulation, respiratory or non-respiratory underlying medical conditions, and propensity to be vaccinated
 COVID-like illness: included acute respiratory illness (e.g., COVID-19, respiratory failure, or pneumonia) or related signs or symptoms (cough, fever, dyspnea, vomiting, or diarrhea)

VISION: mRNA VE against hospitalization, all variants, ages 5-15 years, Apr 9, 2021-Jan 29, 2022



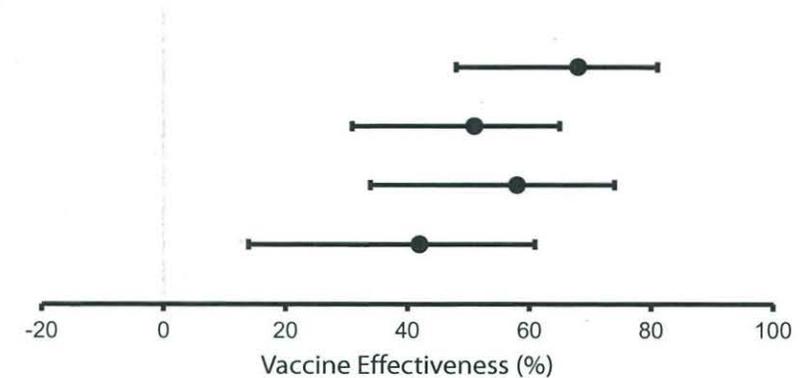
Note: estimates include all variants.
 - 5-11 years: 190 (67%) due to Omicron
 - 12-15 years: 111 (15%) due to Omicron

Overcoming COVID-19 Methods

- **Design:** Case-control test-negative design
- **Population:** Children and adolescents hospitalized at 31 pediatric medical centers in 23 U.S. states
- **Case status (RT-PCR or antigen)**
 - Cases tested SARS-CoV-2 positive
 - Controls tested SARS-CoV-2 negative
- **Vaccination status (documented or plausible self-report)**
 - Fully vaccinated with Pfizer-BioNTech vaccine (dose 2 is ≥ 14 days prior to illness onset)
 - Or unvaccinated by illness onset
- **Logistic regression to estimate VE against hospitalization (VE_s)**
 - Comparing odds of being fully vaccinated vs unvaccinated in COVID-19 cases and controls
 - $VE_s = 100 \times (1 - \text{adjusted odds ratio})$
 - Adjusting for admission date, hospital region, age, sex, race/ethnicity

Overcoming COVID-19 platform: VE for 2 doses of Pfizer-BioNTech vaccine against hospitalization, Dec 19, 2021-Apr 27, 2022

	No. vaccinated COVID-19 patients/Total no. COVID-19 patients (%)	Adjusted VE % (95% CI)
5–11 years*	25/325 (8)	68 (48-81)
12–18 years	109/286 (38)	51 (31-65)
2–22 weeks since vaccination	42/219 (19)	58 (34-74)
23–45 weeks since vaccination	67/244 (27)	42 (14-61)

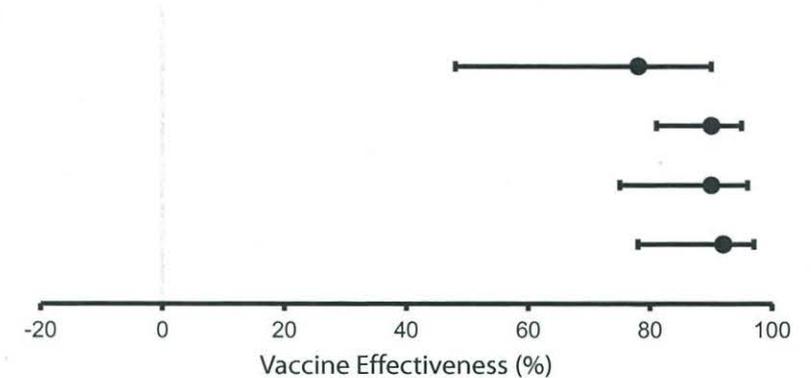


*median time from vaccination to hospitalization is 37 days

CDC preliminary unpublished data. Methods from: Price AM, Olson SM, Newhams MM, Halasa NB, Boom JA, Sahni LC, Pannaraj PS, Irby K, Blinc KE, Maddux AB, Nofziger RA, Cameron MA, Walker TC, Schwartz SP, Mack EH, Smallcomb L, Schuster JE, Hobbs CV, Kamidani S, Tarquinio KM, Bradford TT, Levy ER, Chiotos K, Bhumbra SS, Cvijanovich NZ, Heidemann SM, Cullimore ML, Gertz SJ, Coates BM, Staat MA, Zinter MS, Kong M, Chatani BM, Hume JR, Typpo KV, Maamari M, Flori HR, Tenforde MW, Zambrano LD, Campbell AP, Patel MM, Randolph AG; Overcoming Covid-19 Investigators. BNT162b2 Protection against the Omicron Variant in Children and Adolescents. *N Engl J Med.* 2022 Mar 30. doi: 10.1056/NEJMoa2202826. Epub ahead of print. PMID: 35353976.

Overcoming COVID-19 platform: VE for 2 doses of Pfizer-BioNTech vaccine against MIS-C, Jul 1, 2021-Apr 7, 2022

	No. vaccinated MIS-C patients/Total no. MIS-C patients (%)	Adjusted VE % (95% CI)
5–11 years	10/144 (7)	78 (48-90)
12–18 years	14/160 (9)	90 (81-95)
28-120 days since vaccination	7/153 (5)	90 (75-96)
≥121 days since vaccination	7/131 (5)	92 (78-97)

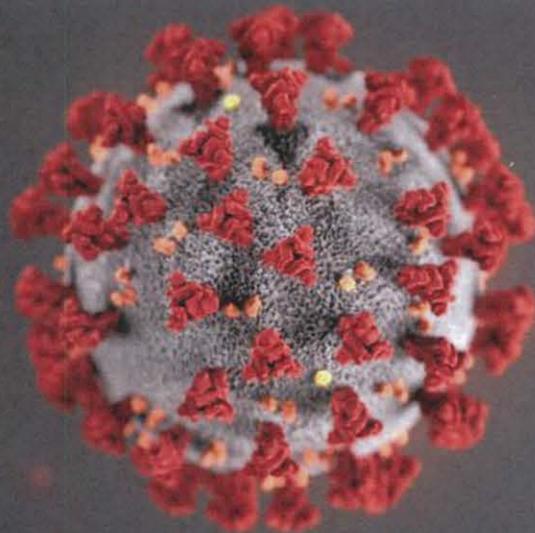


Summary

- Infection
 - 2-dose VE declines quickly in children and adolescents, following similar pattern to adults during Omicron
 - A booster dose in adolescents significantly improved VE at least 6 weeks-3 months after the 3rd dose
- Emergency department/urgent care visits
 - 2-dose VE was higher for ED/UC visits compared to infection.
 - Declined once >60 days after the 2nd dose for adolescents
 - A booster doses in ages 12-15 years significantly improved VE
- Severe disease: hospitalization and MIS-C
 - 2-doses provided protection for both children and adolescents, with some waning evident for hospitalization in adolescents
 - Not enough data to assess waning in 5-11 or impact of booster dose in 12-15

Acknowledgements

- Tamara Pilishvili
- Sara Oliver
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 - Samantha Olson
 - Manish Patel
 - Mark Thompson
 - Laura Zambrano



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.



ORIGINAL ARTICLE

BNT162b2 Protection against the Omicron Variant in Children and Adolescents

A.M. Price, S.M. Olson, M.M. Newhams, N.B. Halasa, J.A. Boom, L.C. Sahni, P.S. Pannaraj, K. Irby, K.E. Blaine, A.B. Maddux, R.A. Nofziger, M.A. Cameron, T.C. Walker, S.P. Schwartz, E.H. Mack, L. Smallcomb, J.E. Schuster, C.V. Hobbs, S. Kamidani, K.M. Tarquinio, T.T. Bradford, E.R. Levy, K. Chiotos, S.S. Bhumbra, N.Z. Cvijanovich, S.M. Heidemann, M.L. Cullimore, S.J. Gertz, B.M. Coates, M.A. Staat, M.S. Zinter, M. Kong, B.M. Chatani, J.R. Hume, K.V. Typpo, M. Maamari, H.R. Flori, M.W. Tenforde, L.D. Zambrano, A.P. Campbell, M.M. Patel, and A.G. Randolph, for the Overcoming Covid-19 Investigators*

ABSTRACT

BACKGROUND

Spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) B.1.1.529 (omicron) variant, which led to increased U.S. hospitalizations for coronavirus disease 2019 (Covid-19), generated concern about immune evasion and the duration of protection from vaccines in children and adolescents.

METHODS

Using a case-control, test-negative design, we assessed vaccine effectiveness against laboratory-confirmed Covid-19 leading to hospitalization and against critical Covid-19 (i.e., leading to receipt of life support or to death). From July 1, 2021, to February 17, 2022, we enrolled case patients with Covid-19 and controls without Covid-19 at 31 hospitals in 23 states. We estimated vaccine effectiveness by comparing the odds of antecedent full vaccination (two doses of BNT162b2 messenger RNA vaccine) at least 14 days before illness among case patients and controls, according to time since vaccination for patients 12 to 18 years of age and in periods coinciding with circulation of B.1.617.2 (delta) (July 1, 2021, to December 18, 2021) and omicron (December 19, 2021, to February 17, 2022) among patients 5 to 11 and 12 to 18 years of age.

RESULTS

We enrolled 1185 case patients (1043 [88%] of whom were unvaccinated, 291 [25%] of whom received life support, and 14 of whom died) and 1627 controls. During the delta-predominant period, vaccine effectiveness against hospitalization for Covid-19 among adolescents 12 to 18 years of age was 93% (95% confidence interval [CI], 89 to 95) 2 to 22 weeks after vaccination and was 92% (95% CI, 80 to 97) at 23 to 44 weeks. Among adolescents 12 to 18 years of age (median interval since vaccination, 162 days) during the omicron-predominant period, vaccine effectiveness was 40% (95% CI, 9 to 60) against hospitalization for Covid-19, 79% (95% CI, 51 to 91) against critical Covid-19, and 20% (95% CI, -25 to 49) against noncritical Covid-19. During the omicron period, vaccine effectiveness against hospitalization among children 5 to 11 years of age was 68% (95% CI, 42 to 82; median interval since vaccination, 34 days).

CONCLUSIONS

BNT162b2 vaccination reduced the risk of omicron-associated hospitalization by two thirds among children 5 to 11 years of age. Although two doses provided lower protection against omicron-associated hospitalization than against delta-associated hospitalization among adolescents 12 to 18 years of age, vaccination prevented critical illness caused by either variant. (Funded by the Centers for Disease Control and Prevention.)

This is the exhibit marked "GT-13" referred to in the annexed Affidavit of GEORGE IAN TOWN affirmed at Christchurch this 10th day of June 2022 before me:


Emma Louise Spratt
Solicitor of the High Court
Christchurch

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Patel can be contacted at aul3@cdc.gov or at the Influenza Division, Centers for Disease Control and Prevention, 1600 Clifton Rd. NE, H24-7, Atlanta, GA 30329-4027.

*A list of the Overcoming Covid-19 Investigators is provided in the Supplementary Appendix, available at NEJM.org.

Ms. Price, Ms. Olson, Dr. Patel, and Dr. Randolph contributed equally to this article.

This article was published on March 30, 2022, at NEJM.org.

N Engl J Med 2022;386:1899-909.

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IN THE UNITED STATES, THE MESSENGER RNA (mRNA) vaccine BNT162b2 (Pfizer–BioNTech) is currently authorized for use in persons 5 to 18 years of age.^{1,2} Real-world evaluations have shown the BNT162b2 vaccine to be highly effective at reducing the risk of hospitalization and death from coronavirus disease 2019 (Covid-19) among adolescents 12 to 18 years of age, but data on its effectiveness among children 5 to 11 years of age are limited.^{3–8} Moreover, the studies involving adolescents have been limited to measuring effectiveness for approximately 3 months after vaccination, and they preceded circulation of the B.1.1.529 (omicron) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Studies in adult populations indicate that the effectiveness of two vaccine doses against Covid-19 wanes and is lower against the omicron variant than against the B.1.617.2 (delta) variant.^{9–11}

The durability of protection against severe Covid-19 after full vaccination (i.e., after receipt of two doses of BNT162b2) is uncertain but is important to understand as time since vaccination increases. Furthermore, the recent emergence of the omicron variant, against which the neutralization efficiency of BNT162b2 is reduced, coupled with increases in Covid-19 hospitalizations among children, has prompted concerns about immune evasion.¹² In this analysis, we examined the duration of protection among adolescents 12 to 18 years of age during the delta-predominant period, as well as protection against omicron variant-associated hospitalizations among children and adolescents 5 to 18 years of age. We also evaluated the effectiveness of two doses of BNT162b2 vaccine against Covid-19 leading to hospitalization and against Covid-19 leading to receipt of life-supporting interventions or to death among adolescents 12 to 18 years of age during the period from July 1, 2021, through February 17, 2022, in the United States.

METHODS

STUDY DESIGN

We used a case–control, test-negative design to assess vaccine effectiveness against Covid-19 leading to hospitalization and against critical Covid-19 (i.e., leading to life-supporting interventions or death). In this design, vaccine effectiveness is estimated by comparing the odds of antecedent vaccination among hospitalized case patients who have laboratory-confirmed Covid-19 and control

patients without Covid-19.^{13–17} The dates of emergency use authorization for BNT162b2 varied among the age groups of 16 to 18 years (December 2020), 12 to 15 years (May 2021), and 5 to 11 years (October 2021). Because the time since vaccination was longer among adolescents 12 to 18 years of age than in the other age groups, we assessed duration of protection by comparing effectiveness from 2 to 22 weeks and more than 23 weeks after full vaccination among patients admitted to the hospital during the delta-predominant period (defined as July 1, 2021, to December 18, 2021) or during the period of omicron-variant circulation (defined as December 19, 2021, to February 17, 2022).^{11,18–20} For the age group of 5 to 11 years, estimation of effectiveness was possible only during the omicron period because vaccination had only recently been approved for this age group.

The surveillance protocol, available with the full text of this article at NEJM.org, was reviewed by the Centers for Disease Control and Prevention (CDC) and other participating institutions and was determined to be public health surveillance and not subject to informed-consent requirements; this review was conducted in accordance with applicable federal laws and CDC policy.²¹ The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

STUDY POPULATION

Participants included in this study were identified through active surveillance for Covid-19–associated hospitalizations in 31 pediatric hospitals across 23 states in the CDC-funded Overcoming Covid-19 Network.^{4,22} Case patients were identified through review of hospital admission logs or electronic medical records and included those hospitalized with Covid-19 as the primary reason for admission or with a clinical syndrome consistent with acute Covid-19 (one or more of the following: fever, cough, shortness of breath, loss of taste, loss of smell, gastrointestinal symptoms, receipt of respiratory support, or new pulmonary findings on chest imaging). All case patients had to have had a positive SARS-CoV-2 reverse-transcriptase–polymerase-chain-reaction (RT-PCR) or antigen test result within 10 days after symptom onset or within 72 hours after hospital admission.

We classified control patients as hospitalized patients with a negative SARS-CoV-2 RT-PCR or

antigen test result, with or without Covid-19–associated symptoms.^{4,5} Each matched control patient was selected from among the patients who were hospitalized within the same institution as the case patient, were in the same age category as the case patient (5 to 11 years, 12 to 15 years, or 16 to 18 years), and were hospitalized within 4 weeks before or after the date of admission for the case patient.

We excluded patients who received the SARS-CoV-2 test result more than 10 days after illness onset or more than 72 hours after the admission date, those who were partially vaccinated, those who were vaccinated 0 to 13 days before symptom onset, those whose vaccination status was unknown, and those who had received the mRNA-1273 (Moderna) or Ad26.COV2.S (Johnson & Johnson–Janssen) vaccine, neither of which was authorized for adolescents younger than 18 years of age during the study period. Patients admitted for reasons not related to Covid-19 (e.g., trauma or suicide attempt) who had a positive SARS-CoV-2 test during admission were identified by the enrolling site and excluded from the analysis. Patients who had received a third dose of BNT162b2 were also excluded from the analytic data set because the sample size (12 case patients and 30 control patients) was insufficient for an evaluation of booster-dose protection.

DATA COLLECTION

Demographic characteristics, clinical information about the current illness, and SARS-CoV-2 testing history were obtained through interviews with the patients' parents or guardians and review of electronic medical records. Parents or guardians were asked about Covid-19 vaccination history, including vaccination dates, the number of doses of vaccine, whether the most recent dose occurred in the last 14 days, the location where vaccination occurred, the vaccine manufacturer, and the availability of a Covid-19 vaccination card. Study personnel searched state immunization information systems, electronic medical records, and other sources (including documentation from pediatricians) to verify reported or unknown vaccination status.

VACCINATION STATUS

For this analysis, patients were considered to be vaccinated against Covid-19 on the basis of source documentation or plausible reporting by the patient's parents or guardians if vaccination dates

and location were provided at the time of the interview. Patients were categorized as unvaccinated if BNT162b2 had not been received before illness onset and were categorized as fully vaccinated if the second dose of BNT162b2 had been administered at least 14 days before illness onset.

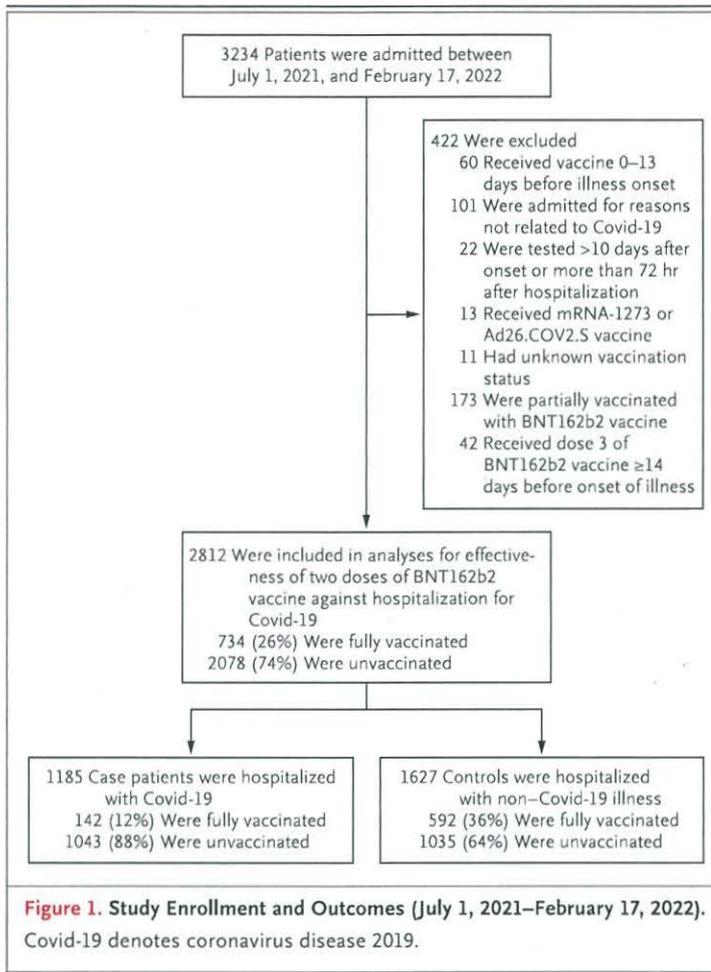
CHARACTERIZATION OF COVID-19 SEVERITY

To evaluate vaccine protection against a gradient of disease severity, we distinguished patients with critical Covid-19 (i.e., Covid-19 leading to life-supporting interventions or death) during their hospital stay. Life-supporting interventions were defined as noninvasive mechanical ventilation (bilevel positive airway pressure or continuous positive airway pressure), invasive mechanical ventilation, vasoactive infusions, or extracorporeal membrane oxygenation during the hospital stay.

STATISTICAL ANALYSIS

Vaccine effectiveness against Covid-19–associated hospitalization was estimated with the use of logistic regression, comparing odds ratios of antecedent vaccination (fully vaccinated vs. unvaccinated) in case patients as compared with controls with the following equation: vaccine effectiveness = $100 \times (1 - \text{odds ratio})$ (Tables S1, S2, and S3 and the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org). We adjusted models a priori for U.S. Census region, calendar time of admission (biweekly intervals), age, sex, and race and ethnic group.^{4,15,23} Using a change-in-estimate approach, we assessed other potential confounding factors (the presence of any underlying health conditions, specific underlying conditions, and the score on the Social Vulnerability Index) that were not included in the final models because these factors did not change the odds ratio for vaccination by more than 5%.^{15,24} We also adjusted the standard error for clustering according to hospital, an analysis that did not substantially alter the results. Time-varying vaccine effectiveness models (a priori) were then constructed by adding a categorical term (2 to 22 weeks vs. >22 weeks, dichotomized on the basis of the median time since vaccination among case patients) for interval from receipt of the second vaccine dose and illness onset.^{18,20} Unvaccinated patients were assigned a value of 0 weeks since vaccination.

To assess vaccine effectiveness against a gradient of disease severity, we conducted analyses



ation for Statistical Computing), and SAS software, version 9.4 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PATIENTS

Among the 3234 eligible patients enrolled during the period from July 1, 2021, to February 17, 2022, a total of 422 (13%) were excluded (Fig. 1). Our analysis involving adolescents included 918 case patients and 1357 control patients who were between 12 and 18 years of age and were admitted to the hospital during the delta period (684 case patients) or omicron period (234 case patients). Among these case patients, the median age was 16 years, and 78% had at least one underlying health condition (Table 1). Among control patients, the median age was 15 years, and 67% had at least one underlying condition. Among the 918 adolescent case patients, 122 (13%) were fully vaccinated and 796 (87%) were unvaccinated. In contrast, among the 1357 adolescent control patients, 542 (40%) were fully vaccinated and 815 (60%) were unvaccinated.

We enrolled 267 case patients and 270 control patients who were children 5 to 11 years of age, all whom were admitted during the omicron period. Among case patients in this age group, the median age was 8 years, and 82% had at least one underlying health condition. Among the control patients, the median age was 8 years, and 73% had at least one underlying condition. Among the 267 case patients, 20 (7%) were fully vaccinated and 247 (93%) were unvaccinated (Table 1). Among 270 control patients, 50 (19%) were fully vaccinated and 220 (81%) were unvaccinated.

CLINICAL SEVERITY OF COVID-19 CASES

Among the 1185 case patients overall, 291 (25%) had critical Covid-19, including 14 who died. Among the 918 case patients who were 12 to 18 years of age, 249 (27%) had critical Covid-19, including 22 (2%) patients who received extracorporeal membrane oxygenation and 13 (1%) who died (Table 2). Among the 249 adolescents with critical Covid-19, 232 (93%) were unvaccinated.

Among the 267 children 5 to 11 years of age with Covid-19, 42 (16%) had critical Covid-19, including 2 patients who received extracorporeal membrane oxygenation and 1 who died. Among the 42 children 5 to 11 years of age with critical Covid-19, 38 (90%) were unvaccinated.

of subgroups defined according to receipt of life-supporting interventions or death in the hospital, with separately constructed models. In addition, models evaluating vaccine effectiveness during the delta period and the omicron period were generated for adolescents 12 to 18 years of age who were age-eligible for vaccination and had sufficient vaccination uptake during both periods. For children 5 to 11 years of age, vaccine effectiveness was calculated only for the omicron period, since these children were not eligible for vaccination until October 29, 2021. Subgroup analyses of time-varying vaccine effectiveness and severity were not possible for children 5 to 11 years of age because of sample-size limitations.

The widths of the confidence intervals were not adjusted for multiplicity, and therefore the intervals should not be used to infer vaccine effectiveness for the subgroup analyses. Statistical analyses were conducted with R software, version 4.0.2 (R Foun-

VACCINE EFFECTIVENESS DURING CIRCULATION OF THE DELTA AND OMICRON VARIANTS

Vaccine effectiveness during the delta and omicron periods combined was similar in the group of patients who were 12 to 15 years of age and the group of patients who were 16 to 18 years of age (83% [95% CI, 77 to 88] and 82% [95% CI, 74 to 88], respectively) (Fig. 2). Effectiveness against Covid-19–associated hospitalization among adolescents 12 to 18 years of age was higher during the delta period than during the omicron period (92% [95% CI, 89 to 95] vs. 40% [95% CI, 9 to 60]).

In the analysis in which time since vaccination was taken into account, vaccine effectiveness against hospitalization for Covid-19 during the delta period among adolescents 12 to 18 years of age was 93% (95% CI, 89 to 95) during the 2 to 22 weeks after full vaccination and 92% (95% CI, 80 to 97) in the 23 to 44 weeks after full vaccination. In contrast, during the omicron period, vaccine effectiveness against hospitalization for Covid-19 was similar during the 2 to 22 weeks and 23 to 44 weeks after full vaccination (43% [95% CI, –1 to 68] and 38% [95% CI, –3 to 62], respectively).

Among children 5 to 11 years of age, vaccine effectiveness was 68% (95% CI, 42 to 82) against Covid-19–associated hospitalization during the omicron period. The interval from vaccination to Covid-19 hospitalization during the omicron period was longer among participants 12 to 18 years of age than among those 5 to 11 years of age (median, 162 days vs. 34 days).

VACCINE EFFECTIVENESS ACCORDING TO DISEASE SEVERITY AMONG ADOLESCENTS

During the delta period, vaccine effectiveness against critical Covid-19 among adolescents 12 to 18 years of age was 96% (95% CI, 90 to 98), as compared with 91% (95% CI, 86 to 94) against hospitalization without life support. During the omicron period, vaccine effectiveness was 79% (95% CI, 51 to 91) against critical Covid-19, as compared with 20% (95% CI, –25 to 49) against noncritical Covid-19 (Fig. 3). Sample sizes were insufficient for subgroup analysis involving children 5 to 11 years of age.

DISCUSSION

In a multicenter network made up of 31 pediatric hospitals covering 23 states, in which 1185

hospitalized case patients with Covid-19 who were 5 to 18 years of age and 1627 control patients of similar age without Covid-19 were enrolled during the period from July 2021 through February 2022, the effectiveness of two doses of the BNT162b2 vaccine against hospitalization for Covid-19 was sustained through the period of delta-variant circulation. However, during the omicron period, the effectiveness of two doses of BNT162b2 against hospitalization for Covid-19 decreased to 40% among adolescents 12 to 18 years of age, with similar point estimates of effectiveness among those in whom Covid-19 developed within 2 to 22 weeks after vaccination (43%; 95% CI, –1 to 68) or at least 23 weeks after vaccination (38%; 95% CI, –3 to 62). Among adolescents, the estimated effectiveness against omicron-related critical illness was 79% (95% CI, 51 to 91), as compared with 20% (95% CI, –25 to 49) against hospitalization for less-severe illness. For children 5 to 11 years of age, who had only recently been authorized to receive the vaccine and on average had been vaccinated 1 month earlier (median, 34 days), vaccination reduced the risk of hospitalization for Covid-19 during the period of omicron circulation by 68%.

Several studies have shown that the BNT162b2 vaccine was highly effective at reducing the risk of hospitalization and life-threatening illness in adolescents during the delta period,^{3-7,17} but data on duration of protection, protection against omicron, and protection among children 5 to 11 years of age have been limited. A recent study showed a decline in effectiveness against emergency department and urgent care Covid-19 visits among adolescents 12 to 18 years of age, but effectiveness improved with a booster dose among those 16 to 17 years of age.⁸ The study was not powered to assess effectiveness against hospitalization for Covid-19 during the omicron period alone. In adult populations, the protection conferred by two vaccine doses against Covid-19 wanes (more against milder infection than against severe disease) and is lower for omicron than for delta.⁹⁻¹¹ However, a booster dose increases protection, including protection against omicron.

In our analysis involving adolescents 12 to 18 years of age, during the period of delta-variant circulation in the United States, we did not find a decline in protection from two BNT162b2 vaccine doses against hospitalization for Covid-19 for more than 6 months after vaccination. In con-

Table 1. Characteristics of Hospitalized Case Patients and Controls from 31 Pediatric Hospitals in 23 States, July 2021–February 2022.*

Characteristic	Overall (5–18 Yr)		5–11 Yr		12–18 Yr	
	Case Patients (N=1185)	Control Patients (N=1627)	Case Patients (N=267)	Control Patients (N=270)	Case Patients (N=918)	Control Patients (N=1357)
Median age (IQR) — yr	15 (12–17)	15 (14–17)	8 (6–10)	8 (7–10)	16 (14–17)	15 (14–17)
Female sex — no. (%)	574 (48)	787 (48)	115 (43)	121 (45)	459 (50)	666 (49)
Race and ethnic group — no. (%) [†]						
White, non-Hispanic	433 (37)	679 (42)	89 (33)	98 (36)	344 (37)	581 (43)
Black, non-Hispanic	304 (26)	336 (21)	63 (24)	61 (23)	241 (26)	275 (20)
Hispanic, any race	302 (25)	400 (25)	74 (28)	80 (30)	228 (25)	320 (24)
Other, non-Hispanic	69 (6)	114 (7)	18 (7)	14 (5)	51 (6)	100 (7)
Unknown	77 (6)	98 (6)	23 (9)	17 (6)	54 (6)	81 (6)
Median Social Vulnerability Index (IQR) [‡]	0.6 (0.4–0.9)	0.6 (0.2–0.8)	0.6 (0.3–0.8)	0.6 (0.1–0.8)	0.7 (0.4–0.9)	0.6 (0.2–0.8)
Census region — no. (%)						
Northeast	135 (11)	156 (10)	43 (16)	35 (13)	92 (10)	121 (9)
Midwest	300 (25)	442 (27)	57 (21)	97 (36)	243 (26)	345 (25)
South	488 (41)	604 (37)	104 (39)	74 (27)	384 (42)	530 (39)
West	262 (22)	425 (26)	63 (24)	64 (24)	199 (22)	361 (27)
Month of admission — no. (%)						
July 2021	46 (4)	60 (4)	—	—	46 (5)	60 (4)
August 2021	175 (15)	218 (13)	—	—	175 (19)	218 (16)
September 2021	196 (17)	334 (21)	—	—	196 (21)	334 (25)
October 2021	107 (9)	292 (18)	—	—	107 (12)	292 (22)
November 2021	96 (8)	181 (11)	—	—	96 (10)	181 (13)
December 2021	197 (17)	189 (12)	65 (24)	59 (22)	132 (14)	130 (10)
January 2022	326 (28)	295 (18)	180 (67)	175 (65)	146 (16)	120 (9)
February 2022	42 (4)	58 (4)	22 (8)	36 (13)	20 (2)	22 (2)

Underlying health conditions — no./total no. (%)						
At least one underlying condition, including obesity	901/1145 (79)	1089/1598 (68)	207/251 (82)	182/250 (73)	694/894 (78)	907/1348 (67)
Respiratory, including asthma	414/1144 (36)	455/1592 (29)	99/251 (39)	101/250 (40)	315/893 (35)	354/1342 (26)
Cardiovascular	135/1144 (12)	124/1617 (8)	45/251 (18)	16/248 (6)	90/893 (10)	108/1341 (8)
Neurologic or neuromuscular	243/1144 (21)	314/1594 (20)	91/251 (36)	49/250 (20)	152/893 (17)	265/1344 (20)
Immunosuppression or autoimmune	102/1145 (9)	156/1596 (10)	42/251 (17)	22/250 (9)	60/834 (7)	134/1346 (10)
Endocrine, including diabetes	178/1143 (16)	150/1593 (9)	35/250 (14)	15/247 (6)	143/893 (16)	135/1346 (10)
Diabetes	102/1140 (9)	90/1592 (6)	11/249 (4)	9/247 (4)	91/891 (10)	81/1345 (6)
Other chronic conditions§	592/1144 (52)	640/1594 (40)	136/251 (54)	95/250 (38)	456/893 (51)	545/1344 (41)
In-person school attendance — no./total no. (%)¶						
Previous hospitalizations in past year — no./total no. (%)¶	463/727 (64)	683/983 (69)	80/155 (52)	120/170 (71)	383/572 (67)	563/813 (69)
Vaccination status — no. (%)						
Unvaccinated	1043 (88)	1035 (64)	247 (93)	220 (81)	796 (87)	815 (60)
Fully vaccinated	142 (12)	592 (36)	20 (7)	50 (19)	122 (13)	542 (40)
If fully vaccinated, median days from second vaccine to illness onset (IQR)**	145 (81–201)	99 (55–152)	34 (23–52)	39 (25–48)	162 (111–206)	106 (64–156)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.

† Race and ethnic group were reported by the patients or by their parents or guardians or were extracted from the medical record.

‡ Data were missing for 6 patients (2 case patients and 4 controls). Scores on the Social Vulnerability Index range from 0 to 1.0, with higher scores indicating greater social vulnerability. Details regarding this index are available at <https://www.atsdr.cdc.gov/placeandhealth/svi/index.html>. The median scores on the Social Vulnerability Index were based on 2018 data.

§ Other chronic conditions included, but were not limited to, rheumatologic or autoimmune disorder, hematologic disorder, renal or urologic dysfunction, gastrointestinal or hepatic disorder, metabolic or confirmed or suspected genetic disorder, and atopic or allergic condition.

¶ In-person school attendance and previous hospitalization in the past year were based on information reported by parent or guardian.

|| Patients were defined as unvaccinated if they had not received any coronavirus disease 2019 (Covid-19) vaccine before illness onset. Patients were defined as fully vaccinated if they had received both doses of a two-dose BNT162b2 vaccination regimen, with the second dose received at least 14 days before illness onset.

** Dates are based on patients with documented vaccination (138 case patients and 577 controls), not plausible self-report. We used the date of illness onset for case patients and controls with Covid-19–like illness with median value imputed if missing. For controls without Covid-19–like illness, we used the date of admission as the date of illness onset.

Table 2. Clinical Outcomes and Severity among Children and Adolescents Hospitalized with Covid-19.*

Characteristic	Children 5–11 Yr		Adolescents 12–18 Yr			
	Total (N = 267)	Unvaccinated (N = 247)	Fully Vaccinated (N = 20)†	Total (N = 918)	Unvaccinated (N = 796)	Fully Vaccinated (N = 122)‡
ICU admission — no./total no (%)	60/262 (23)	55/244 (23)	5/18 (28)	326/912 (36)	306/790 (39)	20/122 (16)
Critical Covid-19 — no./total no. (%)‡	42/259 (16)	38/241 (16)	4/18 (22)	249/910 (27)	232/789 (29)	17/121 (14)
Invasive mechanical ventilation	18/259 (7)	17/241 (7)	1/18 (6)	96/905 (11)	88/784 (11)	8/121 (7)
Noninvasive mechanical ventilation	26/258 (10)	24/240 (10)	2/18 (11)	195/907 (21)	182/786 (23)	13/121 (11)
Vasoactive infusion	11/259 (4)	9/241 (4)	2/18 (11)	75/908 (8)	69/787 (9)	6/121 (5)
Extracorporeal membrane oxygenation	2/259 (1)	2/241 (1)	0/18	22/907 (2)	21/786 (3)	1/121 (1)
Death before discharge from hospital	1/249 (<1)	1/232 (<1)	0/17	13/879 (1)	11/765 (1)	2/114 (2)
Median hospital length of stay (IQR) — days§	2 (1–5)	2 (1–5)	3 (1–3)	4 (2–7)	4 (2–8)	3 (2–5)

* ICU denotes intensive care unit.

† Patients were described as being fully vaccinated if they had received a second dose of the BNT162b2 vaccine at least 14 days before the onset of illness.

‡ Critical Covid-19 was defined as Covid-19 leading to life support (i.e., noninvasive mechanical ventilation [bilevel positive airway pressure or continuous positive airway pressure] or invasive mechanical ventilation, vasoactive infusions, or extracorporeal membrane oxygenation) or death.

§ Data on length of hospital stay were missing for 20 children 5 to 11 years of age (17 unvaccinated and 3 fully vaccinated) and for 58 adolescents 12 to 18 years of age (47 unvaccinated and 11 fully vaccinated).

trast, effectiveness declined during the omicron period. The lower effectiveness among adolescents 12 to 18 years of age was temporally associated with both a longer time since vaccination and the emergence of the omicron variant. However, the sustained protection in the analysis according to time since vaccination during the delta and omicron periods among adolescents 12 to 18 years of age, with an overall lower effectiveness during the omicron period, suggests that evasion of immunity contributed more to the decline in protection than waning immunity. During the omicron period, effectiveness was also relatively lower among children 5 to 11 years of age than was expected on the basis of an efficacy of 91% against infection, which was observed in a randomized, controlled trial before the omicron variant emerged.²⁵ Reduced neutralization efficiency of the BNT162b2 vaccine against the recently emerged omicron variant has been observed.^{12,26} Ongoing surveillance and future analyses of time since vaccination as more omicron-associated hospitalizations accumulate will help to address whether protection against severe disease is sustained during the omicron period. Evaluations of vaccine effectiveness can also address whether observed declines are related to waning protection that would be bolstered by booster doses of current vaccines (or increasing antigen content) or are instead related to immune evasion, which might require other strategies, such as updates to the vaccine strain.

Our study provides strong evidence for the benefits of vaccination in preventing the most severe forms of disease related to the delta and omicron variants in children and adolescents. During the omicron period, vaccine protection among adolescents 12 to 18 years of age was higher against critical illness (79%) than against noncritical illness (20%). Breakthrough infections can occur in persons who have been vaccinated against respiratory viruses such as SARS-CoV-2 and influenza because sterilizing immunity providing lifelong protection against infection is untenable; variants can emerge against which vaccine-induced antibodies have reduced neutralization efficiency, and preexisting antibodies wane with time.^{27,28} However, these breakthrough infections would be expected to invoke memory B- and T-cell responses, which can limit the progression of disease.^{29–31} Our findings support the premise that vaccination-induced immunity at

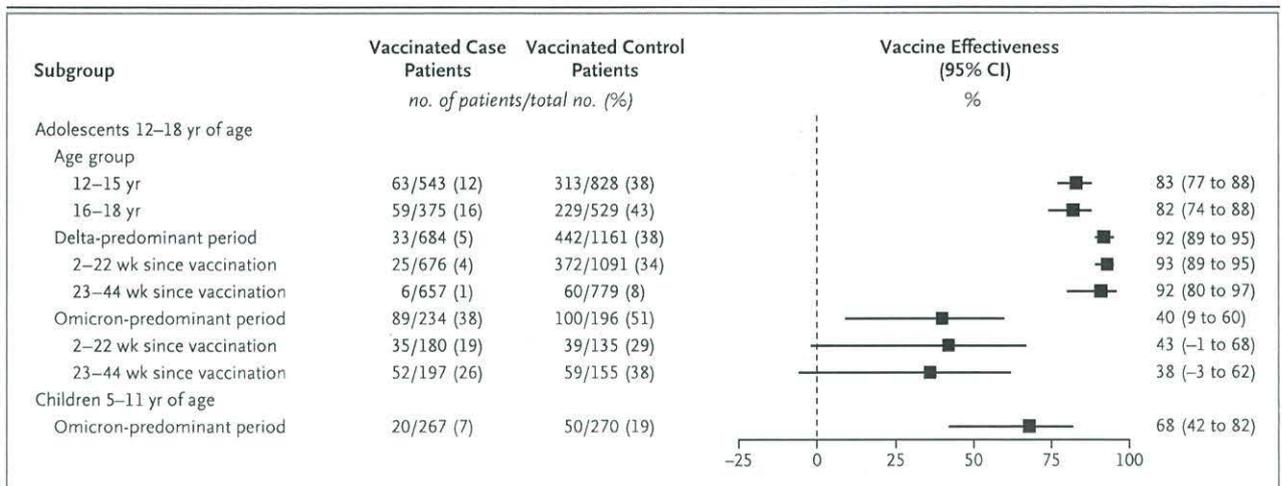


Figure 2. Effectiveness of the BNT162b2 Vaccine against Hospitalization for Covid-19, Stratified According to Age and Variant.

The delta-predominant period was defined as July 1, 2021, through December 18, 2021. The omicron-predominant period was defined as December 19, 2021, to February 17, 2022. For children 5 to 11 years of age, evaluation was limited to the omicron period because of the recent introduction of vaccination in this group (on October 29, 2021). For the subgroup analysis of time since vaccination, 4 case patients were not included because of missing dates of vaccination. Vaccine effectiveness was calculated as $(1 - \text{adjusted odds ratio}) \times 100$, where the odds ratio is the odds of vaccination in case patients as compared with controls.

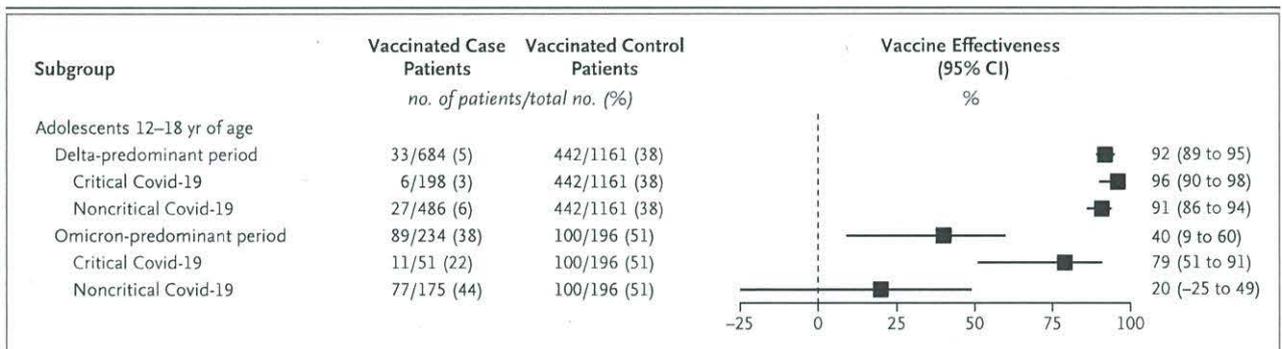


Figure 3. Effectiveness of the BNT162b2 Vaccine against Hospitalization for Critical as Compared with Noncritical Covid-19 in Adolescents 12 to 18 Years of Age, Stratified According to Variant.

Numbers were insufficient to stratify the analysis according to disease severity among children 5 to 11 years of age. In this analysis, only subgroups of case patients were based on disease severity; the entire control group (regardless of disease severity) served as the basis for comparison. Critical Covid-19 was defined as Covid-19 leading to life support (i.e., noninvasive mechanical ventilation [bilevel positive airway pressure or continuous positive airway pressure] or invasive mechanical ventilation, vasoactive infusions, or extracorporeal membrane oxygenation) or death. Information on this outcome was missing for 8 case patients admitted during the omicron period. Vaccine effectiveness was calculated as $(1 - \text{adjusted odds ratio}) \times 100$, where the odds ratio is the odds of vaccination in case patients as compared with controls.

tenuated Covid-19 disease severity without fully eliminating the risk of breakthrough infections in vaccinated children and adolescents. Although no such previous data are available for children, studies evaluating Covid-19 in vaccinated as compared with unvaccinated adults have shown similar disease attenuation.^{10,32} With waning protection against infection and recurrent emergence of variants that evade immunity, ongoing moni-

toring is necessary to ensure that Covid-19 vaccines provide sustained attenuation of illness severity and prevent life-threatening disease.

Our analysis has some limitations. We estimated effectiveness only for the BNT162b2 vaccine, which was widely available for adolescents 12 to 18 years of age in the United States. Because of the recent authorization of the BNT162b2 vaccine for children 5 to 11 years of age in the United

States, the sample and the duration of follow-up since full vaccination were limited. As the pandemic evolves, additional analyses with longer durations of follow-up since vaccination will be important to assess the durability of protection against Covid-19–associated hospitalization, critical illness, and death. Misclassification due to reduced sensitivity of the SARS-CoV-2 assay cannot be ruled out, especially because the use of antigen assays was permitted, although in most case patients (94%) Covid-19 was diagnosed by RT-PCR. Finally, we could not evaluate vaccine effectiveness after a booster dose because eligibility for booster doses was not expanded to include adolescents 12 to 15 years of age until January 2022, and only a small number of patients received a booster dose during the surveillance period in this analysis.

The effectiveness of two doses of BNT162b2 against any hospitalization for Covid-19 was

lower during the omicron period than during the delta period in adolescents 12 to 18 years of age, but vaccination prevented most life-threatening Covid-19 in both periods. Vaccination also reduced the risk of hospitalization for Covid-19 among children 5 to 11 years of age by two thirds during the omicron period, and most children with critical Covid-19 were unvaccinated. Continued monitoring of vaccine effectiveness against severe Covid-19 will be important to inform vaccination strategies as the time since vaccination increases or if new SARS-CoV-2 variants emerge.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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ATAGI recommendations on the use of the paediatric Pfizer COVID-19 vaccine in children aged 5 to 11 years in Australia

21 February 2022

What has changed:

- Third primary dose recommendations for children aged 5-11 years who are severely immunocompromised have been added
- COVID-19 vaccination can be deferred for 4 months (reduced from 6 months) following SARS-CoV-2 infection.

Introduction

A paediatric formulation of the Pfizer COVID-19 vaccine (Comirnaty) has been provisionally approved for use in children aged 5-11 years by the Therapeutic Goods Administration (TGA). This approval is based on the results of a clinical trial demonstrating that the vaccine is highly effective and that most side effects are mild and transient. ATAGI notes that real-world evidence on the safety of this vaccine in children aged 5-11 years is rapidly accumulating overseas, including data on the low rate of rare adverse events following immunisation, notably myocarditis, which the clinical trial was insufficiently powered to assess.

The recommended dose for this age group is 10µg (0.2mL), a third of the recommended 30µg dose for people aged 12 years and over.

ATAGI's recommendations take into account:

- the direct benefits of vaccination for the child in preventing illness
- the indirect benefits of vaccination for the child, their family and for the broader community. To realise some of these benefits, a large proportion of the 5-11 year age group needs to be vaccinated
- adequate supply of the paediatric Pfizer COVID-19 vaccine is available to vaccinate all children aged 5-11 in Australia.

Recommendations

ATAGI provides the following recommendations:

Eligibility

- ATAGI recommends vaccination with the paediatric Pfizer COVID-19 vaccine for all children aged 5-11 years.
- Children aged 5-11 years with medical risk factors for severe illness, Aboriginal and Torres Strait Islander children and children living in crowded conditions or outbreak areas are most likely to benefit from COVID-19 vaccination, given their increased risk of severe outcomes and/or exposure.
- Children aged 5-11 years who have previously had SARS-CoV-2 infection can receive the paediatric Pfizer COVID-19 vaccine. This is recommended following recovery from their illness or vaccination, and can be deferred for up to 4 months. This includes children with a past history of PIMS-TS or post COVID-19 condition ('long COVID').

Schedule

This is the exhibit marked "GT-14" referred to in the annexed Affidavit of **GEORGE IAN TOWN** affirmed at **Christchurch** this 10th day of **June 2022** before me:


Solicitor of the High Court of New Zealand

Emma Louise Spratt
Solicitor
Christchurch

- The recommended schedule for vaccination in this age group is 2 doses, 8 weeks apart.
 - It is appropriate to consider shortening the interval in special circumstances to a minimum of 3 weeks, including:
 - in those due a 3rd dose as part of their primary course due to significant immunosuppression (see below)
 - in those at high risk of severe COVID (for more information, see 'Medical Conditions' at the following link: www.health.gov.au/initiatives-and-programs/covid-19-vaccines/advice-for-providers/clinical-guidance/clinical-features)
 - prior to international travel.
- Severely immunocompromised children aged 5 to 11 years are recommended to receive a 3rd primary dose of COVID-19 vaccine, from 2 months after their second dose, in line with other severely immunocompromised age cohorts.
 - For more information, see: www.health.gov.au/resources/publications/atagi-recommendations-on-the-use-of-a-third-primary-dose-of-covid-19-vaccine-in-individuals-who-are-severely-immunocompromised.
- Children who turn 12 after their first dose should be given the adolescent/adult formulation of the Pfizer COVID-19 vaccine for their second dose.
- The recommended dose interval for children who turn 12 in between their first and second dose is 3–8 weeks and will depend on:
 - the potential for improved immunogenicity and fewer rare side effects with a longer interval
 - local epidemiology
 - individual circumstances, including the underlying risk of COVID-19 to the child and parental wishes.
- ATAGI recommends against use of the adolescent/adult Pfizer COVID-19 vaccine formulation in children aged 5-11 years.

Co-administration

- The paediatric Pfizer COVID-19 vaccine can be co-administered with other vaccines. Parents and guardians should be aware that this may be associated with an increase in mild-moderate adverse events.

Restrictions based on vaccination status

- While vaccination is recommended for children aged 5 to 11 years, ATAGI does not support restricting the activities of children in this age group who are not vaccinated or have only received one dose.

Background

COVID-19 in children

Acute Infection

Most children with SARS-CoV-2 infection are asymptomatic or experience a mild illness. Those who are symptomatic typically have a short illness with a median duration of 5 days (interquartile range [IQR] 2–9 days)¹.

Disease burden in children in Australia

Data from the Australian National Notifiable Diseases Surveillance System from June 6 to October 17, 2021 (during the Delta outbreak), covering jurisdictions for which complete data were available, showed that children aged 5-11 years (8.9% of the total population) were the least likely of all age groups to require hospitalisation or ICU admission for COVID-19. Children aged 5 to 11 years accounted for 0.7% of COVID-19 related hospitalisations in Australia and for 0.04% of COVID-19 related ICU admissions over this period.

This reported proportion of hospitalised cases is likely to be an overestimate of severe disease, since children are often hospitalised for social indications (e.g., if their carers are hospitalised with COVID-19).²

Deaths in children due to COVID-19 are rare. Data from the United Kingdom suggest that 2 per every 1 million children infected with the virus died of COVID-19.³

Risk factors for severe illness in children aged 5-11 years

Children with certain medical conditions have an increased risk of severe outcomes from COVID-19. In a large meta-analysis, pre-existing obesity, chronic pulmonary disease, congenital heart disease and neurological disease were found to increase the odds of death due to COVID-19 by approximately 9-fold compared with children with no risk conditions.⁴ The odds for ICU admission were two-fold higher for children with obesity and congenital heart disease and three-fold higher for chronic pulmonary disease.

More detailed data on children in this age group are available from a large study from the USA, assessing the association between the risk of severe COVID-19 and underlying conditions using ICD codes.⁵ Among children hospitalised with SARS-CoV-2 infection, 63% had underlying medical conditions. Obesity was associated with a 3.7-fold higher risk of hospitalisation compared to children with COVID-19 who had no medical risk factors. Other conditions that were associated with an increased rate of hospitalisation from COVID-19 in this age group were neurodevelopmental disorders, epilepsy and/or convulsions and asthma (with risk ratios ranging from 1.4 to 2.2).

Estimates of the prevalence of medical conditions associated with severe COVID-19 disease among Australian children are available from National Health Survey data in 2017-18. In this study, 8.2% of Australian children aged 2-17 were obese.⁶ In a cohort study among children in NSW, the prevalence of underlying medical conditions broadly similar to the risk conditions for severe COVID-19 was 7-8% in those aged 5-10 years.⁷

Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS)

Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS; also known as multisystem inflammatory syndrome in children, MIS-C) is a rare post-infectious inflammatory condition unique to SARS-CoV-2 infection. The estimated incidence of PIMS-TS/MIS-C is 1 in 2,469 cases.⁸ It typically occurs 2-6 weeks following infection with SARS-CoV-2 in children with a median age of 9 years (IQR 5-13 years).⁹ The severity ranges from mild to life-threatening; it can include severe heart disease. Treatment requires hospitalisation and the use of potent anti-inflammatory agents.

Post-COVID-19 condition ('Long COVID')

Post-COVID-19 condition (also known as 'long COVID') describes the presence of a broad array of symptoms for over 3 months following infection with SARS-CoV-2. Published data regarding the prevalence of post-COVID-19 condition in children are limited and few studies have compared symptoms post COVID-19 to those in uninfected children living in similar environments, to determine the attributable risk.¹⁰ Studies suggest that the post-COVID-19 condition is less severe and of shorter duration in children than in adults.¹

Benefits of vaccinating children against COVID-19

Direct benefits against COVID-19 in children

The paediatric Pfizer COVID-19 vaccine has been demonstrated to reduce COVID-19 in children 5-11 years of age. Within an ongoing clinical trial evaluating the paediatric Pfizer COVID-19 vaccine in children aged 6 months to 11 years, results have been reported for the age group 5 to 11 years.¹¹ Among 2,186 trial participants aged 5 to 11 years without evidence of prior COVID-19 infection, two doses of 10µg of paediatric Pfizer COVID-19 vaccine were 90.7% effective (95% CI [confidence interval]: 67.7 to 98.3%) at preventing laboratory-confirmed symptomatic COVID-19 from day 7 after dose 2 (with an interval of 3 weeks between doses). This was based on 3 observed cases among 1,305 paediatric Pfizer COVID-19 vaccine recipients compared to 16 cases among 663 placebo recipients reported between July and September 2021. The three cases in the paediatric Pfizer COVID-19 vaccine group were mild and without fever, whereas most cases in the placebo group had documented fever. Multiple other symptoms were also observed more frequently among cases in the placebo group. There were no cases of severe COVID-19 in either group.

The paediatric Pfizer COVID-19 vaccine has been shown to be immunogenic. Neutralising antibody titres after two 10µg doses of the paediatric Pfizer COVID-19 vaccine in 264 participants aged 5 to 11 years were comparable to those observed in 253 trial participants aged 16- to 25-year-old who received two 30µg doses of the adolescent/adult formulation, with a geometric mean ratio of 1.04 (95% CI: 0.93 to 1.18).¹¹ The proportion achieving seroconversion was 99.2%. Additionally, in a small subset of 34 children studied who received the paediatric Pfizer COVID-19 vaccine, the increase in neutralisation titre against the Delta variant strain from pre-vaccination to after dose 2 was similar to the fold-increase observed for the reference strain (29.5- and 36.5-fold, respectively).

Vaccine effectiveness data from real world experience are not yet available for children aged 5-11 years but are expected in coming months. As of 8 February 2021, over 8.9 million children aged 5-11 years have received at least one dose of the paediatric Pfizer COVID-19 vaccine in the United States, and over 6.6 million have received two doses.¹²

The paediatric Pfizer COVID-19 vaccine is the only vaccine recommended for this age group. Additional SARS-CoV-2 vaccines suitable for use for children aged 5-11 years may become available over time.

Clinical trials were conducted prior to the emergence of the Omicron variant, and the results reflect vaccine efficacy against older strains of SARS-CoV-2. Vaccine efficacy or effectiveness against the Omicron strain in children aged 5-11 years is not yet known.

Indirect benefits to the child

In addition to the reduction in COVID-19 illness, vaccination of young children has the anticipated benefit of reducing the likelihood of school closures and disruptions to extra-curricular and social activities resulting from COVID-19 related public health measures.

Vaccination of this age group is also anticipated to reduce parental absenteeism and isolation of children and their families. These disruptions disproportionately impact on vulnerable groups of children, such as those with disabilities, chronic medical or mental illness, financial hardship, Aboriginal and Torres Strait Islander children, migrant and refugee children, and children in residential care or rural locations.¹³

Reducing disruption of usual activities may have positive impacts on the mental health and well-being of children and their families in allowing them to resume and maintain normal activities that contribute to their educational, physical, psychological and social development. Worldwide, approximately one quarter of children experienced clinically important symptoms of depression during the pandemic, and one in five experienced anxiety symptoms; both of these important types of symptoms increased when compared to pre-pandemic prevalence.¹⁴

In Australia specifically, there was a marked increase in children aged 5-12 years who contacted the Kids Helpline during the first lockdown of the pandemic.¹⁵ The Victorian Commission for Children and Young People found a negative impact of the pandemic on young children's mental health, with increased stress and loneliness due to remote learning.¹⁶

Indirect benefits to close contacts and the community

At the population level, reduced transmission of SARS-CoV-2 among young children may lead to lower SARS-CoV-2 incidence in all age groups. Several published modelling studies suggest that a vaccination program for young children may have an impact on reducing COVID-19 hospitalisations, ICU admissions and deaths in the overall population.¹⁷⁻¹⁹ Because children are a greater proportion of many Aboriginal and Torres Strait Islander communities, these indirect benefits are expected to be greater in these settings.

Children aged 5-11 years who contract SARS-CoV-2 within a school setting have a high likelihood of transmitting to unvaccinated household contacts. The household secondary attack rate was 68% in a study conducted in New South Wales during the 2021 Delta variant outbreak, at a time when COVID-19 vaccine coverage rates were low.²⁰ Transmission to close contacts within the school setting was much less likely, with a secondary attack rate of 3.1% in primary school settings where the index case was a child.²⁰

Rationale for an extended dosing interval

The manufacturer's recommended schedule is 2 doses, 3 weeks apart.

ATAGI recommends a schedule of 2 doses, 8 weeks apart for children 5-11 years of age.

An extended dosing interval may improve immunogenicity and the effectiveness after the second vaccine dose. In adult populations, extending the interval (e.g. to 8 weeks or longer) has resulted in higher antibody concentrations, improved vaccine effectiveness and potentially a longer duration of protection compared with the standard interval.²¹⁻²³ Extended dosing intervals have not yet been directly studied in children, but the same principles apply. The recommendation for an 8 week interval between doses is consistent with other National Immunisation Technical Advisory Groups, such as NACI, Canada.²⁴

A longer dosing interval may also reduce the risk of myocarditis and pericarditis after vaccination. In a population-based cohort study evaluating passive vaccine safety surveillance data in Ontario, Canada, rates of myocarditis and pericarditis after the Pfizer COVID-19 vaccine in people aged 12 years and over were higher in those with an inter-dose interval of 30 days or less, and were lowest in those with an inter-dose interval of 56 days or more.²⁵ However, it should be noted that this study did not include children aged 5-11 years. Furthermore, an 8 week dosing interval will enable a longer time period for observation of international data regarding potential rare adverse events in this age group, such as myocarditis.

It is appropriate to consider shortening the interval in special circumstances to a minimum of 3 weeks, including:

- in those due a 3rd dose as part of their primary course due to significant immunosuppression
- in those at high risk of severe COVID
 - for more information, see 'Medical Conditions' at the following link: www.health.gov.au/initiatives-and-programs/covid-19-vaccines/advice-for-providers/clinical-guidance/clinical-features)
- prior to international travel.

Severely immunocompromised children aged 5 to 11 years are recommended to receive a 3rd primary dose of COVID-19 vaccine, from 2 months after their second dose, in line with other severely immunocompromised age cohorts. For more information, see: www.health.gov.au/resources/publications/atagi-recommendations-on-the-use-of-a-third-primary-dose-of-covid-19-vaccine-in-individuals-who-are-severely-immunocompromised.

Risks relating to vaccine adverse events

The paediatric Pfizer COVID-19 vaccine was demonstrated to be well tolerated in 5-11 year old children in the phase II/III clinical trial, with most adverse events being mild and transient.¹¹

Pain at the injection site was the most frequently reported adverse event (in 74.1% of participants after dose 1 and 71.0% after dose 2). Although infrequent, local redness and swelling were more common in children than in young adults. Conversely, systemic adverse reactions after both dose 1 and dose 2 were less frequently observed in 5-11 year old children than in 16-to-25 year olds. The systemic adverse reactions most frequently reported were fatigue, headache, muscle pain, chills and fever, with the latter occurring in 6.5% of children after dose 2. There were no serious adverse events reported in the trial that were considered to be related to vaccination. Local and systemic adverse events in the 5-11 year age group were milder than in the 16-25 year age group.²⁶

The Pfizer clinical trial and safety expansion population included a total of approximately 3000 children who received the trial vaccine. The trial was therefore not powered to detect any rare unanticipated adverse events or to assess rates of myocarditis and pericarditis following immunisation in this age group. As of 8 February 2021, over 8.9 million children aged 5-11 years have received at least one dose of the paediatric Pfizer COVID-19 vaccine in the United States, and over 6.6 million have received two doses.¹²

Data on the safety of the vaccine is available in this large real-world population, which is already greater in number than the total population aged 5-11 years in Australia of 2.3 million.

Myocarditis and pericarditis following mRNA vaccines

Myocarditis and pericarditis have been associated with the use of mRNA COVID-19 vaccines. Both are very rare adverse events. The people at highest risk of developing myocarditis and/or pericarditis after mRNA COVID-19 vaccines are males under the age of 30 years (particularly adolescent males) with no other risk factors currently identified.

Most cases of myocarditis associated with mRNA COVID-19 vaccines in people aged ≥ 16 years have resolved within several weeks. However, some symptoms can persist for a few weeks to months. In an ongoing study conducted by the US CDC, about 50% of these patients reported no symptoms at 10-12 weeks post-vaccination, and about a quarter of patients reported fatigue, palpitations, shortness of breath or chest pain.²⁷ At 3 months post-vaccination, about 90% of patients were assessed by their healthcare provider to be either 'fully recovered' (74%) or 'probably fully recovered, awaiting additional information' (17%).

The risk of myocarditis after Pfizer second dose COVID-19 vaccination in children aged 5-11 years from US surveillance networks is estimated to be 2.0 per million doses for females and 4.3 per millions for males.²⁸ This is several-fold lower than the reporting rates in adolescents and young adults²⁸. Myocarditis due to other (non COVID-19) causes is more common in male children than in females, and is more common in adolescents than in children aged 5-11 years.^{29,30}

Anticipated uptake of COVID-19 vaccine in children and young adolescents

In Australia, COVID-19 vaccination in the 12- to-15-year-old age group commenced on 13 September 2021. This age group is eligible to receive either the adolescent/adult Pfizer COVID-19 vaccine (30 μ g per dose) or the Moderna COVID-19 vaccine. As of 7 February 2022, 77.4% of this cohort was fully vaccinated, and 84.1% had received at least one vaccine dose.³¹ This rapid uptake indicates a high willingness to vaccinate in this age group.

COVID-19 vaccination in 5-11-year-old age group commenced on 10 January 2022. As of 7 February 2021, 0.2% of this cohort was fully vaccinated, and 45.5% had received at least one vaccine dose.¹²

Similarly high levels of vaccine acceptance in younger children are anticipated over time. Survey data suggest that around 80% of Australian adults with children would definitely or probably get their children vaccinated when they are eligible.³² ATAGI emphasise it is very important to provide parents, guardians, and children, as well as immunisation providers, with Australia-specific evidence-based information on COVID-19 epidemiology among children, and vaccine uptake and safety to optimise vaccine coverage. Local surveys on knowledge of COVID-19 vaccines and intent to vaccinate among children and their caregivers will help tailor information.

Issues relating to paediatric and adolescent/adult vaccine formulations

The paediatric Pfizer COVID-19 vaccine is supplied in a 10-dose vial and requires dilution with 1.3mL of normal saline. Each dose administered is 0.2mL containing 10 μ g of mRNA vaccine. The dilution volume, final concentration for administration, and components (excipients) of the vaccine formulation for use in this younger age group differ from the adolescent/adult formulations.

ATAGI recommends using the specific Pfizer COVID-19 vaccine formulation provided for the respective registered age group, for the following reasons:

- There is the potential for administration errors leading to under- or overdose if the adolescent/adult formulation is used to vaccinate children aged 5-11 years.
- Delivering a 10 μ g dose using the adolescent/adult formulation would require accurately drawing and administering up 0.1mL, whereas for the 5-11 year formulation the dose volume is 0.2mL.

- Inadvertent administration of a 30µg dose to a child aged 5–11 years may lead to an increased number or severity of adverse events. In the phase I clinical trial in this age group, the severity of local and systemic adverse events for the 30µg dose level were deemed unacceptable to proceed with using this dose.

It is noted that there may be three separate formulations available concurrently in Australia in the near future:

- two for use in adolescents (aged from 12 years) and in adults: the purple top (PBS buffered formulation requiring diluent to be added; each dose 30ug in 0.3mL), and the grey top: (Tris/sucrose buffered liquid formulation, not requiring dilution; each dose 30ug in 0.3mL)
- one for children aged 5-11 years: (orange top: Tris/sucrose buffered requiring dilution; each dose 10ug in 0.2mL).

Each have different reconstitution requirements and storage times. This reinforces the need for clear guidance, communications and training for providers to reduce the potential for error.

Recommendations regarding co-administration

ATAGI supports co-administration of other childhood vaccines with COVID-19 vaccines, given the importance of ensuring protection against other vaccine-preventable diseases and maintaining high vaccine uptake.

While there are limited data on the immunogenicity and safety of COVID-19 vaccines co-administered with other vaccines³³, based on first principles it is unlikely there will be an impact on the immunogenicity or effectiveness of vaccines given on the same day. Expected adverse events such as local reactions and fever may be increased in the setting of co-administration. It is recommended that parents and guardians be made aware of this prior to vaccine administration.

Recommendations regarding vaccine mandates, restrictions on activities and related public health measures

ATAGI believes the benefits of vaccination, including both direct and indirect benefits to the child, close contact and community warrant a recommendation for vaccination in this age group. Unvaccinated children will remain at greater risk of adverse outcomes related to the COVID-19 pandemic.

There are significant detrimental impacts of exclusion from education and other community settings on children. ATAGI therefore recommends that vaccination should not be mandatory in this age group and being unvaccinated should not be a reason to routinely exclude children from school and other activities critical to their development and well-being.

ATAGI supports the right of children and their guardians to make an informed decision about vaccination.

ATAGI notes:

1. the balance of direct benefits over potential vaccine risks (such as rare cases of myocarditis) is more limited in this age group compared to older individuals
2. the available evidence suggests that the transmissibility of infection in younger children is lower than in older age groups
3. there are significant detrimental effects of exclusion from educational or other settings for any child
4. children in this age group are too young to individually consent for a COVID-19 vaccine and rely on their parents/carers decision-making
5. there may be some exceptional settings where the consequences of transmission may be extreme and may justify exclusion of unvaccinated children (e.g., transplant wards) but these should be considered carefully.

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"GT-15"

An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Recommendation on the use of the Pfizer-BioNTech
COVID-19 vaccine (10 mcg) in children 5-11 years of
age

Published: November 19, 2021

This is the exhibit marked "GT-15" referred to in
the annexed Affidavit of **GEORGE IAN TOWN**
affirmed at **Christchurch** this **10** day of **June 2022**
before me:

Solicitor of the High Court of New Zealand

Emma-Louise Sprott
Solicitor
Christchurch

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH



Public Health
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Canada

PREAMBLE

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI Statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

BACKGROUND

The Pfizer-BioNTech (Comirnaty) mRNA COVID-19 vaccine is the first COVID-19 vaccine authorized in Canada for use in pediatric populations under the age of 12 years. Pfizer-BioNTech [10 microgram (mcg) dose] was approved for children 5-11 years of age on November 19, 2021. The Pfizer-BioNTech (Comirnaty) COVID-19 vaccine has been previously authorized by Health Canada as follows:

- December 9, 2020 for individuals 16 years of age and over under an Interim Order using a 30 mcg dose
- May 18, 2021 for individuals 12 to 15 years of age under an Interim Order using a 30 mcg dose
- September 16, 2021 for individuals 12 years of age and over as a full authorization under the name Comirnaty using a 30 mcg dose

On May 18, 2021, following Health Canada authorization of the Pfizer-BioNTech vaccine (30 mcg dose) for individuals 12 to 15 years of age under the Interim Order, NACI recommended the use of the vaccine in adolescents (Strong NACI Recommendation) based on a review of available evidence including additional clinical trial results in the adolescent population. On August 27, 2021, Health Canada expanded the Interim Order authorization for the Moderna (SpikeVax) COVID-19 vaccine to also include adolescents 12 to 17 years of age. That same day, NACI issued updated guidance on the use of [mRNA COVID-19 vaccines in adolescents](#), incorporating additional evidence including clinical data on the efficacy, safety, and immunogenicity of the Moderna COVID-19 vaccine in adolescents as well as post-market safety and effectiveness reports on both mRNA COVID-19 vaccines. Subsequently, Moderna received full authorization on September 16, 2021 for individuals 12 years of age and over under the name Spikevax.

For further information on the use of the Pfizer-BioNTech vaccine in individuals 12 years of age and older, please refer to [NACI's Recommendations on the use of COVID-19 vaccines](#) and NACI's [Recommendation on the use of mRNA COVID-19 vaccines in adolescents 12 to 17 years of age](#).

NACI's recommendations are aligned with the following goals of the Canadian COVID-19 Immunization Program, updated in October, 2021: i) to enable as many Canadians as possible to be immunized as quickly as possible against COVID-19, while ensuring that high risk populations be prioritized; ii) minimize serious illness and overall deaths while preserving health system capacity; and iii) reduce transmission to protect high risk populations.

METHODS

On October 26, 2021 and November 2, 2021, NACI reviewed the available evidence on the use of the Pfizer-BioNTech COVID-19 vaccine (10 mcg dose) in children 5-11 years of age (including manufacturer's clinical data in the regulatory submission to Health Canada, modeling projections on the impact of a pediatric vaccine program, and post-market safety data for the 30 mcg dose in older age groups). Ethical considerations related to COVID-19 vaccination in pediatric populations were discussed with the Public Health Ethics Consultative Group (PHECG) on May 3, 2021, July 6, 2021 and September 21, 2021. The Canadian Immunization Committee (CIC) provided feedback on key policy questions to ensure alignment with program needs on October 21, 2021. NACI approved their recommendations on the use of mRNA COVID-19 vaccines in children 5-11 years of age on November 11, 2021.

Details of NACI's evidence-informed recommendation development process can be found elsewhere ^(1, 2).

SUMMARY OF EVIDENCE

COVID-19 burden of disease in children

Children 5-11 years of age generally present with mild or asymptomatic SARS-CoV-2 infection. Among the 12 jurisdictions currently reporting detailed age data to PHAC, severe outcomes from COVID-19 such as hospitalization and death are very infrequent in children, occurring in <0.3% and <0.002% of confirmed SARS-CoV-2 infections in children aged 5-11 years. As of November 09, 2021, children aged 5-11 years represent 7.5% of confirmed SARS-CoV-2 infections, 0.3% of COVID-19 associated hospitalizations, 0.3% of COVID-19 associated ICU admissions, and 0.007% of COVID-19 deaths in Canada ⁽³⁾. Persons 12 years of age and older have been eligible to receive COVID-19 vaccines since at least May 2021, depending on age, and recently children 5-11 years of age have represented the population with the highest incidence of confirmed SARS-CoV-2 infection, although hospitalization rates in this age group have remained low during the fourth wave of the pandemic. While the exact prevalence of SARS-CoV-2 seropositivity among children aged 5-11 years is unknown, seroprevalence estimates in children from studies based in Quebec and British Columbia suggest case-level data is likely an underestimate of infection in this age group ⁽⁴⁾.

Children and adolescents are at risk of multisystem inflammatory syndrome in children (MIS-C) following infection with SARS-CoV-2 ⁽⁵⁾. In these age groups, MIS-C is a serious, though uncommon, condition. MIS-C is more frequently reported in males and members of racialized groups or populations, with infrequent comorbidities reported aside from obesity ^(6, 7). A large international cohort study on children with COVID-19 estimated MIS-C to affect between 0.5%-3.1% of all diagnosed pediatric COVID-19 patients and between 0.9%-7.6% of hospitalized

pediatric COVID-19 patients ⁽⁸⁾. As of October 16, 2021, 272 cases of MIS-C in individuals 0-19 years of age have been reported in Canada ⁽⁹⁾. Of these nationally reported cases, over half (59%) were in males, and 40% of cases occurred in children aged 5-11 years, with a median age of 6 years (range: 1 week to 18 years), and 40% of cases occurred in children aged 5 to 11 years. The majority of MIS-C cases in Canada have fully recovered with medical intervention, with no MIS-C associated deaths ⁽⁹⁾.

Myocarditis can also occur as a complication of SARS-CoV-2 infection, including [very rarely] in children ⁽¹⁰⁾.

While evidence is limited in pediatric populations, children may also be at risk of a post-COVID-19 condition (i.e., long COVID or post acute COVID-19 syndrome ⁽¹¹⁾). However, current evidence suggests the risk is lower in children compared to older age groups ^(12, 13).

Children are also at risk of collateral harms of the COVID-19 pandemic. Prolonged schooling disruptions, social isolation, and reduced access to academic and extra-curricular resources have had profound impact on the mental and physical well-being of children and their families. These harms can disproportionately affect some Canadian children and families as compared to others, and the impacts of these harms may further exacerbate social inequities among racialized and Indigenous communities, refugees and other newcomers to Canada, persons living in low-income settings, as well as children with disabilities ⁽¹⁴⁻¹⁹⁾.

Risk factors most frequently associated with severe disease in school-aged children

There is limited evidence on clinical risk factors for severe COVID-19 disease in children aged 5-11 years ⁽²⁰⁾. While not specific to pediatric populations, a rapid review of age-independent risk factors for severe COVID-19 conducted by the Alberta Research Centre for Health Evidence (ARCHE) ⁽²¹⁾ identified strong evidence (moderate or high certainty) for a ≥ 2 -fold increase in mortality from COVID-19, for individuals with Down Syndrome, end-stage kidney disease, epilepsy, neurological disorders including motor neuron disease, multiple sclerosis, myasthenia gravis, and Huntington's disease, as well as type 1 and 2 diabetes. Obesity (BMI > 40) was also identified as a risk factor for a ≥ 2 -fold increase in mortality from COVID-19 (low certainty of evidence). Specifically for individuals 21 years of age and younger, having multiple (≥ 2) chronic comorbidities was identified as a risk factor for severe COVID-19 (moderate certainty of evidence) ⁽²¹⁾. Several recent cohort studies in children and adolescents (≤ 18 years of age) hospitalized for COVID-19 identified the presence of multiple comorbidities ^(22, 23), obesity ⁽²²⁻²⁴⁾, neurological disorders ^(22, 24), feeding tube dependence ⁽²³⁾, and congregate living settings ⁽²³⁾ as independent risk factors for severe COVID-19. Although the relative risk for severe outcomes of COVID-19 may be substantial for children with the comorbidities specified above, the magnitude of the absolute excess risk remains small.

Implications of the SARS-CoV-2 Delta variant on COVID-19 in children

Due to its increased transmissibility compared to other variants of concern, the SARS-CoV-2 Delta variant may pose a higher risk of infection for children when in congregate settings, including in-person schooling, compared to other variants. The Delta variant has been the predominant circulating SARS-CoV-2 strain in Canada since June 2021. A recent rapid review conducted by the Public Health Agency of Canada estimates the Delta variant has increased transmissibility over the Alpha variant by 43-115% ⁽²⁵⁾. However, data from Canada ⁽²⁶⁾ and the United States (US) ⁽²⁷⁾ suggest that COVID-19 disease severity in children since June 2021 remains consistent with previous waves of the pandemic.

Clinical trial data on the Pfizer-BioNTech mRNA COVID-19 vaccine in children 5-11 years of age

Trial design: The Pfizer-BioNTech COVID-19 vaccine was evaluated in an ongoing, randomized, observer-blind, placebo-controlled Phase 1/2/3 clinical trial in healthy children from 6 months to 11 years of age (C4591007) ⁽²⁸⁾. In the Phase 1 dose finding trial, due to the frequency and severity of reactogenicity observed with a 30 mcg dose in the first 4 children 5-11 years of age that received two doses, 30 mcg each, the internal review committee (IRC) recommended that the 30 mcg dose be discontinued and the remaining participants who received 30 mcg as dose 1 received 10 mcg for dose 2 instead (n=12). Based on the reactogenicity and immunogenicity observed in the initial cohort of children 5-11 years of age in the Phase 1 trial, a dose of 10 mcg was selected for the Phase 2/3 trial for this age group. At time of regulatory submission, two cohorts totalling 4,647 participants (initial enrolment cohort: n=2,268; a further safety cohort: n=2,379) 5-11 years of age were randomized 2:1 to receive either two doses of the vaccine (10 mcg mRNA; n=3,109) or placebo (n=1,538), 21 days apart. Follow-up is planned for up to approximately 2 years following the second dose.

Study population: All pediatric study participants for the Phase 2/3 trial were recruited from the US, Finland, Poland and Spain. Children with a history of prior SARS-CoV-2 infection or clinical symptoms/signs of COVID-19, children with known HIV, hepatitis B or hepatitis C, or stable pre-existing disease (defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment) were included. Children with an immunocompromising or immunodeficiency disorder, those with a history of MIS-C, or those receiving immunosuppressive therapy (including cytotoxic agents and systemic glucocorticoids) were excluded.

Cohort 1: 1,518 participants randomized to receive the Pfizer-BioNTech COVID-19 vaccine (10 mcg); 750 randomized to receive placebo, with a minimum duration of safety follow-up of 2-months post second dose (median duration of follow-up 3.3 months; data cut-off October 8, 2021). A preliminary descriptive efficacy analysis was also based on this cohort. A randomly selected subset of Cohort 1 was included in the immunogenicity analysis detailed below.

Cohort 2: 1,591 participants randomized to receive the Pfizer-BioNTech COVID-19 vaccine (10 mcg); 788 randomized to receive placebo, with a median duration of safety follow-up of 2.4 weeks post second dose (data cut-off October 8, 2021). Interim safety data from Cohort 2 were provided at the time of regulatory submission.

Immunogenicity comparator group: This was a randomly selected subset (n=300) of participants aged 16- 25 years from the earlier Phase 2/3 study C4591001 who received two doses of the Pfizer-BioNTech COVID-19 vaccine (30 mcg), 21 days apart.

Demographics: Demographic characteristics were similar in Cohort 1 and Cohort 2 study participants. Overall, 48.6% of participants were female, the median age at vaccination was 8.0 years (range: 5-11 years), 20% of participants had an underlying comorbidity, and the most commonly reported comorbidity was obesity (BMI \geq 95th percentile; 11.4% of participants). 8.7% of participants in Cohort 1 and 10.3% of participants in Cohort 2 reported a positive baseline status for SARS-CoV-2 infection. No participants aged 5-11 years with known HIV were enrolled in the trial.

Safety: Overall, the Pfizer-BioNTech COVID-19 vaccine was well tolerated in children 5-11 years of age. The frequencies of reported solicited local and systemic events are provided in the Appendix. Local reactions were very common and mostly mild to moderate in severity. The median onset of solicited local reactions was 1-2 days after any dose and reactions resolved after a median of 1-2 days. Compared to Phase 3 participants \geq 12 years of age in study C4591001 (who received a 30 mcg dose), children 5-11 years of age that received a 10 mcg dose had similar frequencies of pain at the injection site and higher frequencies of swelling and redness.

Systemic events were predominantly fatigue, headaches, muscle pain, chills, fever, and joint pain (in order of descending frequency) and occurred more frequently after the second dose. Fatigue after dose 1 occurred at similar rates in the vaccinated and placebo group, but was higher in the vaccinated group, compared to placebo, after dose 2. The median onset day for most solicited systemic events after either dose of vaccine was 1 to 4 days post-vaccination, with a median duration of 1 day. Most systemic events were mild or moderate in severity. In the vaccine group, the highest frequencies of systemic events graded as severe after dose 1 and dose 2 were for fatigue (0.3% and 0.7%); fever $> 38.9^{\circ}\text{C}$ after dose 1 and dose 2 was reported in 0.2% and 0.6% of participants. One vaccinated participant had a fever of 40.0°C that occurred 2 days after dose 2 and resolved within 1 day.

Compared to Phase 3 participants \geq 12 years of age in study C4591001 (who received a 30 mcg dose), systemic reactogenicity in children 5-11 years of age receiving a 10 mcg dose was comparable and less frequent for some events (such as fever, chills, headache, and fatigue).

Serious adverse events and other adverse events of interest

In Cohort 1 participants 5-11 years of age (vaccine, n=1,518 and placebo n=750), vaccination-related lymphadenopathy (unsolicited adverse event [AE]) occurred in 0.7% of vaccine recipients. A 6-year-old female in the vaccine group, had an AE of Henoch-Schonlein purpura which was

diagnosed 21 days after dose 1 and was considered non-serious. A 5-year-old female in the vaccine group with transient neutropenia reported at baseline, had an AE of severe neutropenia (worsening from baseline) which was diagnosed 3 days after dose 1 and was considered non-serious and related to the intervention. The patient was withdrawn from the study and dose 2 was not administered. No allergic events or anaphylactoid reactions were reported after either dose. No serious adverse events (SAE) related to the vaccine, no cases of MIS-C, myocarditis/pericarditis or deaths were reported. Given the trial was limited to n=3,109 participants randomized to receive the Pfizer-BioNTech vaccine, it is unlikely that any AE occurring at a frequency less often than 1 in 1,000 would be detected.

Expanded safety data

The findings for Cohort 2 participants (vaccine, n= 1,591 and placebo, n= 778 for placebo) were limited to a median follow-up duration of 2.4 weeks after dose 2 at time of data cut-off.

Preliminary safety data available on Cohort 2 participants suggested a similar profile to the initial safety dataset ⁽²⁹⁾. No cases of myocarditis/pericarditis, MIS-C, anaphylaxis or anaphylactoid reactions or deaths were reported.

Concurrent administration with other vaccines

A small percentage ($\leq 0.8\%$) of trial participants were administered a different non COVID-19 vaccine concurrently with the Pfizer-BioNTech vaccine or placebo. No analyses were performed to determine the impact of concurrent administration of other vaccines on safety or other outcomes.

Immunogenicity: The humoral immune response was evaluated based on SARS-CoV-2 50% neutralizing antibody titres (NT-50) assessed one month following the second dose. A 1.5-fold non-inferiority criterion was pre-established to compare immune responses in children 5-11 years of age to that in adolescents and young adults 16-25 years of age (point estimate of the geometric mean ratio [GMR] of titres ≥ 0.8 and lower bound of the 2-sided 95% confidence interval (CI) for the GMR of titres > 0.67). The GMR of titres in children 5-11 years of age (n=264) relative to those in 16- 25 years of age (n=253) was 1.04 (95% CI: 0.93 to 1.18), meeting both criteria for non-inferiority. Immunogenicity data in children following dose 1 and prior to dose 2 were not assessed.

A smaller randomly selected subset of 38 participants aged 5-11 years were assessed for neutralization titres against both the Delta variant and wild-type strain using a non-validated plaque reduction neutralization assay. Of the 38 participants, 34 received the vaccine and 4 received placebo, and all were without evidence of prior SARS-CoV-2 infection. Neutralization of both the wild-type strain and the Delta variant were comparable by NT-50 assay in participants that received the vaccine, one month following dose 2 [GMT: 365.3 (95% CI: 279.0 to 478.4) for the wild-type strain, and 294.0 (95% CI: 214.6 to 405.3) for the Delta variant]. Participants that received the placebo had a GMT of 10 (95% CI: 10 to 10) for both the wild-type and the Delta variant.

Recent evidence suggesting that neutralizing antibodies may serve as a correlate of protection for vaccines against SARS-CoV-2 in humans is evolving⁽³⁰⁾. However, since no correlate of protection has been established for COVID-19 at this time, it is unknown how reported immune responses are related to prevention of SARS-CoV-2 infection or disease or the ability to transmit infection to others.

Efficacy: Preliminary efficacy data were limited to the evaluable efficacy population from Cohort 1 (individuals who did not have evidence of SARS-CoV-2 infection prior to dose 2; 1,305 randomized to receive the vaccine; 663 randomized to receive placebo). As of October 8, 2021 (data cut-off date for analysis), a total of 19 confirmed, symptomatic cases of COVID-19 were identified at least 7 days after dose 2 of the Pfizer-BioNTech COVID-19 vaccine or placebo in study participants 5-11 years of age. The estimated efficacy of the vaccine against symptomatic COVID-19 from 7 days after dose 2 was 90.7% (95% CI: 67.7 to 98.3%; 3 cases identified in the vaccine group and 16 cases in the placebo group). An analysis of efficacy by various subgroups (sex, race, and ethnicity, presence of comorbidities, and country of recruitment) resulted in point estimates of vaccine efficacy (all above 85%) that were similar to the overall estimate. However, many of the subgroup efficacy estimates were based on a small number of cases, resulting in large confidence intervals around these point estimates.

The majority of confirmed cases in study participants were identified in August and September 2021, at a time when the Delta variant was the predominant circulating strain in the US and globally. However, no sequence analysis was reported on case isolates to determine whether they were caused by the Delta variant or another variant.

None of the identified cases met the pre-defined criteria for a severe case of COVID-19, therefore the data did not include estimates of vaccine efficacy against severe outcomes such as hospitalization, MIS-C or death⁽³¹⁾.

Myocarditis and/or pericarditis and MIS-C/A following mRNA COVID-19 vaccination

Cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining around the heart) have been reported following vaccination with mRNA COVID-19 vaccines in Canada and internationally among individuals aged 12 years and older who received the 30 mcg formulation of the Pfizer-BioNTech COVID-19 vaccine or 100 mcg formulation of the Moderna COVID-19 vaccine; however, the risk is considered rare. Symptoms of myocarditis/pericarditis can include shortness of breath, chest pain, or the feeling of a rapid or abnormal heart rhythm. Symptoms can be accompanied by abnormal test results (e.g., electrocardiogram, serum troponins, echocardiogram)⁽³²⁾. Available data indicate that most individuals affected have responded well to conservative therapy and have recovered quickly⁽³³⁾.

Cases of myocarditis/pericarditis following COVID-19 mRNA vaccination occur most commonly in adolescents and young adults (12 to 30 years of age), more often after the second dose, more

often in males than females, more often after Moderna than Pfizer-BioNTech, and usually within a week of vaccination. Emerging Canadian safety surveillance data suggest an extended interval between the first and second dose may reduce the risk of myocarditis/pericarditis associated with the second dose of an mRNA COVID-19 vaccine (note this data is currently under preparation for publication). Data from the US suggest the risk of myocarditis/pericarditis following mRNA COVID-19 vaccination may be higher in older adolescents aged 16-17 years compared to younger adolescents aged 12-15 years⁽³³⁾.

Myocarditis following mRNA COVID-19 vaccination tends to have a similar epidemiologic profile to classic myocarditis (unrelated to COVID-19), as it occurs more commonly in adolescents and young adult males. Classic myocarditis is less common in younger children 5-11 years of age. It is unknown whether myocarditis/pericarditis will occur after the lower doses of mRNA present within pediatric COVID-19 vaccines for children 5-11 years of age⁽³³⁾.

Very rare cases of MIS-C/A (multisystem inflammatory syndrome; in children and in adults, respectively) have been reported following vaccination with COVID-19 mRNA vaccines in Canada and internationally among individuals aged 12 years and older. However, on October 29, 2021, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (EMA-PRAC) issued a statement that there is currently insufficient evidence on a possible link between mRNA COVID-19 vaccines and very rare cases of MIS-C/A⁽³⁴⁾.

Adult/adolescent and pediatric formulations of the Pfizer-BioNTech vaccine

Table 1. Adult/adolescent and pediatric formulations of the Pfizer-BioNTech vaccine

	Adult/adolescent formulation	Pediatric formulation^a
Age	12 years of age and over	5-11 years
Vial Cap Colour	Purple	Orange
Diluent (ONLY use 0.9% Sodium Chloride Injection, USP as the diluent)	1.8 mL	1.3 mL
Dose	0.3 mL (30 micrograms)	0.2 mL (10 micrograms)
Doses per vial	6	10
Potential allergens	Polyethylene glycol (PEG)	Polyethylene glycol (PEG) Tromethamine (Tris, Trometamol) ^b

Post-dilution time Can be at room temperature	6 hours	12 hours
Ancillary supplies	Low dead volume needle/syringe	Low dead volume needle/syringe
Storage^{c,e}	<ul style="list-style-type: none"> • Ultra-frozen until expiry date printed on the label ^g • Frozen for up to 2 weeks ^{f, g} • Refrigerated ^d for up to 1 month • Room temperature ^d for: <ul style="list-style-type: none"> ○ up to 2 hours prior to dilution; ○ up to 6 hours after dilution (i.e., post first puncture) 	<ul style="list-style-type: none"> • Ultra-frozen up to 6 months from the date of manufacture printed on the vial and cartons ^a • Do not store frozen • Refrigerated ^d for up to 10 weeks • Room temperature ^d for: <ul style="list-style-type: none"> ○ up to 12 hours prior to dilution; ○ up to 12 hours after dilution (i.e., post first puncture)
Transport^c	<ul style="list-style-type: none"> • Ultra-frozen full cartons containing vials ^g • Frozen vials up to 2 weeks (included in 2-week limit for frozen storage) ^{f, g} • Refrigerated ^d thawed vials up to 12 hours (included in 1-month limit for refrigerated storage) 	<ul style="list-style-type: none"> • Ultra-frozen full cartons containing vials • Refrigerated ^d full cartons or individual undiluted vials

^a Regardless of storage condition, vaccines should not be used after 6 months from the date of manufacture printed on the vial and cartons.

^b Tromethamine (Tris or trometamol) is used as a buffer in vaccines and medications, including those for use in children, to improve stability and prevent pH fluctuations in the solution. No safety concerns have been identified with tromethamine ⁽³⁵⁾. While tromethamine has been identified as a potential allergen, a review of existing evidence did not identify any cases of allergic reactions to tromethamine in children ⁽³⁶⁾.

^c Ultra Frozen is -90°C to -60°C; Frozen is -25°C to -15°C; Refrigerated is +2°C to +8°C; Room temperature is up to +25°C.

^d Once vials are thawed, they should not be refrozen.

^e During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

^f Frozen vials stored for up to 2 weeks at -25°C to -15°C may be returned one time to ultra-frozen storage. Total cumulative time the vials are stored at -25°C to -15°C should not exceed 2 weeks.

^g Vials must be kept frozen and protected from light, in the original cartons, until ready to thaw.

For complete prescribing information for the pediatric and adult formulations of the Pfizer-BioNTech vaccine, consult the product leaflet or information contained within Health Canada's authorized product monographs available through the [Drug Product Database](#).

Schedule

Refer to Table 2 for a summary of immunization schedules for authorized COVID-19 vaccines for children 5-11 years of age.

Table 2. Immunization schedule for primary series, by COVID-19 vaccine

Vaccine Product	Dose	Immunization Schedule	Minimum Interval	Authorized Interval	NACI - Recommended Interval ¹
Pfizer-BioNTech (Comirnaty; 10 mcg)	0.2mL	2-dose schedule	19 days	21 days	At least 8 weeks

¹There is emerging evidence that longer intervals between the first and second doses of COVID-19 vaccines result in more robust and durable immune response and higher vaccine effectiveness. See Evidence to inform an optimum dosing interval for the primary series of an mRNA COVID-19 vaccine section below. NACI will continue to monitor the evidence and update this interval as needed.

Evidence to inform an optimum dosing interval for the primary series of an mRNA COVID-19 vaccine

Shorter intervals between doses of COVID-19 mRNA vaccines result in lower antibody titres, which may wane to below protective levels more quickly over time. Currently, there is no direct evidence to establish an optimal interval between doses in pediatric populations. However, evidence on COVID-19 mRNA vaccines in adult populations indicates that a longer dose interval such as 8 weeks, compared with the authorized 21-day interval, improves the immune response and is associated with greater vaccine effectiveness that may last longer, which is consistent with general principles of vaccinology⁽³⁷⁻⁴⁰⁾. In addition, emerging Canadian safety surveillance data suggest an extended interval between the first and second dose may reduce the risk of myocarditis/pericarditis following the second dose of an mRNA COVID-19 vaccine (note this data is currently under preparation for publication).

Ethics considerations on the use of the Pfizer-BioNTech COVID-19 vaccine in children 5-11 years of age

The guiding consideration for COVID-19 pediatric vaccine recommendations should be whether vaccination is in children's best interests. Decisions regarding pediatric COVID-19 vaccination programs should not only evaluate the direct and indirect benefits and risks of vaccination in this age group, but also consider principles such as the precautionary principle, equity, trust, and proportionality. There are multiple and intersecting uncertainties at play, including those related to the impact of COVID-19 on children's health; the long-term effectiveness of vaccination in this age group; potential safety concerns (e.g., uncertainty around the risk of myocarditis and pericarditis); and the future progression of the pandemic, including the emergence of variants of

concern. While it is not justified to vaccinate children only to benefit others, the indirect, population-level benefits of vaccination can also benefit children.

The overall safety and effectiveness data are limited for children. While it is justifiable to make recommendations based on available data for children 5-11 years of age, including following the dosing intervals associated with the clinical trial data, the precautionary principle also justifies taking action under conditions of scientific uncertainty to mitigate vaccine-related risks, including through active post-market surveillance. This includes using data available from other age groups and applying vaccination principles.

Generally, a vaccination program is justified if its anticipated benefits outweigh its potential risks. Children aged 5-11 years are unlikely to be deemed capable of consenting to vaccination, and decisions related to their vaccination will likely be made by parents or guardians. Given the short-term uncertainties surrounding pediatric vaccination at this time, children and their parents or guardians should be supported and respected in their decisions regarding COVID-19 vaccinations for the child, whatever decisions they make, and should not be stigmatised for accepting, or not accepting, the vaccination offer.

RECOMMENDATIONS

NACI recommends that a complete series with the Pfizer-BioNTech COVID-19 vaccine (10 mcg) may be offered to children 5-11 years of age who do not have contraindications to the vaccine, with a dosing interval of at least 8 weeks between first and second dose. (Discretionary NACI Recommendation)

- The Phase 2/3 clinical trial had 1,518 children who received the Pfizer-BioNTech COVID-19 vaccine (10 mcg), and 750 who received the placebo; both groups were followed a minimum of 2 months. A further safety cohort of 1,591 received the vaccine and were followed for a median of 2.4 weeks. Interim findings did not indicate any safety concerns and preliminary efficacy against symptomatic COVID-19 was 90.7%. No cases of myocarditis/pericarditis or any other SAE were reported. Any uncommon, rare, or very rare AE that occurs at the frequency less often than 1 in 1,000 would not be detected with this trial size. NACI will closely review emerging evidence and will update their recommendation, as well as its strength, as the evidence base evolves.
- **Children aged 5-11 years with a history of previous SARS-CoV-2 infection (confirmed by PCR or antigen testing from a respiratory specimen) should no longer be considered infectious based on [current criteria](#), and symptoms of an acute illness should be completely resolved prior to vaccination.** Consistent with current recommendations for adolescents and adults with previous infection, two doses of a COVID-19 vaccine may be offered to children with a previous history of SARS-CoV-2 infection. NACI will closely review emerging evidence and will update their recommendation as the evidence base evolves.
- **For children with a previous history of MIS-C, vaccination should be postponed until clinical recovery has been achieved or until it has been ≥ 90 days since diagnosis, whichever is longer.**

- Unlike adolescent and adult populations with defined risk estimates for rare and very rare AEs following COVID-19 vaccination, thorough post-market safety surveillance will be required to inform risk estimates of any AEs that may occur in children 5-11 years of age. Therefore, considering the risk of erroneous attribution of an AEFI to a given vaccine, it may be preferential during early program rollout to refrain from offering concomitant administration of COVID-19 vaccines and other vaccines for children 5-11 years of age. However, feasibility may be challenging for both healthcare providers and parents if multiple visits to healthcare providers are required to administer all recommended immunizations. Concomitant administration or a shortened interval between COVID-19 vaccines and other vaccines may be warranted on an individual basis in some circumstances at the clinical discretion of the healthcare provider. Given these considerations, in the early program rollout:
 - **COVID-19 vaccines for children 5-11 years old should not routinely be given concomitantly (i.e., same day) with other vaccines (live or non-live).** In the absence of evidence, it would be prudent to wait for a period of at least 14 days BEFORE or AFTER the administration of another vaccine before administering a COVID-19 vaccine to prevent erroneous attribution of an AEFI to one particular vaccine or the other. This suggested minimum waiting period between vaccines is **precautionary** at this time.
- Children who receive the 10 mcg Pfizer-BioNTech COVID-19 vaccine for their first dose and who have turned 12 years of age by the time the second dose is due may receive the 30 mcg Pfizer-BioNTech COVID-19 vaccine that is authorized for individuals aged 12 years and older to complete their primary series. If the second dose of 10 mcg is given, the dose should still be considered valid and the series complete.
- Risk of severe outcomes of COVID-19 may be an important element of individual decision-making, and the literature is evolving and emerging to clarify areas of heightened risk with infection. Children at increased risk for severe outcomes may include children who are obese, children who are medically fragile/ have medical complexities, children with more than one comorbidity, children with neurological disorders, and children with immune dysregulation associated with Down Syndrome and other immunocompromising conditions.

Additional Considerations, Summary of Evidence, and Rationale

- The Pfizer-BioNTech COVID-19 vaccine (10 mcg dose) met non-inferiority criteria for generating a humoral immune response to the vaccine in children aged 5-11 years compared to young adults and adolescents aged 16 to 25 years (who received a 30 mcg dose). Interim phase 2/3 findings in children 5-11 years of age suggest the vaccine is efficacious at preventing symptomatic COVID-19, with a similar estimate of vaccine efficacy against symptomatic COVID-19 to that observed in individuals aged 12 years and over. The systemic reactogenicity profile in children ages 5-11 years (10 mcg dose) was lower than that observed for adolescents and young adults (who received a 30 mcg dose).

- The Pfizer-BioNTech vaccine for children 5-11 years of age is authorized as a primary series of two 10 mcg doses given 21 days apart. In adults, emerging evidence suggests that longer intervals between the first and second doses of a primary series result in a stronger immune response and higher vaccine effectiveness that is expected to last longer, compared to shorter intervals. Data from older age groups also suggests an extended interval may also be associated with a reduced risk of myocarditis/pericarditis following a second dose of an mRNA COVID-19 vaccine.
- Rare cases of myocarditis and/or pericarditis have been reported following administration of the Pfizer-BioNTech vaccine (30 mcg dose) in adolescents and young adults 12 years of age and older, most commonly after dose 2 and in males.
- Currently, the risk of myocarditis/pericarditis in children following immunization with the 10 mcg dose of the Pfizer-BioNTech vaccine is unknown. Safety surveillance data from individuals aged 12 and older does not suggest the risk of myocarditis/pericarditis following mRNA COVID-19 vaccination would be greater in children aged 5-11 years compared to older populations. Additionally, the impact of a reduced vaccine dose (10 mcg vs 30 mcg) is also unknown. Real-world evidence in large pediatric populations is required to provide risk estimates of myocarditis/pericarditis and any other AE that may occur in children aged 5-11 years at a frequency less often than 1 in 1,000.
- As a precautionary measure, and consistent with current recommendations for adolescents and adults, **the second dose in the mRNA COVID-19 vaccination series should be deferred in children who experience myocarditis or pericarditis following the first dose of the Pfizer-BioNTech COVID-19 vaccine until more information is available. Children who have a history of myocarditis unrelated to mRNA COVID-19 vaccination should consult their clinical team for individual considerations and recommendations.** If they are no longer followed clinically for cardiac issues, they may receive the vaccine. NACI will continue to monitor the evidence and update recommendations as needed. Caregivers are advised to seek medical attention for children if they develop symptoms including chest pain, shortness of breath, or palpitations following receipt of the Pfizer-BioNTech vaccine.
- The exact prevalence of SARS-CoV-2 seropositivity among children aged 5-11 years is unknown and likely underestimated when inferred by case-level data due to the frequency of mild/asymptomatic infections that may not be captured.
- While most children with COVID-19 have mild or no symptoms, some do become ill and require hospitalization.
- Children with SARS-CoV-2 infection are at risk of MIS-C, a rare but serious syndrome that can occur several weeks following SARS-CoV-2 infection.
- Program planning should ensure equitable access to vaccination information and services and minimize inequities in vaccine acceptance and uptake based on socioeconomic status.
- It is essential that children aged 5-11 years and their parents are supported and respected in their decisions regarding COVID-19 vaccinations for their children, whatever decisions they make, and are not stigmatised for accepting, or not accepting, the vaccination offer.
- Adults, including caregivers and youth who interact with children, should be vaccinated to ensure protection for themselves and to offer additional protection to children.

- In addition to vaccination, public health measures are very important for preventing transmission in children. It is important that everyone, regardless of vaccination status, continue to follow recommended public health measures.
- The Pfizer-BioNTech COVID-19 vaccine is not authorized for use in children under 5 years of age at this time.

RESEARCH PRIORITIES

- NACI recommends continuous monitoring of data on the safety, immunogenicity, efficacy, and effectiveness of the Pfizer-BioNTech COVID-19 vaccine in children through clinical trials and studies in real-world settings, including clinical implications of previous SARS-CoV-2 infection, MIS-C, or myocarditis or pericarditis on the safety, efficacy, and effectiveness of COVID-19 vaccines in pediatric populations and in children considered moderately to severely immunocompromised.
- NACI recommends continuous monitoring of vaccine uptake, particularly according to the socioeconomic status of families with children aged 5-11 years, and for decision makers to consider measures to reduce the risk of socioeconomic disparities in vaccine confidence and uptake.
- NACI recommends vigilant reporting across Canadian jurisdictions for timely assessment of myocarditis and pericarditis cases as well as other potential rare or very rare AEs in pediatric populations following COVID-19 vaccination. In addition, efforts should be made to facilitate investigation of previous SARS-CoV-2 infection in cases of suspected AEFI. Global collaboration should be prioritized to enable data sharing so decision makers around the world can weigh benefits and risks of COVID-19 vaccination for their own specific pediatric populations.
- NACI recommends that further evaluations of dosage intervals and the impact of the interval on effectiveness and safety in children aged 5-11 years should be undertaken.

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ABBREVIATIONS

<i>Abbreviation</i>	<i>Term</i>
AE	Adverse event
AEFI	Adverse event following immunization
ARCHE	Alberta Research Center for Health Evidence
CI	Confidence Interval
CIC	Canadian Immunization Committee
COVID-19	Coronavirus disease 2019
GMR	Geometric mean ratio
GMT	Geometric mean titre
ICU	Intensive Care Unit
MCG	microgram
MIS-C	Multisystem Inflammatory Syndrome in Children
mL	Millilitre
mRNA	Messenger Ribonucleic Acid
NACI	National Advisory Committee on Immunization
NT-50	SARS-CoV-2 50% neutralizing titres
PHAC	Public Health Agency of Canada
PHECG	Public Health Ethics Consultative Group
PCR	Polymerase Chain Reaction
SAE	Serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
US	United States
VE	Vaccine efficacy

APPENDIX A: FREQUENCY OF SOLICITED ADVERSE EVENTS FOLLOWING IMMUNIZATION FOR COVID-19 IN CLINICAL TRIALS

Table 1. Frequency of solicited local AEs in 5 to 11 year olds for the Pfizer-BioNTech COVID-19 vaccine (Comirnaty™)^{a,b}

AEFI	Vaccine		Placebo control	
	Dose 1 N=1,511	Dose 2 N=1,501	Dose 1 N=749	Dose 2 N=741
Pain at injection site	74.1%	71.0%	31.3%	29.5%
Redness/erythema	14.7%	18.5%	5.7%	5.4%
Swelling	10.5%	15.3%	2.7%	2.7%

Abbreviations: AEFI: adverse event following immunization vaccine; NS: not solicited

^a Very common = occur in 10% or more of vaccine recipients, common = occur in 1 to less than 10% of vaccine recipients, uncommon = occur in 0.1% to less than 1% of vaccine recipients

^b AEFIs were solicited within 7 days after each dose in a Phase 2/3 clinical trial. The information in this table is up to date as of November 19, 2021. For updated information, please consult the Comirnaty product monograph.

Table 2. Frequency of solicited systemic AEs in 5 to 11 year olds for the Pfizer-BioNTech COVID-19 vaccine (Comirnaty™)^{a,c}

AEFI	Vaccine		Placebo control	
	Dose 1 N=1,511	Dose 2 N=1,501	Dose 1 N=749	Dose 2 N=741
Fatigue	33.6%	39.4%	31.3%	24.3%
Headache	22.4%	28.0%	24.1%	18.6%
Muscle Pain	9.1%	11.7%	6.8%	7.4%
Chills	4.6%	9.8%	4.7%	4.3%
Joint Pain	3.3%	5.2%	5.5%	3.6%
Fever ^b	2.5%	6.5%	1.3%	1.2%
Diarrrhea	5.9%	5.3%	4.1%	4.7%
Vomiting	2.2%	1.9%	1.5%	0.8%

Abbreviations: AEFI: adverse event following immunization vaccine; NS: not solicited

^a Very common = occur in 10% or more of vaccine recipients, common = occur in 1 to less than 10% of vaccine recipients, uncommon = occur in 0.1% to less than 1% of vaccine recipients

^b Fever was objectively reported as having a temperature $\geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$.

^c AEFIs were solicited within 7 days after each dose in a Phase 2/3 clinical trial. The information in this table is up to date as of November 19, 2021. For updated information, please consult the Comirnaty product monograph.

This is the exhibit marked "GT-16" referred to in the annexed Affidavit of **GEORGE IAN TOWN** affirmed at **Christchurch** this 10 day of **June 2022** before me:

Solicitor of the High Court of New Zealand

Emma Louise Sprott
Solicitor
Christchurch

mRNA vaccines — a new era in vaccinology

Norbert Pardi¹, Michael J. Hogan¹, Frederick W. Porter² and Drew Weissman¹

Abstract | mRNA vaccines represent a promising alternative to conventional vaccine approaches because of their high potency, capacity for rapid development and potential for low-cost manufacture and safe administration. However, their application has until recently been restricted by the instability and inefficient *in vivo* delivery of mRNA. Recent technological advances have now largely overcome these issues, and multiple mRNA vaccine platforms against infectious diseases and several types of cancer have demonstrated encouraging results in both animal models and humans. This Review provides a detailed overview of mRNA vaccines and considers future directions and challenges in advancing this promising vaccine platform to widespread therapeutic use.

Vaccines prevent many millions of illnesses and save numerous lives every year¹. As a result of widespread vaccine use, the smallpox virus has been completely eradicated and the incidence of polio, measles and other childhood diseases has been drastically reduced around the world². Conventional vaccine approaches, such as live attenuated and inactivated pathogens and subunit vaccines, provide durable protection against a variety of dangerous diseases³. Despite this success, there remain major hurdles to vaccine development against a variety of infectious pathogens, especially those better able to evade the adaptive immune response⁴. Moreover, for most emerging virus vaccines, the main obstacle is not the effectiveness of conventional approaches but the need for more rapid development and large-scale deployment. Finally, conventional vaccine approaches may not be applicable to non-infectious diseases, such as cancer. The development of more potent and versatile vaccine platforms is therefore urgently needed.

Nucleic acid therapeutics have emerged as promising alternatives to conventional vaccine approaches. The first report of the successful use of *in vitro* transcribed (IVT) mRNA in animals was published in 1990, when reporter gene mRNAs were injected into mice and protein production was detected⁵. A subsequent study in 1992 demonstrated that administration of vasopressin-encoding mRNA in the hypothalamus could elicit a physiological response in rats⁶. However, these early promising results did not lead to substantial investment in developing mRNA therapeutics, largely owing to concerns associated with mRNA instability, high innate immunogenicity and inefficient *in vivo* delivery. Instead, the field pursued DNA-based and protein-based therapeutic approaches^{7,8}.

Over the past decade, major technological innovation and research investment have enabled mRNA to become a promising therapeutic tool in the fields of vaccine development and protein replacement therapy. The use of mRNA has several beneficial features over subunit, killed and live attenuated virus, as well as DNA-based vaccines. First, safety: as mRNA is a non-infectious, non-integrating platform, there is no potential risk of infection or insertional mutagenesis. Additionally, mRNA is degraded by normal cellular processes, and its *in vivo* half-life can be regulated through the use of various modifications and delivery methods^{9–12}. The inherent immunogenicity of the mRNA can be down-modulated to further increase the safety profile^{9,12,13}. Second, efficacy: various modifications make mRNA more stable and highly translatable^{9,12,13}. Efficient *in vivo* delivery can be achieved by formulating mRNA into carrier molecules, allowing rapid uptake and expression in the cytoplasm (reviewed in REFS 10, 11). mRNA is the minimal genetic vector; therefore, anti-vector immunity is avoided, and mRNA vaccines can be administered repeatedly. Third, production: mRNA vaccines have the potential for rapid, inexpensive and scalable manufacturing, mainly owing to the high yields of *in vitro* transcription reactions.

The mRNA vaccine field is developing extremely rapidly; a large body of preclinical data has accumulated over the past several years, and multiple human clinical trials have been initiated. In this Review, we discuss current mRNA vaccine approaches, summarize the latest findings, highlight challenges and recent successes, and offer perspectives on the future of mRNA vaccines. The data suggest that mRNA vaccines have the potential to solve many of the challenges in vaccine development for both infectious diseases and cancer.

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Table 1 | mRNA vaccine complexing strategies for *in vivo* use

Delivery system type	Route of delivery	Species	Target
Commercial transfection reagent	i.n.	Mouse	OVA ¹⁴⁵
Protamine	i.d.	Mouse, ferret, pig and human	Influenza virus ^{18,52} , melanoma ¹⁵⁰ , non-small-cell lung cancer ²⁰⁰ , prostate cancer ^{36,52,151} , rabies virus ⁵⁶ , OVA ^{36,52,155} and Lewis lung cancer ¹⁵⁵
Protamine liposome	i.v.	Mouse	Lung cancer ²⁰¹
Polysaccharide particle	s.c.	Mouse and rabbit	Influenza virus ⁹⁸
Cationic nanoemulsion	i.m.	Mouse, rabbit, ferret and rhesus macaque	Influenza virus ⁹⁶ , RSV ⁵⁰ , HIV-1 (REFS 50,97), HCMV ⁵⁰ , <i>Streptococcus</i> spp. ¹⁰⁰ , HCV and rabies virus ⁸⁷
Cationic polymer	s.c. and i.n.	Mouse	Influenza virus ⁹⁹ , and HIV-1 (REFS 110,111)
Cationic polymer liposome	i.v.	Mouse	Melanoma ^{202,203} , pancreatic cancer ²⁰⁴
Cationic lipid nanoparticle	i.d., i.v. and s.c.	Mouse	HIV-1 (REF. 109) and OVA ¹⁵²
Cationic lipid, cholesterol nanoparticle	i.v., s.c. and i.s.	Mouse	Influenza virus ^{59,108} , melanoma ^{59,141} , Moloney murine leukaemia virus, OVA, HPV and colon cancer ⁵⁹
Cationic lipid, cholesterol, PEG nanoparticle	i.d., i.m. and s.c.	Mouse, cotton rat and rhesus macaque	Zika virus ^{20,85,112} , influenza virus ^{22,94,95,205} , RSV ¹⁹ , HCMV, rabies virus ⁸⁷ and melanoma ¹⁵³
Dendrimer nanoparticle	i.m.	Mouse	Influenza virus, Ebola virus, <i>Toxoplasma gondii</i> ⁸⁹ and Zika virus ⁸⁸

HCMV, human cytomegalovirus; HCV, hepatitis C virus; HPV, human papillomavirus; i.d., intradermal; i.m., intramuscular; i.n., intranasal; i.s., intrasplenic; i.v., intravenous; OVA, ovalbumin-expressing cancer models; PEG, polyethylene glycol; RSV, respiratory syncytial virus; s.c., subcutaneous.

Basic mRNA vaccine pharmacology

mRNA is the intermediate step between the translation of protein-encoding DNA and the production of proteins by ribosomes in the cytoplasm. Two major types of RNA are currently studied as vaccines: non-replicating mRNA and virally derived, self-amplifying RNA. Conventional mRNA-based vaccines encode the antigen of interest and contain 5' and 3' untranslated regions (UTRs), whereas self-amplifying RNAs encode not only the antigen but also the viral replication machinery that enables intracellular RNA amplification and abundant protein expression.

The construction of optimally translated IVT mRNA suitable for therapeutic use has been reviewed previously^{14,15}. Briefly, IVT mRNA is produced from a linear DNA template using a T7, a T3 or an Sp6 phage RNA polymerase¹⁶. The resulting product should optimally contain an open reading frame that encodes the protein of interest, flanking UTRs, a 5' cap and a poly(A) tail. The mRNA is thus engineered to resemble fully processed mature mRNA molecules as they occur naturally in the cytoplasm of eukaryotic cells.

Complexing of mRNA for *in vivo* delivery has also been recently detailed^{10,11}. Naked mRNA is quickly degraded by extracellular RNases¹⁷ and is not internalized efficiently. Thus, a great variety of *in vitro* and *in vivo* transfection reagents have been developed that facilitate cellular uptake of mRNA and protect it from degradation. Once the mRNA transits to the cytosol, the cellular translation machinery produces protein that undergoes post-translational modifications, resulting in

a properly folded, fully functional protein. This feature of mRNA pharmacology is particularly advantageous for vaccines and protein replacement therapies that require cytosolic or transmembrane proteins to be delivered to the correct cellular compartments for proper presentation or function. IVT mRNA is finally degraded by normal physiological processes, thus reducing the risk of metabolite toxicity.

Recent advances in mRNA vaccine technology

Various mRNA vaccine platforms have been developed in recent years and validated in studies of immunogenicity and efficacy^{18–20}. Engineering of the RNA sequence has rendered synthetic mRNA more translatable than ever before. Highly efficient and non-toxic RNA carriers have been developed that in some cases^{21,22} allow prolonged antigen expression *in vivo* (TABLE 1). Some vaccine formulations contain novel adjuvants, while others elicit potent responses in the absence of known adjuvants. The following section summarizes the key advances in these areas of mRNA engineering and their impact on vaccine efficacy.

Optimization of mRNA translation and stability

This topic has been extensively discussed in previous reviews^{14,15}; thus, we briefly summarize the key findings (BOX 1). The 5' and 3' UTR elements flanking the coding sequence profoundly influence the stability and translation of mRNA, both of which are critical concerns for vaccines. These regulatory sequences can be derived from viral or eukaryotic genes and greatly increase the

Box 1 | Strategies for optimizing mRNA pharmacology

A number of technologies are currently used to improve the pharmacological aspects of mRNA. The various mRNA modifications used and their impact are summarized below.

- Synthetic cap analogues and capping enzymes^{26,27} stabilize mRNA and increase protein translation via binding to eukaryotic translation initiation factor 4E (EIF4E)
- Regulatory elements in the 5'-untranslated region (UTR) and the 3'-UTR²³ stabilize mRNA and increase protein translation
- Poly(A) tail²⁵ stabilizes mRNA and increases protein translation
- Modified nucleosides^{9,48} decrease innate immune activation and increase translation
- Separation and/or purification techniques: RNase III treatment (N.P. and D.W., unpublished observations) and fast protein liquid chromatography (FPLC) purification¹³ decrease immune activation and increase translation
- Sequence and/or codon optimization²⁹ increase translation
- Modulation of target cells: co-delivery of translation initiation factors and other methods alters translation and immunogenicity

Dendritic cell

(DC). A professional antigen-presenting cell that can potentially activate CD4⁺ and CD8⁺ T cells by presenting peptide antigens on major histocompatibility complex (MHC) class I and II molecules, respectively, along with co-stimulatory molecules.

Pathogen-associated molecular pattern

(PAMP). Conserved molecular structure produced by microorganisms and recognized as an inflammatory danger signal by various innate immune receptors.

Type I interferon

A family of proteins, including but not limited to interferon- β (IFN β) and multiple isoforms of IFN α , released by cells in response to viral infections and pathogen products. Type I IFN sensing results in the upregulation of interferon-stimulated genes and an antiviral cellular state.

Fast protein liquid chromatography

(FPLC). A form of liquid chromatography that can be used to purify proteins or nucleic acids. High-performance liquid chromatography (HPLC) is a similar approach, which uses high pressure to purify materials.

half-life and expression of therapeutic mRNAs^{23,24}. A 5' cap structure is required for efficient protein production from mRNA²⁵. Various versions of 5' caps can be added during or after the transcription reaction using a vaccinia virus capping enzyme²⁶ or by incorporating synthetic cap or anti-reverse cap analogues^{27,28}. The poly(A) tail also plays an important regulatory role in mRNA translation and stability²⁵; thus, an optimal length of poly(A)²⁴ must be added to mRNA either directly from the encoding DNA template or by using poly(A) polymerase. The codon usage additionally has an impact on protein translation. Replacing rare codons with frequently used synonymous codons that have abundant cognate tRNA in the cytosol is a common practice to increase protein production from mRNA²⁹, although the accuracy of this model has been questioned³⁰. Enrichment of G:C content constitutes another form of sequence optimization that has been shown to increase steady-state mRNA levels *in vitro*³¹ and protein expression *in vivo*¹².

Although protein expression may be positively modulated by altering the codon composition or by introducing modified nucleosides (discussed below), it is also possible that these forms of sequence engineering could affect mRNA secondary structure³², the kinetics and accuracy of translation and simultaneous protein folding^{33,34}, and the expression of cryptic T cell epitopes present in alternative reading frames³⁰. All these factors could potentially influence the magnitude or specificity of the immune response.

Modulation of immunogenicity

Exogenous mRNA is inherently immunostimulatory, as it is recognized by a variety of cell surface, endosomal and cytosolic innate immune receptors (FIG. 1) (reviewed in REF. 35). Depending on the therapeutic application, this feature of mRNA could be beneficial or detrimental. It is potentially advantageous for vaccination because in some cases it may provide adjuvant activity to drive dendritic cell (DC) maturation and thus elicit robust T and B cell immune responses. However, innate immune sensing of mRNA has also been associated with the inhibition of antigen expression and may negatively affect the immune

response^{9,13}. Although the paradoxical effects of innate immune sensing on different formats of mRNA vaccines are incompletely understood, some progress has been made in recent years in elucidating these phenomena.

Studies over the past decade have shown that the immunostimulatory profile of mRNA can be shaped by the purification of IVT mRNA and the introduction of modified nucleosides as well as by complexing the mRNA with various carrier molecules^{9,13,36,37}. Enzymatically synthesized mRNA preparations contain double-stranded RNA (dsRNA) contaminants as aberrant products of the IVT reaction¹³. As a mimic of viral genomes and replication intermediates, dsRNA is a potent pathogen-associated molecular pattern (PAMP) that is sensed by pattern recognition receptors in multiple cellular compartments (FIG. 1). Recognition of IVT mRNA contaminated with dsRNA results in robust type I interferon production¹³, which upregulates the expression and activation of protein kinase R (PKR; also known as EIF2AK2) and 2'-5'-oligoadenylate synthetase (OAS), leading to the inhibition of translation³⁸ and the degradation of cellular mRNA and ribosomal RNA³⁹, respectively. Karikó and colleagues¹³ have demonstrated that contaminating dsRNA can be efficiently removed from IVT mRNA by chromatographic methods such as reverse-phase fast protein liquid chromatography (FPLC) or high-performance liquid chromatography (HPLC). Strikingly, purification by FPLC has been shown to increase protein production from IVT mRNA by up to 1,000-fold in primary human DCs¹³. Thus, appropriate purification of IVT mRNA seems to be critical for maximizing protein (immunogen) production in DCs and for avoiding unwanted innate immune activation.

Besides dsRNA contaminants, single-stranded mRNA molecules are themselves a PAMP when delivered to cells exogenously. Single-stranded oligoribonucleotides and their degradative products are detected by the endosomal sensors Toll-like receptor 7 (TLR7) and TLR8 (REFS 40,41), resulting in type I interferon production⁴². Crucially, it was discovered that the incorporation of naturally occurring chemically modified nucleosides, including but not limited to pseudouridine^{9,43,44} and 1-methylpseudouridine⁴⁵, prevents activation of TLR7, TLR8 and other innate immune sensors^{46,47}, thus reducing type I interferon signalling⁴⁸. Nucleoside modification also partially suppresses the recognition of dsRNA species⁴⁶⁻⁴⁸. As a result, Karikó and others have shown that nucleoside-modified mRNA is translated more efficiently than unmodified mRNA *in vitro*⁹, particularly in primary DCs, and *in vivo* in mice⁴⁵. Notably, the highest level of protein production in DCs was observed when mRNA was both FPLC-purified and nucleoside-modified¹³. These advances in understanding the sources of innate immune sensing and how to avoid their adverse effects have substantially contributed to the current interest in mRNA-based vaccines and protein replacement therapies.

In contrast to the findings described above, a study by Thess and colleagues found that sequence-optimized, HPLC-purified, unmodified mRNA produced higher levels of protein in HeLa cells and in mice than its nucleoside-modified counterpart¹². Additionally, Kauffman

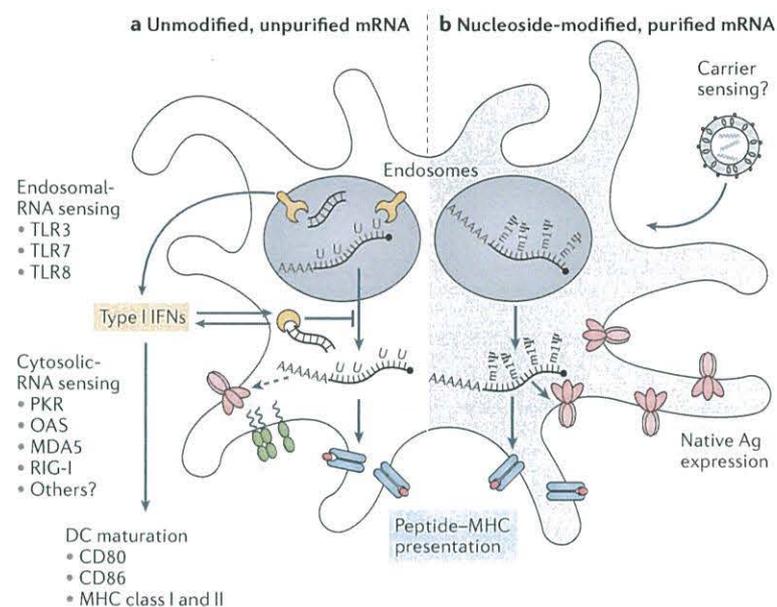


Figure 1 | Innate immune sensing of mRNA vaccines. Innate immune sensing of two types of mRNA vaccine by a dendritic cell (DC), with RNA sensors shown in yellow, antigen in red, DC maturation factors in green, and peptide–major histocompatibility complex (MHC) complexes in light blue and red; an example lipid nanoparticle carrier is shown at the top right. A non-exhaustive list of the major known RNA sensors that contribute to the recognition of double-stranded and unmodified single-stranded RNAs is shown. Unmodified, unpurified (part a) and nucleoside-modified, fast protein liquid chromatography (FPLC)-purified (part b) mRNAs were selected for illustration of two formats of mRNA vaccines where known forms of mRNA sensing are present and absent, respectively. The dashed arrow represents reduced antigen expression. Ag, antigen; PKR, interferon-induced, double-stranded RNA-activated protein kinase; MDA5, interferon-induced helicase C domain-containing protein 1 (also known as IFIH1); IFN, interferon; m1Ψ, 1-methylpseudouridine; OAS, 2′-5′-oligoadenylate synthetase; TLR, Toll-like receptor.

Nucleoside modification

The incorporation of chemically modified nucleosides, such as pseudouridine, 1-methylpseudouridine, 5-methylcytidine and others, into mRNA transcripts, usually to suppress innate immune sensing and/or to improve translation.

Adjuvant

An additive to vaccines that modulates and/or boosts the potency of the immune response, often allowing lower doses of antigen to be used effectively. Adjuvants may be based on pathogen-associated molecular patterns (PAMPs) or on other molecules that activate innate immune sensors.

and co-workers demonstrated that unmodified, non-HPLC-purified mRNA yielded more robust protein production in HeLa cells than nucleoside-modified mRNA, and resulted in similar levels of protein production in mice⁴⁹. Although not fully clear, the discrepancies between the findings of Karikó^{9,13} and these authors^{12,49} may have arisen from variations in RNA sequence optimization, the stringency of mRNA purification to remove dsRNA contaminants and the level of innate immune sensing in the targeted cell types.

The immunostimulatory properties of mRNA can conversely be increased by the inclusion of an adjuvant to increase the potency of some mRNA vaccine formats. These include traditional adjuvants as well as novel approaches that take advantage of the intrinsic immunogenicity of mRNA or its ability to encode immunomodulatory proteins. Self-replicating RNA vaccines have displayed increased immunogenicity and effectiveness after formulating the RNA in a cationic nanoemulsion based on the licensed MF59 (Novartis) adjuvant⁵⁰. Another effective adjuvant strategy is TriMix, a combination of mRNAs encoding three immune activator proteins: CD70, CD40 ligand (CD40L) and constitutively active TLR4. TriMix mRNA augmented the immunogenicity

of naked, unmodified, unpurified mRNA in multiple cancer vaccine studies and was particularly associated with increased DC maturation and cytotoxic T lymphocyte (CTL) responses (reviewed in REF. 51). The type of mRNA carrier and the size of the mRNA–carrier complex have also been shown to modulate the cytokine profile induced by mRNA delivery. For example, the RNAActive (CureVac AG) vaccine platform^{52,53} depends on its carrier to provide adjuvant activity. In this case, the antigen is expressed from a naked, unmodified, sequence-optimized mRNA, while the adjuvant activity is provided by co-delivered RNA complexed with protamine (a polycationic peptide), which acts via TLR7 signalling^{52,54}. This vaccine format has elicited favourable immune responses in multiple preclinical animal studies for vaccination against cancer and infectious diseases^{18,36,55,56}. A recent study provided mechanistic information on the adjuvanticity of RNAActive vaccines in mice *in vivo* and human cells *in vitro*⁵⁴. Potent activation of TLR7 (mouse and human) and TLR8 (human) and production of type I interferon, pro-inflammatory cytokines and chemokines after intradermal immunization was shown⁵⁴. A similar adjuvant activity was also demonstrated in the context of non-mRNA-based vaccines using RNAadjuvant (CureVac AG), an unmodified, single-stranded RNA stabilized by a cationic carrier peptide⁵⁷.

Progress in mRNA vaccine delivery

Efficient *in vivo* mRNA delivery is critical to achieving therapeutic relevance. Exogenous mRNA must penetrate the barrier of the lipid membrane in order to reach the cytoplasm to be translated to functional protein. mRNA uptake mechanisms seem to be cell type dependent, and the physicochemical properties of the mRNA complexes can profoundly influence cellular delivery and organ distribution. There are two basic approaches for the delivery of mRNA vaccines that have been described to date. First, loading of mRNA into DCs *ex vivo*, followed by re-infusion of the transfected cells⁵⁸; and second, direct parenteral injection of mRNA with or without a carrier. *Ex vivo* DC loading allows precise control of the cellular target, transfection efficiency and other cellular conditions, but as a form of cell therapy, it is an expensive and labour-intensive approach to vaccination. Direct injection of mRNA is comparatively rapid and cost-effective, but it does not yet allow precise and efficient cell-type-specific delivery, although there has been recent progress in this regard⁵⁹. Both of these approaches have been explored in a variety of forms (FIG. 2; TABLE 1).

Ex vivo loading of DCs. DCs are the most potent antigen-presenting cells of the immune system. They initiate the adaptive immune response by internalizing and proteolytically processing antigens and presenting them to CD8⁺ and CD4⁺ T cells on major histocompatibility complexes (MHCs), namely, MHC class I and MHC class II, respectively. Additionally, DCs may present intact antigen to B cells to provoke an antibody response⁶⁰. DCs are also highly amenable to mRNA transfection. For these reasons, DCs represent an attractive target for transfection by mRNA vaccines, both *in vivo* and *ex vivo*.

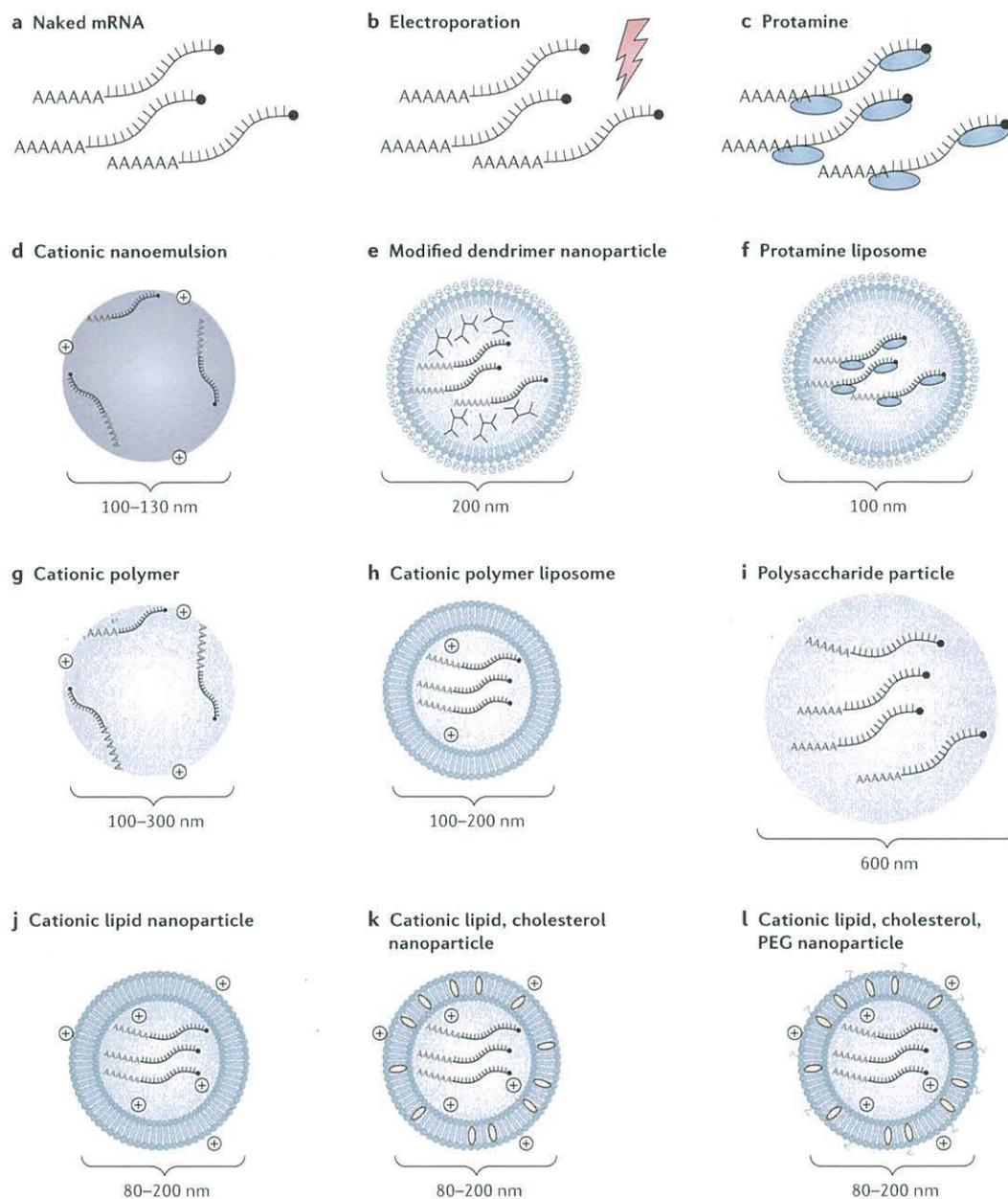


Figure 2 | Major delivery methods for mRNA vaccines. Commonly used delivery methods and carrier molecules for mRNA vaccines along with typical diameters for particulate complexes are shown: naked mRNA (part a); naked mRNA with *in vivo* electroporation (part b); protamine (cationic peptide)-complexed mRNA (part c); mRNA associated with a positively charged oil-in-water cationic nanoemulsion (part d); mRNA associated with a chemically modified dendrimer and complexed with polyethylene glycol (PEG)-lipid (part e); protamine-complexed mRNA in a PEG-lipid nanoparticle (part f); mRNA associated with a cationic polymer such as polyethylenimine (PEI) (part g); mRNA associated with a cationic polymer liposome (part h); mRNA associated with a polysaccharide (for example, chitosan) particle or gel (part i); mRNA in a cationic lipid nanoparticle (for example, 1,2-dioleoyloxy-3-trimethylammoniumpropane (DOTAP) or dioleoylphosphatidylethanolamine (DOPE) lipids) (part j); mRNA complexed with cationic lipids and cholesterol (part k); and mRNA complexed with cationic lipids, cholesterol and PEG-lipid (part l).

MHC class I

A polymorphic set of proteins expressed on the surface of all nucleated cells that present antigen to CD8⁺ (including cytotoxic) T cells in the form of proteolytically processed peptides, typically 8–11 amino acids in length.

MHC class II

A polymorphic set of proteins expressed on professional antigen-presenting cells and certain other cell types, which present antigen to CD4⁺ (helper) T cells in the form of proteolytically processed peptides, typically 11–30 amino acids in length.

Although DCs have been shown to internalize naked mRNA through a variety of endocytic pathways^{61–63}, *ex vivo* transfection efficiency is commonly increased using electroporation; in this case, mRNA molecules pass through membrane pores formed by a high-voltage pulse

and directly enter the cytoplasm (reviewed in REF. 64). This mRNA delivery approach has been favoured for its ability to generate high transfection efficiency without the need for a carrier molecule. DCs that are loaded with mRNA *ex vivo* are then re-infused into the autologous vaccine

recipient to initiate the immune response. Most *ex vivo*-loaded DC vaccines elicit a predominantly cell-mediated immune response; thus, they have been used primarily to treat cancer (reviewed in REF. 58).

Injection of naked mRNA in vivo. Naked mRNA has been used successfully for *in vivo* immunizations, particularly in formats that preferentially target antigen-presenting cells, as in intradermal^{61,65} and intranodal injections^{66–68}. Notably, a recent report showed that repeated intranodal immunizations with naked, unmodified mRNA encoding tumour-associated neoantigens generated robust T cell responses and increased progression-free survival⁶⁸ (discussed further in BOX 2).

Physical delivery methods in vivo. To increase the efficiency of mRNA uptake *in vivo*, physical methods have occasionally been used to penetrate the cell membrane. An early report showed that mRNA complexed with gold particles could be expressed in tissues using a gene gun, a microprojectile method⁶⁹. The gene gun was shown to be an efficient RNA delivery and vaccination method in mouse models^{70–73}, but no efficacy data in large animals or humans are available. *In vivo* electroporation has also been used to increase uptake of therapeutic RNA^{74–76}; however, in one study, electroporation increased the immunogenicity of only a self-amplifying RNA and not a non-replicating mRNA-based vaccine⁷⁴. Physical methods can be limited by increased cell death and restricted access to target cells or tissues. Recently, the field has instead favoured the use of lipid or polymer-based nanoparticles as potent and versatile delivery vehicles.

Protamine. The cationic peptide protamine has been shown to protect mRNA from degradation by serum RNases⁷⁷; however, protamine-complexed mRNA alone demonstrated limited protein expression and efficacy in

a cancer vaccine model, possibly owing to an overly tight association between protamine and mRNA^{36,78}. This issue was resolved by developing the RActive vaccine platform, in which protamine-formulated RNA serves only as an immune activator and not as an expression vector⁵².

Cationic lipid and polymer-based delivery. Highly efficient mRNA transfection reagents based on cationic lipids or polymers, such as TransIT-mRNA (Mirus Bio LLC) or Lipofectamine (Invitrogen), are commercially available and work well in many primary cells and cancer cell lines^{9,13}, but they often show limited *in vivo* efficacy or a high level of toxicity (N.P. and D.W., unpublished observations). Great progress has been made in developing similarly designed complexing reagents for safe and effective *in vivo* use, and these are discussed in detail in several recent reviews^{10,11,79,80}. Cationic lipids and polymers, including dendrimers, have become widely used tools for mRNA administration in the past few years. The mRNA field has clearly benefited from the substantial investment in *in vivo* small interfering RNA (siRNA) administration, where these delivery vehicles have been used for over a decade. Lipid nanoparticles (LNPs) have become one of the most appealing and commonly used mRNA delivery tools. LNPs often consist of four components: an ionizable cationic lipid, which promotes self-assembly into virus-sized (~100 nm) particles and allows endosomal release of mRNA to the cytoplasm; lipid-linked polyethylene glycol (PEG), which increases the half-life of formulations; cholesterol, a stabilizing agent; and naturally occurring phospholipids, which support lipid bilayer structure. Numerous studies have demonstrated efficient *in vivo* siRNA delivery by LNPs (reviewed in REF. 81), but it has only recently been shown that LNPs are potent tools for *in vivo* delivery of self-amplifying RNA¹⁹ and conventional, non-replicating mRNA²¹. Systemically delivered mRNA–LNP complexes mainly target the liver owing to binding of apolipoprotein E and subsequent receptor-mediated uptake by hepatocytes⁸², and intradermal, intramuscular and subcutaneous administration have been shown to produce prolonged protein expression at the site of the injection^{21,22}. The mechanisms of mRNA escape into the cytoplasm are incompletely understood, not only for artificial liposomes but also for naturally occurring exosomes⁸³. Further research into this area will likely be of great benefit to the field of therapeutic RNA delivery.

The magnitude and duration of *in vivo* protein production from mRNA–LNP vaccines can be controlled in part by varying the route of administration. Intramuscular and intradermal delivery of mRNA–LNPs has been shown to result in more persistent protein expression than systemic delivery routes: in one experiment, the half-life of mRNA-encoded firefly luciferase was roughly threefold longer after intradermal injection than after intravenous delivery²¹. These kinetics of mRNA–LNP expression may be favourable for inducing immune responses. A recent study demonstrated that sustained antigen availability during vaccination

Box 2 | Personalized neopeptide cancer vaccines

Sahin and colleagues have pioneered the use of individualized neopeptide mRNA cancer vaccines¹²¹. They use high-throughput sequencing to identify every unique somatic mutation of an individual patient's tumour sample, termed the mutanome. This enables the rational design of neopeptide cancer vaccines in a patient-specific manner, and has the advantage of targeting non-self antigen specificities that should not be eliminated by central tolerance mechanisms. Proof of concept has been recently provided: Kreiter and colleagues found that a substantial portion of non-synonymous cancer mutations were immunogenic when delivered by mRNA and were mainly recognized by CD4⁺ T cells¹⁷⁶. On the basis of these data, they generated a computational method to predict major histocompatibility complex (MHC) class II-restricted neopeptides that can be used as vaccine immunogens. mRNA vaccines encoding such neopeptides have controlled tumour growth in B16-F10 melanoma and CT26 colon cancer mouse models. In a recent clinical trial, Sahin and colleagues developed personalized neopeptide-based mRNA vaccines for 13 patients with metastatic melanoma, a cancer known for its high frequency of somatic mutations and thus neopeptides. They immunized against ten neopeptides per individual by injecting naked mRNA intranodally. CD4⁺ T cell responses were detected against the majority of the neopeptides, and a low frequency of metastatic disease was observed after several months of follow-up⁶⁸. Interestingly, similar results were also obtained in a study of analogous design that used synthetic peptides as immunogens rather than mRNA¹⁷⁷. Together, these recent trials suggest the potential utility of the personalized vaccine methodology.

Box 3 | The germinal centre and T follicular helper cells

The vast majority of potent antimicrobial vaccines elicit long-lived, protective antibody responses against the target pathogen. High-affinity antibodies are produced in specialized microanatomical sites within the B cell follicles of secondary lymphoid organs called germinal centres (GCs). B cell proliferation, somatic hypermutation and selection for high-affinity mutants occur in the GCs, and efficient T cell help is required for these processes¹⁷⁸. Characterization of the relationship between GC B and T cells has been actively studied in recent years. The follicular homing receptor CXCR5-chemokine receptor 5 (CXCR5) was identified on GC B and T cells in the 1990s^{179,180}, but the concept of a specific lineage of T follicular helper (T_{FH}) cells was not proposed until 2000 (REFS 181,182). The existence of the T_{FH} lineage was confirmed in 2009 when the transcription factor specific for T_{FH} cells, B cell lymphoma 6 protein (BCL-6), was identified^{183–185}. T_{FH} cells represent a specialized subset of CD4⁺ T cells that produce critical signals for B cell survival, proliferation and differentiation in addition to signals for isotype switching of antibodies and for the introduction of diversifying mutations into the immunoglobulin genes. The major cytokines produced by T_{FH} cells are interleukin-4 (IL-4) and IL-21, which play a key role in driving the GC reaction. Other important markers and functional ligands expressed by T_{FH} cells include CD40 ligand (CD40L), Src homology domain 2 (SH2) domain-containing protein 1A (SH2D1A), programmed cell death protein 1 (PD1) and inducible T cell co-stimulator (ICOS)¹⁸⁶. The characterization of rare, broadly neutralizing antibodies to HIV-1 has revealed that unusually high rates of somatic hypermutation are a hallmark of protective antibody responses against HIV-1 (REF. 187). As T_{FH} cells play a key role in driving this process in GC reactions, the development of new adjuvants or vaccine platforms that can potentially activate this cell type is urgently needed.

was a driver of high antibody titres and germinal centre (GC) B cell and T follicular helper (T_{FH}) cell responses⁸⁴. This process was potentially a contributing factor to the potency of recently described nucleoside-modified mRNA–LNP vaccines delivered by the intramuscular and intradermal routes^{20,22,85}. Indeed, T_{FH} cells have been identified as a critical population of immune cells that vaccines must activate in order to generate potent and long-lived neutralizing antibody responses, particularly against viruses that evade humoral immunity⁸⁶. The dynamics of the GC reaction and the differentiation of T_{FH} cells are incompletely understood, and progress in these areas would undoubtedly be fruitful for future vaccine design (BOX 3).

mRNA vaccines against infectious diseases

Development of prophylactic or therapeutic vaccines against infectious pathogens is the most efficient means to contain and prevent epidemics. However, conventional vaccine approaches have largely failed to produce effective vaccines against challenging viruses that cause chronic or repeated infections, such as HIV-1, herpes simplex virus and respiratory syncytial virus (RSV). Additionally, the slow pace of commercial vaccine development and approval is inadequate to respond to the rapid emergence of acute viral diseases, as illustrated by the 2014–2016 outbreaks of the Ebola and Zika viruses. Therefore, the development of more potent and versatile vaccine platforms is crucial.

Preclinical studies have created hope that mRNA vaccines will fulfil many aspects of an ideal clinical vaccine: they have shown a favourable safety profile in animals, are versatile and rapid to design for emerging infectious diseases, and are amenable to scalable good manufacturing practice (GMP) production (already under

way by several companies). Unlike protein immunization, several formats of mRNA vaccines induce strong CD8⁺ T cell responses, likely owing to the efficient presentation of endogenously produced antigens on MHC class I molecules, in addition to potent CD4⁺ T cell responses^{56,87,88}. Additionally, unlike DNA immunization, mRNA vaccines have shown the ability to generate potent neutralizing antibody responses in animals with only one or two low-dose immunizations^{20,22,85}. As a result, mRNA vaccines have elicited protective immunity against a variety of infectious agents in animal models^{19,20,22,56,89,90} and have therefore generated substantial optimism. However, recently published results from two clinical trials of mRNA vaccines for infectious diseases were somewhat modest, leading to more cautious expectations about the translation of preclinical success to the clinic^{22,91} (discussed further below).

Two major types of RNA vaccine have been utilized against infectious pathogens: self-amplifying or replicon RNA vaccines and non-replicating mRNA vaccines. Non-replicating mRNA vaccines can be further distinguished by their delivery method: *ex vivo* loading of DCs or direct *in vivo* injection into a variety of anatomical sites. As discussed below, a rapidly increasing number of preclinical studies in these areas have been published recently, and several have entered human clinical trials (TABLE 2).

Self-amplifying mRNA vaccines

Most currently used self-amplifying mRNA (SAM) vaccines are based on an alphavirus genome⁹², where the genes encoding the RNA replication machinery are intact but the genes encoding the structural proteins are replaced with the antigen of interest. The full-length RNA is ~9 kb long and can be easily produced by IVT from a DNA template. The SAM platform enables a large amount of antigen production from an extremely small dose of vaccine owing to intracellular replication of the antigen-encoding RNA. An early study reported that immunization with 10 µg of naked SAM vaccine encoding RSV fusion (F), influenza virus haemagglutinin (HA) or louping ill virus pre-membrane and envelope (prM-E) proteins resulted in antibody responses and partial protection from lethal viral challenges in mice⁹³. The development of RNA complexing agents brought remarkable improvement to the efficacy of SAM vaccines. As little as 100 ng of an RNA replicon vaccine encoding RSV F, complexed to LNP, resulted in potent T and B cell immune responses in mice, and 1 µg elicited protective immune responses against RSV infection in a cotton rat intranasal challenge system¹⁹. SAM vaccines encoding influenza virus antigens in LNPs or an oil-in-water cationic nanoemulsion induced potent immune responses in ferrets and conferred protection from homologous and heterologous viral challenge in mice^{94–96}. Further studies demonstrated the immunogenicity of this vaccine platform against diverse viruses in multiple species, including human cytomegalovirus (CMV), hepatitis C virus and rabies virus in mice, HIV-1 in rabbits, and HIV-1 and human CMV in rhesus macaques^{50,87,97}. Replicon RNA encoding influenza antigens, complexed with chitosan-containing LNPs or polyethylenimine (PEI), has elicited

Good manufacturing practice (GMP). A collection of guidelines and practices designed to guarantee the production of consistently high-quality and safe pharmaceutical products. GMP-grade materials must be used for human clinical trials.

Table 2 | Clinical trials with mRNA vaccines against infectious diseases

Sponsoring institution	Vaccine type (route of administration)	Targets	Trial numbers (phase)	Status
Argos Therapeutics	DC EP with autologous viral Ag and CD40L mRNAs (i.d.)	HIV-1	• NCT00672191 (II) • NCT01069809 (II) • NCT02042248 (I)	• Completed ¹⁰⁵ • Completed; results NA • Completed; results NA
CureVac AG	RNActive viral Ag mRNA (i.m., i.d.)	Rabies virus	NCT02241135 (I)	Active ^{56,91}
Erasmus Medical Center	DC loaded with viral Ag mRNA with TriMix (i.nod.)	HIV-1	NCT02888756 (II)	Recruiting
Fundació Clínic per la Recerca Biomèdica	Viral Ag mRNA with TriMix (NA)	HIV-1	NCT02413645 (I)	Active
Massachusetts General Hospital	DC loaded with viral Ag mRNA (i.d.)	HIV-1	NCT00833781 (II)	Completed ¹⁰⁴
McGill University Health Centre	DC EP with autologous viral Ag and CD40L mRNAs (i.d.)	HIV-1	NCT00381212 (I/II)	Completed ¹⁰²
Moderna Therapeutics	Nucleoside-modified viral Ag mRNA (i.m.)	Zika virus Influenza virus	NCT03014089 (I/II) NCT03076385 (I)	Recruiting ⁸⁵ Ongoing ²²

The table summarizes the clinical trials registered at ClinicalTrials.gov as of 5 May 2017. Ag, antigen; CD40L, CD40 ligand; DC, dendritic cell; EP, electroporated; i.d., intradermal; i.m., intramuscular; i.nod., intranodal; NA, not available.

T and B cell immune responses in mice after subcutaneous delivery^{98,99}. Chahal and colleagues developed a delivery platform consisting of a chemically modified, ionizable dendrimer complexed into LNPs⁸⁹. Using this platform, they demonstrated that intramuscular delivery of RNA replicons encoding influenza virus, Ebola virus or *Toxoplasma gondii* antigens protected mice against lethal infection⁸⁹. The same group recently demonstrated that vaccination with an RNA replicon encoding Zika virus prM-E formulated in the same manner elicited antigen-specific antibody and CD8⁺ T cell responses in mice⁸⁸. Another recent study reported immunogenicity and moderate protective efficacy of SAM vaccines against bacterial pathogens, namely *Streptococcus* (groups A and B) spp., further demonstrating the versatility of this platform¹⁰⁰.

One of the advantages of SAM vaccines is that they create their own adjuvants in the form of dsRNA structures, replication intermediates and other motifs that may contribute to their high potency. However, the intrinsic nature of these PAMPs may make it difficult to modulate the inflammatory profile or reactivity of SAM vaccines. Additionally, size constraints of the insert are greater for SAM vaccines than for mRNAs that do not encode replicon genes, and the immunogenicity of the replication proteins may theoretically limit repeated use.

Dendritic cell mRNA vaccines

As described above, *ex vivo* DC loading is a heavily pursued method to generate cell-mediated immunity against cancer. Development of infectious disease vaccines using this approach has been mainly limited to a therapeutic vaccine for HIV-1: HIV-1-infected individuals on highly active antiretroviral therapy were treated with autologous DCs electroporated with mRNA encoding various HIV-1 antigens, and cellular

immune responses were evaluated¹⁰¹⁻¹⁰⁶. This intervention proved to be safe and elicited antigen-specific CD4⁺ and CD8⁺ T cell responses, but no clinical benefit was observed. Another study in humans evaluated a CMV pp65 mRNA-loaded DC vaccination in healthy human volunteers and allogeneic stem cell recipients and reported induction or expansion of CMV-specific cellular immune responses¹⁰⁷.

Direct injection of non-replicating mRNA vaccines

Directly injectable, non-replicating mRNA vaccines are an appealing vaccine format owing to their simple and economical administration, particularly in resource-limited settings. Although an early report demonstrated that immunization with liposome-complexed mRNA encoding influenza virus nucleoproteins elicited CTL responses in mice¹⁰⁸, the first demonstration of protective immune responses by mRNA vaccines against infectious pathogens was published only a few years ago¹⁸. This seminal work demonstrated that intradermally administered uncomplexed mRNA encoding various influenza virus antigens combined with a protamine-complexed RNA adjuvant was immunogenic in multiple animal models and protected mice from lethal viral challenge.

Immunization with the protamine-based RNActive platform encoding rabies virus glycoprotein has also induced protective immunity against a lethal intracerebral virus challenge in mice and potent neutralizing antibody responses in pigs⁵⁶. In a recently published seminal work, Alberer and colleagues evaluated the safety and immunogenicity of this vaccine in 101 healthy human volunteers⁹¹. Subjects received 80–640 µg of mRNA vaccine three times by needle-syringe or needle-free devices, either intradermally or intramuscularly. Seven days after vaccination, nearly all participants reported mild to moderate injection site reactions, and 78% experienced a systemic reaction (for example, fever,

headache and chills). There was one serious adverse event that was possibly related to the vaccine: a transient and moderate case of Bell palsy. Surprisingly, the needle-syringe injections did not generate detectable neutralizing antibodies in 98% of recipients. By contrast, needle-free delivery induced variable levels of neutralizing antibodies, the majority of which peaked above the expected protective threshold but then largely waned after 1 year in subjects who were followed up long term. Elucidating the basis of the disparate immunogenicity between the animals and humans who received this vaccine and between the two routes of delivery will be informative for future vaccine design using this platform.

Other infectious disease vaccines have successfully utilized lipid- or polymer-based delivery systems. Cationic 1,2-dioleoyloxy-3-trimethylammoniumpropane (DOTAP) and dioleoylphosphatidylethanolamine (DOPE) lipid-complexed mRNA encoding HIV-1 gag generated antigen-specific CD4⁺ and CD8⁺ T cell responses after subcutaneous delivery in mice¹⁰⁹. Two other studies demonstrated that PEI-complexed mRNAs could be efficiently delivered to mice to induce HIV-1-specific immune responses: subcutaneously delivered mRNA encoding HIV-1 gag elicited CD4⁺ and CD8⁺ T cell responses, and intranasally administered mRNA encoding the HIV-1 envelope gp120 subunit crossed the nasal epithelium and generated antigen-specific immune responses in the nasal cavity^{110,111}. Kranz and colleagues also performed intravenous immunizations in mice using lipid-complexed mRNA encoding influenza virus HA and showed evidence of T cell activation after a single dose⁵⁹.

Nucleoside-modified mRNA vaccines represent a new and highly efficacious category of mRNA vaccines. Owing to the novelty of this immunization platform, our knowledge of efficacy is limited to the results of four recent publications that demonstrated the potency of such vaccines in small and large animals. The first published report demonstrated that a single intradermal injection of LNP-formulated mRNA encoding Zika virus prM-E, modified with 1-methylpseudouridine and FPLC purification, elicited protective immune responses in mice and rhesus macaques with the use of as little as 50 µg (0.02 mg kg⁻¹) of vaccine in macaques²⁰. A subsequent study by a different group tested a similarly designed vaccine against Zika virus in mice and found that a single intramuscular immunization elicited moderate immune responses, and a booster vaccination resulted in potent and protective immune responses⁸⁵. This vaccine also incorporated the modified nucleoside 1-methylpseudouridine, but FPLC purification or other methods of removing dsRNA contaminants were not reported. Notably, this report showed that antibody-dependent enhancement of secondary infection with a heterologous flavivirus, a major concern for dengue and Zika virus vaccines, could be diminished by removing a cross-reactive epitope in the E protein. A recent follow-up study evaluated the same vaccine in a model of maternal vaccination and fetal infection¹¹². Two immunizations reduced Zika virus infection in fetal mice by several orders of magnitude and completely rescued a defect in fetal viability.

Another recent report evaluated the immunogenicity of LNP-complexed, nucleoside-modified, non-FPLC-purified mRNA vaccines against influenza HA 10 neuraminidase 8 (H10N8) and H7N9 influenza viruses in mice, ferrets, non-human primates and, for the first time, humans²². A single intradermal or intramuscular immunization with low doses (0.4–10 µg) of LNP-complexed mRNA encoding influenza virus HA elicited protective immune responses against homologous influenza virus challenge in mice. Similar results were obtained in ferrets and cynomolgus monkeys after immunization with one or two doses of 50–400 µg of a vaccine containing LNP-complexed mRNA encoding HA, corroborating that the potency of mRNA–LNP vaccines translates to larger animals, including non-human primates.

On the basis of encouraging preclinical data, two phase I clinical trials have recently been initiated to evaluate the immunogenicity and safety of nucleoside-modified mRNA–LNP vaccines in humans for the first time. The mRNA vaccine encoding H10N8 HA is currently undergoing clinical testing (NCT03076385), and interim findings for 23 vaccinated individuals have been reported²². Participants received a small amount (100 µg) of vaccine intramuscularly, and immunogenicity was measured 43 days after vaccination. The vaccine proved to be immunogenic in all subjects, as measured by haemagglutination inhibition and microneutralization antibody assays. Promisingly, antibody titres were above the expected protective threshold, but they were moderately lower than in the animal models. Similarly to the study by Alberer *et al.*⁹¹, most vaccinated subjects reported mild to moderate reactogenicity (injection site pain, myalgia, headache, fatigue and chills), and three subjects reported severe injection site reactions or a systemic common cold-like response. This level of reactogenicity appears to be similar to that of more traditional vaccine formats^{113,114}. Finally, the Zika virus vaccine described by Richner *et al.*^{85,112} is also entering clinical evaluation in a combined phase I/II trial (NCT03014089). Future studies that apply nucleoside-modified mRNA–LNP vaccines against a greater diversity of antigens will reveal the extent to which this strategy is broadly applicable to infectious disease vaccines.

mRNA cancer vaccines

mRNA-based cancer vaccines have been recently and extensively reviewed^{115–119}. Below, the most recent advances and directions are highlighted. Cancer vaccines and other immunotherapies represent promising alternative strategies to treat malignancies. Cancer vaccines can be designed to target tumour-associated antigens that are preferentially expressed in cancerous cells, for example, growth-associated factors, or antigens that are unique to malignant cells owing to somatic mutation¹²⁰. These neoantigens, or the neoepitopes within them, have been deployed as mRNA vaccine targets in humans¹²¹ (BOX 2). Most cancer vaccines are therapeutic, rather than prophylactic, and seek to stimulate cell-mediated responses, such as those from CTLs, that are capable of clearing or reducing tumour burden¹²².

The first proof-of-concept studies that not only proposed the idea of RNA cancer vaccines but also provided evidence of the feasibility of this approach were published more than two decades ago^{123,124}. Since then, numerous preclinical and clinical studies have demonstrated the viability of mRNA vaccines to combat cancer (TABLE 3).

DC mRNA cancer vaccines

As DCs are central players in initiating antigen-specific immune responses, it seemed logical to utilize them for cancer immunotherapy. The first demonstration that DCs electroporated with mRNA could elicit potent immune responses against tumour antigens was reported by Boczkowski and colleagues in 1996 (REF. 124). In this study, DCs pulsed with ovalbumin (OVA)-encoding mRNA or tumour-derived RNAs elicited a tumour-reducing immune response in OVA-expressing and other melanoma models in mice. A variety of immune regulatory proteins have been identified in the form of mRNA-encoded adjuvants that can increase the potency of DC cancer vaccines. Several studies demonstrated that electroporation of DCs with mRNAs encoding costimulatory molecules such as CD83, tumour necrosis factor receptor superfamily member 4 (TNFRSF4; also known as OX40) and 4-1BB ligand (4-1BBL) resulted in a substantial increase in the immune stimulatory activity of DCs^{125–128}. DC functions can also be modulated through the use of mRNA-encoded pro-inflammatory cytokines, such as IL-12, or trafficking-associated molecules^{129–131}. As introduced above, TriMix is a cocktail of mRNA-encoded adjuvants (CD70, CD40L and constitutively active TLR4) that can be electroporated in combination with antigen-encoding mRNA or mRNAs¹³². This formulation proved efficacious in multiple preclinical studies by increasing DC activation and shifting the CD4⁺ T cell phenotype from T regulatory cells to T helper 1 (T_H1)-like cells^{132–136}. Notably, the immunization of patients with stage III or stage IV melanoma using DCs loaded with mRNA encoding melanoma-associated antigens and TriMix adjuvant resulted in tumour regression in 27% of treated individuals¹³⁷. Multiple clinical trials have now been conducted using DC vaccines targeting various cancer types, such as metastatic prostate cancer, metastatic lung cancer, renal cell carcinoma, brain cancers, melanoma, acute myeloid leukaemia, pancreatic cancer and others^{138,139} (reviewed in REFS 51, 58).

A new line of research combines mRNA electroporation of DCs with traditional chemotherapy agents or immune checkpoint inhibitors. In one trial, patients with stage III or IV melanoma were treated with ipilimumab, a monoclonal antibody against CTL antigen 4 (CTLA4), and DCs loaded with mRNA encoding melanoma-associated antigens plus TriMix. This intervention resulted in durable tumour reduction in a proportion of individuals with recurrent or refractory melanoma¹⁴⁰.

Direct injection of mRNA cancer vaccines

The route of administration and delivery format of mRNA vaccines can greatly influence outcomes. A variety of mRNA cancer vaccine formats have been developed using common delivery routes (intradermal,

intramuscular, subcutaneous or intranasal) and some unconventional routes of vaccination (intranodal, intravenous, intrasplenic or intratumoural).

Intranodal administration of naked mRNA is an unconventional but efficient means of vaccine delivery. Direct mRNA injection into secondary lymphoid tissue offers the advantage of targeted antigen delivery to antigen-presenting cells at the site of T cell activation, obviating the need for DC migration. Several studies have demonstrated that intranodally injected naked mRNA can be selectively taken up by DCs and can elicit potent prophylactic or therapeutic anti-tumour T cell responses^{62,66}; an early study also demonstrated similar findings with intrasplenic delivery¹⁴¹. Coadministration of the DC-activating protein FMS-related tyrosine kinase 3 ligand (FLT3L) was shown in some cases to further improve immune responses to intranodal mRNA vaccination^{142,143}. Incorporation of the TriMix adjuvant into intranodal injections of mice with mRNAs encoding tumour-associated antigens resulted in potent antigen-specific CTL responses and tumour control in multiple tumour models¹³³. A more recent study demonstrated that intranodal injection of mRNA encoding the E7 protein of human papillomavirus (HPV) 16 with TriMix increased the number of tumour-infiltrating CD8⁺ T cells and inhibited the growth of an E7-expressing tumour model in mice⁶⁷.

The success of preclinical studies has led to the initiation of clinical trials using intranodally injected naked mRNA encoding tumour-associated antigens into patients with advanced melanoma (NCT01684241) and patients with hepatocellular carcinoma (EudraCT: 2012-005572-34). In one published trial, patients with metastatic melanoma were treated with intranodally administered DCs electroporated with mRNA encoding the melanoma-associated antigens tyrosinase or gp100 and TriMix, which induced limited antitumour responses¹⁴⁴.

Intranasal vaccine administration is a needle-free, noninvasive manner of delivery that enables rapid antigen uptake by DCs. Intranasally delivered mRNA complexed with Stemfect (Stemgent) LNPs resulted in delayed tumour onset and increased survival in prophylactic and therapeutic mouse tumour models using the OVA-expressing E.G7-OVA T lymphoblastic cell line¹⁴⁵.

Intratumoural mRNA vaccination is a useful approach that offers the advantage of rapid and specific activation of tumour-resident T cells. Often, these vaccines do not introduce mRNAs encoding tumour-associated antigens but simply aim to activate tumour-specific immunity *in situ* using immune stimulatory molecules. An early study demonstrated that naked mRNA or protamine-stabilized mRNA encoding a non-tumour related gene (*GLB1*) impaired tumour growth and provided protection in a glioblastoma mouse model, taking advantage of the intrinsic immunogenic properties of mRNA¹⁴⁶. A more recent study showed that intratumoural delivery of mRNA encoding an engineered cytokine based on interferon- β (IFN β) fused to a transforming growth factor- β (TGF β) antagonist increased the cytolytic capacity of CD8⁺ T cells and modestly delayed tumour growth in

Table 3 | Clinical trials with mRNA vaccines against cancer

Sponsoring institution	Vaccine type (route of administration)	Targets	Trial numbers (phase)	Status
Antwerp University Hospital	DC EP with TAA mRNA (i.d. or NA)	AML	• NCT00834002 (I) • NCT01686334 (II)	• Completed ^{206,207} • Recruiting
		AML, CML, multiple myeloma	NCT00965224 (II)	Unknown
		Multiple solid tumours	NCT01291420 (I/II)	Unknown ²⁰⁸
		Mesothelioma	NCT02649829 (I/II)	Recruiting
		Glioblastoma	NCT02649582 (I/II)	Recruiting
Argos Therapeutics	DC EP with autologous tumour mRNA with or without CD40L mRNA (i.d. or NA)	Renal cell carcinoma	• NCT01482949 (II) • NCT00678119 (II) • NCT00272649 (I/II) • NCT01582672 (III) • NCT00087984 (I/II)	• Ongoing • Completed ²⁰⁹ • Completed; results NA • Ongoing • Completed; results NA
		Pancreatic cancer	NCT00664482 (NA)	Completed; results NA
Asterias Biotherapeutics	DC loaded with TAA mRNA (NA)	AML	NCT00510133 (II)	Completed ²¹⁰
BioNTech RNA Pharmaceuticals GmbH	Naked TAA or neo-Ag mRNA (i.nod.)	Melanoma	• NCT01684241 (I) • NCT02035956 (I)	• Completed; results NA • Ongoing
		Melanoma	NCT02410733 (I)	Recruiting ⁵⁹
		Breast cancer	NCT02316457 (I)	Recruiting
CureVac AG	RNActive TAA mRNA (i.d.)	Non-small-cell lung cancer	• NCT00923312 (I/II) • NCT01915524 (I)	• Completed ²¹¹ • Terminated ²⁰⁰
		Prostate cancer	• NCT02140138 (II) • NCT00831467 (I/II) • NCT01817738 (I/II)	• Terminated • Completed ²⁵¹ • Terminated ²¹²
Duke University	DC loaded with CMV Ag mRNA (i.d. or ing.)	Glioblastoma, malignant glioma	• NCT00626483 (I) • NCT00639639 (I) • NCT02529072 (I) • NCT02366728 (II)	• Ongoing ²¹³ • Ongoing ^{138,139} • Recruiting • Recruiting
		Glioblastoma	NCT00890032 (I)	Completed; results NA
		Melanoma	NCT01216436 (I)	Terminated
Guangdong 999 Brain Hospital	DC loaded with TAA mRNA (NA)	Glioblastoma	• NCT02808364 (I/II) • NCT02709616 (I/II)	• Recruiting • Recruiting
		Brain metastases	NCT02808416 (I/II)	Recruiting
Herlev Hospital	DC loaded with TAA mRNA (i.d.)	Breast cancer, melanoma	NCT00978913 (I)	Completed ²¹⁴
		Prostate cancer	NCT01446731 (II)	Completed ²¹⁵
Life Research Technologies GmbH	DC, matured, loaded with TAA mRNA (NA)	Ovarian cancer	NCT01456065 (I)	Unknown
Ludwig-Maximilian-University of Munich	DC loaded with TAA and CMV Ag mRNA (i.d.)	AML	NCT01734304 (I/II)	Recruiting
MD Anderson Cancer Center	DC loaded with AML lysate and mRNA (NA)	AML	NCT00514189 (I)	Terminated
Memorial Sloan Kettering Cancer Center	DC (Langerhans) EP with TAA mRNA (i.d.)	Melanoma	NCT01456104 (I)	Ongoing
		Multiple myeloma	NCT01995708 (I)	Recruiting
Oslo University Hospital	DC loaded with autologous tumour or TAA mRNA (i.d. or NA)	Melanoma	• NCT00961844 (I/II) • NCT01278940 (I/II)	• Terminated • Completed ²¹⁶
		Prostate cancer	• NCT01197625 (I/II) • NCT01278914 (I/II)	• Recruiting • Completed; results NA
		Glioblastoma	NCT00846456 (I/II)	Completed ²¹⁷
		Ovarian cancer	NCT01334047 (I/II)	Terminated

REVIEWS

Table 3 (cont.) | Clinical trials with mRNA vaccines against cancer

Sponsoring institution	Vaccine type (route of administration)	Targets	Trial numbers (phase)	Status
Radboud University	DC EP with TAA mRNA (i.d. and i.v. or i.nod)	Colorectal cancer	NCT00228189 (I/II)	Completed ²¹⁸
		Melanoma	<ul style="list-style-type: none"> • NCT00929019 (I/II) • NCT00243529 (I/II) • NCT00940004 (I/II) • NCT01530698 (I/II) • NCT02285413 (II) 	<ul style="list-style-type: none"> • Terminated • Completed^{219,220} • Completed^{220,221} • Completed^{144,220,221} • Completed; results NA
Universitair Ziekenhuis Brussel	DC EP with TAA and TriMix mRNA (i.d. and i.v.)	Melanoma	<ul style="list-style-type: none"> • NCT01066390 (I) • NCT01302496 (II) • NCT01676779 (II) 	<ul style="list-style-type: none"> • Completed¹³⁷ • Completed¹⁴⁰ • Completed; results NA
University Hospital Erlangen	DC, matured, loaded with autologous tumour RNA (i.v.)	Melanoma	NCT01983748 (III)	Recruiting
University Hospital Tübingen	Autologous tumour mRNA with GM-CSF protein (i.d. and s.c.)	Melanoma	NCT00204516 (I/II)	Completed ²²²
		Melanoma	NCT00204607 (I/II)	Completed ¹⁵⁰
University of Campinas, Brazil	DC loaded with TAA mRNA (NA)	AML, myelodysplastic syndromes	NCT03083054 (I/II)	Recruiting
University of Florida	RNAActive* TAA mRNA (i.d.)	Prostate cancer	NCT00906243 (I/II)	Terminated
	DC loaded with CMV Ag mRNA with GM-CSF protein (i.d.)	Glioblastoma, malignant glioma	NCT02465268 (II)	Recruiting

The table summarizes the clinical trials registered at ClinicalTrials.gov as of 5 May 2017. Ag, antigen; AML, acute myeloid leukaemia; CD40L, CD40 ligand; CML, chronic myeloid leukaemia; CMV, cytomegalovirus; DC, dendritic cell; EP, electroporated; GM-CSF, granulocyte-macrophage colony-stimulating factor; i.d., intradermal; ing., inguinal injection; i.nod., intranodal injection; i.v., intravenous; NA, not available; neo-Ag, personalized neoantigen; s.c., subcutaneous; TAA, tumour-associated antigen. *Developed by CureVac AG.

OVA-expressing lymphoma or lung carcinoma mouse models¹⁴⁷. It has also been shown that intratumoural administration of TriMix mRNA that does not encode tumour-associated antigens results in activation of CD8 α^+ DCs and tumour-specific T cells, leading to delayed tumour growth in various mouse models¹⁴⁸.

Systemic administration of mRNA vaccines is not common owing to concerns about aggregation with serum proteins and rapid extracellular mRNA degradation; thus, formulating mRNAs into carrier molecules is essential. As discussed above, numerous delivery formulations have been developed to facilitate mRNA uptake, increase protein translation and protect mRNA from RNases^{10,11,79,80}. Another important issue is the biodistribution of mRNA vaccines after systemic delivery. Certain cationic LNP-based complexing agents delivered intravenously traffic mainly to the liver²¹, which may not be ideal for DC activation. An effective strategy for DC targeting of mRNA vaccines after systemic delivery has recently been described⁵⁹. An mRNA-lipoplex (mRNA-liposome complex) delivery platform was generated using cationic lipids and neutral helper lipids formulated with mRNA, and it was discovered that the lipid-to-mRNA ratio, and thus the net charge of the particles, has a profound impact on the biodistribution of the vaccine. While a positively charged lipid particle primarily targeted the lung, a negatively charged particle targeted DCs in secondary lymphoid tissues and bone marrow. The negatively charged particle induced potent immune responses against tumour-specific antigens that were associated with impressive tumour

reduction in various mouse models⁵⁹. As no toxic effects were observed in mice or non-human primates, clinical trials using this approach to treat patients with advanced melanoma or triple-negative breast cancer have been initiated (NCT02410733 and NCT02316457).

A variety of antigen-presenting cells reside in the skin¹⁴⁹, making it an ideal site for immunogen delivery during vaccination (FIG. 3). Thus, the intradermal route of delivery has been widely used for mRNA cancer vaccines. An early seminal study demonstrated that intradermal administration of total tumour RNA delayed tumour growth in a fibrosarcoma mouse model⁶⁵. Intradermal injection of mRNA encoding tumour antigens in the protamine-based RNAActive platform proved efficacious in various mouse models of cancer³⁶ and in multiple prophylactic and therapeutic clinical settings (TABLE 3). One such study demonstrated that mRNAs encoding survivin and various melanoma tumour antigens resulted in increased numbers of antigen-specific T cells in a subset of patients with melanoma¹⁵⁰. In humans with castration-resistant prostate cancer, an RNAActive vaccine expressing multiple prostate cancer-associated proteins elicited antigen-specific T cell responses in the majority of recipients¹⁵¹. Lipid-based carriers have also contributed to the efficacy of intradermally delivered mRNA cancer vaccines. The delivery of OVA-encoding mRNA in DOTAP and/or DOPE liposomes resulted in antigen-specific CTL activity and inhibited growth of OVA-expressing tumours in mice¹⁵². In the same study, coadministration of mRNA encoding granulocyte-macrophage colony-stimulating factor

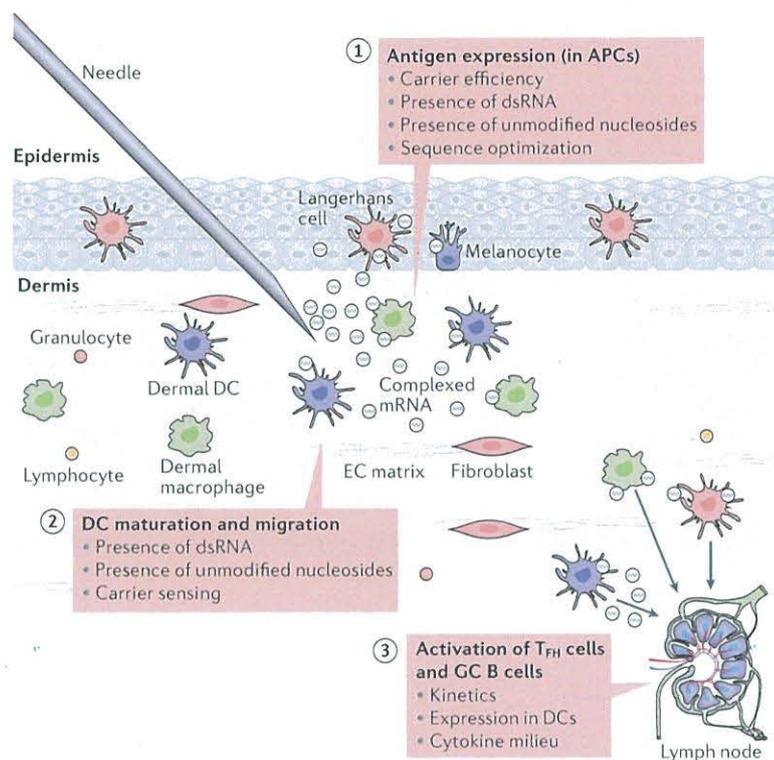


Figure 3 | Considerations for effectiveness of a directly injected mRNA vaccine. For an injected mRNA vaccine, major considerations for effectiveness include the following: the level of antigen expression in professional antigen-presenting cells (APCs), which is influenced by the efficiency of the carrier, by the presence of pathogen-associated molecular patterns (PAMPs) in the form of double-stranded RNA (dsRNA) or unmodified nucleosides and by the level of optimization of the RNA sequence (codon usage, G:C content, 5' and 3' untranslated regions (UTRs) and so on); dendritic cell (DC) maturation and migration to secondary lymphoid tissue, which is increased by PAMPs; and the ability of the vaccine to activate robust T follicular helper (T_{FH}) cell and germinal centre (GC) B cell responses — an area that remains poorly understood. An intradermal injection is shown as an example. EC, extracellular.

(GM-CSF) improved OVA-specific cytolytic responses. Another report showed that subcutaneous delivery of LNP-formulated mRNA encoding two melanoma-associated antigens delayed tumour growth in mice, and co-delivery of lipopolysaccharide (LPS) in LNPs increased both CTL and antitumour activity¹⁵³. In general, mRNA cancer vaccines have proved immunogenic in humans, but further refinement of vaccination methods, as informed by basic immunological research, will likely be necessary to achieve greater clinical benefits.

The combination of mRNA vaccination with adjunctive therapies, such as traditional chemotherapy, radiotherapy and immune checkpoint inhibitors, has increased the beneficial outcome of vaccination in some preclinical studies^{154,155}. For example, cisplatin treatment significantly increased the therapeutic effect of immunizing with mRNA encoding the HPV16 E7 oncoprotein and TriMix, leading to the complete rejection of female genital tract tumours in a mouse model⁶⁷. Notably, it has also been suggested that treatment with antibodies against programmed cell death protein 1

(PD1) increased the efficacy of a neoepitope mRNA-based vaccine against metastatic melanoma in humans, but more data are required to explore this hypothesis⁶⁸.

Therapeutic considerations and challenges

Good manufacturing practice production

mRNA is produced by *in vitro* reactions with recombinant enzymes, ribonucleotide triphosphates (NTPs) and a DNA template; thus, it is rapid and relatively simple to produce in comparison with traditional protein subunit and live or inactivated virus vaccine production platforms. Its reaction yield and simplicity make rapid mRNA production possible in a small GMP facility footprint. The manufacturing process is sequence-independent and is primarily dictated by the length of the RNA, the nucleotide and capping chemistry and the purification of the product; however, it is possible that certain sequence properties such as extreme length may present difficulties (D.W., unpublished observations). According to current experience, the process can be standardized to produce nearly any encoded protein immunogen, making it particularly suitable for rapid response to emerging infectious diseases.

All enzymes and reaction components required for the GMP production of mRNA can be obtained from commercial suppliers as synthesized chemicals or bacterially expressed, animal component-free reagents, thereby avoiding safety concerns surrounding the adventitious agents that plague cell-culture-based vaccine manufacture. All the components, such as plasmid DNA, phage polymerases, capping enzymes and NTPs, are readily available as GMP-grade traceable components; however, some of these are currently available at only limited scale or high cost. As mRNA therapeutics move towards commercialization and the scale of production increases, more economical options may become accessible for GMP source materials.

GMP production of mRNA begins with DNA template production followed by enzymatic IVT and follows the same multistep protocol that is used for research scale synthesis, with added controls to ensure the safety and potency of the product¹⁶. Depending on the specific mRNA construct and chemistry, the protocol may be modified slightly from what is described here to accommodate modified nucleosides, capping strategies or template removal. To initiate the production process, template plasmid DNA produced in *Escherichia coli* is linearized using a restriction enzyme to allow synthesis of runoff transcripts with a poly(A) tract at the 3' end. Next, the mRNA is synthesized from NTPs by a DNA-dependent RNA polymerase from bacteriophage (such as T7, SP6, or T3). The template DNA is then degraded by incubation with DNase. Finally, the mRNA is enzymatically or chemically capped to enable efficient translation *in vivo*. mRNA synthesis is highly productive, yielding in excess of 2 g l⁻¹ of full-length mRNA in multi-gram scale reactions under optimized conditions.

Once the mRNA is synthesized, it is processed through several purification steps to remove reaction components, including enzymes, free nucleotides, residual DNA and truncated RNA fragments. While LiCl precipitation is

Box 4 | mRNA-based passive immunotherapy

Recombinant monoclonal antibodies are rapidly transforming the pharmaceutical market and have become one of the most successful therapeutic classes to treat autoimmune disorders, infectious diseases, osteoporosis, hypercholesterolemia and cancer^{188–192}. However, the high cost of protein production and the need for frequent systemic administration pose a major limitation to widespread accessibility. Antibody-gene transfer technologies could potentially overcome these difficulties, as they administer nucleotide sequences encoding monoclonal antibodies to patients, enabling *in vivo* production of properly folded and modified protein therapeutics¹⁹³. Multiple gene therapy vectors have been investigated (for example, viral vectors and plasmid DNA) that bear limitations such as pre-existing host immunity, acquired anti-vector immunity, high innate immunogenicity, difficulties with *in vivo* regulation of antibody production and toxic effects^{193,194}. mRNA therapeutics combine safety with exquisite dose control and the potential for multiple administrations with no pre-existing or anti-vector immunity. Two early reports demonstrated that dendritic cells (DCs) electroporated with mRNAs encoding antibodies against immuno-inhibitory proteins secreted functional antibodies and improved immune responses in mice^{195,196}. Three recent publications have described the use of injectable mRNA for *in vivo* production of therapeutic antibodies: Pardi and colleagues demonstrated that a single intravenous injection into mice with lipid nanoparticle (LNP)-encapsulated nucleoside-modified mRNAs encoding the heavy and light chains of the anti-HIV-1 neutralizing antibody VRC01 rapidly produced high levels of functional antibody in the serum and protected humanized mice from HIV-1 infection¹⁹⁷; Stadler and co-workers demonstrated that intravenous administration of low doses of TransIT (Mirus Bio LLC)-complexed, nucleoside-modified mRNAs encoding various anticancer bispecific antibodies resulted in the elimination of large tumours in mouse models¹⁹⁸; and Thrall and colleagues¹⁹⁹ utilized an unmodified mRNA–LNP delivery system¹² to express three monoclonal antibodies at levels that protected from lethal challenges with rabies virus, botulinum toxin and a B cell lymphoma cell line. No toxic effects were observed in any of these studies. These observations suggest that mRNA offers a safe, simple and efficient alternative to therapeutic monoclonal antibody protein delivery, with potential application to any therapeutic protein.

routinely used for laboratory-scale preparation, purification at the clinical scale utilizes derivatized microbeads in batch or column formats, which are easier to utilize at large scale^{156,157}. For some mRNA platforms, removal of dsRNA and other contaminants is critical for the potency of the final product, as it is a potent inducer of interferon-dependent translation inhibition. This has been accomplished by reverse-phase FPLC at the laboratory scale¹⁵⁸, and scalable aqueous purification approaches are being investigated. After mRNA is purified, it is exchanged into a final storage buffer and sterile-filtered for subsequent filling into vials for clinical use. RNA is susceptible to degradation by both enzymatic and chemical pathways¹⁵⁷. Formulation buffers are tested to ensure that they are free of contaminating RNases and may contain buffer components, such as antioxidants and chelators, which minimize the effects of reactive oxygen species and divalent metal ions that lead to mRNA instability¹⁵⁹.

Pharmaceutical formulation of mRNAs is an active area of development. Although most products for early phase studies are stored frozen (–70 °C), efforts to develop formulations that are stable at higher temperatures more suitable for vaccine distribution are continuing. Published reports suggest that stable refrigerated or room temperature formulations can be made. The RNActive platform was reported to be active after lyophilization and storage at 5–25 °C for 3 years and at 40 °C for 6 months⁹¹. Another report demonstrated that

freeze-dried naked mRNA is stable for at least 10 months under refrigerated conditions¹⁶⁰. The stability of mRNA products might also be improved by packaging within nanoparticles or by co-formulation with RNase inhibitors¹⁶¹. For lipid-encapsulated mRNA, at least 6 months of stability has been observed (Arbutus Biopharma, personal communication), but longer-term storage of such mRNA–lipid complexes in an unfrozen form has not yet been reported.

Regulatory aspects

There is no specific guidance from the FDA or European Medicines Agency (EMA) for mRNA vaccine products. However, the increasing number of clinical trials conducted under EMA and FDA oversight indicate that regulators have accepted the approaches proposed by various organizations to demonstrate that products are safe and acceptable for testing in humans. Because mRNA falls into the broad vaccine category of genetic immunogens, many of the guiding principles that have been defined for DNA vaccines¹⁶² and gene therapy vectors^{163,164} can likely be applied to mRNA with some adaptations to reflect the unique features of mRNA. A detailed review of EMA regulations for RNA vaccines by Hinz and colleagues highlights the different regulatory paths stipulated for prophylactic infectious disease versus therapeutic applications¹⁶⁵. Regardless of the specific classification within existing guidelines, some themes can be observed in what is stated in these guidance documents and in what has been reported for recently published clinical studies. In particular, the recent report of an mRNA vaccine against influenza virus highlights preclinical and clinical data demonstrating biodistribution and persistence in mice, disease protection in a relevant animal model (ferrets), and immunogenicity, local reactogenicity and toxicity in humans²². As mRNA products become more prominent in the vaccine field, it is likely that specific guidance will be developed that will delineate requirements to produce and evaluate new mRNA vaccines.

Safety

The requirement for safety in modern prophylactic vaccines is extremely stringent because the vaccines are administered to healthy individuals. Because the manufacturing process for mRNA does not require toxic chemicals or cell cultures that could be contaminated with adventitious viruses, mRNA production avoids the common risks associated with other vaccine platforms, including live virus, viral vectors, inactivated virus and subunit protein vaccines. Furthermore, the short manufacturing time for mRNA presents few opportunities to introduce contaminating microorganisms. In vaccinated people, the theoretical risks of infection or integration of the vector into host cell DNA are not a concern for mRNA. For the above reasons, mRNA vaccines have been considered a relatively safe vaccine format.

Several different mRNA vaccines have now been tested from phase I to IIb clinical studies and have been shown to be safe and reasonably well tolerated (TABLES 2, 3). However, recent human trials have demonstrated moderate and in

Table 4 | Leading mRNA vaccine developers: research focus, partners and therapeutic platforms

Institution	mRNA technology	Partners	Indication (disease target)
Argos Biotechnology	mRNA neoantigens (Arcelis platform)	NA	Individualized cancer vaccines, HIV-1
BioNTech RNA Pharmaceuticals GmbH	Nucleoside-modified mRNA (IVAC Mutanome, FixVAC)	Genentech/Roche Bayer AG	Individualized cancer vaccines Veterinary vaccines
CureVac AG	Sequence-optimized, purified mRNA (RNAActive, RNArt, RNAdjuvant)	Boehringer Ingelheim GmbH Johnson & Johnson Sanofi Pasteur BMGF IAVI	Cancer vaccines (lung cancer) Viral vaccines Infectious disease vaccines Infectious disease vaccines HIV vaccines
eTheRNA Immunotherapies	Purified mRNA (TriMix)	NA	Cancer (melanoma, breast), viral vaccines (HBV and/or HPV)
GlaxoSmithKline/Novartis	Self-amplifying mRNA (SAM) (alphavirus replicon)	NA	Infectious disease vaccines
Moderna Therapeutics	Nucleoside-modified mRNA	Merck & Co. BMGF, DARPA, BARDA	Individualized cancer vaccines, viral vaccines Viral vaccines (influenza virus, CMV, HMPV, PIV, chikungunya virus, Zika virus)
University of Pennsylvania	Nucleoside-modified, purified mRNA	NA	Infectious disease vaccines

BARDA, Biomedical Advanced Research and Development Authority; BMGF, Bill & Melinda Gates Foundation; CMV, cytomegalovirus; DARPA, Defense Advanced Research Projects Agency; HBV, hepatitis B virus; HMPV, human metapneumovirus; HPV, human papillomavirus; IAVI, International AIDS Vaccine Initiative; NA, not available; PIV, parainfluenza virus.

rare cases severe injection site or systemic reactions for different mRNA platforms^{22,91}. Potential safety concerns that are likely to be evaluated in future preclinical and clinical studies include local and systemic inflammation, the biodistribution and persistence of expressed immunogen, stimulation of auto-reactive antibodies and potential toxic effects of any non-native nucleotides and delivery system components. A possible concern could be that some mRNA-based vaccine platforms^{54,166} induce potent type I interferon responses, which have been associated not only with inflammation but also potentially with autoimmunity^{167,168}. Thus, identification of individuals at an increased risk of autoimmune reactions before mRNA vaccination may allow reasonable precautions to be taken. Another potential safety issue could derive from the presence of extracellular RNA during mRNA vaccination. Extracellular naked RNA has been shown to increase the permeability of tightly packed endothelial cells and may thus contribute to oedema¹⁶⁹. Another study showed that extracellular RNA promoted blood coagulation and pathological thrombus formation¹⁷⁰. Safety will therefore need continued evaluation as different mRNA modalities and delivery systems are utilized for the first time in humans and are tested in larger patient populations.

Conclusions and future directions

Currently, mRNA vaccines are experiencing a burst in basic and clinical research. The past 2 years alone have witnessed the publication of dozens of preclinical and

clinical reports showing the efficacy of these platforms. Whereas the majority of early work in mRNA vaccines focused on cancer applications, a number of recent reports have demonstrated the potency and versatility of mRNA to protect against a wide variety of infectious pathogens, including influenza virus, Ebola virus, Zika virus, *Streptococcus* spp. and *T. gondii* (TABLES 1, 2).

While preclinical studies have generated great optimism about the prospects and advantages of mRNA-based vaccines, two recent clinical reports have led to more tempered expectations^{22,91}. In both trials, immunogenicity was more modest in humans than was expected based on animal models, a phenomenon also observed with DNA-based vaccines¹⁷¹, and the side effects were not trivial. We caution that these trials represent only two variations of mRNA vaccine platforms, and there may be substantial differences when the expression and immunostimulatory profiles of the vaccine are changed. Further research is needed to determine how different animal species respond to mRNA vaccine components and inflammatory signals and which pathways of immune signalling are most effective in humans.

Recent advances in understanding and reducing the innate immune sensing of mRNA have aided efforts not only in active vaccination but also in several applications of passive immunization or passive immunotherapy for infectious diseases and cancer (BOX 4). Direct comparisons between mRNA expression platforms should clarify which systems are most appropriate for both passive and active immunization. Given the large number of

Passive immunization or passive immunotherapy
In contrast to traditional (active) vaccines, these therapies do not generate *de novo* immune responses but can provide immune-mediated protection through the delivery of antibodies or antibody-encoding genes. Passive vaccination offers the advantage of immediate action but at the disadvantage of high cost.

promising mRNA platforms, further head-to-head comparisons would be of utmost value to the vaccine field because this would allow investigators to focus resources on those best suited for each application.

The fast pace of progress in mRNA vaccines would not have been possible without major recent advances in the areas of innate immune sensing of RNA and *in vivo* delivery methods. Extensive basic research into RNA and lipid and polymer biochemistry has made it possible to translate mRNA vaccines into clinical trials and has led to an astonishing level of investment in mRNA vaccine companies (TABLE 4). Moderna Therapeutics, founded in 2010, has raised almost US\$2 billion in capital with a plan to commercialize mRNA-based vaccines and therapies^{172,173}. The US Biomedical Advanced Research and Development Authority (BARDA) has committed support for Moderna's clinical evaluation of a promising nucleoside-modified mRNA vaccine for Zika virus (NCT03014089). In Germany, CureVac AG has an

expanding portfolio of therapeutic targets¹⁷⁴, including both cancer and infectious diseases, and BioNTech is developing an innovative approach to personalized cancer medicine using mRNA vaccines¹²¹ (BOX 2). The translation of basic research into clinical testing is also made more expedient by the commercialization of custom GMP products by companies such as New England Biolabs and Aldevron¹⁷⁵. Finally, the recent launch of the Coalition for Epidemic Preparedness Innovations (CEPI) provides great optimism for future responses to emerging viral epidemics. This multinational public and private partnership aims to raise \$1 billion to develop platform-based vaccines, such as mRNA, to rapidly contain emerging outbreaks before they spread out of control.

The future of mRNA vaccines is therefore extremely bright, and the clinical data and resources provided by these companies and other institutions are likely to substantially build on and invigorate basic research into mRNA-based therapeutics.

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Competing interests statement

The authors declare competing interests: see Web version for details.

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