The following information resources have been selected by the National Health Library and Knowledge Service Evidence Virtual Team in response to a question from the National Immunisation Advisory Committee (NIAC). The resources are listed in our estimated order of relevance to practicing healthcare professionals confronted with this scenario in an Irish context. In respect of the evolving global situation and rapidly changing evidence base, it is advised to use hyperlinked sources in this document to ensure that the information you are disseminating to the public or applying in clinical practice is the most current, valid and accurate. For further information on the methodology used in the compilation of this document — including a complete list of sources consulted — please see our National Health Library and Knowledge Service Summary of Evidence Protocol.

Question 207

Is there evidence of mRNA vaccine effectiveness with an extended dosing interval? If so, what is the interval?

Question 207 was prepared by the National Health Library and Knowledge Service in collaboration with the Research Subgroup of the National Immunisation Advisory Committee (NIAC).

Is there evidence of mRNA vaccine effectiveness with an extended dosing interval? If so, what is the interval?

Main Points

1. **The WHO and CDC recommend that in exceptional epidemiological circumstances, countries may consider extending the dosing interval to a maximum of 42 days. Currently, only limited data are available on the efficacy of mRNA COVID-19 vaccines administered beyond the 42-day window.**
2. **Modelling studies suggest that initially vaccinating a greater number of people with a single dose will prevent more deaths and hospitalizations than vaccinating a smaller number of people with 2 doses; and that extending the dosing interval shows progressive benefit to population immunity.**
3. **Data suggest that the second dose should not be delayed in those >65 years of age or in immunosuppressed individuals, such as cancer patients or transplant recipients, due to reduced vaccine immunogenicity after the first dose.**

Please refer to the National Health Library Levels of Evidence Table used to grade the levels of evidence included below.

☑	Inclusion criteria:	All levels.
☒	Exclusion criteria:	None.

Please note that individual studies may not have been critically appraised and that designation at a certain level is not a final determination of the quality of a given study.

Summary of Evidence

The World Health Organization (WHO) recommends that countries experiencing exceptional epidemiological circumstances may consider extending the dosing interval for a short period — up to 12 weeks — as a pragmatic approach to maximizing the number of individuals benefiting from a first dose while vaccine supply continues to increase[1]. Countries should ensure that any programme adjustments to dose intervals do not affect the likelihood of receiving the second dose[1, 7]. The United States (US) Centers for Disease Control and Prevention (CDC) recommends that the second dose of mRNA COVID-19 vaccines should be administered as close to the recommended interval as possible, but not earlier than recommended: ie 21 days (Pfizer-BioNTech) or 28 days (Moderna). If it is not feasible to adhere to the recommended interval and a delay in vaccination is unavoidable, the second dose of Pfizer-BioNTech and Moderna COVID-19 vaccines may be administered up to 42 days after the first dose[2, 7, 8]. Currently, only limited data are available on the efficacy of mRNA COVID-19 vaccines administered beyond the 42-day window[1, 2].

In the United Kingdom (UK), the Joint Commission on Vaccination and Immunisation (JCVI) notes that the short-term vaccine efficacy of the first dose of the Pfizer-BioNTech vaccine from 15 days after vaccination is estimated at 89% (95% CI 52% to 97%); and of the first dose of the AstraZeneca vaccine from 22 days after vaccination at 73% (95% CI 48.79% to 85.76%),

with high protection against severe disease[3, 4]. Given the high level of protection afforded by the first dose, modelling studies suggest that initially vaccinating a greater number of people with a single dose will prevent more deaths and hospitalizations than vaccinating a smaller number of people with 2 doses. The JCVI affirms that the second dose is still important to provide longer lasting protection and is expected to be as or more effective when delivered at an interval of 12 weeks from the first dose[3, 4]. The JCVI supports a 2-dose vaccine schedule for the Pfizer-BioNTech and AstraZeneca vaccines, and recommends a maximum interval between the first and second doses of 12 weeks for both vaccines. It can be assumed that protection from the first dose will wane in the medium term, and that the second dose will be required to provide more durable protection[4].

In the US, the Food and Drug Administration (FDA)[6] asserts that changes to authorized dosing or schedules is premature and that available data continue to support the use of 2 specified doses of each authorized vaccine at specified intervals. The FDA cautions that data in submissions from Pfizer-BioNTech and Moderna regarding the first dose are commonly misinterpreted. In the phase 3 trials, 98% of participants in the Pfizer-BioNTech trial and 92% of participants in the Moderna trial received 2 doses of the vaccine at either a 3- or 4-week interval, respectively. Those participants who did not receive 2 vaccine doses at either a 3- or 4-week interval were generally only followed for a short period of time. Therefore, definitive conclusions about the depth or duration of protection after a single dose of vaccine from the single dose percentages reported by Pfizer-BioNTech and Moderna cannot be inferred.

Vasileiou et al.[14] reported that a single dose of the Pfizer-BioNTech or AstraZeneca vaccines resulted in substantial reductions in the risk of COVID-19 related hospitalization. Bernal et al.[17] reported that

vaccination with either a single dose of the Pfizer-BioNTech or AstraZeneca vaccines was associated with a significant reduction in symptomatic SARS-CoV-2 positive cases in adults ≥70 years, with even greater protection against severe disease: a single dose of either vaccine is, combined with their effect against symptomatic disease, ~80% effective at preventing hospitalization; and a single dose of Pfizer-BioNTech, combined with its effect against symptomatic disease, is 85% effective at preventing death from COVID-19. However, Pimenta et al.[31] cautioned that a second dose of the Pfizer-BioNTech vaccine is critical in those aged ≥65 years. The phase 2 trial of the Pfizer-BioNTech COVID-19 vaccine reported a reduced antibody response among participants aged 65-85 compared with those under 55. Recent data from Public Health England (PHE) showed that efficacy against symptomatic disease was 57% among adults over 80 after a single dose, increasing to 85% after the second dose. Antibody surveillance data from the REACT-2 study showed IgG positivity 21 days after one dose of Pfizer-BioNTech vaccine in 80% of adults under 60, but in only 49% and 34% of those aged over 70 and 80, respectively. IgG positivity increased to 93% and 88% respectively after a second dose.

In modelling studies, Nam et al.[20] found that extending mRNA dose intervals from 6 weeks to 12-24 weeks were projected to result in 12.1%-18.9% fewer symptomatic cases, 9.5%-13.5% fewer hospitalizations, and 7.5%-9.7% fewer deaths over a 12-month time horizon. The largest reductions in hospitalizations and deaths were observed in the longest interval of 24 weeks, although benefits were diminishing as intervals extended. Jurgens and Lackner[21] reported that deferring the second dose of mRNA vaccines from 3 weeks to 6 weeks, 12 weeks and 24 weeks showed progressive benefit to population immunity; and that benefits were proportionate to the delay to second dose. Romero-Brufau et al.[24] found that the median cumulative mortality per 100,000 for the standard dose schedule for mRNA vaccines *vs.* a delayed

dose schedule was 226 *vs.* 179, 233 *vs.* 207 and 235 *vs.* 236 for 90%, 80% and 70% first dose efficacy, respectively. The authors assert that under specific conditions — including vaccine efficacy being above 70%, and vaccination rates remaining below 1% of the population per day — a decrease in cumulative mortality, infections and hospitalizations can be achieved when the second vaccine dose is delayed. This decrease was most significant when the second dose was delayed in people <65 years of age, with second doses still prioritized for those ≥65 years.

Moghadas et al.[25] asserted that for Moderna vaccines, a delay of at least 9weeks in administering the second dose could maximize vaccination program effectiveness and avert at least an additional 17.3 (95% CrI: 7.8 – 29.7) infections, 0.69 (95% CrI: 0.52 - 0.97) hospitalizations and 0.34 (95% CrI: 0.25 - 0.44) deaths per 10,000 population compared to the recommended 4-week interval between the 2 doses. Pfizer-BioNTech vaccines also averted an additional 0.60 (95% CrI: 0.37–0.89) hospitalizations and 0.32 (95% CrI: 0.23–0.45) deaths per 10,000 population in a 9-week delayed second dose strategy, compared to the 3-week recommended schedule between doses.

In a cohort study on the safety and efficacy of the Pfizer-BioNTech vaccine in 54 healthy controls and 151 patients with solid and haematological malignancies, Monin-Aldama et al.[16] found significantly different levels of vaccine efficacy across the three cohorts 21 days following a single vaccine dose. In contrast to its very high performance in healthy controls (~97% of healthy controls had a serological response to the vaccine), efficacy of a single dose in solid cancer patients was low (only ~39% of solid cancer patients had a serological response($p<0.0001$)) and very low in haematological cancer patients (only ~13% of haematological cancer patients had a serological response to the vaccine ($p<0.0001$)). Efficacy in solid cancer patients was greatly and rapidly increased by

boosting at 21 days: 95% within 2 weeks of boost. Too few haematological cancer patients were boosted for clear conclusions to be inferred. The authors concluded that study data support prioritisation of cancer patients for an early (21-day) second dose of the Pfizer-BioNTech vaccine.

Benotmane et al.[18] reported that immunosuppressed kidney transplant recipients had a weak anti-SARS-CoV-2 antibody response 28 days after the first dose of the Moderna mRNA COVID-19 vaccine. This was in sharp contrast with immunocompetent subjects who invariably seroconverted after the first dose. The authors advocated not to delay the second vaccine dose in immunocompromised patients. Similarly, Brockman et al.[19] reported a lower immune response in elderly long term care facility residents compared with younger health care workers one month after a single dose of the Pfizer-BioNTech vaccine and concluded that extending the interval between COVID-19 vaccine doses may pose a risk to older persons due to lower vaccine immunogenicity.

Irish and International Guidance

Level 1

World Health Organization (8 January 2021) Interim recommendations for use of the Pfizer-BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing[1]

See Section: CONSIDERATIONS FOR DEFERRING THE SECOND DOSE

WHO acknowledges that a number of countries face exceptional circumstances of vaccine supply constraints combined with a high disease burden. Some countries have therefore considered delaying the administration of the second dose to allow for a higher initial coverage. This is based on the observation that efficacy has been shown to start from day 12 after the first dose and reached about 89% between days 14 and 21 at the time when the second dose was given. No data on longer-term efficacy for a single dose of the mRNA vaccine BNT162b2 currently exist, as the trial participants received 2 doses with an interval between doses in the trial ranging from 19 to 42 days. Of note, neutralizing antibody responses are modest after the first dose and increase substantially after the second dose. Countries experiencing exceptional epidemiological circumstances may consider delaying for a short period the administration of the second dose as a pragmatic approach to maximizing the number of individuals benefiting from a first dose while vaccine supply continues to increase. WHO's recommendation at present is that the interval between doses may be extended up to 12 weeks, on the basis of currently available clinical trial data. Should additional data become available on longer intervals between doses, revision of this recommendation will be considered. Countries should ensure that any such programme

[1]World Health Organisation (8 January 2021). Interim recommendations for use of the Pfiezer-BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing. https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1. Accessed 19/04/2021

adjustments to dose intervals do not affect the likelihood of receiving the second dose.

Level 1

Centers for Disease Control and Prevention (United States) (March 2021) Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States[2]

See Section: INTERVAL BETWEEN mRNA DOSES

The second dose of Pfizer-BioNTech and Moderna vaccines should be administered as close to the recommended interval as possible, but not earlier than recommended: ie 3 weeks (Pfizer-BioNTech) or 1 month (Moderna). However, second doses administered within a period of 4 days earlier than the recommended date for the second dose are still considered fully vaccinated. If it is not feasible to adhere to the recommended interval and a delay in vaccination is unavoidable, the second dose of Pfizer-BioNTech and Moderna COVID-19 vaccines may be administered up to 6 weeks (42 days) after the first dose. Currently, only limited data are available on efficacy of mRNA COVID-19 vaccines administered beyond this window.

Level 1

Joint Committee on Vaccination and Immunisation (Great Britain) Optimising the COVID-19 vaccination programme for maximum short-term impact[3]

The Joint Committee on Vaccination and Immunisation (JCVI) states that rapid delivery of vaccines is required to protect those most vulnerable. Short-term vaccine efficacy from the first dose of the Pfizer-BioNTech

[2]Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States (last reviewed March 2021) https://www.cdc.gov/vaccines/COVID-19/info-by-product/clinical-considerations.html#Administration Accessed 19/04/2021

[3] Joint Committee on Vaccination and Immunisation (Great Britain) Optimising the COVID-19 vaccination programme for maximum short-term impact. https://www.gov.uk/government/publications/prioritising-the-first-covid-19-vaccine-dose-jcvi-statement/optimising-the-covid-19-vaccination-programme-for-maximum-short-term-impact.

vaccine is calculated at around 90%. Short-term vaccine efficacy from the first dose of the AstraZeneca vaccine is calculated at around 70%, with high protection against severe disease.

Given the high level of protection afforded by the first dose, models suggest that initially vaccinating a greater number of people with a single dose will prevent more deaths and hospitalisations than vaccinating a smaller number of people with 2 doses. The second dose is still important to provide longer lasting protection and is expected to be as or more effective when delivered at an interval of 12 weeks from the first dose.

Level 1

Department of Health and Social Care (Great Britain) (2021) [Internet Publication] Optimising the COVID-19 vaccination programme for maximum short-term impact[4]

Considerations

When considering vaccination schedules JCVI often considers first principles, and regularly advises schedules which differ from the marketing authorisation. In every case, the advice of JCVI is aimed at maximising protection in the population.

Published efficacy between the first and second doses of the Pfizer vaccine was 52.4% (95% CI 29.5% to 68.4%). Based on the timing of cases accrued in the phase 3 study, most of the vaccine failures in the period between doses occurred shortly after vaccination, suggesting that short-term protection from the first dose is very high from day 10 after vaccination. Using data for those cases observed between day 15 and 21, efficacy against

[4]Department of Health & Social Care (2021) Optimising the COVID-19 vaccination programme for maximum short-term impact [Internet Publication] https://www.gov.uk/government/publications/prioritising-the-first-COVID-19-vaccine-dose-jcvi-statement/optimising-the-COVID-19-vaccination-programme-for-maximum-short-term-impact. Accessed 19/04/2021

symptomatic COVID-19 was estimated at 89% (95% CI 52% to 97%).

The level of protection gained from a single dose of the AstraZeneca vaccine was assessed in an exploratory analysis. Vaccine efficacy from 22 days after the first dose was 73% (95% CI 48.79% to 85.76%). High protection against hospitalization was seen from 21 days after the first dose until 2 weeks after the second dose, suggesting that a single dose of the AstraZeneca vaccine will provide high short-term protection against severe disease. Protective immunity from the first dose likely lasts for a duration of 12 weeks.

With most vaccines an extended interval between the prime and booster doses leads to a better immune response to the booster dose. There is evidence that a longer interval between the first and second doses promotes a stronger immune response with the AstraZeneca vaccine.

There is currently no strong evidence to expect that the immune response from the Pfizer-BioNTech and AstraZeneca vaccines differ substantially from each other.

The rate of vaccine delivery in Britain is currently limited by vaccine supply rather than by workforce capacity. An extended interval between vaccine doses together with initial prioritisation of the first vaccine dose would increase the flow of vaccine supply in the short term. This will allow for more first doses to be delivered to more people earlier.

Conclusion

Given the epidemiology of COVID-19 in Britain in late 2020 there is a need for rapid, high levels of vaccine uptake among vulnerable persons.

The committee supports a 2-dose vaccine schedule for the Pfizer-BioNTech and AstraZeneca vaccines. Given the data available, and evidence from the use of many other vaccines, JCVI advises a maximum interval between the first and second doses of 12 weeks for both vaccines. It

can be assumed that protection from the first dose will wane in the medium term, and the second dose will still be required to provide more durable protection.

The committee advises initially prioritising delivery of the first vaccine dose as this is highly likely to have a greater public health impact in the short term and reduce the number of preventable deaths from COVID-19.

Level 1

European Centre for Disease Control and Prevention (ECDC) (29 March 2021) Overview of the implementation of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA[5]

Ten countries have extended the timing between vaccine doses to provide the first dose to as many people in priority groups as possible. Regarding the timing between first and second dose, policies vary by country and product as follows:

- Comirnaty: at least 21 days (Italy), 28 days (Ireland, Portugal), 6 weeks (Estonia, Norway), 42 days (Croatia, the Netherlands, Poland, Germany under discussion), and 12 weeks (Finland).
- COVID-19 Vaccine Moderna: 28 days (Italy), 42 days (Germany under discussion), and 12 weeks (Finland), 6 weeks (Norway).
- COVID-19 Vaccine AstraZeneca: 12 weeks (Croatia, Czechia, Estonia, Finland, Ireland, Lithuania, Poland), at least 10 weeks (Italy), 9-12 weeks (Sweden), minimum nine weeks (Norway)

Level 1

[5] European Centre for Disease Prevention and Control. Overview of the implementation of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA – 29 March 2021. ECDC: Stockholm; 2021.

Food and Drug Administration (United States) (January 2021) [Internet Publication] FDA Statement on following the authorised dosing schedules for COVID-19 vaccines[6]

[The FDA] has been following the discussions and news reports about reducing the number of doses, extending the length of time between doses, changing the dose (half-dose), or mixing and matching vaccines in order to immunize more people against COVID-19. These are all reasonable questions to consider and evaluate in clinical trials. However, at this time, suggesting changes to the FDA-authorized dosing or schedules of these vaccines is premature and not rooted solidly in the available evidence. Without appropriate data supporting such changes in vaccine administration, there is a significant risk of placing public health at risk, undermining the historic vaccination efforts to protect the population from COVID-19.

The available data continue to support the use of 2 specified doses of each authorized vaccine at specified intervals. For the Pfizer-BioNTech COVID-19 vaccine, the interval is 21 days between the first and second dose; and for the Moderna COVID-19 vaccine, the interval is 28 days between the first and second dose.

Data in the firms' submissions regarding the first dose is commonly misinterpreted. In the phase 3 trials, 98% of participants in the Pfizer-BioNTech trial and 92% of participants in the Moderna trial received 2 doses of the vaccine at either a 3- or 4-week interval, respectively. Those participants who did not receive 2 vaccine doses at either a 3-or 4-week interval were generally only followed for a short period of time. Therefore, definitive conclusions about the depth or duration of protection after a single dose of vaccine from the single dose percentages reported by the companies cannot be inferred.

[6]United States Food and Drug Administration (January 2021) FDA Statement on following the authorised dosing schedules for COVID-19 vaccines. https://www.fda.gov/news-events/press-announcements/fda-statement-following-authorized-dosing-schedules-COVID-19-vaccines [Internet Publication] Accessed 19/04/2021

Using a single dose regimen and/or administering less than the dose studied in the clinical trials without understanding the nature of the depth and duration of protection that it provides is concerning, as there is some indication that the depth of the immune response is associated with the duration of protection provided. If people do not truly know how protective a vaccine is, there is the potential for harm because they may assume that they are fully protected when they are not, and accordingly, alter their behavior to take unnecessary risks.

Some of these discussions about changing the dosing schedule or dose are based on a belief that changing the dose or dosing schedule can help get more vaccine to the public faster. However, making such changes that are not supported by adequate scientific evidence may ultimately be counterproductive to public health.

Evidence Synopsis Resources

Level 2

BMJ Best Practice (2021) Coronavirus disease 2019 (COVID-19)[7]

See Section: VACCINE DOSE SCHEDULES MAY DIFFER ACROSS LOCATIONS

There have been suggestions about extending the length of time between doses, reducing the number of doses, changing the dose (half-dose), or mixing and matching different COVID-19 vaccines in order to vaccinate more people. However, there is no evidence to support these strategies as yet. The WHO recommends that countries experiencing exceptional epidemiological circumstances may consider delaying the administration of the second

[7]BMJ Best Practice (2021). Coronavirus disease 2019 (COVID-19). https://bestpractice.bmj.com/topics/en-gb/3000201. Accessed 19/04/2021.

dose of mRNA vaccines for a short period (up to 42 days based on currently available clinical trial data) as a pragmatic approach to maximising the number of individuals benefiting from a first dose while vaccine supply continues to increase. However, evidence for this extension is not strong. Countries should ensure that any such programme adjustments to dose intervals do not affect the likelihood of receiving the second dose. WHO does not support altering doses.

In the UK, the JCVI recommends that delivery of the first dose of any vaccine to as many eligible individuals as possible should be initially prioritised over delivery of a second dose. However, there is a lack of evidence to support an extended dose interval between the first and second dose, and an extended dose interval is outside the manufacturer's authorised dose recommendations.

In the US, the CDCrecommends that the second dose of an mRNA vaccine can be scheduled for up to 6 weeks after the first dose if the recommended dosing interval cannot be met. The agency continues to emphasise that the second dose should be given as close to the recommended interval as possible, and states that the 2 mRNA vaccines that are available in the US may be considered interchangeable in exceptional circumstances.

Level 2

UpToDate (2021) COVID-19 vaccines to prevent SARS-CoV-2 infection[8]

See Section: DEVIATIONS FROM RECOMMENDED DOSING INTERVALS

For the mRNA vaccines, which are given as 2-dose series, the second dose should be given as close to the recommended interval as possible, but not earlier than recommended. If necessary, the second dose can be scheduled for up to 6 weeks (42 days) after the first dose. If the second dose is not given within this time

[8]UpToDate (2021) COVID-19 vaccines to prevent SARS-CoV-2 infection. https://www.uptodate.com/contents/COVID-19-vaccines-to-prevent-sars-cov-2-infection. Accessed 20 April 2021.

frame, it should be given as soon as feasible. The US CDC notes that the series does not need to be repeated if the second dose is given too early or given more than 6 weeks after the first dose. The efficacy of administering vaccines outside of the recommended timeframes is uncertain, although with some vaccines, using longer intervals has been associated with higher titer antibody responses.

Irish and International Literature

Level 2

Polack et al (2020) [Randomized Controlled Trial] Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine[9]

METHODS: In an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, the authors randomly assigned persons 16 years of age or older in a 1:1 ratio to receive 2 doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30µg per dose). BNT162b2 is a lipid nanoparticle-formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length Spike protein. The first primary endpoint was the efficacy of BNT162b2 against confirmed COVID-19 with onset at least 7 days after the second dose in participants who had been without serologic or virologic evidence of SARS-CoV-2 infection up to 7 days after the second dose; the second primary endpoint was efficacy in participants with and in participants without evidence of prior infection.

RESULTS: A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of COVID-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing COVID-19 (95% CI, 90.3 to 97.6). Similar vaccine efficacy was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe COVID-19 with onset after the first dose, 9 occurred in placebo recipients

[9] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine. N Engl J Med. 2020 Dec 31;383(27):2603-2615. doi: 10.1056/NEJMoa2034577. Epub 2020 Dec 10. PMID: 33301246; PMCID: PMC7745181.

and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.

Among participants with and those without evidence of prior SARS CoV-2 infection, 9 cases of COVID-19 at least 7 days after the second dose were observed among vaccine recipients and 169 among placebo recipients, corresponding to 94.6% vaccine efficacy (95% CI, 89.9 to 97.3). Between the first dose and the second dose, 39 cases in the BNT162b2 group and 82 cases in the placebo group were observed, resulting in vaccine efficacy of 52% (95% CI, 29.5 to 68.4) during this interval and indicating early protection by the vaccine, starting as soon as 12 days after the first dose.

CONCLUSIONS: A 2-dose regimen of BNT162b2 conferred 95% protection against COVID-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines.

Level 4

Dagan et al (2021) [Cohort Study] BNT162b2 mRNA COVID-19 Vaccine in a Nationwide Mass Vaccination Setting[10]

BACKGROUND: As mass vaccination campaigns against COVID-19 commence worldwide, vaccine effectiveness needs to be assessed for a range of outcomes across diverse populations in a non-controlled setting. In this study, data from Israel's largest health care organization were used to evaluate the effectiveness of the BNT162b2 mRNA vaccine.

METHODS: All persons who were newly vaccinated during the period from December 20, 2020, to February 1, 2021, were matched to unvaccinated controls in a 1:1 ratio according to demographic and clinical characteristics. Study

[10] Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, Hernán MA, Lipsitch M, Reis B, Balicer RD. BNT162b2 mRNA COVID-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021 Apr 15;384(15):1412-1423. doi: 10.1056/NEJMoa2101765. Epub 2021 Feb 24. PMID: 33626250; PMCID: PMC7944975.

outcomes included documented infection with the SARS-CoV-2, symptomatic COVID-19, COVID-19-related hospitalization, severe illness, and death. Vaccine effectiveness for each outcome was measured as 1 minus the risk ratio, using the Kaplan-Meier estimator.

RESULTS: Each study group included 596,618 persons. Estimated vaccine effectiveness for the study outcomes at days 14 through 20 after the first dose and at 7 or more days after the second dose was as follows: for documented infection, 46% (95% CI 40 to 51) and 92% (95% CI, 88 to 95); for symptomatic COVID-19, 57% (95% CI, 50 to 63) and 94% (95% CI, 87 to 98); for hospitalization, 74% (95% CI, 56 to 86) and 87% (95% CI, 55 to 100); and for severe disease, 62% (95% CI, 39 to 80) and 92% (95% CI, 75 to 100), respectively. Estimated effectiveness in preventing death from COVID-19 was 72% (95% CI, 19 to 100) for days 14 through 20 after the first dose. Estimated effectiveness in specific subpopulations assessed for documented infection and symptomatic COVID-19 was consistent across age groups, with potentially slightly lower effectiveness in persons with multiple coexisting conditions.

CONCLUSIONS: This study in a nationwide mass vaccination setting suggests that the Pfizer-BopNTech mRNA vaccine is effective for a wide range of COVID-19-related outcomes, a finding consistent with that of the randomized trial.

Level 4

Hall et al (2021) [Cohort Study] COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study[11]

BACKGROUND: BNT162b2 mRNA and ChAdOx1 nCOV-19 adenoviral

[11] Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, Wellington E, Stowe J, Gillson N, Atti A, Islam J, Karagiannis I, Munro K, Khawam J, Chand MA, Brown CS, Ramsay M, Lopez-Bernal J, Hopkins S; SIREN Study Group. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. Lancet. 2021 May 8;397(10286):1725-1735. doi: 10.1016/S0140-6736(21)00790-X. Epub 2021 Apr 23. PMID: 33901423; PMCID: PMC8064668.

vector vaccines have been rapidly rolled out in the UK from December 2020. The authors aimed to determine the factors associated with vaccine coverage for both vaccines and documented vaccine effectiveness of the BNT162b2 mRNA vaccine in a cohort of health-care workers undergoing regular asymptomatic testing.

METHODS: The SIREN study is a prospective cohort study among staff aged ≥18 years working in publicly-funded hospitals in the UK Participants were assigned into either the positive cohort (antibody positive or history of infection indicated by previous positivity of antibody or PCR tests) or the negative cohort (antibody negative with no previous positive test) at the beginning of the follow-up period. Baseline risk factors were collected at enrolment; symptom status was collected every 2 weeks; and vaccination status was collected through linkage to the National Immunisations Management System and questionnaires. Participants had fortnightly asymptomatic SARS-CoV-2 PCR testing and monthly antibody testing, and all tests including symptomatic testing outside SIREN were captured. Data cut-off for the analysis was February 5, 2021. The follow-up period was December 7, 2020, to February 5, 2021. The primary outcomes were vaccinated participants (binary ever vaccinated variable; indicated by at least one vaccine dose recorded by at least one of the two vaccination data sources) for the vaccine coverage analysis and SARS-CoV-2 infection confirmed by a PCR test for the vaccine effectiveness analysis. A mixed-effect logistic regression analysis was carried out to identify factors associated with vaccine coverage. A piecewise exponential hazard mixed-effects model (shared frailty-type model) using a Poisson distribution was used to calculate hazard ratios to compare time-to-infection in unvaccinated and vaccinated participants and to estimate the impact of the BNT162b2 vaccine on all asymptomatic and symptomatic PCR-positive infections. This study is registered with ISRCTN [ISRCTN11041050], and is ongoing.

FINDINGS: 23,324 participants from 104 sites (all in England) met inclusion criteria for the analysis and were

enrolled. Included participants had a median age of 46·1 years (IQR 36·0-54·1) and 19,692 (84%) were female; 8,203 (35%) were assigned to the positive cohort at the start of the analysis period, and 15,121 (65%) assigned to the negative cohort. Total follow-up time was 2 calendar months and 1,106,905 person-days (396,318 vaccinated and 710,587 unvaccinated). Vaccine coverage was 89% on February 5, 2021, 94% of whom had BNT162b2 vaccine. Significantly lower coverage was associated with previous infection, gender, age, ethnicity, job role, and Index of Multiple Deprivation score. During follow-up, there were 977 new infections in the unvaccinated cohort, an incidence density of 14 infections per 10,000 person-days; the vaccinated cohort had 71 new infections 21 days or more after their first dose (incidence density of eight infections per 10,000 person-days) and nine infections 7 days after the second dose (incidence density four infections per 10,000 person-days). In the unvaccinated cohort, 543 (56%) participants had typical COVID-19 symptoms and 140 (14%) were asymptomatic on or 14 days before their PCR positive test date, compared with 29 (36%) with typical COVID-19 symptoms and 15 (19%) asymptomatic in the vaccinated cohort. A single dose of BNT162b2 vaccine showed vaccine effectiveness of 70% (95% CI 55-85) 21 days after first dose and 85% (95% CI 74-96) 7 days after 2 doses in the study population.

INTERPRETATION: These findings show that the BNT162b2 vaccine can prevent both symptomatic and asymptomatic infection in working-age adults. This cohort was vaccinated when the dominant variant in circulation was B.1.1.7 and shows effectiveness against the variant.

Level 4

Britton et al (2021) [Retrospective Cohort Study] Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine Among Residents of Two Skilled Nursing Facilities Experiencing COVID-19 Outbreaks - Connecticut, December

2020-February 2021[12]

Residents of long-term care facilities (LTCFs), particularly those in skilled nursing facilities (SNFs), have experienced disproportionately high levels of COVID-19-associated morbidity and mortality and were prioritized for early COVID-19 vaccination. However, residents of LTCFs and SNFs were not included in COVID-19 vaccine clinical trials, and limited post-authorization vaccine effectiveness data are available for this critical population. It is not known how well COVID-19 vaccines protect SNF residents, who typically are more medically frail, are older, and have more underlying medical conditions than the general population. In addition, immunogenicity of the Pfizer-BioNTech vaccine was found to be lower in adults aged 65-85 years than in younger adults. Through the CDC Pharmacy Partnership for Long-Term Care Program, SNF residents and staff members in Connecticut began receiving the Pfizer-BioNTech COVID-19 vaccine on December 18, 2020. Administration of the vaccine was conducted during several on-site pharmacy clinics. In late January 2021, the Connecticut Department of Public Health (CT DPH) identified two SNFs experiencing COVID-19 outbreaks among residents and staff members that occurred after each facility's first vaccination clinic. CT DPH, in partnership with CDC, performed electronic chart reviews in these facilities to obtain information on resident vaccination status and infection with SARS-CoV-2. Partial vaccination, defined as the period from >14 days after the first dose through 7 days after the second dose, had an estimated effectiveness of 63% (95% CI 33%-79%) against SARS-CoV-2 infection, regardless of symptoms, among residents within these SNFs.This is similar to estimated effectiveness for a single dose of the Pfizer-BioNTech COVID-19 vaccine in adults across a range of age groups in non-congregate

[12] Britton A, Jacobs Slifka KM, Edens C, Nanduri SA, Bart SM, Shang N, Harizaj A, Armstrong J, Xu K, Ehrlich HY, Soda E, Derado G, Verani JR, Schrag SJ, Jernigan JA, Leung VH, Parikh S. Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine Among Residents of Two Skilled Nursing Facilities Experiencing COVID-19 Outbreaks - Connecticut, December 2020-February 2021. MMWR Morb Mortal Wkly Rep. 2021 Mar 19;70(11):396-401. doi: 10.15585/mmwr.mm7011e3. PMID: 33735160; PMCID: PMC7976620.

settings and suggests that to optimize vaccine impact, high coverage with the complete 2-dose series should be recommended for SNF residents and staff members.

Level 4

Chodick et al (2021) [Preprint] [Retrospective Cohort Study] The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence[13]

BACKGROUND: BNT162b2 vaccines showed high efficacy against COVID-19 in a randomised controlled phase 3 trial. A vaccine effectiveness evaluation in real life settings is urgently needed, especially given the global disease surge. The authors assessed the short-term effectiveness of the first dose of BNT162b2 vaccine against SARS-CoV-2 infection 13 to 24 days after immunization. Given the BNT162b2 phase 3 results, the authors hypothesized that the cumulative incidence of SARS-CoV-2 infection among vaccinees would decline after 12 days following immunization compared to the incidence during the preceding days.

METHODS: A comparative effectiveness study was conducted. The study population consisted of all members aged ≥16 years who were vaccinated with one dose of the BNT162b2 vaccine between December 19, 2020 and January 15, 2021 in Israel. The authors collected information regarding medical history and positive SARS-CoV-2 PCR tests from days after first dose to January 17, 2021. Daily and cumulative infection rates in days 13-24 were compared to days 1-12 after first dose using Kaplan-Meier survival analysis and generalized linear models.

FINDINGS: Data of 503,875 individuals (mean age 59·7 years, standard deviation [SD]=14·7, 47·6% males) were analysed, of whom 351,897 had 13-24 days of follow-up.

[13] The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence.
Gabriel Chodick, Lilac Tene, Tal Patalon, Sivan Gazit, Amir Ben Tov, Dani Cohen, Khitam Muhsen.
medRxiv 2021.01.27.21250612; doi: https://doi.org/10.1101/2021.01.27.21250612.

The cumulative incidence of SARS-CoV-2 infection was 0·57% (n=2484) during days 1-12 and 0·27% (n=614) in days 13-24. A 51·4% relative risk reduction (RRR) was calculated in weighted-average daily incidence of SARS-CoV-2 infection from 43·41 infections per 100,000 population (standard error [SE]=12·07) in days 1-12 to 21·08 infections per 100,000 population (SE=6·16) in days 13-24 following immunization. The decrement in incidence was evident from day 18 after first dose. Similar RRRs were calculated in individuals aged 60 or above (44.5%), individuals aged <60 years (50.2%), females (50.0%) and males (52.1%). Findings were similar in sub-populations and patients with various comorbidities.

CONCLUSIONS: This is the first and largest phase 4 study on the effectiveness of the BNT162b2 mRNA COVID-19 vaccine in real-world settings. The findings showed that the first dose of the vaccine is associated with an approximately 51% reduction in the incidence of PCR-confirmed SARS-CoV-2 infections at 13 to 24 days after immunization compared to the rate during the first 12 days. Similar levels of effectiveness were found across age groups, sex, as well as among individuals residing in Arab or ultra-orthodox Jewish communities that display an increased COVID-19 risk.

IMPLICATIONS OF ALL THE AVAILABLE EVIDENCE: Together our findings and the 95% efficacy shown in the phase 3 trial suggest that the BNT162b2 vaccine should be administered in 2 doses to achieve maximum protection and impact in terms of disease burden reduction and possibly reducing SARS-CoV-2 transmission. Global efforts should be made to accelerate COVID-19 vaccine deployment.

Level 4

Vasileiou et al (2021) [Preprint] [Cohort Study] Effectiveness of First Dose of COVID-19 Vaccines Against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 Million People[14]

[14] Vasileiou, Eleftheria and Simpson, Colin R. and Robertson, Chris and Shi, Ting and Kerr,

BACKGROUND: The BNT162b2 mRNA (Pfizer-BioNTech) and ChAdOx1 (Oxford-AstraZeneca) COVID-19 vaccines have demonstrated high efficacy against infection in phase 3 clinical trials and are now being used in national vaccination programmes in the UK and several other countries. There is an urgent need to study the real-world effects of these vaccines. The aim of the present study was to estimate the effectiveness of the first dose of these COVID-19 vaccines in preventing hospital admissions.
METHODS: A prospective cohort study using the Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) database comprising of linked vaccination, primary care, PCR testing, hospitalization and mortality records for 5.4 million people in Scotland (covering ~99% of the population). A time-dependent Cox model and Poisson regression models were fitted to estimate effectiveness against COVID-19 related hospitalization following the first dose of vaccine.
FINDINGS: The first dose of the BNT162b2 vaccine was associated with a vaccine effect of 85% (95% CI 76 to 91) for COVID-19 related hospitalization at 28-34 days post-vaccination. Vaccine effect at the same time interval for the ChAdOx1 vaccine was 94% (95% CI 73 to 99). Results of combined vaccine effect for prevention of COVID-19 related hospitalization were comparable when restricting the analysis to those aged ≥80 years (81%; 95% CI 65 to 90 at 28-34 days post-vaccination).
INTERPRETATION: A single dose of the BNT162b2 mRNA and ChAdOx1 vaccines resulted in substantial reductions in the risk of COVID-19 related hospitalization in Scotland.

Steven and Agrawal, Utkarsh and Akbari, Ashley and Bedston, Stuart and Beggs, Jillian and Bradley, Declan and Chuter, Antony and de Lusignan, Simon and Docherty, Annemarie and Ford, David and Hobbs, F.D. Richard and Joy, Mark and Katikireddi, Srinivasa Vittal and Marple, James and McCowan, Colin and McGagh, Dylan and McMenamin, Jim and Moore, Emily and Murray, Josephine-L.K and Pan, Jiafeng and Ritchie OBE FRSE, Professor Sir Lewis and Shah, Syed Ahmar and Stock, Sarah and Torabi, Fatemeh and Tsang, Ruby S. M. and Wood, Rachael and Woolhouse, Mark and Sheikh, Aziz, Effectiveness of First Dose of COVID-19 Vaccines Against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 Million People. Available at
SSRN: https://ssrn.com/abstract=3789264 or http://dx.doi.org/10.2139/ssrn.3789264.

Level 4

Thompson et al (2021) [Cohort Study] Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight US Locations, December 2020-March 2021[15]

mRNA BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) COVID-19 vaccines have been shown to be effective in preventing symptomatic COVID-19 in randomized placebo-controlled phase 3 trials; however, the benefits of these vaccines for preventing asymptomatic and symptomatic SARS-CoV-2 infection, particularly when administered in real-world conditions, is less well understood. Using prospective cohorts of health care personnel, first responders and other essential and frontline workers in eight US locations from December 14, 2020 to March 13, 2021, CDC routinely tested for SARS-CoV-2 infections every week regardless of symptom status and at the onset of symptoms consistent with COVID-19-associated illness. Among 3,950 participants with no previous laboratory documentation of SARS-CoV-2 infection, 2,479 (62.8%) received both recommended mRNA doses and 477 (12.1%) received only one dose of mRNA vaccine. Among unvaccinated participants, 1.38 SARS-CoV-2 infections were confirmed by PCR per 1,000 person-days. In contrast, among fully immunized (≥14 days after second dose) persons, 0.04 infections per 1,000 person-days were reported; and among partially immunized (≥14 days after first dose and before second dose) persons, 0.19 infections per 1,000 person-days were reported. Estimated mRNA vaccine effectiveness for prevention of infection, adjusted for study site, was 90% for full immunization

[15] Thompson MG, Burgess JL, Naleway AL, Tyner HL, Yoon SK, Meece J, Olsho LEW, Caban-Martinez AJ, Fowlkes A, Lutrick K, Kuntz JL, Dunnigan K, Odean MJ, Hegmann KT, Stefanski E, Edwards LJ, Schaefer-Solle N, Grant L, Ellingson K, Groom HC, Zunie T, Thiese MS, Ivacic L, Wesley MG, Lamberte JM, Sun X, Smith ME, Phillips AL, Groover KD, Yoo YM, Gerald J, Brown RT, Herring MK, Joseph G, Beitel S, Morrill TC, Mak J, Rivers P, Harris KM, Hunt DR, Arvay ML, Kutty P, Fry AM, Gaglani M. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight US Locations, December 2020-March 2021. MMWR Morb Mortal Wkly Rep. 2021 Apr 2;70(13):495-500. doi: 10.15585/mmwr.mm7013e3. PMID: 33793460; PMCID: PMC8022879.

and 80% for partial immunization. These findings indicate that authorized mRNA COVID-19 vaccines are effective for preventing SARS-CoV-2 infection, regardless of symptom status, among working-age adults in real-world conditions. COVID-19 vaccination is recommended for all eligible persons.

Level 4

Monin-Aldama et al (2021) [Preprint] [Cohort Study] Interim results of the safety and immune-efficacy of 1 versus 2 doses of COVID-19 vaccine BNT162b2 for cancer patients in the context of the UK vaccine priority guidelines[16]

BACKGROUND: The efficacy and safety profile of vaccines against SARS-CoV-2 have not been definitively established in immunocompromised patient populations. Patients with a known cancer diagnosis were hitherto excluded from trials of the vaccines currently in clinical use.

METHODS: This study presents data on the safety and immune efficacy of the BNT162b2 (Pfizer-BioNTech) vaccine in 54 healthy controls and 151 mostly elderly patients with solid and haematological malignancies, respectively, and compares results for patients who were boosted with BNT162b2 at 3 weeks versus those who were not. Immune efficacy was measured as antibody seroconversion, T cell responses, and neutralisation of SARS-CoV-2 Wuhan strain and of a variant of concern (VOC) (B.1.1.7). The authors also collected safety data for the BNT162b2 vaccine up to 5 weeks following first dose.

FINDINGS: The vaccine was largely well tolerated.

[16] Interim results of the safety and immune-efficacy of 1 versus 2 doses of COVID-19 vaccine BNT162b2 for cancer patients in the context of the UK vaccine priority guidelines. Leticia Monin-Aldama, Adam G. Laing, Miguel Muñoz-Ruiz, Duncan R McKenzie, Irene del Molino del Barrio, Thanussuyah Alaguthurai, Clara Domingo-Vila, Thomas S. Hayday, Carl Graham, Jeffrey Seow, Sultan Abdul-Jawad, Shraddha Kamdar, Elizabeth Harvey-Jones, Rosalind Graham, Jack Cooper, Muhammad Khan, Jennifer Vidler, Helen Kakkassery, Sinha Shubhankar, Richard Davis, Liane Dupont, Isaac Francos Quijorna, Puay Lee, Josephine Eum, Maria Conde Poole, Magdalene Joseph, Daniel Davies, Yin Wu, Ana Montes, Mark Harries, Anne Rigg, James Spicer, Michael H Malim, Paul Fields, Piers Patten, Francesca Di Rosa, Sophie Papa, Tim Tree, Katie Doores, Adrian C. Hayday, Sheeba Irshad. medRxiv 2021.03.17.21253131; doi: https://doi.org/10.1101/2021.03.17.21253131.

However, when study participants were examined for anti-S IgG titres at ~21 days following a single vaccine inoculum, significantly different levels of vaccine efficacy across the three cohorts were observed. In contrast to its very high performance in healthy controls (~97% (31/32) of healthy controls had a serological response to vaccination), immune efficacy of a single inoculum in solid cancer patients was low (only ~39% (21/54) of solid cancer patients had a serological response ($p<0.0001$)) and very low in haematological cancer patients (only ~13% (5/39) of haematological cancer patients had a serological response ($p<0.0001$)).

Of note, efficacy in solid cancer patients was greatly and rapidly increased by boosting at 21-days: 95% within 2 weeks of boost. Too few haematological cancer patients were boosted for clear conclusions to be inferred.

CONCLUSIONS: Delayed boosting potentially leaves most solid and haematological cancer patients wholly or partially unprotected, with implications for their own health, their environment and the evolution of VOC strains. Prompt boosting of solid cancer patients quickly overcomes the poor efficacy of the primary inoculum in solid cancer patients.

EVIDENCE BEFORE THIS STUDY: Some cancer patients have been shown to exhibit sustained immune dysregulation, inefficient seroconversion and prolonged viral shedding as a consequence of SARS-CoV-2 infection. Consequently, their exclusion and, in particular, the exclusion of patients receiving systemic anti-cancer therapies, from the registry trials of the approved COVID-19 vaccines raises questions about the efficacy and safety of SARS-CoV-2 vaccination in this patient population. In addition, while the change in the dosing interval to 12 weeks aimed to maximise population coverage in the UK, it is unclear whether this strategy is appropriate for cancer patients and those on systemic anti-cancer therapies.

IMPLICATIONS OF ALL THE AVAILABLE EVIDENCE: In cancer patients, one dose of 30ug of BNT162b2 yields poor

vaccine efficacy, as measured by seroconversion rates, viral neutralisation capacity and T cell responses, at 3- and 5-weeks following the first inoculum. Patients with solid cancers exhibited a significantly greater response following a booster at 21-days. These data support prioritisation of cancer patients for an early (21-day) second dose of the BNT162b2 vaccine. Given the globally poor responses to vaccination in patients with haematological cancers, post-vaccination serological testing, creation of herd immunity around these patients using a strategy of ring vaccination, and careful follow-up should be prioritised.

Level 5

Bernal et al (2021) [Preprint] [Case-Control Study] Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalizations and mortality in older adults in England[17]

OBJECTIVES: To estimate the real-world effectiveness of the Pfizer-BioNTech BNT162b2 vaccine and AstraZeneca ChAdOx1 vaccine against confirmed COVID-19, hospitalizations and deaths.

DESIGN: Test negative case control design.

SETTING: Community COVID-19 PCR testing in England.

PARTICIPANTS: All adults in England aged 70 years and older (over 7.5 million). All COVID-19 testing in the community among eligible individuals who reported symptoms between 8 December 2020 and 19 February 2021 was included in the analysis.

INTERVENTIONS: One and 2 doses of BNT162b2 vaccine. One dose of ChAdOx1 vaccine.

[17] Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalizations and mortality in older adults in England. Jamie
Lopez Bernal, Nick Andrews, Charlotte Gower, Julia Stowe, Chris Robertson, Elise Tessier, Ruth Simmons, Simon Cottrell, Richard Roberts, Mark O'Doherty, Kevin Brown, Claire Cameron, Diane Stockton, Jim McMenamin, Mary Ramsay.
medRxiv 2021.03.01.21252652; doi: https://doi.org/10.1101/2021.03.01.21252652.

MAIN OUTCOME MEASURES: Symptomatic PCR confirmed SARS-CoV-2 infection, hospitalizations and deaths with COVID-19.

RESULTS: Individuals aged ≥80 years vaccinated with BNT162b2 prior to 4 January had a higher odds of testing positive in the first 9 days after vaccination (OR up to 1.48, 95% CI 1.23-1.77), indicating that those initially targeted had a higher underlying risk of infection. Vaccine effectiveness was therefore estimated relative to the baseline post-vaccination period. Vaccine effects were noted from 10-13 days after vaccination, reaching an effectiveness of 70% (95% CI 59-78%) from 28-34 days, then plateauing. From 14 days after the second dose a vaccine effectiveness of 89% (95% CI: 85-93%) was seen.

Individuals aged ≥70 years vaccinated from 4 January had a similar underlying risk of COVID-19 to unvaccinated individuals. With BNT162b2, vaccine effectiveness reached 61% (95% CI 51-69%) from 28-34 days after vaccination, then plateauing. With the ChAdOx1 vaccine, vaccine effects were seen from 14-20 days after vaccination reaching an effectiveness of 60% (95% CI 41-73%) from 28-34 days and further increasing to 73% (95% CI 27-90%) from day 35 onwards.

On top of the protection against symptomatic disease, cases who had been vaccinated with one dose of BNT162b2 had an additional 43% (95% CI 33-52%) lower risk of emergency hospitalization and an additional 51% (95%CI 37-62%) lower risk of death. Cases who had been vaccinated with one dose of ChAdOx1 had an additional 37% (95% CI 3-59%) lower risk of emergency hospitalization. There was insufficient follow-up to assess the effect of ChAdOx1 on mortality due to the later rollout of this vaccine. Combined with the effect against symptomatic disease, these results indicate that a single dose of either vaccine is approximately 80% effective at preventing hospitalization and a single dose of BNT162b2 is 85% effective at preventing death from COVID-19.

CONCLUSION: Vaccination with either a single dose of

BNT162b2 or ChAdOx1 COVID-19 vaccination was associated with a significant reduction in symptomatic SARS-CoV-2 positive cases in older adults and with even greater protection against severe disease. Both vaccines show similar effects. Protection was maintained for the duration of follow-up (>6 weeks). A second dose of BNT162b2 provides further protection against symptomatic disease but second doses of ChAdOx1 have not yet been rolled out in England.

Level 6

Benotmane et al (2021) [Observational Study] Weak anti-SARS-CoV-2 antibody response after the first injection of an mRNA COVID-19 vaccine in kidney transplant recipients[18]

In an effort to shed light on the efficacy and safety of an mRNA COVID-19 vaccine in kidney transplant recipients (KTRs), the authors conducted a preliminary study to investigate the anti–SARS-CoV-2 antibody response after the first injection.

242 KTRs who received the first injection of the Moderna mRNA-1273 vaccine (100 µg) at Strasbourg University Hospital (Strasbourg, France) between January 21 and 28, 2021 were examined. All had a negative history for COVID-19 and tested negative for anti–SARS-CoV-2 antibodies on the day of the first injection. The anti–SARS-CoV-2 antibody response against the Spike protein was assessed at 28 days after injection using the ARCHITECT IgG II Quant test (Abbott, Abbott Park, IL), with titers >50 arbitrary units (AUs)/ml being considered as positive (detection range, 6.8–40,000 AUs/ml; positive agreement, 99.4%; negative agreement, 99.6%).

One patient developed mild symptomatic COVID-19 7 days after injection, and only 26 (10.8%) KTRs had a positive

[18] Benotmane I, Gautier-Vargas G, Cognard N, Olagne J, Heibel F, Braun-Parvez L, Martzloff J, Perrin P, Moulin B, Fafi-Kremer S, Caillard S. Weak anti-SARS-CoV-2 antibody response after the first injection of an mRNA COVID-19 vaccine in kidney transplant recipients. Kidney Int. 2021 Jun;99(6):1487-1489. doi: 10.1016/j.kint.2021.03.014. Epub 2021 Mar 26. PMID: 33775674; PMCID: PMC7997264.

serology at 28 days after injection. The median IgG titer was 224 AUs/ml (interquartile range, 76–496 AUs/ml), whereas the median IgG titer in the seronegative group was <6.8 AUs/ml. Patients who seroconverted had longer time from transplantation, received less immunosuppression, and had a better kidney function.

In summary, the burden of immunosuppression may induce a weak anti–SARS-CoV-2 antibody response in KTRs after the first injection of an mRNA COVID-19 vaccine. These findings are in sharp contrast with immunocompetent subjects who invariably seroconverted after the first injection. The authors advocate not to delay the second vaccine injection in immunocompromised patients. Close surveillance is also recommended to discuss the opportunity of a third dose in less responsive patients.

Level 6

Brockman et al (2021) [Preprint] [Observational Study] Weak humoral immune reactivity among residents of long-term care facilities following one dose of the BNT162b2 mRNA COVID-19 vaccine[19]

BACKGROUND: Several Canadian provinces are extending the interval between COVID-19 vaccine doses to increase population vaccine coverage more rapidly. However, immunogenicity of these vaccines after one dose is incompletely characterized, particularly among the elderly, who are at greatest risk of severe COVID-19.

METHODS: The authors assessed SARS-CoV-2 humoral responses pre-vaccine and one month following the first dose of BNT162b2 mRNA vaccine in 12 COVID-19 seronegative residents of long-term care facilities (median age, 82 years), 18 seronegative healthcare workers (HCWs; median age, 36 years) and 4 convalescent HCWs. Total antibody responses to SARS-CoV-2 nucleocapsid (N) and Spike

[19] Brockman MA, Mwimanzi F, Sang Y, Ng K, Agafitei O, Ennis S, Lapointe H, Young L, Umviligihozo G, Burns L, Brumme C, Leung V, Montaner JSG, Holmes D, DeMarco M, Simons J, Niikura M, Pantophlet R, Romney MG, Brumme ZL. Weak humoral immune reactivity among residents of long-term care facilities following one dose of the BNT162b2 mRNA COVID-19 vaccine. medRxiv [Preprint]. 2021 Mar 24:2021.03.17.21253773. doi: 10.1101/2021.03.17.21253773. PMID: 33791737; PMCID: PMC8010769.

protein receptor binding domain (S/RBD) were assessed using commercial immunoassays. IgG and IgM responses to S/RBD were quantified and the ability of antibodies to block S/RBD binding to ACE2 receptor was determined using ELISA. Neutralizing antibody activity was also assessed using pseudovirus and live SARS-CoV-2.

RESULTS: After one vaccine dose, binding antibodies against S/RBD were ~4-fold lower in residents compared to HCWs ($p<0.001$). Inhibition of ACE2 binding was 3-fold lower in residents compared to HCWs ($p=0.01$) and pseudovirus neutralizing activity was 2-fold lower ($p=0.003$). While 6 (33%) seronegative HCWs neutralized live SARS-CoV-2, only one (8%) resident did ($p=0.19$). In contrast, convalescent HCWs displayed 7- to 20-fold higher levels of binding antibodies and substantial ability to neutralize live virus after one dose.

INTERPRETATION: Extending the interval between COVID-19 vaccine doses may pose a risk to the elderly due to lower vaccine immunogenicity in this group. The authors recommend that second doses not be delayed in elderly individuals.

Level 6

Nam et al (2021) [Preprint] [Modelling Study] Modelling the impact of extending dose intervals for COVID-19 vaccines in Canada[20]

BACKGROUND: Dual dose SARS-CoV-2 vaccines demonstrate high efficacy and will be critical in public health efforts to mitigate the COVID-19 pandemic and its health consequences; however, many jurisdictions face very constrained vaccine supply. The authors examined the impacts of extending the interval between 2 doses of mRNA vaccines in Canada in order to inform deliberations of Canada's National Advisory Committee on Immunization.

[20] Modelling the impact of extending dose intervals for COVID-19 vaccines in Canada
Austin Nam, Raphael Ximenes, Man
Wah Yeung, Sharmistha Mishra, Jianhong Wu, Matthew Tunis, Beate Sander
medRxiv 2021.04.07.21255094; doi: https://doi.org/10.1101/2021.04.07.21255094.

METHODS: The authors developed an age-stratified, deterministic, compartmental model of SARS-CoV-2 transmission and disease to reproduce the epidemiologic features of the epidemic in Canada. Simulated vaccination comprised mRNA vaccines with explicit examination of effectiveness against disease (67% [first dose], 94% [second dose]), hospitalization (80% [first dose], 96% [second dose]), and death (85% [first dose], 96% [second dose]) in adults aged 20 years and older. Effectiveness against infection was assumed to be 90% relative to the effectiveness against disease. A 6-week mRNA dose interval was used as a base case (consistent with early program rollout across Canadian and international jurisdictions) and compared extended intervals of 12 weeks, 16 weeks, and 24 weeks. Vaccinations commenced on January 1, 2021, and simulated a third wave on April 1, 2021.

RESULTS: Extending mRNA dose intervals were projected to result in 12.1%-18.9% fewer symptomatic cases, 9.5%-13.5% fewer hospitalizations, and 7.5%-9.7% fewer deaths in the population over a 12-month time horizon. The largest reductions in hospitalizations and deaths were observed in the longest interval of 24 weeks, although benefits were diminishing as intervals extended. Benefits of extended intervals stemmed largely from the ability to accelerate coverage in individuals aged 20-74 years as older individuals were already prioritized for early vaccination. Conditions under which mRNA dose extensions led to worse outcomes included: first-dose effectiveness <65% against death; or protection following first dose waning to 0% by month 3 before the scheduled 2nd dose at 24-weeks. Probabilistic simulations from a range of likely vaccine effectiveness values did not result in worse outcomes with extended intervals.

CONCLUSION: Under real-world effectiveness conditions, our results support a strategy of extending mRNA dose intervals across all age groups to minimize symptomatic cases, hospitalizations and deaths while vaccine supply is constrained.

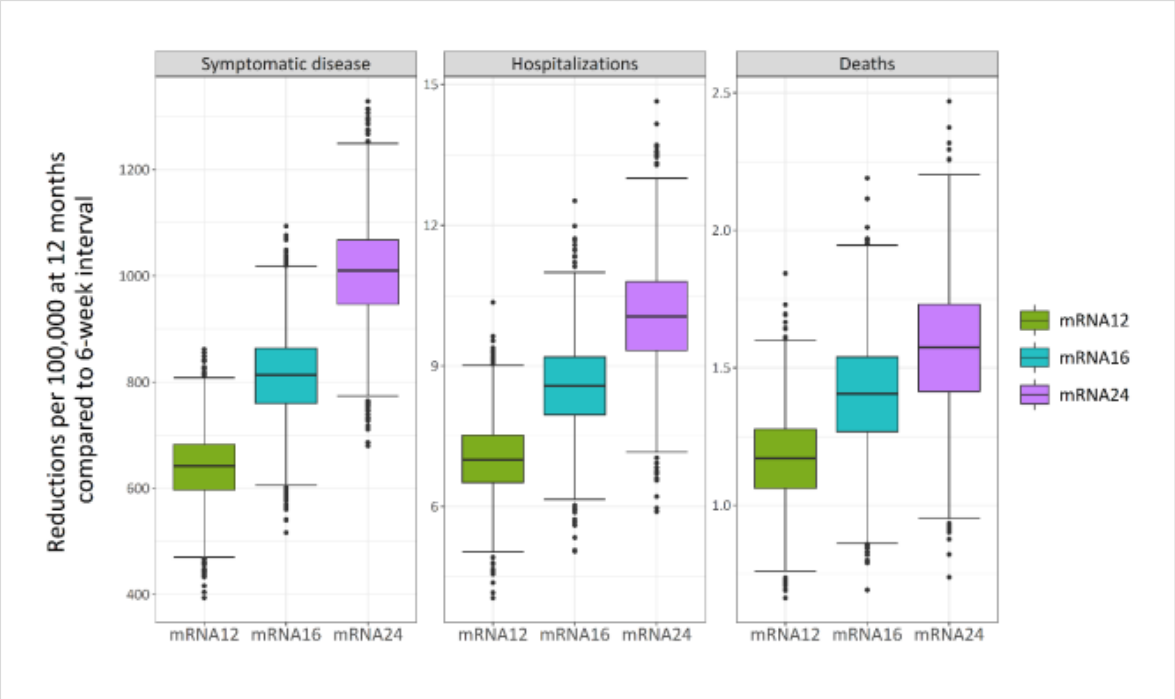

Figure: Reductions in symptomatic disease, hospitalizations and deaths at 12 months compared to a 6-week interval (mRNA6) from probabilistic simulations of 2,000 samples. Vaccine effectiveness against infection = 80-95% of vaccine effectiveness against symptomatic disease.

Level 6

Jurgens and Lackner (2021) [Preprint] [Modelling Study] Modelled Optimization of SARS-Cov-2 Vaccine Distribution: an Evaluation of Second Dose Deferral Spacing of 6, 12, and 24 weeks[21]

BACKGROUND: Multiple recent studies have shown strong first dose vaccine efficacy for both Moderna mRNA-1273 and Pfizer-BioNTech BNT 162b2, which has stimulated discussion of maximizing initial population immunity during a time of vaccine shortage by using a deferred second dose strategy for these vaccines.

METHODS: The present model examines the size of the effect of spacing of the second dose with 6-, 12- and 24-

[21] Modelled Optimization of SARS-Cov-2 Vaccine Distribution: an Evaluation of Second Dose Deferral Spacing of 6, 12, and 24 weeks. GT Jurgens, K Lackner. medRxiv 2021.02.28.21252638; doi: https://doi.org/10.1101/2021.02.28.21252638.

week deferred spacing regimens relative to 3-week spacing.

RESULTS: Deferring the second dose from 3 weeks to 6 weeks, 12 weeks and 24 weeks shows progressive benefit to population immunity for any given time period, even with significant one dose efficacy decay. The benefits to population immunity were proportionate to the delay to second dose. Deferring the second dose to 12 weeks had approximately twice the benefit as deferring to 6 weeks, but only halfthe benefit of the 24-week regimen. Absolute population immunity gains of 2-20 percentage points were reported. These gains are increased significantly if the vaccine supply is more robust.

CONCLUSION: The longer the second dose is deferred the larger the benefit in initial population immunity, provided one dose efficacy does not significantly wane. Monitoring one dose efficacy duration minimizes this risk, as the gathered data will help ensure the second dose is given at an optimal time. How this information is implemented should vary depending on the population and whether the goal is to optimally protect high risk groups or to increase total population immunity as quickly as possible. Benefits of deferring the second dose are influenced by the length of deferral, one dose efficacy, and vaccine supply per capita. The time to herd immunity could be shortened by 4 weeks with the implementation of a 12-week spacing regimen or 10 weeks with a 24-week spacing regimen.

Level 6

Maier et al (2021) [Preprint] [Modelling Study] Potential benefits of delaying the second mRNA COVID-19 vaccine dose[22]

Vaccination against COVID-19 with the recently approved mRNA vaccines BNT162b2 (BioNTech/Pfizer) and mRNA-1273 (Moderna) is currently underway in a large number of

[22] Maier et al (2021) Potential benefits of delaying the second mRNA COVID-19 vaccine dose. https://arxiv.org/abs/2102.13600.

countries. However, high incidence rates and rapidly spreading SARS-CoV-2 variants are concerning. In combination with acute supply deficits in Europe in early 2021, the question arises: Does extending the vaccine, for instance by delaying the second dose, make a significant contribution to preventing deaths, despite associated risks such as lower vaccine efficacy, the potential emergence of escape mutants, enhancement, waning immunity, reduced social acceptance of off-label vaccination, and liability shifts? A quantitative epidemiological assessment of risks and benefits of non-standard vaccination protocols remains elusive. Using conditions in Germany as a reference point, the authors show that delaying the second vaccine dose is expected to prevent deaths in the 4- to 5-digit range, should incidence resurge. This considerable public health benefit relies on the fact that both mRNA vaccines provide substantial protection against severe COVID-19 and death beginning 12 to 14 days after the first dose. The benefits of a protocol change are attenuated should vaccine compliance decrease substantially. To quantify the impact of a protocol change on vaccination adherence, the authors performed a large-scale online survey and found that, in Germany, changing vaccination protocols may lead to small reductions in vaccination intention. Therefore, the authors anticipate that the benefits of a strategy change to remain substantial and stable.

Level 6

Harizi et al (2021) [Preprint] [Modelling Study] Should We Delay the Second COVID-19 Vaccine Dose?[23]

Due to the shortage in COVID-19 vaccine supplies and the alarming sanitary situation engendered by the COVID-19 pandemic, some countries have opted to delay the second dose of mRNA COVID-19 vaccines for some period of time, aiming to get the first dose of the vaccine to a larger number of people before proceeding with second dose administration. This strategy has generated heated debate, and no clear expert consensus has been reached. The authors tried to answer the following question from a pure mathematical perspective: Should the second dose of the vaccine be delayed? The answer depends on the efficacy of the first and second COVID-19 vaccine doses. In fact, if the efficacy of the first dose $\alpha 1$ is greater than $\alpha 2/(1+0.01\alpha 2)$, the optimal strategy to maximize the number of effectively vaccinated people is to delay the second dose of the vaccine as much as possible up to the maximum period prescribed by clinical recommendations.

Efficacy of the first BNT162b2 dose was reported as 92.6% (95% CI: 69.0–98.3) after 14 days. With such a high first dose efficacy, these theoretical findings support the fact that the benefits of the BNT162b2 vaccine could be maximized by deferring second doses until all of the population (or at least the priority group members) are offered at least one dose. The same conclusion may be derived for the Moderna mRNA-1273 vaccine, which achieved efficacy of 94.1% (95% CI: 89.3-96.8%) with a 2-dose regimen, and efficacy of ~92.1% (95% CI: 68.8-99.1%) 14 days after the first dose. Although results may be considered primarily for general population vaccination strategies and decision making, different approaches may be required for high-risk sub-populations. The maximum delay between doses will require efficacy data from ongoing programs; however, the approach described here

[23] Intissar Harizi, Soulaimane Berkane, Abdelhamid Tayebi, Michael S. Silverman, Saverio Stranges
medRxiv 2021.02.13.21251652; doi: https://doi.org/10.1101/2021.02.13.21251652.

will help inform policy makers in assessing these data.

Level 6

Romero-Brufau et al (2021) [Modelling Study] Public health impact of delaying second dose of BNT162b2 or mRNA-1273 COVID-19 vaccine: simulation agent based modeling study[24]

OBJECTIVE: To estimate population health outcomes with delayed second dose versus standard schedule of SARS-CoV-2 mRNA vaccination.

DESIGN: Simulation agent based modeling study.

SETTING: Simulated population based on real world US data.

PARTICIPANTS: The simulation included 100,000 agents, with a representative distribution of demographics and occupations. Networks of contacts were established to simulate potentially infectious interactions through occupation, household and random interactions.

INTERVENTIONS: Simulation of standard COVID-19 vaccination versus delayed second dose vaccination prioritizing the first dose. The simulation runs were replicated 10 times. Sensitivity analyses included first dose vaccine efficacy of 50%, 60%, 70%, 80% and 90% after day 12 post-vaccination; vaccination rate of 0.1%, 0.3% and 1% of population per day; assuming the vaccine prevents only symptoms but not asymptomatic spread (that is, non-sterilizing vaccine); and an alternative vaccination strategy that implements delayed second dose for people under 65 years of age, but not until all those above this age have been vaccinated.

MAIN OUTCOME MEASURES: Cumulative COVID-19 mortality, cumulative SARS-CoV-2 infections, and cumulative hospital admissions due to COVID-19 over 180 days.

[24] Romero-Brufau S, Chopra A, Ryu AJ, Gel E, Raskar R, Kremers W, Anderson KS, Subramanian J, Krishnamurthy B, Singh A, Pasupathy K, Dong Y, O'Horo JC, Wilson WR, Mitchell O, Kingsley TC. Public health impact of delaying second dose of BNT162b2 or mRNA-1273 COVID-19 vaccine: simulation agent based modeling study. BMJ. 2021 May 12;373:n1087. doi: 10.1136/bmj.n1087. Erratum in: BMJ. 2021 May 25;373:n1334. PMID: 33980718; PMCID: PMC8114182.

RESULTS: Over all simulation replications, the median cumulative mortality per 100,000 for standard dosing versus delayed second dose was 226 *vs.* 179, 233 *vs.* 207, and 235 *vs.* 236 for 90%, 80% and 70% first dose efficacy, respectively. The delayed second dose strategy was optimal for vaccine efficacies at or above 80% and vaccination rates at or below 0.3% of the population per day, under both sterilizing and non-sterilizing vaccine assumptions, resulting in absolute cumulative mortality reductions between 26 and 47 per 100,000. The delayed second dose strategy for people under 65 performed consistently well under all vaccination rates tested.

CONCLUSIONS: The results suggest that under specific conditions a decrease in cumulative mortality, infections and hospitalizations can be achieved when the second vaccine dose is delayed. This was most significant in the group where the vaccine was delayed in those below 65 years of age, but not in those older. The conditions where these benefits were observed included first dose vaccine efficacy being above 70%, and vaccination rates remaining below 1% of the population per day.

Level 6

Moghadas et al (2021) [Preprint] [Modelling Study] Evaluation of COVID-19 vaccination strategies with a delayed second dose[25]

COVID-19 vaccines currently approved in the USrequire 2 doses, administered 3 to 4 weeks apart. Constraints in vaccine supply and distribution capacity, together with the rise of COVID-19 cases and hospitalizations and the emergence of SARS-CoV-2 variants, have generated a policy debate on whether to vaccinate more individuals with the first dose of available vaccines and delay the second dose, or to continue with the recommended 2-dose series as tested in clinical trials. The authors developed an agent-based model of COVID-19 transmission to compare the

[25] Moghadas SM, Vilches TN, Zhang K, Nourbakhsh S, Sah P, Fitzpatrick MC, Galvani AP. Evaluation of COVID-19 vaccination strategies with a delayed second dose. medRxiv [Preprint]. 2021 Jan 29:2021.01.27.21250619. doi: 10.1101/2021.01.27.21250619. Update in: PLoS Biol. 2021 Apr 21;19(4):e3001211. PMID: 33532805; PMCID: PMC7852256.

impact of these two vaccination strategies, while varying the temporal waning of vaccine efficacy against disease following the first dose, vaccine efficacy against infection, and the level of pre-existing immunity in the population. Results show that following the first dose of the Moderna vaccine, a delay of at least 9weeks could maximize vaccination program effectiveness and avert at least an additional 17.3 (95% CrI: 7.8 – 29.7) infections, 0.69 (95% CrI: 0.52 - 0.97) hospitalizations, and 0.34 (95% CrI: 0.25 - 0.44) deaths per 10,000 population compared to the recommended 4-week interval between the 2 doses. Following the first dose of the Pfizer-BioNTech vaccine, a 9-week delayed second dose strategy averted an additional 0.60 (95% CrI: 0.37–0.89) hospitalizations and 0.32 (95% CrI: 0.23–0.45) deaths per 10,000 population, compared to the 3-week recommended schedule between doses. However, there was no clear advantage for delaying the second dose beyond the 3-week tested schedule, unless the efficacy of the first dose did not wane over time. These findings underscore the importance of quantifying the durability of vaccine-induced protection after the first dose, as well as vaccine efficacy against infection in order to determine the optimal time interval between the 2 doses.

Level 6

Hill et al (2021) [Preprint] [Modelling Study] Comparison between one and 2 dose SARS-CoV-2 vaccine prioritisation for a fixed number of vaccine doses[26]

BACKGROUND: The swift development of vaccines targeting SARS-CoV-2, which have been shown to generate significant immune responses and offer considerable protection against disease, has been met with worldwide commendation. However, in the context of an ongoing pandemic there is an interplay between infection and vaccination. While infection can grow exponentially,

[26] Comparison between one and two dose SARS-CoV-2 vaccine prioritisation for a fixed number of vaccine doses.Edward M. Hill, Matt J. Keeling. medRxiv 2021.03.15.21253542; doi: https://doi.org/10.1101/2021.03.15.21253542.

potentially overwhelming healthcare resources, vaccination rates are generally limited by both supply and logistics. With the first SARS-CoV-2 vaccines receiving medical approval requiring 2 doses, there has been scrutiny on the spacing between doses; an elongated period between doses would allow more of the population to receive a first vaccine dose in the short-term generating wide-spread partial immunity.

METHODS: Focusing on data from England, the authors investigated prioritisation of a 1-dose or 2-dose vaccination schedule given a fixed number of vaccine doses and with respect to a measure of maximising averted deaths. The authors optimised outcomes for two different estimates of population size and relative risk of mortality for at-risk groups within the phase 1 vaccine priority order in England, for different amounts of available vaccine and for different vaccine efficacies.

FINDINGS: Vaccines offering relatively high protection from the first dose (compared to the efficacy derived from 2 doses) favour strategies that prioritise giving more people one dose rather than a smaller number of people 2 doses. The optimal mix of one and 2 doses between the defined priority groups of phase 1 shows a pattern of returning to give second doses to the highest risk groups as the number of available doses increases. For the age-only estimate of relative risk, the separation between prioritising first dose or second doses was relatively smooth. For low numbers of available doses (< 2 million) and greater than 50% relative efficacy, the optimal policy is to prioritise one dose. For larger stockpiles of vaccine, the relative efficacy needs to be higher to prioritise giving one dose to as many people as possible. Within the plausible range of relative efficacy values (75% - 90%), the authors found a steady switch to prioritising the second dose as the amount of available vaccine increases from 4 million to 18 million doses. For the priority group estimate, the very high relative risk associated with care home residents and workers (priority group 1) means that, for a low number of doses and a low relative efficacy, it can

be optimal to prioritise giving 2 doses to the care home group. With this estimated set of relative risks, there was also an even stronger effect (compared to the age-only estimate) of high relative first dose efficacy, leading to a wider parameter space where the first dose was prioritised.

DISCUSSION: Although an optimal timing of first and second doses between the phase 1 priority groups can substantially reduce overall mortality risk to the population, there also needs to be careful consideration of the precise timing between first and second doses as well as the logistics of vaccine delivery.

Level 7

Plotkin et al (2021) [Letter] Accelerate COVID-19 Vaccine Rollout by Delaying the Second Dose of mRNA Vaccines[27]

The authors pose 3 questions: Will one dose protect more people than 2 doses? Will antibodies and efficacy persist for several months after a single dose? And will a second dose give a boost if delayed?

On question 1, the authors demonstrate that if the vaccines are highly efficacious, more people will be protected if all are given one dose, than if fewer are given two doses.

On question 2, the authors state that data on persistence of antibodies is not available, but in view of the apparent low level of antibodies that correlated with protection by the mRNA vaccine, efficacy is likely to last for several months.

On question 3, B cell memory after mRNA vaccination has been clearly demonstrated, which supports the hypothesis that antibodies will be boosted by a second mRNA dose given months later. Priming of the immune system generates good responses to second doses of most vaccines for at least 6 months and perhaps longer.

[27] Plotkin SA, Halsey N. Accelerate COVID-19 Vaccine Rollout by Delaying the Second Dose of mRNA Vaccines. Clin Infect Dis. 2021 Jan 27:ciab068. doi: 10.1093/cid/ciab068. Epub ahead of print. PMID: 33502467; PMCID: PMC7929065.

Level 7

Iacobucci et al (2021) [Commentary] COVID-19 vaccination: What's the evidence for extending the dosing interval?[28]

In a joint statement, Pfizer and BioNTech said "The safety and efficacy of the vaccine has not been evaluated on different dosing schedules as the majority of trial participants received the second dose within the window specified in the study design. There is no data to demonstrate that protection after the first dose is sustained after 21 days." The European Medicines Agency has said that the gap between the first and second doses of the Pfizer-BioNTech vaccine should not exceed 42 days. "Any change to this would require a variation to the marketing authorisation as well as more clinical data to support such a change, otherwise it would be considered as 'off-label use.'"

Level 7

Quek et al (2021) [Editorial] COVID-19 vaccines: what happened to evidence-based medicine?[29]

The UK government recently decided to extend the interval between the first dose of the Pfizer BioNTech and AstraZeneca COVID-19 vaccines from 3 weeks to 12 weeks to maximise the number of people receiving the initial dose, despite the trials only providing vaccine efficacy data based on a schedule of 21 days between doses. This editorial discusses whether there is evidence to support this policy change, and concludes there is not.

Level 7

Kadire et al (2021) [Editorial] Delayed Second Dose versus Standard Regimen for COVID-19 Vaccination[30]

[28] Iacobucci G, Mahase E. COVID-19 vaccination: What's the evidence for extending the dosing interval? BMJ. 2021 Jan 6;372:n18. doi: 10.1136/bmj.n18. PMID: 33408068.
[29] Quek E, Tahir H. COVID-19 vaccines: what happened to evidence-based medicine? Br J Hosp Med (Lond). 2021 Feb 2;82(2):1-4. doi: 10.12968/hmed.2021.0047. Epub 2021 Feb 3. PMID: 33646036.

[30] Kadire SR, Wachter RM, Lurie N. Delayed Second Dose versus Standard Regimen for COVID-19 Vaccination. N Engl J Med. 2021 Mar 4;384(9):e28. doi: 10.1056/NEJMclde2101987. Epub 2021

Consideration must be given to the current [*c.* March 2021] circumstances: a slow vaccine rollout, a limited vaccine supply, and the recent emergence of more infectious SARS-CoV-2 variants. Our current COVID-19 crisis offers a classic case in which the plan —— by protecting too few people too slowly, in the face of a growing threat —— may represent the riskier option.

Feb 17. PMID: 33596347.

Level 7

Pimenta et al (2021) [Editorial] Delaying the second dose of COVID-19 vaccines[31]

Delaying the second dose of COVID-19 vaccines may be a particular concern for older adults. The phase 2 trial of the Pfizer-BioNTech vaccine reported a reduced antibody response among participants aged 65-85 compared with those under 55. Recent data from PHE showed efficacy against symptomatic disease was 57% among adults over 80 after a single dose, increasing to 85% after the second dose. Antibody surveillance data from the REACT-2 study showed IgG positivity 21 days after one dose of Pfizer-BioNTech vaccine in 80% of adults under 60, but in only 49% and 34% of those aged over 70 and 80, respectively. IgG positivity increased to 93% and 88%, respectively, after a second dose, suggesting that the second dose is critical in these vulnerable age groups.

Level 7

Bieniasz (2021) [Letter] The case against delaying SARS-CoV-2 mRNA vaccine boosting doses[32]

The purported efficacy of prime-only regimens is based on a small number of infections that occurred over an extremely short time period (approximately day 12 to approximately day 21 or 28), between the prime and the boost. The author argued that it is not known whether prime-only recipients will be protected beyond day 21 or 28. This has not been tested in any clinical trial, and assertions about effectiveness beyond day 21–28 are speculative.

[31] Pimenta D, Yates C, Pagel C, Gurdasani D. Delaying the second dose of COVID-19 vaccines. BMJ. 2021 Mar 18;372:n710. doi: 10.1136/bmj.n710. PMID: 33737404.

[32] Bieniasz P. The case against delaying SARS-CoV-2 mRNA vaccine boosting doses. Clin Infect Dis. 2021 Jan 27:ciab070. doi: 10.1093/cid/ciab070. Epub ahead of print. PMID: 33503230; PMCID: PMC7929009.

Level 7

Humphreys and Godkin (2021) [Commentary] The potential risks of delaying the second vaccine dose during the SARS-CoV-2 pandemic[33]

The authors argue that is not a trivial decision to alter the evidence-based vaccination schedule, and there is a risk that it may increase the chances of virulent mutations of SARS-CoV-2 emerging.

Level 8: UNCLASSIFIED

Tauzin et al (2021) [Preprint] A single BNT162b2 mRNA dose elicits antibodies with Fc-mediated effector functions and boost pre-existing humoral and T cell responses[34]

The standard dosing of the Pfizer/BioNTech BNT162b2 mRNA vaccine validated in clinical trials includes 2 doses administered three weeks apart. While the decision by some public health authorities to space the doses because of limiting supply has raised concerns about vaccine efficacy, the authors assert that data indicate a single dose is up to 90% effective starting 14 days after its administration. The authors analyzed humoral and T cell responses three weeks after a single dose of the Pfizer-BioNTech mRNA vaccine. Despite the proven efficacy of the vaccine, no neutralizing activity were elicited in SARS-CoV-2 naïve individuals. However, the authors detected strong anti-receptor binding domain (RBD) and Spike antibodies with Fc-mediated effector functions and cellular responses dominated by the CD4 + T cell component. A single dose of this mRNA vaccine to

[33] Humphreys IR, Godkin AJ. The potential risks of delaying the second vaccine dose during the SARS-CoV-2 pandemic. QJM. 2021 May 19;114(3):163-165. doi: 10.1093/qjmed/hcab046. PMID: 33677593; PMCID: PMC7989192.

[34] Tauzin A, Nayrac M, Benlarbi M, Gong SY, Gasser R, Beaudoin-Bussières G, Brassard N, Laumaea A, Vézina D, Prévost J, Anand SP, Bourassa C, Gendron-Lepage G, Medjahed H, Goyette G, Niessl J, Tastet O, Gokool L, Morrisseau C, Arlotto P, Stamatatos L, McGuire AT, Larochelle C, Uchil P, Lu M, Mothes W, Serres G, Moreira S, Roger M, Richard J, Martel-Laferrière V, Duerr R, Tremblay C, Kaufmann DE, Finzi A. A single BNT162b2 mRNA dose elicits antibodies with Fc-mediated effector functions and boost pre-existing humoral and T cell responses. bioRxiv [Preprint]. 2021 Mar 18:2021.03.18.435972. doi: 10.1101/2021.03.18.435972. PMID: 33758857; PMCID: PMC7987016.

individuals previously infected by SARS-CoV-2 boosted all humoral and T cell responses measured, with strong correlations between T helper and antibody immunity. Neutralizing responses were increased in both potency and breadth, with distinctive capacity to neutralize emerging variant strains. These results highlight the importance of vaccinating uninfected and previously infected individuals and shed new light into the potential role of Fc-mediated effector functions and T cell responses in vaccine efficacy. The results also provide support to spacing the doses of 2-vaccine regimens to vaccinate a larger pool of the population in the context of vaccine scarcity against SARS-CoV-2.

Produced by the members of the National Health Library and Knowledge Service Evidence Team†. Current as at 10 May 2021. This evidence summary collates the best available evidence at the time of writing and does not replace clinical judgement or guidance. Emerging literature or subsequent developments in respect of COVID-19 may require amendment to the information or sources listed in the document. Although all reasonable care has been taken in the compilation of content, the National Health Library and Knowledge Service Evidence Team makes no representations or warranties expressed or implied as to the accuracy or suitability of the information or sources listed in the document. This evidence summary is the property of the National Health Library and Knowledge Service and subsequent re-use or distribution in whole or in part should include acknowledgement of the service.

The following PICO(T) was used as a basis for the evidence summary:

Population	COVID-19 VACCINE RECIPIENTS
Intervention	mRNA VACCINE AT MANUFACTURER-SPECIFIED INTERVAL
Comparison	mRNA VACCINE AT EXTENDED INTERVAL
Outcome	REDUCTION IN MORTALITY; REDUCTION IN SEVERE DISEASE AND HOSPITALIZATION; INCREASED POPULATION IMMUNITY

The following search strategy was used:

```
1     exp Coronavirinae/ (51787)
2     COVID-19.ab,ti. (117014)
3     coronavirus.ab,ti. (57592)
4     "corona virus".ab,ti. (2028)
5     (Wuhan adj3 virus).ab,ti. (115)
6     ("2019-nCoV" or "2019 ncov").ab,ti. (1268)
7     "severe acute respiratory syndrome coronavirus 2".ab,ti. (12363)
8     ("2019" and (new or novel) and coronavirus).ab,ti. (9773)
9     1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (149780)
10     exp vaccination/ (177465)
11     exp immunization/ (295475)
12     exp mass immunization/ (3716)
13     exp vaccine/ (345954)
14     "vaccin*".ab,ti. (381647)
15     10 or 11 or 12 or 13 or 14 (557391)
16     9 and 15 (14681)
17     exp messenger RNA/ (597274)
18     (messenger RNA or messenger ribonucleic acid or mRNA).ab,ti. (657725)
19     (BNT162b2 or Pfizer or Pfizer-BioNTech or Comirnaty or mrna-1273 or Moderna or
CX-024414).ab,ti. (7198)
20     17 or 18 or 19 (792396)
21     16 and 20 (830)
22     ((first or prime) adj4 (dose or dosing or dosage or administ* or
injection)).ab,ti. (60685)
23     ((second or boost*) adj4 (dose or dosing or dosage or administ* or
injection)).ab,ti. (33138)
24     22 or 23 (87315)
25     21 and 24 (125)
26     ((interval adj2 (dose or dosing or dosage)) and ((Coronavirinae or COVID-19 or
coronavirus or "corona virus" or (Wuhan adj3 virus) or ("2019-nCoV" or "2019 ncov") or
"severe acute respiratory syndrome coronavirus 2" or ("2019" and (new or novel) and
coronavirus)) and (vaccination or immunization or mass immunization or vaccine or
"vaccin*"))).ab,ti. (9)
27     20 and 26 (2)
28     ((delay* or postpone* or increase* or extend* or accelerate*) and
((Coronavirinae or COVID-19 or coronavirus or "corona virus" or (Wuhan adj3 virus) or
("2019-nCoV" or "2019 ncov") or "severe acute respiratory syndrome coronavirus 2" or
("2019" and (new or novel) and coronavirus)) and (vaccination or immunization or mass
immunization or vaccine or "vaccin*") and (messenger RNA or (messenger RNA or
messenger ribonucleic acid or mRNA) or (BNT162b2 or Pfizer or Pfizer-BioNTech or
Comirnaty or mrna-1273 or Moderna or CX-024414)))).ab,ti. (118)
29     25 or 27 or 28 (203)
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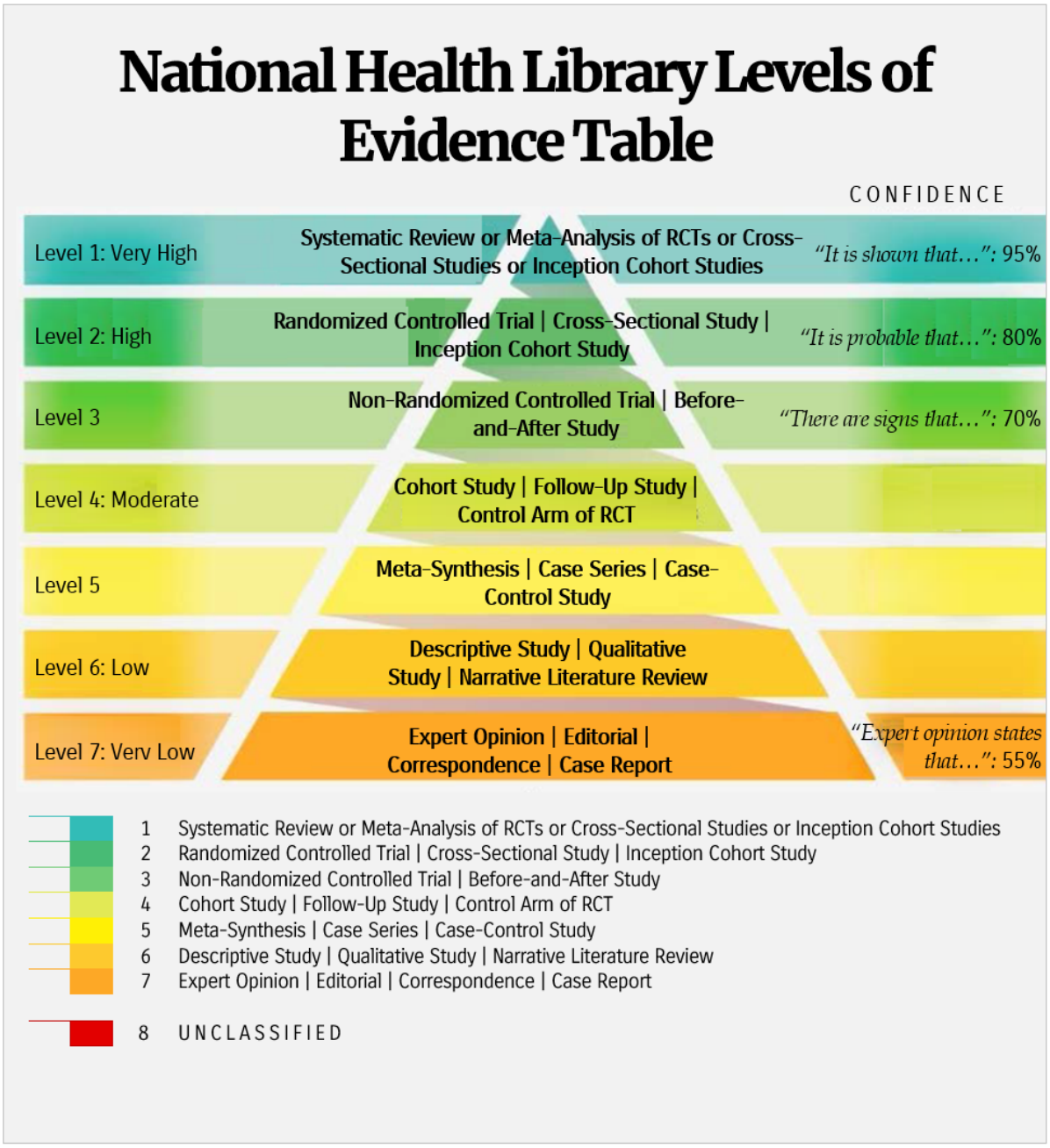
The following schema was used to grade the levels of evidence included:



† Brendan Leen, Area Library Manager, HSE South [Author, Editor]; Gethin White, Librarian, Dr. Steevens' Hospital, Dublin [Author]; Marie Carrigan, Librarian, St. Luke's Radiation Oncology Network, Rathgar, Dublin [Author]; NIAC Subgroup Contributors: Dr. Peter O'Reilly; Dr. Niamh Bambury; Dr. Geraldine Casey; Dr. Kenneth Beatty; Dr. Paul Mullane; Dr. Philippa White.