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 219

Is a booster COVID-19 vaccination required for older people?

Main Points

1. Data suggest that vaccine protection against SARS-CoV-2 infection wanes over time. However, protection against hospitalisation and severe COVID-19 appears to be preserved.
2. Although overall vaccine effectiveness (VE) against severe disease and hospitalisation appears largely preserved, VE is lower in older adults, among whom there may be some decline in effectiveness over time.
3. Age of vaccinated individuals has a significant negative correlation with antibody response, with reduced magnitude and durability of humoral immune responses to COVID-19 mRNA vaccines among older adults.
4. Because of the possibility of waning immunity and decreased VE against variants that might escape the immune response targeted by the original vaccines, several countries have initiated a booster vaccine in specific higher-risk populations, including older people.

Summary of Evidence

Data from observational studies have suggested that vaccine protection against SARS-CoV-2 infection wanes over time. However, protection against hospitalisation and severe COVID-19 appears to be preserved[13, 16, 20]. Although overall vaccine effectiveness (VE) against severe disease and hospitalisation appears largely preserved, the same observational studies suggest that VE is lower in older adults, among whom there may be some decline in effectiveness over time[14-21, 23-24, 27].

Because of the possibility of waning immunity and decreased efficacy against variants that might escape the immune response targeted by the original vaccines, several countries have initiated a booster vaccine in specific higher-risk populations, including older people[8]. In the United States, the Centers for Disease Control and Prevention (CDC) recommends that among those who received a primary mRNA vaccination series, adults 65 years or older or adults 50 years or older at risk for severe COVID-19 because of comorbidities should receive a booster dose 6 months after the primary series[4]. In Britain, the Joint Committee on Vaccination and Immunisation (JCVI) has advised that people who were vaccinated during the first phase of the vaccination programme in priority groups — including adults ≥50 years of age and people living in residential care homes — should be offered a booster dose no earlier than 6 months after completion of their primary course[6].

In a study of the dynamics of antibody response to the Pfizer-BioNTech COVID-19 vaccine, Naaber et al[14] found that the age of vaccinated individuals had a significant negative correlation with antibody response. Similarly, Brockman et al[15] observed reduced magnitude and durability of humoral immune responses to COVID-19 mRNA vaccines among older adults. In multivariable analyses, binding antibodies, ACE2 competition and neutralizing activities

remained significantly lower with age. Older adults also displayed reduced ability to block ACE2 binding by the Delta variant. At one month after the second dose, the median anti-RBD IgG titers in older adults were 3-fold lower than in healthcare personnel (HCP) ($p<0.0001$). A second dose had significantly less of an impact on the ability of binding antibodies to displace ACE2 in older adults compared to HCP ($p=0.0003$). On multivariable analysis, age remained significantly associated with anti-RBD IgG titers ($p=0.0005$), ACE2 displacement activity ($p<0.0001$) and virus neutralization activity ($p=0.006$) after two doses. Collier et al[19] report that neutralising antibody responses after the first vaccine dose diminished with increasing age, with a marked drop in participants over 80 years of age. In an evaluation of SARS-CoV-2 S-antibody response in 478 residents of a large Italian long-term care facility two months after complete vaccination with BNT162B2, Caimi et al found that advanced age was one of the predictors of a risk of null response[23]. Andrews et al[21] report that waning of vaccine effectiveness against symptomatic disease is greater in older adults and suggest that these individuals should be prioritised for booster doses.

In a large study of the protection offered by COVID-19 vaccine booster doses to adults aged ≥60 in Israel, Bar-On et al report that 12 days or more after the booster dose, an 11.4-fold (95% CI, 10.0 to 12.9) decrease in the relative risk of confirmed infection, and a >10-fold decrease in the relative risk of severe illness was found among those in receipt of the booster dose[17-18].

The European Centre for Disease Prevention and Control (ECDC) states that it is important to distinguish between *'booster'* doses for people who responded adequately to a primary vaccination series and additional doses for those with compromised immune systems who did not respond adequately. On the one hand, booster doses are given to vaccinated individuals — *ie* those who have completed a primary series of COVID-19 vaccination — to restore protection after waning of immune response; on the other hand, additional doses as part of a primary vaccination series may be given to

immunocompromised or immunosuppressed individuals who may not achieve an adequate level of protection from the standard primary vaccination[2].

When assessing the need for possible booster doses of COVID-19 vaccine from a public health perspective, the ECDC states that it is important to keep in mind the main objective of the vaccination strategy: preventing severe cases of COVID-19. Vaccine effectiveness against severe disease should be chosen as the primary outcome of interest for assessing whether or not there is a clear need for a booster dose in specific groups[2].

Irish and/or International Guidance

Level 1

World Health Organization (2021) Interim statement on COVID-19 vaccine booster doses[1]

The World Health Organization (WHO) states that there are several reasons why COVID-19 vaccine booster doses may be needed: waning protection against infection or disease — in particular severe disease, over time (*ie* waning immunity); reduced protection against variants of concern (VOC); inadequate protection from the currently recommended primary series for some risk groups for which evidence from phase III clinical trials may have been lacking. The rationale for booster doses may differ by vaccine product, epidemiological setting, risk group, and vaccine coverage rates.

The WHO cautions that administration of booster doses will exacerbate inequities. The focus for the time being remains on increasing global vaccination coverage with the primary vaccination series. To date, the evidence remains limited and inconclusive on any widespread need for booster doses following a primary vaccination series.

Level 1

European Centre for Disease Prevention and Control (ECDC) (2021) Interim public health considerations for the provision of additional COVID-19 vaccine doses[2]

The European Centre for Disease Prevention and Control (ECDC) states that providing all eligible individuals with the recommended dose regimen should remain the current priority for COVID-19 vaccination programmes in the European Union/European Economic Area (EU/EEA). The ECDC states that it is important to distinguish between *'booster'* doses for people who responded adequately to a

[1] World Health Organization (2021) Interim statement on COVID-19 vaccine booster doses. Accessed 18/10/2021.
[2] European Centre for Disease Prevention and Control (ECDC) (2021). Interim public health considerations for the provision of additional COVID-19 vaccine doses. Accessed 19/10/22021.

primary vaccination series and additional doses for those with compromised immune systems who did not respond adequately. On the one hand, booster doses are given to vaccinated individuals — *ie* those who have completed a primary series of COVID-19 vaccination — to restore protection after waning of immune response; on the other hand, additional doses as part of a primary vaccination series may be given to immunocompromised or immunosuppressed individuals who may not achieve an adequate level of protection from the standard primary vaccination.

When assessing the need for possible booster doses of COVID-19 vaccine from a public health perspective, the ECDC states that it is important to keep in mind the main objective of the vaccination strategy: preventing severe cases of COVID-19. Vaccine effectiveness against severe disease should be chosen as the primary outcome of interest for assessing whether or not there is a clear need for a booster dose in specific groups.

The available evidence regarding real world vaccine effectiveness and duration of protection shows that all vaccines authorised in the EU/EEA are currently highly protective against COVID-19-related hospitalisation, severe disease and death. Therefore, the ECDC suggests that there is no urgent need for the administration of booster doses of vaccines to fully vaccinated individuals in the general population.

The option of administering an additional vaccine dose to people who may experience a limited response to the primary series of COVID-19 vaccination such as some categories of immunocompromised individuals should be considered now, according to the ECDC. This is to be seen as an extension of the primary vaccination series for these specific groups, and not as a booster. Consideration could also be given to providing an additional dose as a precautionary measure to older frail individuals, in particular those living in closed settings: *eg* residents of long-term care facilities.

The ECDC further states that full vaccination against COVID-19 of all eligible family contacts and close contacts — including professionals providing care — of immunocompromised and

vulnerable individuals should also be considered.

The ECDC reaffirms that non-pharmaceutical interventions such as physical distancing, mask-wearing and hand hygiene should always complement vaccination, in particular in high-risk settings such as long-term care facilities or hospital wards with patients at risk of severe COVID-19.

More solid data are needed to inform future policies on booster doses. Knowledge gaps are particularly related to the appropriate correlate of protection to consider for the different population groups and the time from primary vaccination series until a booster dose should be given, and duration of immunity according to different age and risk groups, vaccine product, dosing interval, variant of concern, and homologous/heterologous schedule. Prospective vaccine effectiveness studies as well as surveillance of breakthrough infections in the general population and in specific groups are needed to answer these questions.

The benefits and risks of possible booster doses need to be clearly outlined and compared. Benefits may include increased protection against severe disease, mild-to-moderate disease, post COVID-19 condition (often called *'long COVID'*), SARS-CoV-2 infection, and virus transmission. Risks include possible safety concerns and public health implications such as a potential impact on vaccine confidence and uptake, and global availability of vaccines. In the context of many countries outside of the EU/EEA still struggling to receive and administer enough vaccine doses to their populations, special consideration should be given to the current global shortage of COVID-19 vaccines, which could be further worsened by the administration of booster COVID-19 vaccine doses for the general population in EU/EEA countries.

Level 1

European Centre for Disease Prevention and Control ECDC (2021) Interim analysis of COVID-19 vaccine effectiveness against Severe Acute Respiratory Infection due to laboratory-confirmed SARS-CoV-2 among individuals aged 65 years and older, ECDC multi-country study[3]

Monitoring vaccine effectiveness (VE) in real-world conditions is essential for informed decision-making with regards to vaccination strategies. The ECDC is building infrastructure to allow for regular monitoring of COVID-19 VE over time using a multi-national approach that involves studies implemented in different settings. This document presents results from the first interim analysis of COVID-19 VE against severe acute respiratory infection due to laboratory-confirmed SARS-CoV-2 among individuals aged 65 years and older.

A total of 10 European Union (EU) countries — including Ireland — have joined the study. This first interim analysis presents data from 6 of these countries for the period 27 December 2020 to 30 June 2021.

Interim results suggest a good VE against laboratory-confirmed SARS-CoV-2 for COVID-19 vaccines deployed during the first 6 months of the vaccination campaign across the EU/EEA, albeit with wide confidence intervals. The effectiveness of a complete vaccination course with two doses of COVID-19 vaccine was better than for a single dose for those vaccines with a two-dose schedule. Estimated results were in the range of estimates published in other studies for similar outcomes in this population during the pre-Delta period.

Real-world studies of VE estimates in the hospital setting are important to understand the extent of protection the vaccines may have against severe outcomes such as hospitalisation, ICU admission or death. More extensive analyses will be conducted to assess factors that may affect VE such as different variants and length of time since vaccination.

[3] ECDC (2021). Interim analysis of COVID-19 vaccine effectiveness against Severe Acute Respiratory Infection due to laboratory-confirmed SARS-CoV-2 among individuals aged 65 years and older: ECDC multi-country study. Accessed 19/10/2021.

Level 1

Centers for Disease Control and Prevention (United States) (2021) CDC Statement on ACIP Booster Recommendations[4]

In the United States, the Centers for Disease Control and Prevention (CDC) recommend that individuals 65 years and older and residents in long-term care settings should receive a booster shot of the Pfizer-BioNTech COVID-19 vaccine at least 6 months after their Pfizer-BioNTech primary series; and that individuals aged 50–64 years with underlying medical conditions should receive a booster shot of the Pfizer-BioNTech COVID-19 vaccine at least 6 months after their Pfizer-BioNTech primary series.

Level 1

Food and Drug Administration (United States) (24th September 2021) [Press Release] FDA Authorizes Booster Dose of Pfizer-BioNTech COVID-19 Vaccine for Certain Populations[5]

On 24 September 2021, the United States Food and Drug Administration (FDA) amended the emergency use authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine to allow for use of a single booster dose, to be administered at least 6 months after completion of the primary series in:

- ☐ individuals 65 years of age and older
- ☐ individuals 18 through 64 years of age at high risk of severe COVID-19; and
- ☐ individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19

"Today's authorization applies only to the Pfizer-BioNTech COVID-

[4] Centers for Disease Control and Prevention (CDC) (2021). CDC Statement on ACIP Booster Recommendations. Accessed 19/10/2021.
[5] Food and Drug Association (United States) (2021). FDA Authorizes Booster Dose of Pfizer-BioNTech COVID-19 Vaccine for Certain Populations. Accessed 18/10/2021.

19 Vaccine."

To support the authorization for emergency use of a single booster dose, the FDA analyzed safety and immune response data from a subset of participants from the original clinical trial of the Pfizer-BioNTech COVID-19 vaccine. In addition, consideration was given to real-world data on the vaccine's efficacy over a sustained period of time provided by both US and international sources. The immune responses of approximately 200 participants 18 through 55 years of age who received a single booster dose approximately 6 months after their second dose were assessed. The antibody response against SARS-CoV-2 virus one month after a booster dose of the vaccine compared to the response one month after the two-dose primary series in the same individuals demonstrated a booster response.

Additional analysis conducted by the manufacturer as requested by the FDA compared the rates of COVID-19 accrued during the current Delta variant surge among original clinical trial participants who completed the primary two-dose vaccination series early in the clinical trial to those who completed a two-dose series later in the study. The analysis submitted by the company showed that during the study period of July and August 2021, the incidence of COVID-19 was higher among the participants who completed their primary vaccine series earlier. The FDA determined that the rate of breakthrough COVID-19 reported during this time period translates to a modest decrease in the efficacy of the vaccine among those vaccinated earlier.

Safety was evaluated in 306 participants 18 through 55 years of age and 12 participants 65 years of age and older who were followed for an average of over two months. The most commonly reported side effects by the clinical trial participants who received the booster dose of the vaccine were pain, redness and swelling at the injection site, as well as fatigue, headache, muscle or joint pain and chills. Of note, swollen lymph nodes in the underarm were observed more frequently following the booster dose than after the primary two-dose series.

Level 1

Joint Committee on Vaccination and Immunisation (Great Britain) (14 September 2021) JCVI statement regarding a COVID-19 booster vaccine programme for winter 2021 to 2022[6]

The Joint Committee on Vaccination and Immunisation (JCVI) has been asked by the Secretary of State for Health and Social Care in the United Kingdom to consider the options for and timing of a booster programme to re-vaccinate adults in order to reduce mortality, morbidity and hospitalisations from COVID-19 over the 2021 to 2022 winter period as well as to minimise the COVID-19 case infection rate and the chance of new variants emerging.

JCVI advises that for the 2021 COVID-19 booster vaccine programme individuals who received vaccination during the first phase of the COVID-19 vaccination programme — priority groups 1 to 9 — should be offered a third dose COVID-19 booster vaccine. This includes:

- those living in residential care homes for older adults
- all adults aged 50 years or over
- frontline health and social care workers
- all those aged 16 to 49 years with underlying health conditions that put them at higher risk of severe COVID-19
- adult household contacts (aged ≥16 years) of immunosuppressed individuals

The JCVI states that insufficient time has passed to know what levels of protection might be expected 6 to 12 months after the primary course. Taking a precautionary position, the JCVI considers that on balance it is preferable to maintain a high level of protection in vulnerable adults throughout the winter period.

[6] Joint Committee on Vaccination and Immunisation (Great Britain) (14 September 2021) JCVI statement regarding a COVID-19 booster vaccine programme for winter 2021 to 2022. Accessed 27/10/2021.

Evidence Synopsis Resources

Level 2

BMJ Best Practice (2021) Coronavirus Disease 2019 (COVID-19): Prevention[7]

See Section: BOOSTER DOSES

Observational data to support the safety and efficacy of booster doses are emerging, but their follow-up periods are too short to assess long-term effectiveness, and the number of trial participants is small. The studies also focus on plasma neutralising antibodies and don't take into account the protection provided by cellular immunity.

In the US, the Food and Drug Administration has authorised an additional (third) dose of the Pfizer-BioNTech and Moderna mRNA vaccines in moderately to severely immunocompromised people at least 28 days after the completion of the initial vaccine series. It has also authorised a single booster dose of the Pfizer-BioNTech vaccine to be administered at least 6 months after the completion of the primary series in certain people. The US Centers for Disease Control and Prevention recommends that the following groups *should* receive a booster dose: people aged ≥65 years and residents in long-term care settings; and people aged 50 to 64 years with certain underlying medical conditions. It recommends that the following groups *may* receive a booster dose: people aged 18 to 49 years with certain underlying medical conditions based on their individual benefits and risks; and people aged 18 to 64 years who are at increased risk for exposure and transmission because of occupational or institutional setting based on their individual benefits and risks.

In the United Kingdom, the JCVI advises that a third primary dose be offered to people aged ≥12 years with severe immunosuppression. The third primary dose should ideally be given at least 8 weeks after the second dose, with special attention paid to current or planned immunosuppressive therapies. Choice of vaccine depends on age and the previous vaccine used. The JCVI has also advised that people who

[7] BMJ Best Practice (2021). Coronavirus Disease 2019 (COVID-19): Prevention. Accessed 01/11/2021.

were vaccinated during the first phase of the vaccination programme in priority groups [adults ≥50 years of age, frontline health and social care workers, people living in residential care homes, people aged 16 to 49 years with underlying conditions that put them at higher risk and their adult carers, adult household contacts of immunosuppressed people] should be offered a booster dose no earlier than 6 months after completion of their primary course. Influenza and COVID-19 vaccines may be administered together where operationally practical.

Level 2

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

See Section: ROLE OF BOOSTER VACCINATIONS

Because of the possibility of waning immunity and decreased efficacy against variants that might escape the immune response directed against Spike proteins targeted by the original vaccines, several countries have initiated or announced plans to administer a booster vaccine for individuals who have been fully vaccinated. In the United States, the Food and Drug Administration (FDA) has authorized and the CDC recommends a booster doses in specific populations for all available vaccines.

Among individuals who received a primary mRNA vaccine series (BNT162b2 [Pfizer COVID-19 vaccine] or mRNA-1273 [Moderna COVID-19 vaccine]), the CDC recommends a booster dose 6 months after the primary series for certain high-risk adults:

- Adults 65 years or older *should* receive a booster dose.
- Adults 50 years or older at risk for severe COVID-19 because of comorbidities [eg cancer, cerebrovascular disease, chronic kidney disease, COPD, diabetes mellitus, heart conditions such as heart failure or cardiomyopathies, HIV, neurologic conditions, obesity, solid organ or blood stem cell

[8] UpToDate (2021). COVID-19: Vaccines to prevent SARS-CoV-2 infection. Accessed 01/11/2021.

transplantation, use of corticosteroids or other immunosuppressive medications] *should* receive a booster dose.

- Adults aged 18 to 50 years and at risk for severe COVID-19 because of comorbidities *may* receive a booster dose after weighing the individual risks and benefits.
- Adults aged 18 to 64 years who have occupational or institutional risk of exposure to SARS-CoV-2 such as health care workers or those living in congregate settings *may* receive a booster dose after weighing the individual risks and benefits.

Among individuals who received a primary vaccine series with Ad26.COV2.S (Janssen COVID-19 vaccine), the CDC recommends a booster dose at least two months after the primary series.

Booster doses following a primary vaccine series are a distinct issue from administering a third dose of an mRNA vaccine for the primary series in certain immunocompromised patients.

Data from observational studies have suggested that vaccine protection against SARS-CoV-2 infection wanes over time. However, protection against hospitalization and severe COVID-19 appears to be preserved. A review of data on nursing home residents reported to a national database in the United States suggested that vaccine effectiveness against laboratory-confirmed SARS-CoV-2 infection among this population declined from 75% in March to May 2021 to 53% during June to July 2021. Similarly, in a study of state-wide data in New York that included approximately 10 million vaccinated adults, age-adjusted vaccine effectiveness against SARS-CoV-2 infection declined from 92% to 75% from May to July 2021; however, effectiveness against hospitalization remained stable over that time at 90% to 95%. Another study of 3000 hospitalized patients estimated vaccine effectiveness against COVID-19-related hospitalization as 86% 2 to 14 weeks after vaccination and 84% 13 to 24 weeks after vaccination.

Although overall vaccine effectiveness against severe disease and hospitalization appears largely preserved, the same observational studies suggest that it is lower among older adults, among whom

there may be some decline in effectiveness over time.

Evidence that a booster vaccine may improve vaccine effectiveness is limited to observational data and data on immunogenicity. In an observational study from Israel of over one million individuals 60 years or older who had received two doses of BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) at least 5 months previously, receipt of a booster dose was associated with an 11-times lower rate of infection compared with those who did not receive a booster (absolute difference 87 infections per 100,000 days) and a 20-times lower rate of severe illness (absolute difference 7.5 cases per 100,000 days). Given the observational design, it is uncertain whether some of these differences could have been related to other variables such as exposure risk or testing differences; there was also limited follow-up time following receipt of the booster.

Data on immunogenicity are consistent with the observational data. In a small trial of 23 individuals who had received two doses of BNT162b2 (Pfizer-BioNTech COVID-19 vaccine), neutralizing antibody titers against wild-type virus, the Beta variant and the Delta variant following receipt of a third dose 8 to 9 months later were higher than those detected following the initial two vaccine series. The rate and severity of adverse reactions following the booster dose were similar to those following the second dose in prior trials. Similar findings from a larger trial were included in a report to the FDA. Data presented to that FDA indicate that booster doses of mRNA-1273 and AD26.COV2.S also result in increases in binding and neutralizing antibody titers compared with pre-boost with similar reactogenicity profiles to those with the primary series. Efficacy data from trials evaluating two doses of AD26.COV2.S also support use of a booster for this vaccine.

Irish and/or International Literature

Level 2

Atmar et al (2021) [Preprint] Heterologous SARS-CoV-2 Booster Vaccinations – Preliminary Report[9]

While Coronavirus disease 2019 (COVID-19) vaccines are highly effective, breakthrough infections are occurring. Booster vaccinations have recently received emergency use authorization (EUA) for certain populations but are restricted to homologous mRNA vaccines. The authors evaluated homologous and heterologous booster vaccination in persons who had received an EUA COVID-19 vaccine regimen.

METHODS: In this phase I/II open-label clinical trial conducted at 10 US sites, adults who received one of three EUA COVID-19 vaccines at least 12 weeks prior to enrolment and had no reported history of SARS-CoV-2 infection received a booster injection with one of three vaccines (Moderna mRNA-1273 100-µg, Janssen Ad26.COV2.S 5×1010 virus particles, or Pfizer-BioNTech BNT162b2 30-µg). The primary outcomes were safety, reactogenicity, and humoral immunogenicity on study days 15 and 29.

RESULTS: 458 individuals were enrolled. 154 received mRNA-1273, 150 received Ad26.CoV2.S, and 153 received BNT162b2 booster vaccines. Reactogenicity was similar to that reported for the primary series. Injection site pain, malaise, headache and myalgia occurred in more than half the participants. Booster vaccines increased the neutralizing activity against a D614G pseudovirus (4.2-76-fold) and binding antibody titers (4.6-56-fold) for all combinations; homologous boost increased neutralizing antibody titers 4.2-20-fold whereas heterologous boost increased titers 6.2-76-fold. Day 15 neutralizing and binding antibody titers varied by 28.7-fold and 20.9-

[9] Atmar RL, Lyke KE, Deming ME, Jackson LA, Branche AR, El Sahly HM, Rostad CA, Martin JM, Johnston C, Rupp RE, Mulligan MJ, Brady RC, Frenck RW, Bäcker M, Kottkamp AC, Babu TM, Rajakumar K, Edupuganti S, Dobryzynski D, Posavad CM, Archer JI, Crandon S, Nayak SU, Szydlo D, Zemanek J, Islas CPD, Brown ER, Suthar MS, McElrath MJ, McDermott AB, O'Connell SE, Montefiori DC, Eaton A, Neuzil KM, Stephens DS, Roberts PC, Beigel JH; DMID 21-0012 Study Group. Heterologous SARS-CoV-2 Booster Vaccinations - Preliminary Report. medRxiv [Preprint]. 2021 Oct 15:2021.10.10.21264827. doi: 10.1101/2021.10.10.21264827. PMID: 34671773; PMCID: PMC8528081.

fold, respectively, across the nine prime-boost combinations. In the 65 years and older cohort, VE with BNT162b2 was 86.7% (80.1% to 91.1%) and with Ad26.CoV2.S was 76.4% (58.8% to 86.5%)).

CONCLUSION: Homologous and heterologous booster vaccinations were well-tolerated and immunogenic in adults who completed a primary COVID-19 vaccine regimen at least 12 weeks earlier.

Level 3

Seyahi et al (2021) Antibody response to inactivated COVID-19 vaccine (CoronaVac) in immune-mediated diseases: a controlled study among hospital workers and elderly[10]

OBJECTIVE: To assess antibody response to inactivated COVID-19 vaccine in patients with immune-mediated diseases (IMD) among hospital workers and people aged 65 and older.

METHODS: A controlled study of 82 hospital workers with IMD (mean age: 42.2 ± 10.0 years) and 300 (mean age: 41.7 ± 9.9 years) controls. Among + 65 aged population, 22 (mean age: 71.4 ± 4.5 years) patients and 47 controls (mean age: 70.9 ± 4.8 years) were studies. All study subjects had a negative history for COVID-19. Sera were obtained after at least 21 days following the second vaccination. Anti-Spike IgG antibody titers were measured quantitatively using a commercially available immunoassay method.

RESULTS: Patients with IMD were significantly less likely to have detectable antibodies than healthy controls both among the hospital workers (92.7% vs 99.7%, $p < 0.001$) and older population (77.3% vs 97.9%, $p = 0.011$). Among patients with IMD, those using immunosuppressive or immune-modulating drugs (64/75, 85.3%) were significantly less likely to have detectable antibodies compared to those off treatment (29/29, 100%) ($p = 0.029$). Additionally, a negative association between age and the antibody titer categories among patients ($r = -0.352$; $p < 0.001$) and controls ($r = -0.258$; $p <$

[10] Seyahi E, Bakhdiyarli G, Oztas M, Kuskucu MA, Tok Y, Sut N, Ozcifci G, Ozcaglayan A, Balkan II, Saltoglu N, Tabak F, Hamuryudan V. Antibody response to inactivated COVID-19 vaccine (CoronaVac) in immune-mediated diseases: a controlled study among hospital workers and elderly. Rheumatol Int. 2021 Aug;41(8):1429-1440. doi: 10.1007/s00296-021-04910-7. Epub 2021 Jun 9. PMID: 34109466; PMCID: PMC8188953.

0.001) were demonstrated. A statistically significant drop in antibody levels after age 60 was observed. In multivariate analysis including age >60, gender, BMI, smoking and presence of immunocompromising condition, age >60 was independently associated with a negative antibody result (OR 4.32 95%CI 1.2-15.5).

CONCLUSIONS: Among hospital workers, the vast majority of patients with IMD and immunocompetent controls developed a significant humoral response following the administration of the second dose of inactivated COVID-19 vaccine. This was also true for the older population, albeit with lower antibody titers. Immunosuppressive use significantly reduced antibody titers. Antibody titers were significantly lower among those aged ≥ 60 years both in patient and control populations.

Level 3

Alencar et al (2021) High Effectiveness of SARS-CoV-2 Vaccines in Reducing COVID-19-Related Deaths in over 75-Year-Olds, Ceará State, Brazil[11]

In Brazil, the SARS-CoV-2 vaccination program has so far prioritized people over 75 years of age. By the end of March 2021, in Ceará State, a total of 313,328 elderly people had received at least one dose of vaccine (45% Oxford-AstraZeneca/Fiocruz and 55% CoronaVac-Sinovac/Butantan), and 159,970 had received two doses (83% CoronaVac-Sinovac/Butantan and 17% Oxford-AstraZeneca/Fiocruz). After a single dose, there was already a significant reduction in COVID 19-related deaths (protection ratio: 19.31 (95% CI: 18.20-20.48), attributable protection ratio: 94.8%); higher protection ratios were observed after the application of two doses of the vaccine (132.67; 95% CI: 109.88-160.18), with an attributable protection ratio of 99.2%.

For Vaxrevia, deaths among unvaccinated older people were 834.45 times higher compared to those who received 2 doses of the vaccine,

[11] Alencar CH, Cavalcanti LPG, Almeida MM, Barbosa PPL, Cavalcante KKS, Melo DN, de Brito Alves BCF, Heukelbach J. High Effectiveness of SARS-CoV-2 Vaccines in Reducing COVID-19-Related Deaths in over 75-Year-Olds, Ceará State, Brazil. Trop Med Infect Dis. 2021 Jul 13;6(3):129. doi: 10.3390/tropicalmed6030129. PMID: 34287384; PMCID: PMC8293450.

with a protection ratio for deaths of 99.8%.

Level 3

Victora et al (2021) Estimating the early impact of vaccination against COVID-19 on deaths among elderly people in Brazil: Analyses of routinely-collected data on vaccine coverage and mortality[12]

The authors assessed whether there was an impact of vaccinations on the mortality of older individuals in a context of wide transmission of the SARS-CoV-2 Gamma (P.1) variant.

METHODS: By May 15, 2021, 238,414 COVID-19 deaths had been reported to the Brazilian Mortality Information System. Denominators for mortality rates were calculated by correcting population estimates for all-cause deaths reported in 2020. Proportionate mortality at ages 70–79 and 80+ years relative to deaths at all ages were calculated for deaths due to COVID-19 and to other causes, as were COVID-19 mortality rate ratios relative to individuals aged 0–69 years. Vaccine coverage data were obtained from the Ministry of Health. All results were tabulated by epidemiological weeks 1–19, 2021.

FINDINGS: The proportion of all COVID-19 deaths at ages 80+ years was over 25% in weeks 1–6 and declined rapidly to 12.4% in week 19, whereas proportionate COVID-19 mortality for individuals aged 70–79 years started to decline by week 15. Trends in proportionate mortality due to other causes remained stable. Mortality rates were over 13 times higher in the 80+ years age group compared to that of 0–69 year olds up to week 6, and declined to 5.0 times in week 19. Vaccination coverage (first dose) of 90% was reached by week 9 for individuals aged 80+ years and by week 13 for those aged 70–79 years. Coronavac accounted for 65.4% and AstraZeneca for 29.8% of all doses administered in weeks 1–4, compared to 36.5% and 53.3% in weeks 15–19, respectively.

[12] Victora PC, Castro PMC, Gurzenda S, Medeiros AC, França GVA, Barros PAJD. Estimating the early impact of vaccination against COVID-19 on deaths among elderly people in Brazil: Analyses of routinely-collected data on vaccine coverage and mortality. EClinicalMedicine. 2021 Aug;38:101036. doi: 10.1016/j.eclinm.2021.101036. Epub 2021 Jul 16. PMID: 34308302; PMCID: PMC8283303.

INTERPRETATION: Rapid scaling up of vaccination coverage among older Brazilians was associated with important declines in relative mortality compared to younger individuals in a setting where the Gamma variant predominates. Had mortality rates among older people remained proportionate to what was observed up to week 6, an estimated additional 43,802 COVID-related deaths would have been expected up to week 19.

Level 3

Haas et al (2021) Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data[13]

The authors estimated the real-world effectiveness of two doses of BNT162b2 against a range of SARS-CoV-2 outcomes and evaluated the nationwide public-health impact following the widespread introduction of the vaccine in Israel.

METHODS: National surveillance data from the first 4 months of the nationwide vaccination campaign were used to ascertain incident cases of laboratory-confirmed SARS-CoV-2 infections and outcomes, as well as vaccine uptake in residents of Israel aged 16 years and older. Vaccine effectiveness against SARS-CoV-2 outcomes — asymptomatic infection, symptomatic infection, and COVID-19-related hospitalisation, severe or critical hospitalisation, and death — was calculated on the basis of incidence rates in fully vaccinated individuals compared with rates in unvaccinated individuals, with use of a negative binomial regression model adjusted for age-group, sex, and calendar week. The proportion of Spike gene target failures on PCR test among a nationwide convenience-sample of SARS-CoV-2-

[13] Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, Brooks N, Smaja M, Mircus G, Pan K, Southern J, Swerdlow DL, Jodar L, Levy Y, Alroy-Preis S. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet. 2021 May 15;397(10287):1819-1829. doi: 10.1016/S0140-6736(21)00947-8. Epub 2021 May 5. Erratum in: Lancet. 2021 Jul 17;398(10296):212. PMID: 33964222; PMCID: PMC8099315.

positive specimens was used to estimate the prevalence of the B.1.1.7 variant.

FINDINGS: During the analysis period (Jan 24 to April 3, 2021), there were 232 268 SARS-CoV-2 infections, 7694 COVID-19 hospitalisations, 4481 severe or critical COVID-19 hospitalisations, and 1113 COVID-19 deaths in people aged 16 years or older. By April 3, 2021, 4 714 932 (72.1%) of 6 538 911 people aged 16 years and older were fully vaccinated with two doses of BNT162b2. Adjusted estimates of vaccine effectiveness at 7 days or longer after the second dose were 95.3% (95% CI 94.9-95.7; incidence rate 91.5 per 100 000 person-days in unvaccinated vs 3.1 per 100 000 person-days in fully vaccinated individuals) against SARS-CoV-2 infection, 91.5% (90.7-92.2; 40.9 vs 1.8 per 100 000 person-days) against asymptomatic SARS-CoV-2 infection, 97.0% (96.7-97.2; 32.5 vs 0.8 per 100 000 person-days) against symptomatic COVID-19, 97.2% (96.8-97.5; 4.6 vs 0.3 per 100 000 person-days) against COVID-19-related hospitalisation, 97.5% (97.1-97.8; 2.7 vs 0.2 per 100 000 person-days) against severe or critical COVID-19-related hospitalisation, and 96.7% (96.0-97.3; 0.6 vs 0.1 per 100 000 person-days) against COVID-19-related death. In all age groups, as vaccine coverage increased, the incidence of SARS-CoV-2 outcomes declined. 8006 of 8472 samples tested showed a spike gene target failure, giving an estimated prevalence of the B.1.1.7 variant of 94.5% among SARS-CoV-2 infections.

INTERPRETATION: Two doses of BNT162b2 are highly effective across all age groups (≥16 years, including older adults aged ≥85 years) in preventing symptomatic and asymptomatic SARS-CoV-2 infections and COVID-19-related hospitalisations, severe disease, and death, including those caused by the B.1.1.7 SARS-CoV-2 variant. There were marked and sustained declines in SARS-CoV-2 incidence corresponding to increasing vaccine coverage. These findings suggest that COVID-19 vaccination can help to control the pandemic.

Level 4

Naaber et al (2021) Dynamics of antibody response to BNT162b2 vaccine after six months: a longitudinal prospective study[14]

METHODS: The authors studied the antibody and memory T cell responses after the two-dose Pfizer-BioNTech vaccine in 122 volunteers up to 6 months and correlated the findings with age and side effects.

FINDINGS: A robust antibody response to Spike protein after the second dose was observed. However, the antibody levels declined at 12 weeks and 6 months post-vaccination, indicating a waning of the immune response over time. At 6 months after the second dose, the Spike antibody levels were similar to the levels in persons vaccinated with one dose or in COVID-19 convalescent individuals. The antibodies efficiently blocked ACE2 receptor binding to SARS-CoV-2 Spike protein of five variants of concern at one week, but protection was diminished at three months. 87% of individuals developed Spike-specific memory T cell responses, which were lower in individuals with increased proportions of immunosenescent CD8+ TEMRA cells. Antibody response was found to correlate negatively with age and positively with the total score of vaccination side effects. The age of vaccinated individuals had a significant negative correlation with S-RBD IgG response. This was the strongest before the second dose (r= -0·47, p<0·0001) and 1 week after the second dose (r= -0·34, p<0·0003), but weaker at 6 weeks after the second dose (r= -0·19, p=0·077), 12 weeks after the second dose (r= -0·25, p=0·017), and 6 months after the second dose (r= -0·29, p=0·007).

INTERPRETATION: The mRNA vaccine induces a strong antibody response to SARS-CoV-2 and five VOCs at 1 week post-vaccination that decreases thereafter. T cell responses, although detectable in the majority, were lower in individuals with higher T cell

[14] Naaber P, Tserel L, Kangro K, Sepp E, Jürjenson V, Adamson A, Haljasmägi L, Rumm AP, Maruste R, Kärner J, Gerhold JM, Planken A, Ustav M, Kisand K, Peterson P. Dynamics of antibody response to BNT162b2 vaccine after six months: a longitudinal prospective study. Lancet Reg Health Eur. 2021 Nov;10:100208. doi: 10.1016/j.lanepe.2021.100208. Epub 2021 Sep 6. PMID: 34514454; PMCID: PMC8418937.

immunosenescence. The deterioration of vaccine response suggests the need to monitor for the potential booster vaccination.

Factors influencing the vaccination response

The age of vaccinated individuals had a significant negative correlation with S-RBD IgG response. This was the strongest at B2D time-point (r= -0·47, p<0·0001) and 1wA2D (r= -0·34, p<0·0003), but weaker at 6wA2D (r= -0·19, p=0·077), 12wA2D (r= -0·25, p=0·017), and 6mA2D (r= -0·29, p=0·007).

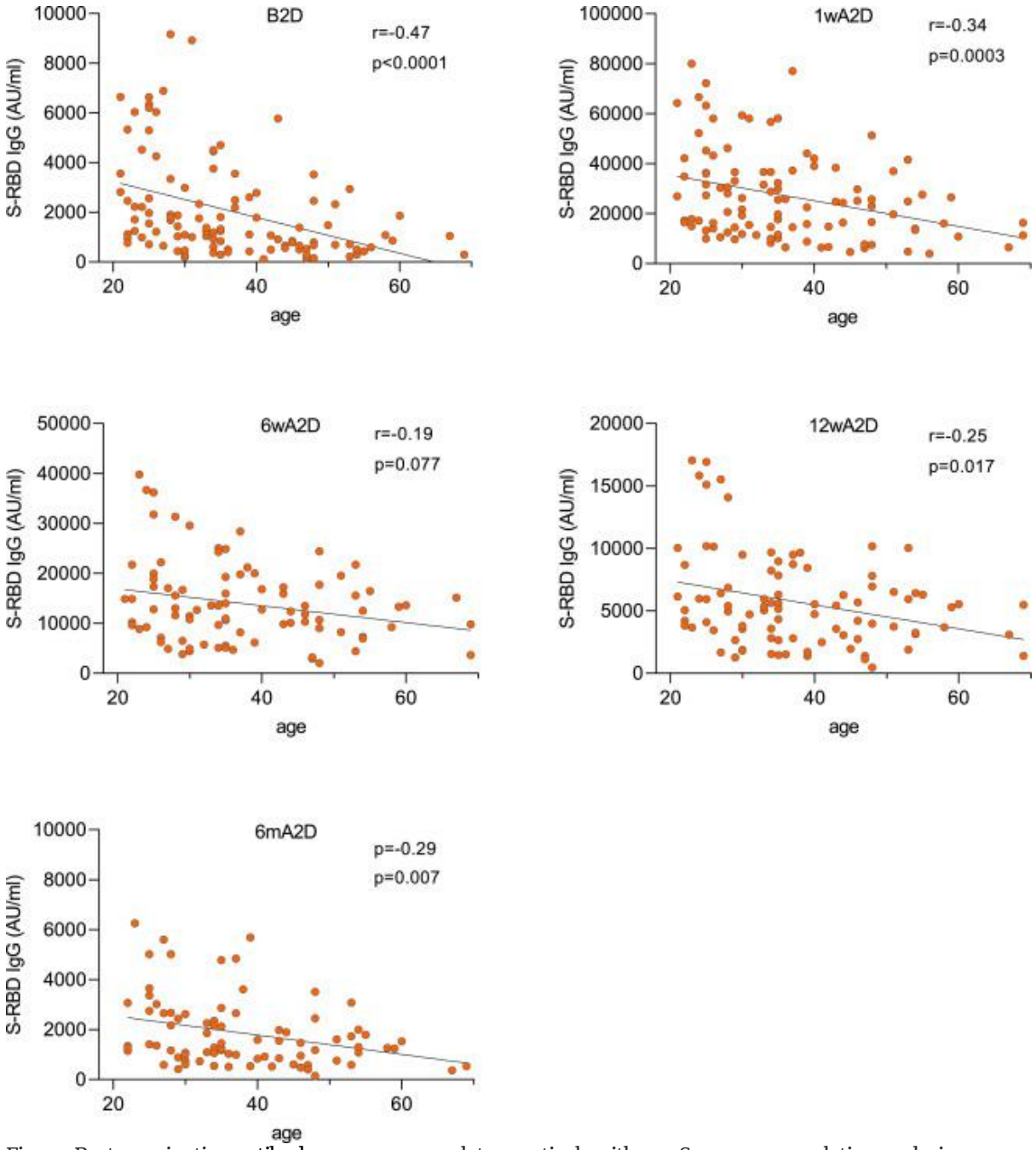

Figure: Post-vaccination antibody responses correlate negatively with age. Spearman correlation analysis between age and S-RBD IgG levels before the second dose (B2D, n=111), 1 week (1wA2D, n=106), 6 weeks (6wA2D,

n=89), 12 weeks (12wA2D, n=90), and 6 months (6mA2D, n=84) after the second dose. Spearman correlation coefficient and exact p-values are given.

Level 4

Brockman et al (2021) Reduced magnitude and durability of humoral immune responses by COVID-19 mRNA vaccines among older adults[15]

mRNA vaccines reduce COVID-19 incidence and severity, but the durability of vaccine-induced immune responses, particularly among the elderly, remains incompletely characterized.

METHODS: Anti-spike RBD antibody titers, ACE2 competition and virus neutralizing activities were longitudinally assessed in 151 healthcare workers and older adults (overall, aged 24-98 years) up to three months after vaccination.

RESULTS: Older adults exhibited lower antibody responses after one and two vaccine doses for all measures. In multivariable analyses correcting for sociodemographic, chronic health and vaccine-related variables, age remained independently associated with all response outcomes. The number of chronic health conditions was additionally associated with lower binding antibody responses after two doses, and male sex with lower ACE2 competition activity after one dose. Responses waned universally at three months after the second dose, but binding antibodies, ACE2 competition and neutralizing activities remained significantly lower with age. Older adults also displayed reduced ability to block ACE2 binding by the Delta variant. At one month after the second dose, the median anti-RBD IgG titers in older adults were 3-fold lower than in HCWs ($p<0.0001$). A second dose had significantly less of an impact on the ability of binding antibodies to

15 Reduced magnitude and durability of humoral immune responses by COVID-19 mRNA vaccines among older adults
Mark A. Brockman, Francis Mwimanzi, Hope R. Lapointe, Yurou Sang, Olga Agafitei, Peter Cheung, Siobhan Ennis, Kurtis Ng, Simran Basra, Li Yi Lim, Fatima Yaseen, Landon Young, Gisele Umviligihozo, F. Harrison Omondi, Rebecca Kalikawe, Laura Burns, Chanson J. Brumme, Victor Leung, Julio S.G. Montaner, Daniel Holmes, Mari DeMarco, Janet Simons, Ralph Pantophlet, Masahiro Niikura, Marc G. Romney, Zabrina L. Brumme
medRxiv 2021.09.06.21263149; doi: https://doi.org/10.1101/2021.09.06.21263149

displace ACE2 in older adults compared to healthcare workers (p=0.0003). On multivariable analysis, age remained significantly associated with anti-RBD IgG titers (p=0.0005), ACE2 displacement activity (p<0.0001) and virus neutralization activity (p=0.006) after two doses.)

CONCLUSIONS: The humoral immune response to COVID-19 mRNA vaccines is significantly weaker with age, and universally wanes over time. This will likely reduce antibody-mediated protection against SARS-CoV-2 and the Delta variant as the pandemic progresses. Older adults may benefit from additional immunizations as a priority.

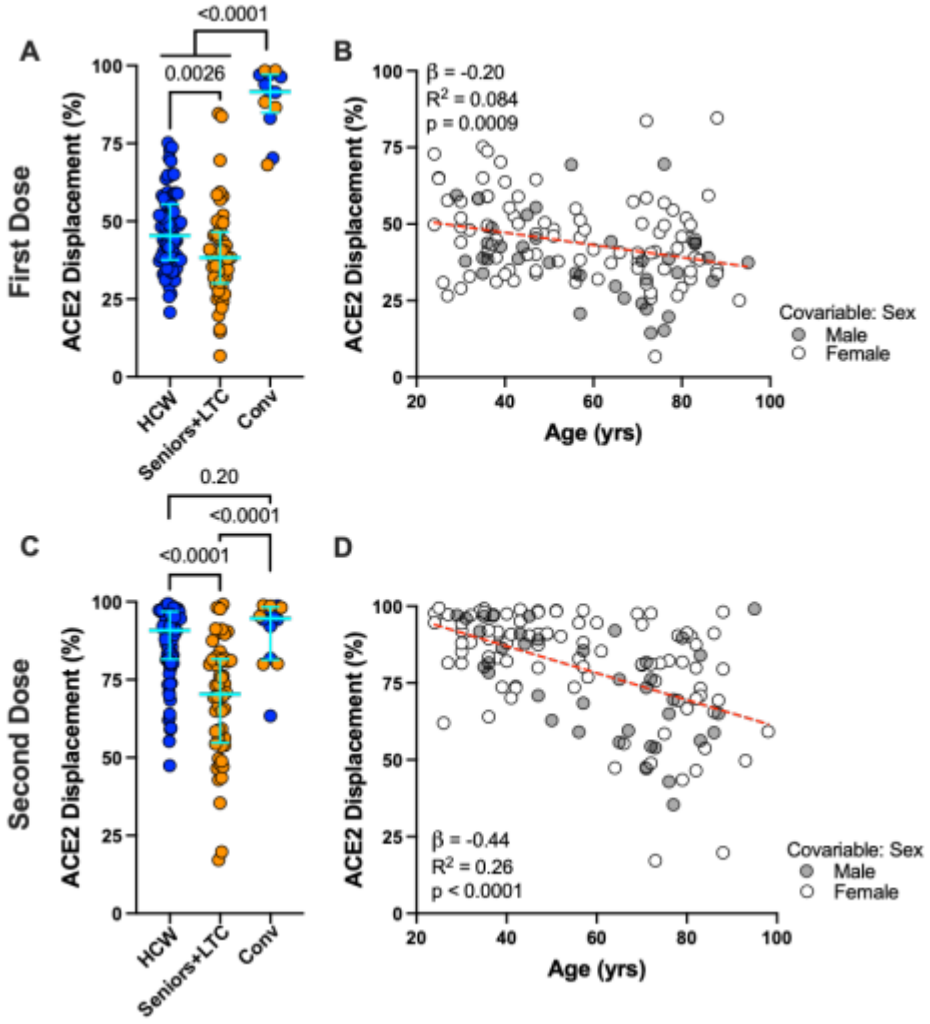

Figure: Ability of vaccine-induced antibodies to block ACE2-receptor binding is weaker in older adults

Level 4

Tartof et al (2021) Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study[16]

Vaccine effectiveness studies have not differentiated the effect of the Delta (B.1.617.2) variant and potential waning immunity in observed reductions in effectiveness against SARS-CoV-2 infections. The authors aimed to evaluate overall and variant-specific effectiveness of BNT162b2 (tozinameran, Pfizer-BioNTech) against SARS-CoV-2 infections and COVID-19-related hospital admissions by time since vaccination among members of a large US health-care system.

METHODS: A retrospective cohort study. The authors analysed electronic health records of individuals (≥12 years) who were members of the health-care organisation Kaiser Permanente Southern California (CA, USA), to assess BNT162b2 vaccine effectiveness against SARS-CoV-2 infections and COVID-19-related hospital admissions for up to 6 months. Participants were required to have 1 year or more previous membership of the organisation. Outcomes comprised SARS-CoV-2 PCR-positive tests and COVID-19-related hospital admissions. Effectiveness calculations were based on hazard ratios from adjusted Cox models.

FINDINGS: Between Dec 14, 2020, and Aug 8, 2021, of 4 920 549 individuals assessed for eligibility, 3 436 957 (median age 45 years [IQR 29-61]; 1 799 395 [52·4%] female and 1 637 394 [47·6%] male) were included. For fully vaccinated individuals, effectiveness against SARS-CoV-2 infections was 73% (95% CI 72-74) and against COVID-19-related hospital admissions was 90% (89-92). Effectiveness against infections declined from 88% (95% CI 86-89) during the first month after full vaccination to 47% (43-51) after 5 months. Among sequenced infections, vaccine effectiveness against infections of the

[16] Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, Frankland TB, Ogun OA, Zamparo JM, Gray S, Valluri SR, Pan K, Angulo FJ, Jodar L, McLaughlin JM. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet. 2021 Oct 16;398(10309):1407-1416. doi: 10.1016/S0140-6736(21)02183-8. Epub 2021 Oct 4. PMID: 34619098; PMCID: PMC8489881.

Delta variant was high during the first month after full vaccination (93% [95% CI 85-97]) but declined to 53% [39-65] after 4 months. Effectiveness against other (non-Delta) variants the first month after full vaccination was also high at 97% (95% CI 95-99), but waned to 67% (45-80) at 4-5 months. Vaccine effectiveness against hospital admissions for infections with the Delta variant for all ages was high overall (93% [95% CI 84-96]) up to 6 months. Stratified by age group, the vaccine effectiveness against infection of those who were fully vaccinated was 61% (57–65) for those aged 65 years and older. Vaccine effectiveness against hospital admissions for infections with the Delta variant for all ages was high overall (93% [95% CI 84–96]) up to 6 months. The age stratified vaccine effectiveness against hospital admissions was 92% (95% CI 88–95) for those aged 16–44 years, and 86% (82–88) for those aged 65 years and older.

INTERPRETATION: Our results provide support for high effectiveness of BNT162b2 against hospital admissions up until around 6 months after being fully vaccinated, even in the face of widespread dissemination of the Delta variant. Reduction in vaccine effectiveness against SARS-CoV-2 infections over time is probably primarily due to waning immunity with time rather than the Delta variant escaping vaccine protection.

Level 4

Bar-On et al (2021) Protection of BNT162b2 Vaccine Booster against COVID-19 in Israel[17]

On July 30, 2021, the administration of a third (booster) dose of the BNT162b2 messenger RNA vaccine (Pfizer-BioNTech) was approved in Israel for persons who were 60 years of age or older and who had received a second dose of vaccine at least 5 months earlier. Data are needed regarding the effect of the booster dose on the rate of confirmed coronavirus 2019 disease (COVID-19) and the rate of severe illness.

[17] Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, Mizrahi B, Alroy-Preis S, Ash N, Milo R, Huppert A. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med. 2021 Oct 7;385(15):1393-1400. doi: 10.1056/NEJMoa2114255. Epub 2021 Sep 15. PMID: 34525275; PMCID: PMC8461568.

METHODS: The authors extracted data for the period from July 30 through August 31, 2021, from the Israeli Ministry of Health database regarding 1,137,804 persons who were 60 years of age or older and had been fully vaccinated (*ie* had received two doses of BNT162b2) at least 5 months earlier. In the primary analysis, the rate of confirmed COVID-19 and the rate of severe illness between those who had received a booster injection at least 12 days earlier (booster group) and those who had not received a booster injection (non-booster group) were compared. In a secondary analysis, the rate of infection 4 to 6 days after the booster dose in comparison to the rate at least 12 days after the booster was evaluated. In all of the analyses, the authors used Poisson regression after adjusting for possible confounding factors.

RESULTS: At least 12 days after the booster dose, the rate of confirmed infection was lower in the booster group than in the non-booster group by a factor of 11.3 (95% CI, 10.4 to 12.3); the rate of severe illness was lower by a factor of 19.5 (95% CI, 12.9 to 29.5). The absolute between-group difference in the rate of severe illness was 7.5 cases per 100,000 person-days. In a secondary analysis, the rate of confirmed infection at least 12 days after vaccination was lower than the rate after 4 to 6 days by a factor of 5.4 (95% CI, 4.8 to 6.1).

CONCLUSIONS: In this study involving participants who were 60 years of age or older and had received two doses of the BNT162b2 vaccine at least 5 months earlier, the authors found that the rates of confirmed COVID-19 and severe illness were substantially lower among those who received a booster (third) dose of the BNT162b2 vaccine.

Level 4

Bar-On et al (2021) BNT162b2 vaccine booster dose protection: A nationwide study from Israel[18]

On July 30, 2021, a third (booster) dose of the Pfizer BNT162b2 vaccine

[18] BNT162b2 vaccine booster dose protection: A nationwide study from Israel
Yinon M. Bar-
On, Yair Goldberg, Micha Mandel, Omri Bodenheimer, Laurence Freedman, Nir Kalkstein, Barak Mizrahi, Sharon Alroy-Preis, Nachman Ash, Ron Milo, Amit Huppert
medRxiv 2021.08.27.21262679; doi: https://doi.org/10.1101/2021.08.27.21262679

was approved in Israel for individuals 60 years or older who had been fully vaccinated at least 5 months previously. Here, the authors estimate the reduction in relative risk for confirmed infection and severe COVID-19 provided by the booster dose.

METHODS: 1,144,690 individuals aged 60 years and older who were eligible for a booster dose were followed between July 30 and August 22, 2021. The authors defined dynamic cohorts in which individuals initially belong to the *'non-booster'* cohort, leave it when receiving the booster dose, and join the *'booster'* cohort 12 days later. Rates of infection and severe COVID-19 outcomes per person-days at risk were compared between the cohorts using Poisson regression, adjusting for possible confounding factors.

RESULTS: 12 days or more after the booster dose, an 11.4-fold (95% CI, 10.0 to 12.9) decrease in the relative risk of confirmed infection, and a >10-fold decrease in the relative risk of severe illness was found. Under a conservative sensitivity analysis, the authors found an approximate 5-fold protection against confirmed infection.

CONCLUSIONS: In conjunction with safety reports, this study demonstrates the effectiveness of a third vaccine dose in both reducing transmission and severe disease and indicates the great potential of curtailing the Delta variant resurgence by administering booster shots.

Level 4

Collier et al (2021) Age-related heterogeneity in immune responses to SARS-CoV-2 vaccine BNT162b2[19]

METHODS: The authors carried out a prospective cohort study of 101 individuals presenting for first dose vaccination, with a subset having the second dose. Following the first and second doses of the BNT162b2 vaccine, binding antibody (IgA, IgG and IgG1-4) responses to Spike

[19] Collier DA, Ferreira IATM, Kotagiri P, Datir RP, Lim EY, Touizer E, Meng B, Abdullahi A; CITIID-NIHR BioResource COVID-19 Collaboration, Elmer A, Kingston N, Graves B, Le Gresley E, Caputo D, Bergamaschi L, Smith KGC, Bradley JR, Ceron-Gutierrez L, Cortes-Acevedo P, Barcenas-Morales G, Linterman MA, McCoy LE, Davis C, Thomson E, Lyons PA, McKinney E, Doffinger R, Wills M, Gupta RK. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. Nature. 2021 Aug;596(7872):417-422. doi: 10.1038/s41586-021-03739-1. Epub 2021 Jun 30. PMID: 34192737; PMCID: PMC8373615.

and Spike RBD, serum neutralising antibody responses to wild type (Wuhan-1 with D614G) and the B.1.1.7 Spike variant using a lentiviral pseudotyping system were measured. B cell repertoires and autoantibodies were measured. Spike specific IFNγ and IL-2 T cell responses and CMV serostatus were measured. The authors correlated age with immune responses and compared responses after the first and second doses.

RESULTS: Median age was 81 years among 101 participants after the first dose of the BNT162b2 vaccine. Geometric mean neutralisation titres in participants over 80 years after the first dose were lower than in younger individuals [83.4 (95% CI 52.0-133.7) vs 46.6 (95% CI 33.5-64.8) p 0.01]. A lower proportion of participants 80 years and older achieved adequate neutralisation titre of >1:20 for 50% neutralisation as compared to those under 80 (21% vs 51%, p 0.003). Binding IgG responses correlated with neutralisation. Sera from participants in both age groups showed significantly lower neutralisation potency against B.1.1.7 Spike pseudotyped viruses as compared to wild type. The adjusted ORs for inadequate neutralisation in the 80 years and above age group were 3.7 (95% CI 1.2-11.2) and 4.4 (95% CI 1.5-12.6) against wild type and B.1.1.7 pseudotyped viruses. A trend towards lower somatic hypermutation in participants with suboptimal neutralisation was observed, and older participants demonstrated clear reduction in class switched somatic hypermutation, driven by the IgA1/2 isotype. SARS-CoV-2 Spike specific T-cell IFNγ and IL-2 responses were impaired in the older age group after 1 dose and although IFNγ increased between vaccine doses, IL-2 responses did not significantly increase.

CONCLUSIONS: Neutralising antibody responses after the first vaccine dose diminished with increasing age, with a marked drop in participants over 80 years of age. Those over 80 were more likely to lack any neutralisation against variants of concern compared to younger participants following the first vaccine dose. The adjusted odds ratio for inadequate neutralisation activity against the B.1.1.7, P.1 and B.1.351 variants in the older versus younger age group was 4.3 (95% CI 2.0-9.3, p<0.001), 6.7 (95% CI 1.7- 26.3, p=0.008) and 1.7 (95% CI 0.5-5.7, p=0.41). There was a significantly higher risk of

suboptimal neutralising antibody and T cell response following first dose vaccination with BNT162b2 in half of participants above the age of 80, persisting up to 12 weeks.

Level 4

Tenforde et al (2021) Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Among Hospitalized Adults Aged ≥65 Years - United States, January-March 2021[20]

Adults aged ≥65 years are at increased risk for severe outcomes from COVID-19 and were identified as a priority group to receive the first COVID-19 vaccines approved for use under an Emergency Use Authorization (EUA) in the United States (1-3). In an evaluation at 24 hospitals in 14 states, the effectiveness of partial or full vaccination with Pfizer-BioNTech or Moderna vaccines against COVID-19-associated hospitalization was assessed among adults aged ≥65 years. Among 417 hospitalized adults aged ≥65 years including 187 case-patients and 230 controls, the median age was 73 years, 48% were female, 73% were non-Hispanic White, 17% were non-Hispanic Black, 6% were Hispanic, and 4% lived in a long-term care facility. Adjusted vaccine effectiveness (VE) against COVID-19-associated hospitalization among adults aged ≥65 years was estimated to be 94% (95% CI = 49%-99%) for full vaccination and 64% (95% CI = 28%-82%) for partial vaccination. These findings are consistent with efficacy determined from clinical trials in the subgroup of adults aged ≥65 years. This multisite US evaluation under real-world conditions suggests that vaccination provided protection against COVID-19-associated hospitalization among adults aged ≥65 years. Vaccination is a critical tool for reducing severe COVID-19 in groups at high risk.

[20] Tenforde MW, Olson SM, Self WH, Talbot HK, Lindsell CJ, Steingrub JS, Shapiro NI, Ginde AA, Douin DJ, Prekker ME, Brown SM, Peltan ID, Gong MN, Mohamed A, Khan A, Exline MC, Files DC, Gibbs KW, Stubblefield WB, Casey JD, Rice TW, Grijalva CG, Hager DN, Shehu A, Qadir N, Chang SY, Wilson JG, Gaglani M, Murthy K, Calhoun N, Monto AS, Martin ET, Malani A, Zimmerman RK, Silveira FP, Middleton DB, Zhu Y, Wyatt D, Stephenson M, Baughman A, Womack KN, Hart KW, Kobayashi M, Verani JR, Patel MM; IVY Network; HAIVEN Investigators. Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Among Hospitalized Adults Aged ≥65 Years - United States, January-March 2021. MMWR Morb Mortal Wkly Rep. 2021 May 7;70(18):674-679. doi: 10.15585/mmwr.mm7018e1. PMID: 33956782.

Level 5

Andrews et al (2021) [Preprint] Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK[21]

Here, the authors estimate vaccine effectiveness over time since the second dose of Comirnaty [Pfizer-BioNTech], Vaxzevria [AstraZeneca] and Spikevax [Moderna] in England.

METHODS: A test-negative case-control design was used to estimate vaccine effectiveness against symptomatic disease, hospitalisation and mortality by age, comorbidity status and over time after the second dose to investigate waning separately for Alpha and Delta variants.

RESULTS: Vaccine effectiveness against symptomatic disease peaked in the early weeks after the second dose and then fell to 47.3 (95% CI 45 to 49.6) and 69.7 (95% CI 68.7 to 70.5) by 20+ weeks against the Delta variant for Vaxzevria and Comirnaty, respectively. Waning of vaccine effectiveness was greater for 65+ year-olds compared to 40-64 year-olds. Vaccine effectiveness fell less against hospitalisations to 77.0 (70.3 to 82.3) and 92.7 (90.3 to 94.6) beyond 20 weeks post-vaccination and 78.7 (95% CI 52.7 to 90.4) and 90.4 (95% CI 85.1 to 93.8) against death for Vaxzevria and Comirnaty, respectively. Greater waning was observed among 65+ year-olds in a clinically extremely vulnerable group and 40-64-year olds with underlying medical conditions compared to healthy adults.

CONCLUSIONS: Limited waning in vaccine effectiveness against hospitalisation and death more than 20 weeks post-vaccination with Vaxzevria or Comirnaty was observed. Waning was greater in older adults and those in a clinical risk group, suggesting that these individuals should be prioritised for booster doses.

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[21] Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK.
Nick Andrews, Elise Tessier, Julia Stowe, Charlotte Gower, Freja Kirsebom, Ruth Simmons, Eileen Gallagher, Meer a Chand, Kevin Brown, Shamez N Ladhani, Mary Ramsay, Jamie Lopez Bernal
medRxiv 2021.09.15.21263583; doi: https://doi.org/10.1101/2021.09.15.21263583

Level 6

Krause et al (2021) Considerations in boosting COVID-19 vaccine immune responses[22]

A new wave of COVID-19 cases caused by the highly transmissible Delta variant is exacerbating the worldwide public health crisis, and has led to consideration of the potential need for, and optimal timing of, booster doses for vaccinated populations. Although the idea of further reducing the number of COVID-19 cases by enhancing immunity in vaccinated people is appealing, any decision to do so should be evidence-based and consider the benefits and risks for individuals and society. COVID-19 vaccines continue to be effective against severe disease, including that caused by the Delta variant. However, most of the observational studies on which this conclusion is based are preliminary and difficult to interpret precisely due to potential confounding and selective reporting. Careful and public scrutiny of the evolving data will be needed to assure that decisions about boosting are informed by reliable science more than by politics. Even if boosting were eventually shown to decrease the medium-term risk of serious disease, current vaccine supplies could save more lives if used in previously unvaccinated populations than if used as boosters in vaccinated populations.

Although the efficacy of most vaccines against symptomatic disease is somewhat less for the Delta variant than for the Alpha variant, there is still high vaccine efficacy against both symptomatic and severe disease due to the Delta variant. The limited supply of these vaccines will save the most lives if made available to people who are at appreciable risk of serious disease and have not yet received any vaccine. Even if some gain can ultimately be obtained from boosting, it will not outweigh the benefits of providing initial protection to the unvaccinated.

[22] Krause PR, Fleming TR, Peto R, Longini IM, Figueroa JP, Sterne JAC, Cravioto A, Rees H, Higgins JPT, Boutron I, Pan H, Gruber MF, Arora N, Kazi F, Gaspar R, Swaminathan S, Ryan MJ, Henao-Restrepo AM. Considerations in boosting COVID-19 vaccine immune responses. Lancet. 2021 Oct 9;398(10308):1377-1380. doi: 10.1016/S0140-6736(21)02046-8. Epub 2021 Sep 14. PMID: 34534516; PMCID: PMC8437678.

Although the benefits of primary COVID-19 vaccination clearly outweigh the risks, there could be risks if boosters are widely introduced too soon, especially with vaccines that can have immune-mediated side-effects. Increasing success in delivering vaccines to large populations will inevitably lead to increasing numbers of breakthrough cases, especially if vaccination leads to behavioural changes in vaccinees.

Level 8: UNCLASSIFIED

Caimi et al (2021) [Preprint] Sero-survey on Long-term Care Facility Residents Reveals Increased Risk of Sub-optimal Antibody Response to BNT162B2: Implications for Breakthrough Prevention[23]

OBJECTIVE: To evaluate SARS-CoV-2 S-IgG antibodies titers in 478 residents and 649 healthcare workers of the largest Italian long-term care facility two months after complete vaccination with BNT162B2. Associations among host-related factors and predictors of humoral response were investigated.

RESULTS: By stratifying levels of humoral responses, the authors found that 62.1%, 21.6%, 12.1% and 4.2% of hosts had high (>1,000 BAU/ml), medium (101-1,000), low (1-100) and null (<1 BAU/mL) S-IgG titers, respectively. Hosts with previous COVID-19 and those with SARS-CoV-2 N-IgG positive serology showed a higher level of serological response ($p<0.001$ and $p<0.001$, respectively), while the administration of corticosteroids or cancer drugs diminished all levels of specific antibodies ($p=0.019$ and $p=0.004$). Significant associations were observed for these parameters in those with suboptimal response ($p<0.001$, $p<0.001$, $p=0.028$ and $p=0.005$), and with a null response ($p=0.005$, $p<0.001$ and $p=0.039$). Predictors of an increased risk of null response were advanced age, corticosteroid therapy and diabetes mellitus ($p=0.025$, $p=0.017$ and $p=0.037$). In contrast, previous diagnosis of COVID-19 resulted strongly associated with a reduced risk of null response to vaccination ($p<0.001$).

[23] Caimi et al (2021). Sero-survey on long-term care facility residents reveals increased risk of sub-optimal antibody response to BNT162B2: Implications for breakthrough prevention. DOI: 10.21203/rs.3.rs-775688/v1.

CONCLUSIONS: SARS-CoV-2 specific antibodies in older individuals need to be measured to consider a third dose of vaccine after mass vaccination for prevention of reinfections in LTCFs despite the maintenance of barrier measures.

Level 8: UNCLASSIFIED

Goldberg et al (2021) Waning Immunity after the BNT162b2 Vaccine in Israel[24]

In December 2020, Israel began a mass vaccination campaign against COVID-19 by administering the BNT162b2 vaccine. After a period with almost no cases of SARS-CoV-2 infection, a resurgent COVID-19 outbreak began in mid-June 2021. Possible reasons for the resurgence were reduced vaccine effectiveness against the Delta (B.1.617.2) variant, and waning immunity. The extent of waning immunity of the vaccine against the delta variant in Israel is unclear.

METHODS: Data on confirmed infection and severe disease collected from an Israeli national database for the period of July 11 to 31, 2021, for all Israeli residents who had been fully vaccinated before June 2021 were collated. A Poisson regression model was used to compare rates of confirmed SARS-CoV-2 infection and severe COVID-19 among persons vaccinated during different time periods, with stratification according to age-group and with adjustment for possible confounding factors.

RESULTS: Among persons 60 years of age or older, the rate of infection in the July 11-31 period was higher among persons who became fully vaccinated in January 2021 (when they were first eligible) than among those fully vaccinated 2 months later, in March (RR 1.6; 95% CI, 1.3 to 2.0). The risk ratio (RR) for severe disease among persons fully vaccinated in the month when they were first eligible as compared with those fully vaccinated in March was 1.8 (95% CI, 1.1 to 2.9) among persons 60 years of age or older and 2.2 (95% CI, 0.6 to 7.7) among those 40 to 59 years of age; due to small numbers, the RR

[24] Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, Milo R, Alroy-Preis S, Ash N, Huppert A. Waning Immunity after the BNT162b2 Vaccine in Israel. N Engl J Med. 2021 Oct 27:NEJMoa2114228. doi: 10.1056/NEJMoa2114228. Epub ahead of print. PMID: 34706170; PMCID: PMC8609604.

could not be calculated among persons 16 to 39 years of age.

CONCLUSIONS: These findings indicate that immunity against the Delta variant of SARS-CoV-2 waned in all age groups a few months after receipt of the second dose of vaccine.

Level 8: UNCLASSIFIED

Juthani et al (2021) Hospitalisation among vaccine breakthrough COVID-19 infections[25]

Emergency use authorisations granted by the US Food and Drug Administration for three SARS-CoV-2 vaccines represent an important milestone in the response to the COVID-19 pandemic. Data presented from the VIVALDI study by Shrotri et al and other phase III clinical trials have shown robust vaccine efficacies (>85%) at preventing severe symptomatic disease. Although rare, emerging reports describe breakthrough SARS-CoV-2 infections in fully vaccinated individuals. The authors describe the impact of vaccination on admission to hospital in patients with confirmed SARS-CoV-2 infection using real-world data collected by the Yale New Haven Health System. The authors reviewed patients admitted to hospital with SARS-CoV-2 confirmed by a positive PCR test at the time of admission between March 23 and July 1, 2021. SARS-CoV-2 vaccination status was recorded. In total, 969 patients who were admitted to a Yale New Haven Health System hospital with a confirmed positive PCR test for SARS-CoV- were identified. Severity of COVID-19 infection was determined on the basis of established guidelines.

172 (18%) of 969 patients had received at least one dose of a COVID-19 vaccine at the time of admission to hospital; and among these, 54 were fully vaccinated. Among the fully vaccinated, 25 (46%) were asymptomatic, 4 (7%) had mild disease, 11 (20%) had moderate disease, and 14 (26%) had severe or critical illness. Among those with

[25] Juthani PV, Gupta A, Borges KA, Price CC, Lee AI, Won CH, Chun HJ. Hospitalisation among vaccine breakthrough COVID-19 infections. Lancet Infect Dis. 2021 Nov;21(11):1485-1486. doi: 10.1016/S1473-3099(21)00558-2. Epub 2021 Sep 7. Erratum in: Lancet Infect Dis. 2021 Nov 15;: PMID: 34506735; PMCID: PMC8423430.

severe or critical illness, the median age was 80.5 years (IQR 76.5–85.0); 4 of 14 patients required intensive care, one required mechanical ventilation, and 3 died. Pre-existing comorbidities in the 14 patients with severe or critical illness included overweight (body–mass index >25 kg/m2; n=9), cardiovascular disease (n=12), lung disease (n=7), malignancy (n=4), type 2 diabetes (n=7), and use of an immunosuppressive agent (n=4).

Level 8: UNCLASSIFIED

Havers et al (2021) [Preprint] COVID-19-associated hospitalizations among vaccinated and unvaccinated adults ≥18 years – COVID-NET, 13 states, January 1 – July 24, 2021[26]

Characteristics of those with vaccine breakthrough resulting in hospitalization and relative rates of hospitalization in unvaccinated and vaccinated persons are not well described, including during late June and July 2021 when the highly transmissible Delta variant predominated.

METHODS: From January 1–June 30, 2021, cases defined as adults aged ≥18 years with laboratory-confirmed SARS-CoV-2 infection were identified from >250 acute care hospitals in the population-based COVID-19-Associated Hospitalization Surveillance Network (COVID-NET). Through chart review for sampled cases, the authors examine characteristics associated with vaccination breakthrough. From January 24–July 24, 2021, state immunization information system data linked to both >37,000 representative cases and the defined surveillance catchment area population were used to compare weekly hospitalization rates in vaccinated and unvaccinated

[26] COVID-19-associated hospitalizations among vaccinated and unvaccinated adults ≥18 years – COVID-NET, 13 states, January 1 – July 24, 2021. Fiona P. Havers, Huong Pham, Christopher A. Taylor, Michael Whitaker, Kadam Patel, Onika Anglin, Anita K. Kambhampati, Jennifer Milucky, Elizabeth Zell, Shua J. Chai, Pam Daily Kirley, Nisha B. Alden, Isaac Armistead, Kimberly Yousey-Hindes, James Meek, Kyle P. Openo, Evan J. Anderson, Libby Reeg, Alexander Kohrman, Ruth Lynfield, Kathryn Como-Sabetti, Elizabeth M. Davis, Cory Cline, Alison Muse, Grant Barney, Sophrena Bushey, Christina B. Felsen, Laurie M. Billing, Eli Shiltz, Melissa Sutton, Nasreen Abdullah, H. Keipp Talbot, William Schaffner, Mary Hill, Andrea George, Bhavini Patel Murthy, Meredith McMorrow medRxiv 2021.08.27.21262356; doi: https://doi.org/10.1101/2021.08.27.21262356

individuals. Unweighted case counts and weighted percentages are presented.

RESULTS: From January 1 – June 30, 2021, fully vaccinated cases increased from 1 (0.01%) to 321 (16.1%) per month. Among 4,732 sampled cases, fully vaccinated persons admitted with COVID-19 were older compared with unvaccinated persons (median age 73 years [Interquartile Range (IQR) 65-80] v. 59 years [IQR 48-70]; p<0.001), more likely to have 3 or more underlying medical conditions (201 (70.8%) v. 2,305 (56.1%), respectively; p<0.001) and be residents of long-term care facilities [37 (14.5%) v. 146 (5.5%), respectively; p<0.001]. From January 24 – July 24, 2021, cumulative hospitalization rates were 17 times higher in unvaccinated persons compared with vaccinated persons (423 cases per 100,000 population v. 26 per 100,000 population, respectively); rate ratios were 23, 22 and 13 for those aged 18-49, 50-64, and ≥65 years respectively. For June 27 – July 24, hospitalization rates were ≥10 times higher in unvaccinated persons compared with vaccinated persons for all age-groups across all weeks.

CONCLUSION: Population-based hospitalization rates show that unvaccinated adults aged ≥18 years are 17 times more likely to be hospitalized compared with vaccinated adults. Rates are far higher in unvaccinated persons in all adult age-groups, including during a period when the Delta variant was the predominant strain of the SARS-CoV-2 virus. Vaccines continue to play a critical role in preventing serious COVID-19 illness and remain highly effective in preventing COVID-19 hospitalizations.

Level 8: UNCLASSIFIED

Grannis et al (2021) Interim Estimates of COVID-19 Vaccine Effectiveness Against COVID-19-Associated Emergency Department or Urgent Care Clinic Encounters and Hospitalizations Among Adults During SARS-CoV-2 B.1.617.2 (Delta) Variant Predominance - Nine States, June-August 2021[27]

Data on COVID-19 vaccine effectiveness (VE) since the B.1.617.2 (Delta) variant of SARS-CoV-2 became the predominant circulating strain in the United States are limited (1-3). CDC used the VISION Network to examine medical encounters (32,867) from 187 hospitals and 221 emergency departments (EDs) and urgent care (UC) clinics across nine states during June-August 2021, beginning on the date the Delta variant accounted for >50% of sequenced isolates in each medical facility's state.

Overall, VE against COVID-19 hospitalization (all vaccines) was 86% (95% CI = 82%–89%). VE was significantly lower among adults aged ≥75 years (76%) than among those aged 18–74 years (89%).

Level 8: UNCLASSIFIED

Cohn et al (2021) [Preprint] Breakthrough SARS-CoV-2 infections in 620,000 U.S. Veterans, February 1, 2021 to August 13, 2021[28]

National data on COVID-19 vaccine breakthrough infections is inadequate but urgently needed to determine US policy during the emergence of the Delta variant. The authors compared SARS CoV-2 infection by vaccination status from February 1, 2021 to August 13, 2021 in the Veterans Health Administration, covering 2.7% of the US population. Vaccine protection declined by mid-August 2021,

[27] Grannis SJ, Rowley EA, Ong TC, Stenehjem E, Klein NP, DeSilva MB, Naleway AL, Natarajan K, Thompson MG; VISION Network. Interim Estimates of COVID-19 Vaccine Effectiveness Against COVID-19-Associated Emergency Department or Urgent Care Clinic Encounters and Hospitalizations Among Adults During SARS-CoV-2 B.1.617.2 (Delta) Variant Predominance - Nine States, June-August 2021. MMWR Morb Mortal Wkly Rep. 2021 Sep 17;70(37):1291-1293. doi: 10.15585/mmwr.mm7037e2. PMID: 34529642; PMCID: PMC8445373.
[28] Breakthrough SARS-CoV-2 infections in 620,000 U.S. Veterans, February 1, 2021 to August 13, 2021 Barbara A. Cohn, Piera M. Cirillo, Caitlin C. Murphy, Nickilou Y. Krigbaum, Arthur W. Wallace medRxiv 2021.10.13.21264966; doi: https://doi.org/10.1101/2021.10.13.21264966

decreasing from 91.9% in March to 53.9% (p<0.01, n=619,755). Declines were greatest for the Janssen vaccine followed by Pfizer–BioNTech and Moderna. Patterns of breakthrough infection over time were consistent by age, despite rolling vaccine eligibility, implicating the Delta variant as the primary determinant of infection. Findings support continued efforts to increase vaccination and an immediate, national return to additional layers of protection against infection.

Level 8: UNCLASSIFIED

Moline et al (2021) Effectiveness of COVID-19 Vaccines in Preventing Hospitalization Among Adults Aged ≥65 Years — COVID-NET, 13 States, February–April 2021[29]

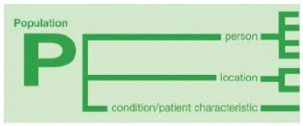
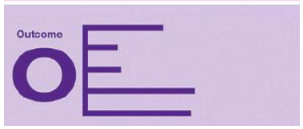
Clinical trials of COVID-19 vaccines currently authorized for emergency use in the United States (Pfizer-BioNTech, Moderna, and Janssen) have shown high efficacy in preventing symptomatic (including moderate to severe) COVID-19. Among adults aged 65–74 years, effectiveness of full vaccination for preventing hospitalization was 96% for Pfizer-BioNTech, 96% for Moderna, and 84% for Janssen COVID-19 vaccines; among adults aged ≥75 years, effectiveness of full vaccination for preventing hospitalization was 91% for Pfizer-BioNTech, 96% for Moderna, and 85% for Janssen COVID-19 vaccines.

Efforts to increase vaccination coverage are critical to reducing the risk for COVID-19–related hospitalization, particularly in older adults.

[29] Moline HL, Whitaker M, Deng L, Rhodes JC, Milucky J, Pham H, Patel K, Anglin O, Reingold A, Chai SJ, Alden NB, Kawasaki B, Meek J, Yousey-Hindes K, Anderson EJ, Farley MM, Ryan PA, Kim S, Nunez VT, Como-Sabetti K, Lynfield R, Sosin DM, McMullen C, Muse A, Barney G, Bennett NM, Bushey S, Shiltz J, Sutton M, Abdullah N, Talbot HK, Schaffner W, Chatelain R, Ortega J, Murthy BP, Zell E, Schrag SJ, Taylor C, Shang N, Verani JR, Havers FP. Effectiveness of COVID-19 Vaccines in Preventing Hospitalization Among Adults Aged ≥65 Years - COVID-NET, 13 States, February-April 2021. MMWR Morb Mortal Wkly Rep. 2021 Aug 13;70(32):1088-1093. doi: 10.15585/mmwr.mm7032e3. PMID: 34383730; PMCID: PMC8360274.

Produced by the members of the National Health Library and Knowledge Service Evidence Team†. Current as at November 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.

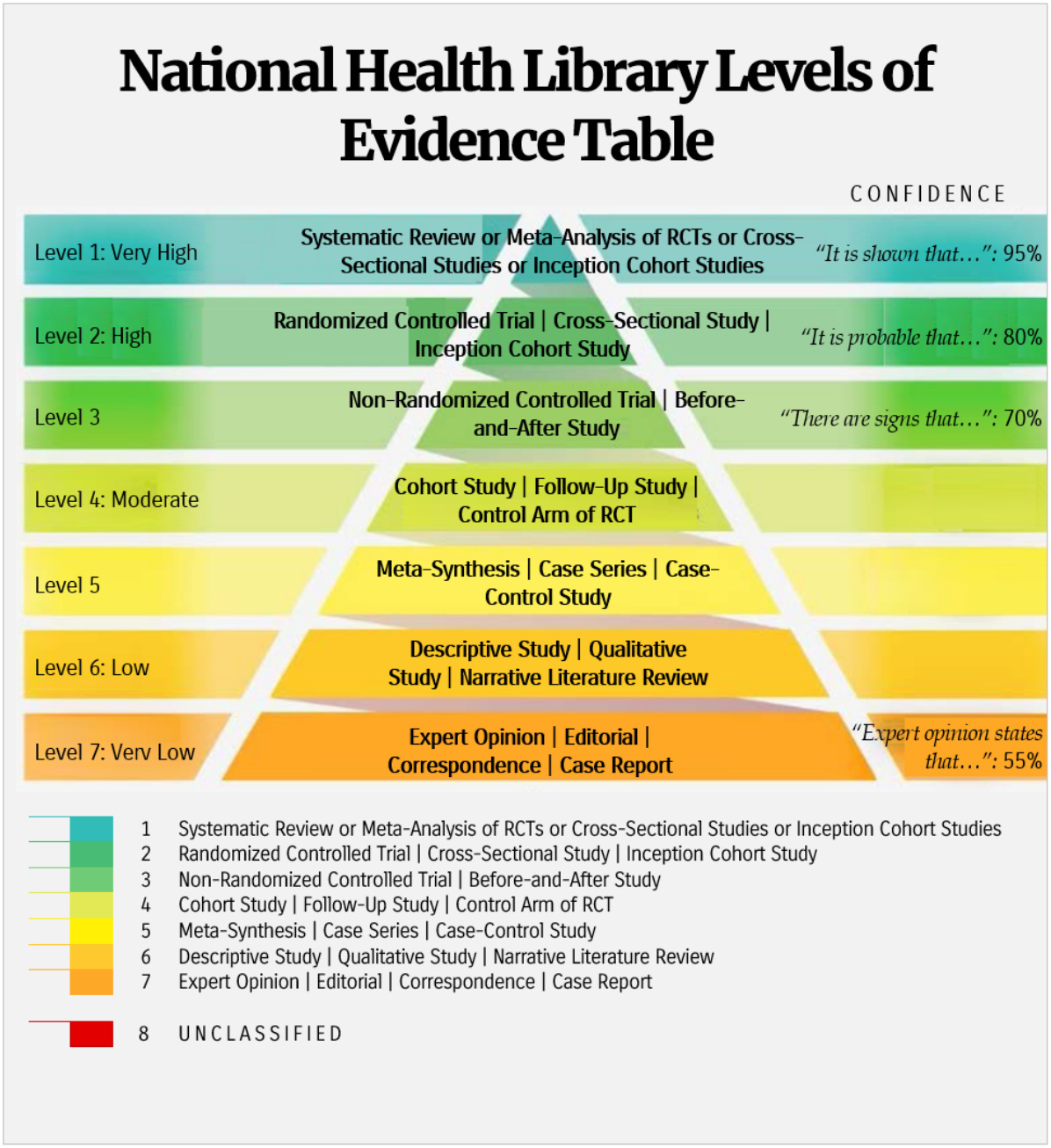
The following PICO(T) was used as a basis for the evidence summary:

	INDIVIDUALS ≥65 YEARS
	COVID-19 BOOSTER VACCINATION
	
	REDUCED INCIDENCE OF SEVERE DISEASE; REDUCED HOSPITALISATION; REDUCED ICU ADMISSION; REDUCED MORTALITY

The following search strategy was used:

1. Coronavirinae/
2. (covid-19 or coronavirus or "corona virus" or "2019-ncov" or "2019 ncov").ab,ti.
3. "severe acute respiratory syndrome coronavirus".ab,ti.
4. ("2019" and (new or novel) and coronavirus).ab,ti.
5. coronavirus disease 2019.ab,ti.
6. exp Coronavirus infection/
7. exp coronavirus disease 2019/
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp vaccination/
10. "vaccin*".ab,ti.
11. vaccine immunogenicity.ab,ti.
12. exp vaccine immunogenicity/
13. 9 or 10 or 11 or 12
14. hospital mortality/ or mortality rate/ or mortality/
15. death/
16. clinical outcome/
17. hospitalization/
18. reinfection/
19. (mortality or death or hospitali*).ab,ti.
20. (severe adj1 (disease or illness)).ab,ti.
21. (ICU or "intensive care" or "critical care").ab,ti.
22. (readmission or admitted).ab,ti.
23. 21 and 22
24. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 23
25. 8 and 13 and 24
26. aged/
27. (older or "older patient" or elderly or "frail elderly" or geriatric or "old age").ab,ti.
28. ("over 65" or "over 65 years").ab,ti.
29. 26 or 27 or 28
30. 25 and 29
31. 30 and 2021:2021.(sa_year).

The following schema was used to grade the levels of evidence included:



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