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 222

Do COVID-19 vaccines prevent SARS-CoV-2 transmission and infection among healthcare workers with specific consideration of the B.1.617.2 (Delta) variant?

Main Points

1. Data from several reports support the efficacy of vaccination in reducing SARS-CoV-2 infections in healthcare personnel (HCP); however, cases of SARS-CoV-2 infection have been reported in fully vaccinated HCP, and data suggest there may be a somewhat higher rate of breakthrough infections with the Delta variant.
2. Vaccination reduces transmission of Delta, but by less than the Alpha variant. The Delta variant may attenuate vaccine-associated reductions in transmission; and transmission reductions may decline over time. It is unclear if the reduction in vaccine effectiveness is due to the Delta variant or waning immunity with increasing time since initial vaccination series.
3. Fully vaccinated individuals with breakthrough infections have peak viral load similar to unvaccinated cases and can efficiently transmit infection.
4. As vaccine uptake has progressed and vaccine supplies have increased, several countries have progressively expanded the rollout and have started recommending additional vaccine doses in certain priority groups including HCP.

Summary of Evidence

Data from several reports support the efficacy of vaccination in reducing SARS-CoV-2 infections in healthcare personnel (HCP)[23-25]; however, cases of SARS-CoV-2 infection have been reported in fully vaccinated HCP, and data suggest there may be a somewhat higher rate of breakthrough infections with the Delta variant, the dominant variant in many countries currently[7, 27, 28, 30, 32, 33].

In a systematic review and meta-analysis of post-vaccination SARS-CoV-2 infection among HCP, Chandan et al[8] found that the pooled proportion of COVID-19 infections was 1.3% (95% CI 0.6-2.9), 2.3% (CI 1.2-4.4) and 10.1% (95% CI 4.5-19.5) among fully vaccinated, partially vaccinated and unvaccinated, respectively. The pooled proportion of fully and partially vaccinated HCP hospitalised was 5.7% (95%CI 3.5-9.1). The pooled proportion of fully and partially vaccinated HCP requiring ICU admission was 2.6% (95% CI 0.4-15.4). The pooled proportion of fully and partially vaccinated HCP dying from COVID-19 was 1.2% (95%CI 0.3-5.7). The authors conclude that the risk of SARS-CoV-2 infection in both partially and fully vaccinated HCP is low in comparison to unvaccinated individuals.

In a study of the effect of vaccination on SARS-CoV-2 transmission in Scotland, Shah et al[10] found that transmission was less common among household members of vaccinated HCP during the period beginning 14 days after the first dose than during the unvaccinated period before the first dose (event rate per 100 person-years, 9.4 before the first dose and 5.93 beginning 14 days after the first dose); and that after the second dose, the rate in HCP household members was lower still (2.98). Eyre et al[11] report that vaccination reduces transmission of Delta, but by less than the Alpha variant: the Delta variant attenuated vaccine-associated reductions in transmission; and transmission reductions declined over time post-second

vaccination for Delta, reaching similar levels to unvaccinated individuals by 12 weeks for the AstraZeneca vaccine and attenuating substantially for the Pfizer-BioNTech vaccine. Singanayagam et al[12] found that vaccination reduces the risk of Delta variant infection and accelerates viral clearance. Nonetheless, fully vaccinated individuals with breakthrough infections have peak viral load similar to unvaccinated cases and can efficiently transmit infection. Siedner et al[13] report that Delta variant breakthrough infections were characterized by higher initial viral load, longer duration of virologic shedding by PCR (median 13.5 vs 4 days, HR 0.45, 95%CI 0.17-1.17), greater likelihood of replication-competent virus at early stages of infection (6/8 [75%] vs 3/14 [23%], P=0.03), and longer duration of culturable virus (median 7 vs 3 days, HR 0.38, 95%CI 0.14-1.02) compared to non-Delta variants. Riemersma et al[15] caution that the Delta variant is highly transmissible and contains mutations that confer partial immune escape.

Fowlkes et al[9] found that vaccine effectiveness (VE) against SARS-CoV-2 infection was 85% (95% CI 68–93) among HCP for whom <4 months had elapsed since completion of full vaccination compared with 73% (95% CI 49–86) among those for whom ≥5 months had elapsed. Adjusted VE against infection when Delta was predominant was 66% (95% CI 26–84) compared with 91% (95% CI 81–96) during the preceding months. 75% of infections in fully vaccinated HCP in the Delta predominant period were symptomatic. The authors conclude that it was unclear if the reduction in VE was due to the Delta variant or waning immunity with increasing time since initial vaccination series.

In a cohort study of 2397 fully vaccinated HCP at a hospital in Lombardy, Italy, Novazzi et al[20] report that between March and August, 2021, 1.5% (n=33) of HCP were detected as positive as part of a surveillance programme. All were asymptomatic. 8 HCP developed symptoms and tested positive outside of the surveillance programme. Mean time to viral clearance was one day for asymptomatic cases vs. 11 days for symptomatic cases. Mean *Ct* values were similar for both groups. Asymptomatic cases had higher

mean IgG post-vaccination compared with symptomatic cases.

Evidence continues to emerge on the duration of vaccine protection and real world vaccine effectiveness against different outcomes such as infection, severe disease and hospitalisation due to the Delta variant[5]. As vaccine uptake has progressed and vaccine supplies have increased, several countries have progressively expanded the rollout and have started recommending additional vaccine doses in certain priority groups including HCP[5]. Saiag et al[22] report high vaccine immunoreactivity in HCP in receipt of a booster dose. In Britain, the Joint Committee on Vaccination and Immunisation (JCVI) recommends a booster vaccine dose for all frontline and social care workers no earlier than 6 months after completion of the primary vaccine course[2]. In Germany, the Standing Committee on Vaccination has recommended that all HCP who are in direct contact with patients should be offered a third vaccine dose 6 months after the completion of the primary vaccination series at the earliest[3]. Similarly, in France, the Conseil d'orientation de la stratégie vaccinale recommends that HCP should be offered a booster dose of a COVID-19 vaccine from 6 months after completion of the primary vaccine series[4]. In the United States, the Advisory Committee on Immunization Practices (ACIP) recommend that HCP aged 18–64 years who received either a Pfizer-BioNTech or Moderna vaccine as part of their primary series may get a booster dose of the Pfizer vaccine at 6 months or more after their initial series[6].

Recent data from the Health Protection Surveillance Centre (HPSC) indicate that the proportion of PCR-confirmed COVID-19 cases who are HCP remains far lower (3.8%) than that seen during the January 2021 surge when 16.4% of cases were HCP[1].

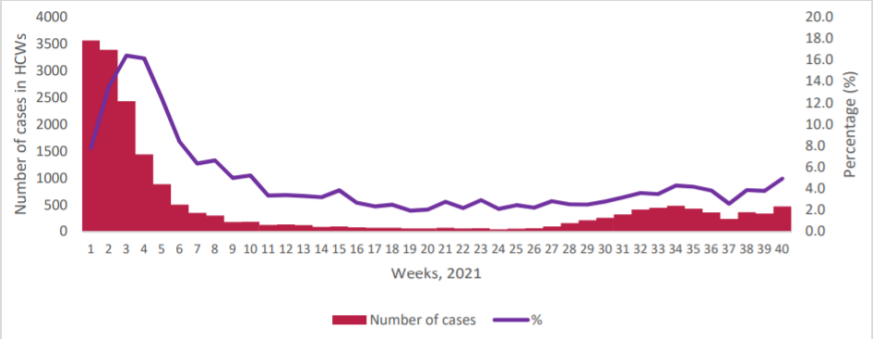
Irish and/or International Guidance

Level 1

Health Protection Surveillance Centre (2021) Interim report of the profile of COVID-19 cases in healthcare workers, 12/09/2021 to 09/10/2021 in Ireland[1]

During 4-week period from September 12, 2021 to October 9, 2021, there were 1,417 PCR-confirmed cases in Irish healthcare workers, representing 3.8% of all cases in Ireland during this time-period. 0.9% of HCW cases (n=13) have been hospitalized and 0.2% (n=2) have been admitted to ICU. 26% (n=371) of HCW cases have been nurses, and 20% (n=282) healthcare assistants. 26% (n=376) of HCW cases are based in acute hospitals, and 17% (n=242) in nursing homes. The total number of HCW cases in this time-period is lower than that seen in the previous 4-week period. The proportion of cases who are HCW remains far lower than that seen during the January 2021 surge when 16.4% (2,433/14,809) of cases were HCW.

Figure: Number of COVID-19 cases and percentage of HCW cases by week in Ireland notified to CIDR (weeks 1-40, 2021).



[1] HPSC (2021) Interim report of the profile of COVID-19 cases in healthcare workers, 12/09/2021 to 09/10/2021 in Ireland. Accessed 21/10/21.

Table: Healthcare worker COVID-19 cases in Ireland by likely transmission source

Total number of cases	N=1417	%
Community transmission	558	39.4
Close contact with a known confirmed case	537	37.9
Healthcare setting acquired: staff	184	13.0
Travel related	41	2.9
Healthcare setting acquired: patient	40	2.8
Under investigation	57	4.0

Level 1

Department of Health and Social Care (Great Britain) (2021) JCVI statement regarding a COVID-19 booster vaccine programme for winter 2021 to 2022[2]

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

With increasing levels of social mixing and close social contact, it is expected that during winter 2021 to 2022 SARS-CoV2 will co-circulate alongside other respiratory viruses, including seasonal influenza virus. Seasonal influenza and SARS-CoV-2 viruses have the potential to add substantially to the winter pressures usually faced by the NHS, particularly if infection waves from both viruses coincide. The timing and magnitude of potential influenza and SARS-CoV2 infection waves for winter 2021 to 2022 are currently unknown.

In JCVI's view, the primary objective of a 2021 COVID-19 booster programme is to maintain protection against severe COVID-19 disease, specifically hospitalisation and deaths, over winter 2021 to 2022. This is exceptional advice aimed at maintaining protection in

[2] Department of Health and Social Care (Great Britain) (2021) JCVI statement regarding a COVID-19 booster vaccine programme for winter 2021 to 2022. Accessed 21/10/21.

those most vulnerable, and to protect the National Health Service.

In respect of healthcare workers, the JCVI recommends a booster vaccine dose for all frontline and social care workers no earlier than 6 months after completion of the primary vaccine course, with a preference for the Pfizer-BioNTech vaccine to be offered as the third booster dose irrespective of which product was used in the primary schedule. Alternatively, individuals may be offered a half dose (50µg) of the Moderna vaccine. Where mRNA vaccines cannot be offered (*eg* due to contraindication), vaccination with the AstraZeneca vaccine may be considered for those who received AstraZeneca in the primary course.

Level 1

Robert Koch Institute (Germany) (2021) Standing Committee on Vaccination[3]

In Germany, the Standing Committee on Vaccination has recommended that all healthcare workers who are in direct contact with patients should be offered a third vaccine dose 6 months after the completion of the primary vaccination series at the earliest, regardless of which vaccine was used in the initial series; and that an mRNA vaccine should be given to those who received mRNA vaccines as part of their primary vaccination series.

Level 1

Conseil d'orientation de la stratégie vaccinale (France) (2021) Note du 13 septembre 2021 relative au rappel vaccinal contre le SARSCoV-2 chez les personnels de santé à l'automne 2021[4]

In France, the Conseil d'orientation de la stratégie vaccinale recommends that healthcare workers should be offered a booster dose of a COVID-19 vaccine from 6 months after completion of the primary

[3] Robert Koch Institute (2021) Standing Committee on Vaccination. Accessed 21/10/21.
[4] Conseil d'orientation de la stratégie vaccinale (2021) Note du 13 septembre 2021 relative au rappel vaccinal contre le SARSCoV-2 chez les personnels de santé à l'automne 2021. Accessed 21/10/21.

vaccine series. The recommended vaccines for boosting is the Pfizer vaccine. The Moderna vaccine is no longer offered as a booster as of October 18, 2021.

Level 1

European Centre for Disease Prevention and Control (2021) Overview of the implementation of COVID-19 vaccination strategies and deployment plans in the EU/EEA 23 September 2021[5]

This report provides an updated overview of the progress of national COVID-19 vaccination strategies in European Union/European Economic Area (EU/EEA) countries, including updates on: overall vaccine uptake and uptake by target group; vaccination strategies and policies; challenges and good practices with the rollout.

As of 7 November 2021, over 599 million vaccine doses have been administered in the EU/EEA, 293 million people have received a complete primary vaccination course (30 countries reporting) and over seven million individuals in the EU/EEA have already received an additional dose following the primary vaccination course (22 countries reporting).

Since the start of COVID-19 vaccine deployment in the EU/EEA in December 2020, the cumulative uptake of a full vaccination course has reached 64.8% (range: 22.5-81.2%) in the total population and 76% (range: 27-92.4%) in the adult population aged 18 years and above (pooled data from 30 reporting countries). However, the pace of weekly increase in vaccine uptake in the EU/EEA as a whole is slowing down and the progress is unequal across countries, with four reporting less than 50% of full vaccination uptake in the total population (Bulgaria, Croatia, Romania and Slovakia).

As vaccine campaigns expanded to include younger age groups, the median uptake of full vaccination among the elderly aged 60 years and above in the EU/EEA, as of 7 November 2021, reached a plateau well above 80%, while still increasing among younger adults (65.9%

[5]European Centre for Disease Prevention and Control (2021) Overview of the implementation of COVID-19 vaccination strategies and deployment plans in the EU/EEA 23 September 2021. Accessed 21/10/21.

in 18-24; 71.6% in 25-49; 79.6% in 50-59), as well as in adolescents and children, with a median uptake of full vaccination of 14.3% among individuals below 18 years (52.9% in 15-17; 19.5% in 10-14).

From the start, vaccinations have been rolled out in phases through various priority groups. Countries initially prioritised elderly people, residents and personnel of long-term care facilities, healthcare workers, social care personnel, and people with certain comorbidities. All EU/EEA countries then opened vaccination to the general population, with all offering vaccination to those aged 12 years and over.

As vaccine uptake has progressed in priority groups such as the elderly, residents in long-term care facilities and healthcare workers, and vaccine supplies have increased, countries have progressively expanded the rollout to include younger age groups. All EU/EEA countries have now opened vaccinations to 12-year-olds and over. Several countries have started recommending additional vaccine doses for immunocompromised individuals, and some have also recommended booster doses for older age groups, healthcare workers, and the general population. Many countries are still discussing the use of additional doses and booster doses as evidence continues to emerge on the duration of vaccine protection and real world vaccine effectiveness against different outcomes such as infection, severe disease and hospitalisation due to the Delta variant of concern.

Level 1

Centers for Disease Control and Prevention (United States) (2021) Advisory Committee on Immunization Practices (ACIP) COVID-19 Vaccine Recommendations[6]

The Advisory Committee on Immunization Practices (ACIP) recommend that healthcare workers aged 18–64 years who received either a Pfizer-BioNTech or Moderna vaccine as part of their primary series may get a booster dose of the Pfizer vaccine at 6 months or

[6] Centers for Disease Control and Prevention (2021) Advisory Committee on Immunization Practices (ACIP) COVID-19 Vaccination Recommendations. Accessed 21/10/21.

more after their initial series.

Evidence Synopsis Resources

Level 2

[UpToDate (2021) COVID-19: Occupational health issues for health care personnel[7]]

See Section: PREVENTING COVID-19 IN HEALTH CARE SETTINGS

Vaccination with one of the available COVID-19 vaccines is indicated for all health care personnel (HCP), unless there is a contraindication such as allergic reactions to the vaccines or their components. In the United States, multiple medical societies support COVID-19 vaccination as a condition of employment for all HCP unless they are exempt due to medical contraindications or subject to other exemptions as specified by federal or state law. This includes non-employees functioning at a health care facility: *eg* students, contract workers, volunteers.

Data from several reports support the efficacy of vaccination in reducing SARS-CoV-2 infections in HCP; however, cases of SARS-CoV-2 infection have been reported in fully vaccinated HCP, and data suggest there may be a somewhat higher rate of breakthrough infections with Delta, the dominant variant in many countries.

After vaccination, systemic signs and symptoms such as fever, fatigue, headache, chills, myalgia, and arthralgia can occur, and it can be challenging to distinguish these clinical manifestations from signs and symptoms of COVID-19 or other infectious diseases.

The United States Centers for Disease Control and Prevention (CDC) has issued guidelines for the management of HCP after vaccination. Institutional policies may vary, but in general, HCP should

[7] UpToDate (2021) COVID-19: Occupational health issues for health care personnel. Accessed 21/10/2021.

be excluded from work pending further evaluation if they: develop fever, fatigue, headache, chills, myalgia, or arthralgias, and had a known unprotected exposure within the past 14 days; have a fever >100.0°F; have symptoms that are unlikely to be due to vaccination: *eg* cough, shortness of breath, rhinorrhea, sore throat, loss of taste or smell.

Other HCP who develop systemic reactions that are typically observed following COVID-19 vaccination can continue to work but should be evaluated by employee health if the symptoms persist for more than 48 hours.

To minimize the impact of post-vaccination signs and symptoms on health care staffing, facilities should consider vaccinating HCP prior to scheduled days off and staggering delivery of vaccine to HCP in the facility so that not all HCP in a single department, service, or unit are vaccinated at the same time.

Irish and/or International Literature

Level 1

Chandan et al (2021) [Systematic Review and Meta-Analysis] Post-vaccination SARS-CoV-2 infection among healthcare workers: A systematic review and meta-analysis[8]

The authors conducted a systematic review and meta-analysis to assess the incidence of post-vaccination SARS-CoV-2 infection among vaccinated healthcare workers (HCW). Multiple databases were searched from inception through August 2021 to identify studies that reported on the incidence of post-vaccination SARS-CoV-2 infection among HCW. Meta-analysis was performed to determine pooled proportions of COVID-19 infection in partially or fully vaccinated as well as unvaccinated individuals. 18 studies with 228 873 HCW were included in the final analysis.

The total number of partially-vaccinated, fully-vaccinated, and unvaccinated HCW were 132 922, 155 673, and 17 505, respectively. Overall, the pooled proportion of COVID-19 infections among partially or fully vaccinated and unvaccinated HCW was 2.1% (95% CI 1.2-3.5). Among partially vaccinated, fully vaccinated and unvaccinated HCW, the pooled proportion of COVID-19 infections was 2.3% (CI 1.2-4.4), 1.3% (95% CI 0.6-2.9), and 10.1% (95% CI 4.5-19.5), respectively. The pooled proportion of fully and partially vaccinated HCW hospitalized was 5.7% (95%CI 3.5-9.1). The pooled proportion of fully and partially vaccinated HCW requiring ICU admission was 2.6% (95%CI 0.4-15.4). The pooled proportion of fully and partially vaccinated HCW dying from COVID-19 was 1.2% (95%CI 0.3-5.7).

Level 4

Fowlkes et al (2021) Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before

[8] Chandan S, Khan SR, Deliwala S, Mohan BP, Ramai D, Chandan OC, Facciorusso A. Postvaccination SARS-CoV-2 infection among healthcare workers: A systematic review and meta-analysis. J Med Virol. 2021 Nov 15. doi: 10.1002/jmv.27457. Epub ahead of print. PMID: 34783055.

and During B.1.617.2 (Delta) Variant Predominance - Eight U.S. Locations, December 2020-August 2021[9]

From December 14, 2020 to April 10, 2021, data from the HEROES-RECOVER network of prospective cohort studies among frontline healthcare workers showed that the Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines were approximately 90% effective in preventing symptomatic and asymptomatic infection with SARS-CoV-2 in real-world conditions. This report updates vaccine effectiveness (VE) estimates including all COVID-19 vaccines available through August 14, 2021, and examines whether VE differs for adults with increasing time since completion of all recommended vaccine doses. VE before and during SARS-CoV-2 B.1.617.2 (Delta) variant predominance, which coincided with an increase in reported COVID-19 vaccine breakthrough infections, were compared.

COVID-naive vaccinated and unvaccinated HCW in eight US locations (n=7,112) were included in the study.

VE against SARS-CoV-2 infection was 85% (68–93) among participants for whom <4 months had elapsed since completion of full vaccination compared with 73% (49–86) among those for whom ≥5 months had elapsed. Adjusted VE against infection when Delta was predominant was 66% (95% CI = 26%–84%) compared with 91% (95% CI = 81%–96%) during the preceding months. 75% of infections in fully vaccinated HCW in the Delta predominant period were symptomatic. The authors stated that it was unclear if the reduction in VE was due to the Delta variant or waning immunity with increasing time since initial vaccination series.

[9] Fowlkes A, Gaglani M, Groover K, Thiese MS, Tyner H, Ellingson K; HEROES-RECOVER Cohorts. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance - Eight U.S. Locations, December 2020-August 2021. MMWR Morb Mortal Wkly Rep. 2021 Aug 27;70(34):1167-1169. doi: 10.15585/mmwr.mm7034e4. PMID: 34437521; PMCID: PMC8389394.

Level 4

Shah et al (2021) [Cohort Study] Effect of Vaccination on Transmission of SARS-CoV-2[10]

The authors investigated the effect of vaccination of healthcare workers in Scotland — one of the earliest groups to be vaccinated worldwide — on the risk of COVID-19 among members of their households.

Data from 194,362 household members (which represented 92,470 households of 2 to 14 persons per household) of 144,525 healthcare workers who had been employed during the period from March 2020 through November 2020 were evaluated. The mean ages of the household members and the healthcare workers were 31 and 44 years, respectively; a majority (>96%) were White. A total of 113,253 healthcare workers (78.4%) had received at least one dose of either the BNT162b2 (Pfizer–BioNTech) mRNA vaccine or the ChAdOx1 nCoV-19 (Oxford–AstraZeneca) vaccine, and 36,227 (25.1%) had received a second dose.

The primary outcome was any confirmed case of COVID-19 that occurred between December 8, 2020, and March 3, 2021. Cases of COVID-19 were less common among household members of vaccinated healthcare workers during the period beginning 14 days after the first dose than during the unvaccinated period before the first dose (event rate per 100 person-years, 9.40 before the first dose and 5.93 beginning 14 days after the first dose). After the healthcare worker's second dose, the rate in household members was lower still (2.98 cases per 100 person-years). These differences persisted after fitting extended Cox models that were adjusted for calendar time, geographic region, age, sex, occupational and socioeconomic factors, and underlying conditions. Relative to the period before each

[10] Shah ASV, Gribben C, Bishop J, Hanlon P, Caldwell D, Wood R, Reid M, McMenamin J, Goldberg D, Stockton D, Hutchinson S, Robertson C, McKeigue PM, Colhoun HM, McAllister DA. Effect of Vaccination on Transmission of SARS-CoV-2. N Engl J Med. 2021 Oct 28;385(18):1718-1720. doi: 10.1056/NEJMc2106757. Epub 2021 Sep 8. PMID: 34496200; PMCID: PMC8451182.

healthcare worker was vaccinated, the hazard ratio for a household member to become infected was 0.70 (95% CI, 0.63 to 0.78) for the period beginning 14 days after the first dose and 0.46 (95% CI, 0.30 to 0.70) for the period beginning 14 days after the second dose. Not all the cases of COVID-19 in the household members were transmitted from the healthcare worker; therefore, the effect of vaccination may be larger.

Level 4

Eyre et al (2021) [Retrospective Cohort Study] [Preprint] The impact of SARS-CoV-2 vaccination on Alpha & Delta variant transmission[11]

Before the emergence of the Delta variant, vaccination reduced SARS-CoV-2 transmission from individuals infected despite vaccination, potentially via reducing viral loads. While vaccination still lowers the risk of infection, similar viral loads in vaccinated and unvaccinated individuals infected with the Delta variant call into question the extent to which vaccination prevents transmission.

METHODS: A retrospective observational cohort study of adult contacts of SARS-CoV-2-infected adult index cases using English contact testing data. The authors used multivariable Poisson regression to investigate associations between transmission and index case and contact vaccination, and how these vary with Alpha and Delta variants (classified using S-gene detection/calendar trends) and time since second vaccination.

RESULTS: 54,667/146,243 (37.4%) PCR-tested contacts of 108,498 index cases were PCR-positive. Two doses of BNT162b2 or ChAdOx1 vaccines in Alpha index cases were independently associated with reduced PCR-positivity in contacts (aRR vs. unvaccinated = 0.32 [95%CI 0.21-0.48] and 0.48 [0.30-0.78] respectively). The Delta variant attenuated vaccine-associated reductions in transmission: two BNT162b2 doses reduced Delta transmission (aRR = 0.50 [0.39-

[11] The impact of SARS-CoV-2 vaccination on Alpha & Delta variant transmission
David W Eyre, Donald Taylor, Mark Purver, David Chapman, Tom Fowler, Koen B Pouwels, A Sarah Walker, Tim EA Peto
medRxiv 2021.09.28.21264260; doi: https://doi.org/10.1101/2021.09.28.21264260

0.65]), more than ChAdOx1 (aRR = 0.76 [0.70-0.82]). Variation in *Ct* values indicative of viral load explained 7-23% of vaccine-associated transmission reductions. Transmission reductions declined over time post-second vaccination for Delta reaching similar levels to unvaccinated individuals by 12 weeks for ChAdOx1 and attenuating substantially for BNT162b2. Protection in contacts also declined in the 3 months post-second vaccination.

CONCLUSIONS: Vaccination reduces transmission of Delta, but by less than the Alpha variant. The impact of vaccination decreased over time. Factors other than PCR *Ct* values at diagnosis are important in understanding vaccine-associated transmission reductions. Booster vaccinations may help control transmission together with preventing infections.

Level 4

Singanayagam et al (2021) [Retrospective Cohort Study] Community transmission and viral load kinetics of the SARS-CoV-2 Delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study[12]

The SARS-CoV-2 Delta (B.1.617.2) variant is highly transmissible and spreading globally, including in populations with high vaccination rates. The authors aimed to investigate transmission and viral load kinetics in vaccinated and unvaccinated individuals with mild Delta variant infection in the community.

METHODS: Between Sept 13, 2020, and Sept 15, 2021, 602 community contacts of 471 COVID-19 index cases were recruited to the Assessment of Transmission and Contagiousness of COVID-19 in Contacts cohort study and contributed 8145 upper respiratory tract samples from daily sampling for up to 20 days. Household and non-

[12] Singanayagam A, Hakki S, Dunning J, Madon KJ, Crone MA, Koycheva A, Derqui-Fernandez N, Barnett JL, Whitfield MG, Varro R, Charlett A, Kundu R, Fenn J, Cutajar J, Quinn V, Conibear E, Barclay W, Freemont PS, Taylor GP, Ahmad S, Zambon M, Ferguson NM, Lalvani A; ATACCC Study Investigators. Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study. Lancet Infect Dis. 2021 Oct 29:S1473-3099(21)00648-4. doi: 10.1016/S1473-3099(21)00648-4. Epub ahead of print. Erratum in: Lancet Infect Dis. 2021 Dec;21(12):e363. PMID: 34756186; PMCID: PMC8554486.

household exposed contacts aged 5 years or older were eligible for recruitment if they could provide informed consent and agree to self-swabbing of the upper respiratory tract. Transmission risk by vaccination status for 231 contacts exposed to 162 epidemiologically linked Delta variant-infected index cases was analysed. Viral load trajectories from fully vaccinated individuals with Delta infection (n=29) with unvaccinated individuals with Delta (n=16), Alpha (B.1.1.7; n=39), and pre-Alpha (n=49) infections were compared. Primary outcomes for the epidemiological analysis were to assess the secondary attack rate (SAR) in household contacts stratified by contact vaccination status and the index cases' vaccination status. Primary outcomes for the viral load kinetics analysis were to detect differences in the peak viral load, viral growth rate, and viral decline rate between participants according to SARS-CoV-2 variant and vaccination status.

FINDINGS: The SAR in household contacts exposed to the Delta variant was 25% (95% CI 18-33) for fully vaccinated individuals compared with 38% (24-53) in unvaccinated individuals. The median time between second vaccine dose and study recruitment in fully vaccinated contacts was longer for infected individuals (median 101 days [IQR 74-120]) than for uninfected individuals (64 days [32-97], p=0.001). SAR among household contacts exposed to fully vaccinated index cases was similar to household contacts exposed to unvaccinated index cases (25% [95% CI 15-35] for vaccinated vs 23% [15-31] for unvaccinated). 12 (39%) of 31 infections in fully vaccinated household contacts arose from fully vaccinated epidemiologically linked index cases, further confirmed by genomic and virological analysis in three index case-contact pairs. Although peak viral load did not differ by vaccination status or variant type, it increased modestly with age (difference of 0Â.39 [95% credible interval -0.03 to 0.79] in peak log10 viral load per mL between those aged 10 years and 50 years). Fully vaccinated individuals with Delta variant infection had a faster mean rate of viral load decline (0.95 log10 copies per mL per day) than did unvaccinated individuals with pre-Alpha (0.69), Alpha (0.82), or Delta (0.79) variant infections. Within individuals, faster viral load growth was correlated with higher peak viral load

(correlation 0.42 [95% credible interval 0.13 to 0.65]) and slower decline (-0.44 [-0.67 to -0.18]).

INTERPRETATION: Vaccination reduces the risk of Delta variant infection and accelerates viral clearance. Nonetheless, fully vaccinated individuals with breakthrough infections have peak viral load similar to unvaccinated cases and can efficiently transmit infection in household settings, including to fully vaccinated contacts. Host-virus interactions early in infection may shape the entire viral trajectory.

Level 4

Siedner et al (2021) [Cohort Study] [Preprint] Duration of viral shedding and culture positivity with post-vaccination breakthrough Delta variant infections[13]

Isolation guidelines for SARS-CoV-2 are largely derived from data collected prior to the emergence of the Delta variant. The authors followed a cohort of ambulatory patients with post-vaccination breakthrough SARS-CoV-2 infections with longitudinal collection of nasal swabs for SARS-CoV-2 viral load quantification, whole genome sequencing, and viral culture. All Delta variant infections (8/8, 100%) in the cohort were symptomatic, compared with 64% (9/14) of non-Delta variant infections. Delta variant breakthrough infections were characterized by higher initial viral load, longer duration of virologic shedding by PCR (median 13.5 vs 4 days, hazard ratio [HR] 0.45, 95%CI 0.17-1.17), greater likelihood of replication-competent virus at early stages of infection (6/8 [75%] vs 3/14 [23%], P=0.03), and longer duration of culturable virus (median 7 vs 3 days, HR 0.38, 95%CI 0.14-1.02) compared to non-Delta variants. Nonetheless, no individuals with Delta variant infections had replication-competent virus by day 10 after symptom onset or 24 hours after resolution of symptoms. These data support current US Center for Disease Control isolation

[13] Duration of viral shedding and culture positivity with post-vaccination breakthrough delta variant infections
Mark J. Siedner, Julie Boucau, Rebecca Gilbert, Rockib Uddin, Jonathan Luu, Sebastien Haneuse, Tammy Vyas, Zahra Reynolds, Surabhi Iyer, Grace Chamberlin, Robert H. Goldstein, Crystal M. North, Chana A. Sacks, James Regan, James P. Flynn, Manish C. Choudhary, Jatin M. Vyas, Amy Barczak, Jacob Lemieux, Jonathan Z. Li
medRxiv 2021.10.14.21264747; doi: https://doi.org/10.1101/2021.10.14.21264747

guidelines and reinforce the importance of prompt testing and isolation among symptomatic individuals with Delta variant breakthrough infections. Additional data are needed to evaluate these relationships among asymptomatic and more severe Delta variant breakthrough infections.

Level 4

Harris et al (2021) [Retrospective Cohort Study] Effect of Vaccination on Household Transmission of SARS-CoV-2 in England[14]

Vaccination against SARS-CoV-2 prevents infection and reduces the severity of COVID-19 in vaccinated persons. The authors investigated whether vaccination would reduce transmission in the household setting in the context of post-vaccination infection.

The authors compared the risk of secondary infection among unvaccinated household contacts of persons with SARS-CoV-2 infection who had received at least one dose of the ChAdOx1 nCoV-19 or BNT162b2 vaccine 21 days or more before testing positive with the risk among unvaccinated household contacts of unvaccinated persons with infection.

Between January 4 and February 28, 2021, there were 960,765 household contacts of unvaccinated index patients, and there were 96,898 secondary cases of COVID-19 (10.1%). Overall, the likelihood of household transmission was approximately 40 to 50% lower in households of index patients who had been vaccinated 21 days or more before testing positive than in households of unvaccinated index patients; the findings were similar for the two vaccines. Most of the vaccinated index patients in the data set (93%) had received only the first dose of vaccine. Assessment of infection risks among household contacts according to the timing of vaccination of the index patient showed protective effects when the vaccine had been administered at least 14 days before the positive test.

[14] Harris RJ, Hall JA, Zaidi A, Andrews NJ, Dunbar JK, Dabrera G. Effect of Vaccination on Household Transmission of SARS-CoV-2 in England. N Engl J Med. 2021 Aug 19;385(8):759-760. doi: 10.1056/NEJMc2107717. Epub 2021 Jun 23. PMID: 34161702; PMCID: PMC8262621.

Level 4

Riemersma et al (2021) [Preprint] Shedding of Infectious SARS-CoV-2 Despite Vaccination[15]

The SARS-CoV-2 Delta variant is highly transmissible and contains mutations that confer partial immune escape. The authors compared RT-PCR cycle threshold (*Ct*) data from 699 test-positive anterior nasal swab specimens from fully vaccinated (n = 310) or unvaccinated (n=389) individuals. Low *Ct* values (<25) in 212 of 310 fully vaccinated (68%) and 246 of 389 (63%) unvaccinated individuals were observed. Testing a subset of these low *Ct* samples revealed infectious SARS-CoV-2 in 15 of 17 specimens (88%) from unvaccinated and 37 of 39 (95%) from vaccinated individuals.

Level 4

Brown et al (2021) [Retrospective Cohort Study] Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings — Barnstable County, Massachusetts, July 2021[16]

During July 2021, 469 cases of COVID-19 associated with multiple summer events and large public gatherings in a town in Barnstable County, Massachusetts, were identified among Massachusetts residents. Vaccination coverage among eligible Massachusetts residents was 69%. Approximately three quarters (346; 74%) of cases occurred in fully vaccinated persons: *ie* those who had completed a two-dose course of an mRNA vaccine [Pfizer-BioNTech or Moderna]

---

[15] Shedding of Infectious SARS-CoV-2 Despite Vaccination
Kasen K. Riemersma, Brittany E. Grogan, Amanda Kita-Yarbro, Peter J. Halfmann, Hannah E. Segaloff, Anna Kocharian, Kelsey R. Florek, Ryan Westergaard, Allen Bateman, Gunnar E. Jeppson, Yoshihiro Kawaoka, David H. O'Connor, Thomas C. Friedrich, Katarina M. Grande
medRxiv 2021.07.31.21261387; doi: https://doi.org/10.1101/2021.07.31.21261387

[16] Brown CM, Vostok J, Johnson H, Burns M, Gharpure R, Sami S, Sabo RT, Hall N, Foreman A, Schubert PL, Gallagher GR, Fink T, Madoff LC, Gabriel SB, MacInnis B, Park DJ, Siddle KJ, Harik V, Arvidson D, Brock-Fisher T, Dunn M, Kearns A, Laney AS. Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings - Barnstable County, Massachusetts, July 2021. MMWR Morb Mortal Wkly Rep. 2021 Aug 6;70(31):1059-1062. doi: 10.15585/mmwr.mm7031e2. PMID: 34351882; PMCID: PMC8367314.

or had received a single dose of the Janssen vaccine ≥14 days before exposure. Genomic sequencing of specimens from 133 patients identified the B.1.617.2 (Delta) variant of SARS-CoV-2 in 119 (89%) cases, and the Delta AY.3 sublineage in one (1%) case. Overall, 274 (79%) vaccinated patients with breakthrough infection were symptomatic. Among 5 COVID-19 patients who were hospitalized, 4 were fully vaccinated; no deaths were reported.

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[17]

A retrospective cohort study of 463 residents of two skilled nursing facilities (SNFs). The investigation period started on the date of each SNF's first vaccination clinic. All residents who had not received a positive test result in the preceding 90 days, regardless of symptoms, received a once-weekly (Facility A) or twice-weekly (Facility B) PCR test. 97 cases of SARS-CoV-2 infection occurred, including 40 (41%) at Facility A and 57 (59%) at Facility B. At least one COVID-19 symptom was reported in 86 (88.7%) cases. By the date of discharge or the last day of the investigation, 304 residents (65.7%) had received two vaccine doses, 72 (15.6%) had received one dose only, and 87 (18.8%) had not received any doses. Estimated effectiveness of partial vaccination in preventing SARS-CoV-2 infection was 63% (95% CI = 33%–79%) and was similar when residents with past SARS-CoV-2 were excluded (VE = 60%, 95% CI = 30%–77%).

Level 4

Ujjainiya et al (2021) [Cohort Study] [Preprint] High failure rate of

[17] 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.

ChAdOx1 in healthcare workers during Delta variant surge: A case for continued use of masks post-vaccination[18]

Immunization is expected to confer protection against infection and severe disease for vaccinees while reducing risks to unimmunized populations by inhibiting transmission. Here, based on serial serological studies, the authors show that during a severe SARS-CoV2 Delta-variant outbreak in Delhi, 25.3% (95% CI 16.9 - 35.2) of previously uninfected, ChAdOx1-nCoV19 double vaccinated healthcare workers (HCW) were infected within a period of less than two months based on serology. Induction of anti-Spike response was similar between groups with breakthrough infection (541 U/ml, IQR 374) or not (342 U/ml, IQR 497), as was induction of neutralization activity to wild-type. Most infections were unrecognized. The Delta-variant thus causes frequent unrecognized breakthrough infections in adequately immunized subjects, reducing any herd effect of immunity, and requiring reinstatement of preventive measures such as masking.

Level 4

Laing et al (2021) [Cohort Study] [Preprint] Durability of antibody responses and frequency of clinical and subclinical SARS-CoV-2 infection six months after BNT162b2 COVID-19 vaccination in healthcare workers[19]

[18] High failure rate of ChAdOx1 in healthcare workers during Delta variant surge: A case for continued use of masks post-vaccination
Rajat Ujjainiya, Akansha Tyagi, Viren Sardana, Salwa Naushin, Nitin Bhatheja, Kartik Kumar, Joydeb Barman, Satyartha Prakash, Rintu Kutum, Akash K Bhaskar, Prateek Singh, Kumardeep Chaudhary, Menka Loomba, Yukti Khanna, Chestha Walecha, Rizwan Ahmed, Ashutosh Yadav, Archana Bajaj, Gaurav Malik, Sahar Qureshi, Swati Waghdhare, Samreen Siddiqui, Kamal Krishan Trehan, Manju Mani, Rajiv Dang, Poonam Das, Pankaj Dougall, Monica Mahajan, Sudipta Sonar, Kamini Jakhar, Reema Kumar, Mahima Tiwari, Shailendra Mani, Sankar Bhattacharyya, Sandeep Budhiraja, Anurag Agrawal, Debasis Dash, Sujeet Jha, Shantanu Sengupta
medRxiv 2021.02.28.21252621; doi: https://doi.org/10.1101/2021.02.28.21252621

[19] Durability of antibody responses and frequency of clinical and subclinical SARS-CoV-2 infection six months after BNT162b2 COVID-19 vaccination in healthcare workers
Eric D. Laing, Carol D. Weiss, Emily C. Samuels, Si'Ana A. Coggins, Wei Wang, Richard Wang, Russell Vassell, Spencer L. Sterling, Marana A. Tso, Tonia Conner, Emilie Goguet, Matthew Moser, Belinda M. Jackson-Thompson, Luca Illinik, Julian Davies, Orlando Ortega, Edward Parmelee, Monique Hollis-Perry, Santina E. Maiolatesi, Gregory Wang, Kathleen F. Ramsey, Anatalio E. Reyes, Yolanda Alcorta, Mimi A. Wong, Alyssa

A cohort study assessing immunity after BNT162b2 vaccination as part of the Prospective Assessment of SARS-CoV-2 Seroconversion (PASS) study. Healthy adult healthcare workers at the Walter Reed National Military Medical Center, Bethesda, Maryland, United States, who underwent monthly serologic assessments (n=244) were included. The geometric mean titer of vaccine-induced nAb against Delta dropped over time, from 279 (95% CI: 219-355) at peak to 38 (95% CI: 31-48) 6 months after the second dose. There was a comparable decay in binding Ab against Delta over time. Of vaccinated subjects, 26.0% (59/227) developed nucleocapsid protein seroconversion between March and August, 2021. Only two had symptomatic breakthrough infections, both of which were mild cases. A similar proportion of vaccinated HCW developed infection compared to unvaccinated HCW, but a much smaller proportion of vaccinated HCW were symptomatic.

Level 4

Novazzi et al (2021) [Cohort Study] Asymptomatic SARS-CoV-2 Vaccine Breakthrough Infections in Healthcare Workers Identified Through Routine Universal Surveillance Testing[20]

METHODS: A cohort study of healthcare workers (HCW) who were fully vaccinated with BNT162 in February 2021 at a hospital in Lombardy, Italy and had 2- or 4-weekly surveillance PCR swabs (n=2,397).

FINDINGS: Between March and August 2021, 1.5% (n=33) of HCW were detected as positive as part of the surveillance programme. All were asymptomatic. 8 HCW developed symptoms and tested positive outside of the surveillance programme. Mean time to viral clearance was one day for asymptomatic cases vs. 11 days for symptomatic cases. Mean *Ct* values were similar for both groups. Asymptomatic cases had

R. Lindrose, Christopher A. Duplessis, David R. Tribble, Allison M.W. Malloy, Timothy H. Burgess, Simon D. Pollett, Cara H. Olsen, Christopher C. Broder, Edward Mitre
medRxiv 2021.10.16.21265087; doi: https://doi.org/10.1101/2021.10.16.21265087

[20] Novazzi F, Taborelli S, Baj A, Focosi D, Maggi F. Asymptomatic SARS-CoV-2 Vaccine Breakthrough Infections in Health Care Workers Identified Through Routine Universal Surveillance Testing. Ann Intern Med. 2021 Oct 19:M21-3486. doi: 10.7326/M21-3486. Epub ahead of print. PMID: 34662153; PMCID: PMC8524618.

higher mean IgG post-vaccination compared with symptomatic cases. Because of the rapid viral clearance in asymptomatic breakthrough infections, it is possible that many other asymptomatic infections were missed.

Level 4

Uschner et al (2021) [Cohort Study] [Preprint] Breakthrough SARS-CoV-2 Infections after Vaccination in North Carolina[21]

Real-world data are needed to assess incidence and factors associated with breakthrough SARS-CoV-2 infections following vaccination.

OBJECTIVE: To estimate incidence of breakthrough infections and assess associations with risk factors using self-reported data from a large North Carolina population sample.

DESIGN: A prospective observational cohort study utilizing daily online survey data to capture information about COVID-19 symptoms, testing, and vaccination status.

SETTING: 6 healthcare systems in North Carolina with data collected between January 15, 2021 and September 24, 2021.

PARTICIPANTS: Adult study participants who reported full vaccination with a COVID-19 mRNA or Janssen non-replicating viral vector vaccine (n =16,020).

EXPOSURES: Potential community exposure to SARS-CoV-2.

MAIN OUTCOME AND MEASURES: Self-reported breakthrough infection.

RESULTS: SARS-CoV-2 infection after vaccination was self-reported in 1.9% of participants, with an incidence rate of 7.3 per 100,000 person-years. Younger age (45-64 vs. 18-44: HR (95% CI) = 0.65 (0.51

[21] Breakthrough SARS-CoV-2 Infections after Vaccination in North Carolina
Diane Uschner, Matthew Bott, Michele Santacatterina, Mihili Gunaratne, Lida M. Fette, Brian Burke, Greg Strylewicz, Sharon L. Edelstein, William H Lagarde, Kristen Miller, William S. Weintraub, Joseph Keating, John Schieffelin, Joshua Yukich, Hazel Tapp, Amina Ahmed, Andrea A. Berry, Iqra Munawar, Austin Lyles Seals, John Williamson, David Herrington, John W. Sanders, Michael Runyon, for the COVID-19 Community Research Partnership
medRxiv 2021.10.10.21264812; doi: https://doi.org/10.1101/2021.10.10.21264812

- 0.82); 65+ vs. 18-44: HR (95% CI) = 0.59 (0.39 - 0.90)), and vaccination with Janssen Ad26.COV2.S were associated with a higher risk of breakthrough infection compared to vaccination with Pfizer BNT162b2 (Ad26.COV2.S vs. BNT162b2: HR (95% CI) = 2.23 (1.40 - 3.56)), while participants vaccinated with mRNA-1273 (mRNA-1273 vs. BNT162b2: HR (95% CI) = 0.69 (0.50 – 0.96) and those residing in urban counties experienced a lower rate of SARS-CoV-2 breakthrough infection compared with those from suburban (HR (95% CI) = 1.39 (1.01 – 1.90) or rural (HR (95% CI) = 1.57 (1.16 – 2.11) counties. There was no significant association between breakthrough infection and participant sex, race, healthcare worker status, prior COVID-19 infection, routine mask use, or overall vaccination rate in the county of residence.

CONCLUSIONS AND RELEVANCE: This community-based observational study showed that the proportion of the cohort who self-report breakthrough SARS-CoV-2 infections was 7.3 events per 100,000 person-years. Younger adults, those vaccinated with Janssen Ad26.COV2.S, and those residing in suburban or rural counties were at higher risk of breakthrough infections and should be targeted for additional risk mitigation strategies to decrease community transmission.

Level 4

Saiag et al (2021) Immunogenicity of a BNT162b2 vaccine booster in healthcare workers[22]

The Pfizer-BioNTech mRNA COVID19 vaccine (BNT162b2) was found to be highly efficacious against symptomatic SARS-CoV-2 infection, with a vaccine efficacy of 94% in a randomised clinical trial and an effectiveness of 94–95% in real-world studies in Israel. Similar effectiveness rates (97% against symptomatic infection and 86% against asymptomatic infection) were found in healthcare workers. Waning vaccine effectiveness, concurrent with the spread of the Delta

[22] Saiag E, Goldshmidt H, Sprecher E, Ben-Ami R, Bomze D. Immunogenicity of a BNT162b2 vaccine booster in health-care workers. Lancet Microbe. 2021 Oct 11;2(12):e650. doi: 10.1016/S2666-5247(21)00272-X. Epub ahead of print. PMID: 34661180; PMCID: PMC8504922.

(B.1.617.2) variant, prompted the Israeli Ministry of Health to recommend, in early August 2021, a booster dose for individuals aged 60 years or older who were administered a second dose of the vaccine at least 5 months earlier.

The authors report on the effect of a third dose of BNT162b2 on anti-SARS-CoV-2 IgG concentrations in employees of the Tel-Aviv Medical Center vaccinated between August 1 and August 18, 2021. Anti-Spike protein concentrations were established with the ADVIA Centaur SARS-CoV-2 IgG assay, which provides an index value up to 150.00, where an index equal to or greater than 1.00 is considered reactive (positive) for SARS-CoV-2 IgG antibodies.

A total of 346 healthcare workers received a BNT162b2 booster dose. The median age was 67 years (IQR 64–73 years); 215 were women and 131 were men. The median time between the first and third vaccine doses was 32.0 weeks (IQR 31.7–32.1 weeks). All workers had their antibody concentrations measured at baseline, and a second sample was obtained approximately 10 days after the booster dose was administered (median 10 days, IQR 10–11 days). The median ADVIA Centaur SARS-CoV-2 IgG index at baseline was 3.67 (IQR 2.00–7.10), and increased to >150 (the upper limit of quantification) in 95.7% of vaccine recipients. Only two recipients were non-reactive after immunisation for reasons that are as of yet unknown; a follow-up study is ongoing. No serious adverse events were reported.

These results show high vaccine immunoreactivity in healthcare workers who are generally immunocompetent. Further follow-up is needed to ascertain the effect of a third dose on clinical outcomes such as symptomatic illness, hospitalisation, and death.

The cohort was older than most Irish HCW (median age = 67 years, IQR 64–73).

Level 4

Bianchi et al (2021) [Cohort Study] BNT162b2 mRNA COVID-19 Vaccine Effectiveness in the Prevention of SARS-CoV-2 Infection and Symptomatic Disease in Five-Month Follow-Up: A

Retrospective Cohort Study[23]

This retrospective cohort study evaluated the effectiveness of the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine against documented SARS-CoV-2 infection and symptomatic diseases in the medium- to long-term. Healthcare workers at Bari Policlinico University Hospital, Italy who completed the vaccination schedule were matched with HCW who had refused vaccination; the two groups were followed for 5 months (January–May 2021).

Vaccine effectiveness (VE) against infection was 97.7% (95.4–99.0%) at 14–34 days after the first dose, and 94.8% (87.0–97.8%), 83.0% (65.0–92.0%), and 81.0% (42.0–94.0%) at 14–41, 42–69, and >69 days, respectively, after the second dose. The estimated VE for documented symptomatic disease was 99.2% (96.4–99.8%) at 14–34 days after the first dose and 97.2% (90.3–99.2%), 85.0% (63.0–94.2%), and 88.0% (42.0–97.6%) at 14–41, 42–69, and >69 days, respectively, after the second dose. During a median follow-up period of 139 days (IQR 135–143) the incidence of documented infection was 19.9 per 10,000 person days in the unvaccinated group and 0.7 per 10,000 person days in the vaccinated group (IRR 0.03 [95%CI: 0.02–0.05; p < 0.0001]). The incidence of symptomatic disease was 12.4 per 10,000 person days in the unvaccinated group and 0.3 per 10,000 person days in the vaccinated group (IRR 0.02 [95%CI: 0.01–0.04; p < 0.0001]). There were 9 hospitalizations (8 unvaccinated, 1 vaccinated). The authors assert that efforts to increase vaccination rates should be strengthened, including mandatory vaccination for HCW and greater incentives to increase vaccine acceptance by the general population.

Level 4

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

[23] Bianchi FP, Tafuri S, Migliore G, Vimercati L, Martinelli A, Lobifaro A, Diella G, Stefanizzi P, Group OBOTCRW. BNT162b2 mRNA COVID-19 Vaccine Effectiveness in the Prevention of SARS-CoV-2 Infection and Symptomatic Disease in Five-Month Follow-Up: A Retrospective Cohort Study. Vaccines (Basel). 2021 Oct 7;9(10):1143. doi: 10.3390/vaccines9101143. PMID: 34696252; PMCID: PMC8538139.

study[24]

BNT162b2 mRNA and ChAdOx1 nCOV-19 adenoviral vector vaccines have been rapidly rolled out in the United Kingdom 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 healthcare 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 England. 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 of SIREN were captured. Data cut-off for this analysis was February 5, 2021. The follow-up period was from December 7, 2020 to February 5, 2021. The primary outcomes were vaccinated participants for the vaccine coverage analysis and SARS-CoV-2 infection confirmed by a PCR test for the vaccine effectiveness analysis.

FINDINGS: 23 324 participants from 104 sites met the inclusion criteria for this 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; 8203 (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

[24] 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.

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 8 infections per 10 000 person-days), and nine infections 7 days after the second dose (incidence density of 4 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% (74-96) 7 days after two 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 B1.1.7 and shows effectiveness against this variant.

Level 4

Bouton et al (2021) [Cohort Study] Coronavirus Disease 2019 Vaccine Impact on Rates of Severe Acute Respiratory Syndrome Coronavirus 2 Cases and Postvaccination Strain Sequences Among Healthcare Workers at an Urban Academic Medical Center: A Prospective Cohort Study[25]

The authors examine the impact of vaccination on SARS-CoV-2 case rates and viral diversity among healthcare workers (HCW) during a

[25] Bouton TC, Lodi S, Turcinovic J, Schaeffer B, Weber SE, Quinn E, Korn C, Steiner J, Schechter-Perkins EM, Duffy E, Ragan EJ, Taylor BP, Miller N, Davidoff R, Hanage WP, Connor J, Pierre C, Jacobson KR. Coronavirus Disease 2019 Vaccine Impact on Rates of Severe Acute Respiratory Syndrome Coronavirus 2 Cases and Postvaccination Strain Sequences Among Health Care Workers at an Urban Academic Medical Center: A Prospective Cohort Study. Open Forum Infect Dis. 2021 Sep 17;8(10):ofab465. doi: 10.1093/ofid/ofab465. PMID: 34646910; PMCID: PMC8500299.

high community prevalence period.

METHODS: In this prospective cohort study, HCW received 2 doses of BNT162b2 or mRNA-1273. Confirmed cases among HCW from 9 December 2020 to 23 February 2021 were included in the analysis. Weekly SARS-CoV-2 rates per 100,000 person-days and by time from first injection (1-14 and ≥15 days) were compared with surrounding community rates. Viral genomes were sequenced. HCW were screened daily for COVID-19 symptoms and tested if symptomatic. Asymptomatic testing was available to HCW for workplace exposures, following out-of-state travel, and per request. Routine asymptomatic serial screening for SARS-CoV-2 infection was not performed.

RESULTS: Post-vaccination SARS-CoV-2 cases occurred in 96 of 7109 (1.3%) HCW who received at least 1 dose, 17 of 5913 (0.3%) HCW given both doses, and 329 of 3481 (9.5%) unvaccinated HCW. 70% (67/96) of post-vaccination SARS-CoV-2 cases occurred within 14 days of the initial dose.

CONCLUSIONS: These results demonstrate an early positive impact of vaccines on SARS-CoV-2 case rates. Post-vaccination isolates did not show unusual genetic diversity or selection for mutations of concern.

Level 4

Hulme et al (2021) [Cohort Study] [Preprint] Comparative effectiveness of ChAdOx1 versus BNT162b2 COVID-19 vaccines in Health and Social Care workers in England: A cohort study using OpenSAFELY[26]

OBJECTIVE: To compare the effectiveness of the BNT162b2 mRNA (Pfizer-BioNTech) and the ChAdOx1 (Oxford-AstraZeneca) COVID-19

[26] Comparative effectiveness of ChAdOx1 versus BNT162b2 COVID-19 vaccines in Health and Social Care workers in England: a cohort study using OpenSAFELY
William J Hulme, Elizabeth J Williamson, Amelia Green, Krishnan Bhaskaran, Helen I McDonald, Christopher T Rentsch, Anna Schultze, John Tazare, Helen J Curtis, Alex J Walker, Laurie Tomlinson, Tom Palmer, Elsie Horne, Brian MacKenna, Caroline E Morton, Amir Mehrkar, Louis Fisher, Seb Bacon, Dave Evans, Peter Inglesby, George Hickman, Simon Davy, Tom Ward, Richard Croker, Rosalind M Eggo, Angel YS Wong, Rohini Mathur, Kevin Wing, Harriet Forbes, Daniel Grint, Ian J Douglas, Stephen JW Evans, Liam Smeeth, Chris Bates, Jonathan Cockburn, John Parry, Frank Hester, Sam Harper, Jonathan AC Sterne, Miguel Hernán, Ben Goldacre
medRxiv 2021.10.13.21264937; doi: https://doi.org/10.1101/2021.10.13.21264937

vaccines against infection and COVID-19 disease in health and social care workers.

DESIGN: A cohort study emulating a comparative effectiveness trial using linked primary care, hospital and COVID-19 surveillance records available within the OpenSAFELY-TPP research platform.

PARTICIPANTS: 317,341 health and social care workers vaccinated between 4 January and 28 February, 2021, registered with a GP practice using the TPP SystmOne clinical information system in England and not clinically extremely vulnerable.

INTERVENTIONS: Vaccination with either BNT162b2 or ChAdOx1 administered as part of the national COVID-19 vaccine roll-out.

MAIN OUTCOME MEASURES: Recorded SARS-CoV-2 positive test, or COVID-19 related Accident and Emergency attendance or hospital admission occurring within 20 weeks of vaccination.

RESULTS: The cumulative incidence of each outcome was similar for both vaccines during the first 20 weeks post-vaccination. The cumulative incidence of recorded SARS-CoV-2 infection 6 weeks after vaccination with BNT162b2 was 19.2 per 1000 people (95%CI 18.6 to 19.7) and with ChAdOx1 was 18.9 (95%CI 17.6 to 20.3), representing a difference of -0.24 per 1000 people (95%CI -1.71 to 1.22). The difference in the cumulative incidence per 1000 people of COVID-19 Accident and Emergency attendance at 6 weeks was 0.01 per 1000 people (95%CI -0.27 to 0.28). For COVID-19 hospital admission, the difference was 0.03 per 1000 people (95%CI -0.22 to 0.27).

CONCLUSIONS: The authors found no substantial differences in the incidence of SARS-CoV-2 infection or COVID-19 disease up to 20 weeks after vaccination. Incidence dropped sharply after 3-4 weeks and there were very few COVID-19 hospital attendance and admission events after this period. This is in line with expected onset of vaccine-induced immunity, and suggests strong protection against COVID-19 disease for both vaccines.

Level 4

Keehner et al (2021) SARS-CoV-2 Infection after Vaccination in

Healthcare Workers in California[27]

Both the University of California, San Diego (UCSD) and the University of California, Los Angeles (UCLA) health systems began to vaccinate healthcare workers on December 16, 2020. On December 2, in addition to defining a low threshold for testing of symptomatic persons, UCSD mandated that asymptomatic healthcare workers undergo weekly testing by PCR assay of nasal swabs. On December 26, UCLA instituted an optional testing program for asymptomatic healthcare workers with PCR assay of nasal swabs. This program has allowed for increased detection of asymptomatic SARS-CoV-2 infections after vaccination.

Pooled data were obtained in de-identified format from an electronic employee health record system at UCSD and UCLA.

From December 16, 2020, through February 9, 2021, a total of 36,659 healthcare workers received the first dose of vaccine, and 28,184 of these persons (77%) received the second dose. Among vaccinated healthcare workers, 379 unique persons tested positive for SARS-CoV-2 at least 1 day after vaccination, and the majority (71%) of these persons tested positive within the first 2 weeks after the first dose. After receiving both vaccinations, 37 healthcare workers tested positive; of these workers, 22 had positive test results 1 to 7 days after the second dose. Only 8 healthcare workers tested positive 8 to 14 days after the second vaccination, and 7 tested positive 15 or more days after the second vaccination. As of February 9, a total of 5455 healthcare workers at UCSD and 9535 at UCLA had received the second dose 2 or more weeks previously; these findings correspond to a positivity rate of 0.05%.

In the study cohort, the absolute risk of testing positive for SARS-CoV-2 after vaccination was 1.19% among healthcare workers at UCSD and 0.97% among those at UCLA; these rates are higher than the risks reported in the trials of mRNA-1273 vaccine and BNT162b2 vaccine.

[27] Keehner J, Horton LE, Pfeffer MA, Longhurst CA, Schooley RT, Currier JS, Abeles SR, Torriani FJ. SARS-CoV-2 Infection after Vaccination in Health Care Workers in California. N Engl J Med. 2021 May 6;384(18):1774-1775. doi: 10.1056/NEJMc2101927. Epub 2021 Mar 23. PMID: 33755376; PMCID: PMC8008750.

Level 5

Bergwerk M et al (2021) COVID-19 Breakthrough Infections in Vaccinated Healthcare Workers[28]

Despite the high efficacy of the BNT162b2 messenger RNA vaccine against SARS-CoV-2, rare breakthrough infections have been reported, including infections among healthcare workers. Data are needed to characterize these infections and define correlates of breakthrough and infectivity.

METHODS: At the largest medical center in Israel, the authors identified breakthrough infections by performing extensive evaluations of healthcare workers who were symptomatic (including mildly symptomatic) or had known infection exposure. These evaluations included epidemiologic investigations, repeat RT-PCR assays, antigen-detecting rapid diagnostic testing (Ag-RDT), serologic assays, and genomic sequencing. Correlates of breakthrough infection were assessed in a case-control analysis. The study matched patients with breakthrough infection who had antibody titers obtained within a week before SARS-CoV-2 detection with four to five uninfected controls and used generalized estimating equations to predict the geometric mean titers among cases and controls and the ratio between the titers in the two groups. The authors also assessed the correlation between neutralizing antibody titers and N gene cycle threshold (*Ct*) values with respect to infectivity.

RESULTS: Among 1497 fully vaccinated healthcare workers for whom RT-PCR data were available, 39 SARS-CoV-2 breakthrough infections were documented. Neutralizing antibody titers in case patients during the peri-infection period were lower than those in matched uninfected controls (case-to-control ratio, 0.361; 95% CI, 0.165 to 0.787). Higher peri-infection neutralizing antibody titers were associated with lower infectivity (higher *Ct* values). Most

[28] Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, Mandelboim M, Levin EG, Rubin C, Indenbaum V, Tal I, Zavitan M, Zuckerman N, Bar-Chaim A, Kreiss Y, Regev-Yochay G. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. N Engl J Med. 2021 Oct 14;385(16):1474-1484. doi: 10.1056/NEJMoa2109072. Epub 2021 Jul 28. PMID: 34320281; PMCID: PMC8362591.

breakthrough cases were mild or asymptomatic, although 19% had persistent symptoms (>6 weeks). The B.1.1.7 (Alpha) variant was found in 85% of samples tested. A total of 74% of case patients had a high viral load (*Ct* value, <30) at some point during their infection; however, of these patients, only 17 (59%) had a positive result on concurrent Ag-RDT. No secondary infections were documented.

CONCLUSIONS: Among fully vaccinated healthcare workers, the occurrence of breakthrough infections with SARS-CoV-2 was correlated with neutralizing antibody titers during the peri-infection period. Most breakthrough infections were mild or asymptomatic, although persistent symptoms did occur.

Level 5

Deng et al (2021) [Case Series] Breakthrough Infections with Multiple Lineages of SARS-CoV-2 Variants Reveals Continued Risk of Severe Disease in Immunosuppressed Patients[29]

The pandemic of COVID-19 caused by SARS-CoV-2 infection continues to spread around the world. Vaccines that elicit protective immunity have reduced infection and mortality; however, new viral variants are arising that may evade vaccine-induced immunity or cause disease in individuals who are unable to develop robust vaccine-induced responses. Investigating the role of viral variants in causing severe disease, evading vaccine-elicited immunity and infecting vulnerable individuals is important for developing strategies to control the pandemic.

Here, the authors report 14 breakthrough infections of SARS-CoV-2 in vaccinated individuals at Loyola University Medical Center, Chicago between 29 March 2021 and 29 April 2021 with symptoms ranging from asymptomatic/mild (6/14) to severe disease (8/14). High viral loads with a median *Ct* value of 19.6 were detected in the nasopharyngeal specimens from subjects regardless of disease

[29] Deng X, Evdokimova M, O'Brien A, Rowe CL, Clark NM, Harrington A, Reid GE, Uprichard SL, Baker SC. Breakthrough Infections with Multiple Lineages of SARS-CoV-2 Variants Reveals Continued Risk of Severe Disease in Immunosuppressed Patients. Viruses. 2021 Sep 1;13(9):1743. doi: 10.3390/v13091743. PMID: 34578324; PMCID: PMC8472867.

severity. Sequence analysis revealed four distinct virus lineages, including Alpha and Gamma variants of concern. Immunosuppressed individuals were more likely to be hospitalized after infection (p = 0.047); however, no specific variant was associated with severe disease. These results highlight the high viral load that can occur in asymptomatic breakthrough infections and the vulnerability of immunosuppressed individuals to post-vaccination infections by diverse variants of SARS-CoV-2.

Level 5

Teran et al (2021) [Case Series] Postvaccination SARS-CoV-2 infections among skilled nursing facility residents and staff members - Chicago, Illinois, December 2020-March 2021[30]

The authors describe 22 cases of breakthrough SARS-CoV-2 infection among over 14,000 fully vaccinated skilled nursing facility (SNF) residents and staff. The majority of infections were asymptomatic or were associated with mild symptoms, and there was no intra-facility spread. The authors suggest that post-vaccination breakthrough infections are rare, but also confirm that vaccines do not offer 100% protection, even in non-immunosuppressed hosts. Nearly two thirds (14 of 22; 64%) of persons with breakthrough infections were asymptomatic; two residents were hospitalized because of COVID-19, and one died.

Level 5

Farinholt et al (2021) Transmission event of SARS-CoV-2 Delta variant reveals multiple vaccine breakthrough infections[31]

OBJECTIVE: To determine the SARS-CoV-2 variant responsible for 6

[30] Teran RA, Walblay KA, Shane EL, Xydis S, Gretsch S, Gagner A, Samala U, Choi H, Zelinski C, Black SR. Postvaccination SARS-CoV-2 Infections Among Skilled Nursing Facility Residents and Staff Members - Chicago, Illinois, December 2020-March 2021. MMWR Morb Mortal Wkly Rep. 2021 Apr 30;70(17):632-638. doi: 10.15585/mmwr.mm7017e1. PMID: 33914721; PMCID: PMC8084122.
[31] Farinholt T, Doddapaneni H, Qin X, Menon V, Meng Q, Metcalf G, Chao H, Gingras MC, Avadhanula V, Farinholt P, Agrawal C, Muzny DM, Piedra PA, Gibbs RA, Petrosino J. Transmission event of SARS-CoV-2 delta variant reveals multiple vaccine breakthrough infections. BMC Med. 2021 Oct 1;19(1):255. doi: 10.1186/s12916-021-02103-4. PMID: 34593004; PMCID: PMC8483940.

cases of vaccine breakthrough in Houston, Texas.

DESIGN: Nasopharyngeal swabs from suspected vaccine breakthrough cases were tested for SARS-CoV-2. Positive samples were then sequenced by Swift Normalase Amplicon Panels to determine the causal variant.

PARTICIPANTS: 6 fully vaccinated patients were investigated. Three males and three females ranged from 53 to 69 years old. One patient suffered from diabetes while three others were classified as overweight. No significant other comorbidities were identified. None of the patients had a history of failed vaccination.

FINDINGS: Viral sequencing revealed 6 vaccinated patients were infected with the Delta SARS-CoV-2 variant. With no histories of vaccine breakthrough, this suggests that the Delta variant may possess immune evasion in patients that received the Pfizer BNT162b2, Moderna mRNA-1273 or Covaxin BBV152 vaccines.

INTERPRETATION: The Delta variant may pose the highest risk out of any currently circulating SARS-CoV-2 variants with increased transmissibility over the Alpha variant and possible vaccine breakthrough.

Level 5

Keehner et al (2021) Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce[32]

In December 2020, the University of California San Diego Health (UCSDH) workforce experienced a dramatic increase in SARS-CoV-2 infections. Vaccination with mRNA vaccines began in mid-December 2020; by March, 76% of the workforce had been fully vaccinated, and by July, the percentage had risen to 87%. Infections had decreased dramatically by early February 2021. Between March and June, fewer than 30 healthcare workers tested positive each month. However, coincident with the end of California's mask mandate on June 15 and

[32] Keehner J, Horton LE, Binkin NJ, Laurent LC, Pride D, Longhurst CA, Abeles SR, Torriani FJ. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. N Engl J Med. 2021 Sep 30;385(14):1330-1332. doi: 10.1056/NEJMc2112981. Epub 2021 Sep 1. PMID: 34469645; PMCID: PMC8451183.

the rapid dominance of the B.1.617.2 (Delta) variant that first emerged in mid-April and accounted for over 95% of UCSDH isolates by the end of July, infections increased rapidly, including cases among fully vaccinated persons. Institutional review board approval was obtained for use of administrative data on vaccinations and case-investigation data to examine mRNA SARS CoV-2 vaccine effectiveness.

UCSDH has a low threshold for SARS-CoV-2 testing, which is triggered by the presence of at least one symptom during daily screening or by an identified exposure, regardless of vaccination status. From March 1 to July 31, 2021, a total of 227 UCSDH healthcare workers tested positive for SARS-CoV-2 by RT-qPCR assay of nasal swabs; 130 of the 227 workers (57.3%) were fully vaccinated. Symptoms were present in 109 of the 130 fully vaccinated workers (83.8%) and in 80 of the 90 unvaccinated workers (88.9%). The remaining 7 workers were only partially vaccinated. No deaths were reported in either group; one unvaccinated person was hospitalized for SARS-CoV-2–related symptoms.

Vaccine effectiveness was calculated for each month from March through July; the case definition was a positive PCR test and one or more symptoms among persons with no previous COVID-19 infection. Vaccine effectiveness exceeded 90% from March through June but fell to 65.5% (95% CI, 48.9 to 76.9) in July. July case rates were analyzed according to the month in which workers with COVID-19 completed the vaccination series; in workers completing vaccination in January or February, the attack rate was 6.7 per 1000 persons (95% CI, 5.9 to 7.8), whereas the attack rate was 3.7 per 1000 persons (95% CI, 2.5 to 5.7) among those who completed vaccination during the period from March through May. Among unvaccinated persons, the July attack rate was 16.4 per 1000 persons (95% CI, 11.8 to 22.9).

The SARS CoV-2 mRNA vaccines, BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna), have previously shown efficacy rates of 95% and 94.1%, respectively, in their initial clinical trials, and for the BNT162b2 vaccine, sustained albeit slightly decreased effectiveness (84%) 4 months after the second dose. In England, where an extended dosing interval of up to 12 weeks was used, Lopez Bernal et al reported

a preserved vaccine effectiveness of 88% against symptomatic disease associated with the Delta variant. As observed by others in populations that received mRNA vaccines according to standard Emergency Use Authorization intervals, these data suggest that vaccine effectiveness against any symptomatic disease is considerably lower against the Delta variant and may wane over time since vaccination.

The dramatic change in vaccine effectiveness from June to July is likely to be due to both the emergence of the Delta variant and waning immunity over time, compounded by the end of masking requirements in California and the resulting greater risk of exposure in the community. These findings underline the importance of rapidly reinstating nonpharmaceutical interventions such as indoor masking and intensive testing strategies in addition to continued efforts to increase vaccinations as strategies to prevent avoidable illness and deaths and to avoid mass disruptions to society during the spread of the Delta variant. Furthermore, if the findings on waning immunity are verified in other settings, booster doses may be indicated.

Level 5

Tyagi et al (2021) Breakthrough COVID-19 infections after vaccinations in healthcare and other workers in a chronic care medical facility in New Delhi, India[33]

BACKGROUND AND AIMS: To ascertain the number of breakthrough COVID-19 infections after vaccination in a chronic care Diabetes healthcare facility in India.

METHODS: Review of rigorously maintained data of vaccinations, health status, symptoms of COVID-19 and RT-PCR testing of all staff in the healthcare facility from January 16, 2021 to date.

RESULTS: Out of 123 employees, 113 were vaccinated (Covaxin, 28; Covishield, 85). Second dose was completed in 107 (94.7%) and first dose in 6 persons (5.3%). Symptomatic COVD-19 infections occurred

[33] Tyagi K, Ghosh A, Nair D, Dutta K, Singh Bhandari P, Ahmed Ansari I, Misra A. Breakthrough COVID19 infections after vaccinations in healthcare and other workers in a chronic care medical facility in New Delhi, India. Diabetes Metab Syndr. 2021 May-Jun;15(3):1007-1008. doi: 10.1016/j.dsx.2021.05.001. Epub 2021 May 3. PMID: 33991805; PMCID: PMC8091733.

in 19 persons (16.9%) post any dose of vaccine. Symptomatic breakthrough infections > 14 days after the second dose occurred in 15 persons (13.3%). With the exception of one HCW who required hospitalisation, the other 14 had mild COVID-19 disease.

Level 5

Chen et al (2021) Excess mortality associated with the COVID-19 pandemic among Californians 18-65 years of age, by occupational sector and occupation: March through November 2020[34]

METHODS AND FINDINGS: Using autoregressive integrated moving average models and California Department of Public Health data representing 356,188 decedents 18-65 years of age who died between January 1, 2016 and November 30, 2020, the authors estimated pandemic-related excess mortality by occupational sector and occupation, with additional stratification of the sector analysis by race/ethnicity. During these first 9 months of the COVID-19 pandemic, working-age adults experienced 11,628 more deaths than expected, corresponding to 22% relative excess and 46 excess deaths per 100,000 living individuals. Sectors with the highest relative and per-capita excess mortality were Food/Agriculture (39% relative excess; 75 excess deaths per 100,000), Transportation/Logistics (31%; 91 per 100,000), Manufacturing (24%; 61 per 100,000), and Facilities (23%; 83 per 100,000). Across racial and ethnic groups, Latino working-age Californians experienced the highest relative excess mortality (37%) with the highest excess mortality among Latino workers in Food and Agriculture (59%; 97 per 100,000). Black working-age Californians had the highest per-capita excess mortality (110 per 100,000), with relative excess mortality highest among Transportation/Logistics workers (36%). Asian working-age Californians had lower excess mortality overall, but notable relative excess mortality among Health/Emergency workers (37%), while White Californians had high per-capita excess deaths among Facilities

[34] Chen YH, Glymour M, Riley A, Balmes J, Duchowny K, Harrison R, Matthay E, Bibbins-Domingo K. Excess mortality associated with the COVID-19 pandemic among Californians 18-65 years of age, by occupational sector and occupation: March through November 2020. PLoS One. 2021 Jun 4;16(6):e0252454. doi: 10.1371/journal.pone.0252454. PMID: 34086762; PMCID: PMC8177528.

workers (70 per 100,000). Health and Emergency workers had a relative excess of 17% (95% PI: 15-19%) and 30 (95% PI: 27-34) excess deaths per 100,000 living individuals. 395/611 (64.6%) excess deaths in HCW were recorded as due to COVID 19.

CONCLUSIONS: Certain occupational sectors are associated with high excess mortality during the pandemic, particularly among racial and ethnic groups disproportionately affected by COVID-19. The authors assert that in-person essential work is a likely venue of transmission of coronavirus infection and must be addressed through vaccination and strict enforcement of health orders in workplace settings.

Level 5

Cucunawangsih et al (2021) Post-vaccination cases of COVID-19 among healthcare workers at Siloam Teaching Hospital, Indonesia[35]

Healthcare workers (HCW) are at increased risk of exposure to SARS-CoV-2 compared with the general population. Therefore, they are given priority for the COVID-19 vaccine in the national COVID-19 vaccination campaign in Indonesia. However, although the daily number of new COVID-19 cases remains high, and data regarding the efficacy of the vaccine in healthcare settings remain unavailable, vaccinated HCW remain at risk of COVID-19 infection and further transmission.

OBJECTIVE: To identify cases of COVID-19 among vaccinated HCW at Siloam Teaching Hospital, Indonesia via active and passive surveillance conducted by the hospital's COVID-19 infection prevention and control unit.

RESULTS: Of 1040 HCW who had received two doses of the COVID-19 vaccine, 13 (1.25%) tested positive for SARS-CoV-2 RNA on RT-PCR assay between 2 and 11 days (median 5 days) after the second vaccination.

CONCLUSION: Laboratory-confirmed COVID-19 among vaccinated

[35] Cucunawangsih C, Wijaya RS, Lugito NPH, Suriapranata I. Post-vaccination cases of COVID-19 among healthcare workers at Siloam Teaching Hospital, Indonesia. Int J Infect Dis. 2021 Jun;107:268-270. doi: 10.1016/j.ijid.2021.05.020. Epub 2021 May 13. PMID: 33992761; PMCID: PMC8117534.

HCW soon after the second vaccination indicates that HCW remain at risk of COVID-19. Therefore, the presence of symptoms soon after full vaccination cannot be considered as vaccine-related symptoms, and regular COVID-19 testing should be conducted among HCW.

Level 7

Hetemäki et al (2021) [Case Report] An outbreak caused by the SARS-CoV-2 Delta variant (B.1.617.2) in a secondary care hospital in Finland, May 2021[36]

An outbreak caused by the SARS-CoV-2 Delta variant (B.1.617.2) spread from one inpatient in a secondary care hospital to three primary care facilities, resulting in 58 infections including 18 deaths in patients and 45 infections in healthcare workers. Only one of the deceased cases was fully vaccinated. 17/18 patients who died were unvaccinated; 18 (40%) of HCW cases were fully-vaccinated. Transmission occurred despite the use of personal protective equipment by the healthcare workers, as advised in national guidelines, and a high two-dose COVID-19 vaccination coverage among permanent staff members in the COVID-19 cohort ward.

Level 7

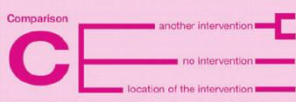
Orsi A et al (2021) [Case Report] Outbreak of SARS-CoV-2 Lineage 20I/501Y.V1 in a Nursing Home Underlines the Crucial Role of Vaccination in Both Residents and Staff[37]

The authors report on an epidemiological and serological investigation of a SARS-CoV-2 outbreak in an Italian nursing home. Among the nursing home residents, all but one (19/20) were vaccinated against SARS-CoV-2. In mid-February 2021, a non-

[36] Hetemäki I, Kääriäinen S, Alho P, Mikkola J, Savolainen-Kopra C, Ikonen N, Nohynek H, Lyytikäinen O. An outbreak caused by the SARS-CoV-2 Delta variant (B.1.617.2) in a secondary care hospital in Finland, May 2021. Euro Surveill. 2021 Jul;26(30):2100636. doi: 10.2807/1560-7917.ES.2021.26.30.2100636. PMID: 34328076; PMCID: PMC8323455.
[37] Orsi A, Domnich A, Pace V, Ricucci V, Caligiuri P, Bottiglieri L, Vagge R, Cavalleri MA, Orlandini F, Bruzzone B, Icardi G. Outbreak of SARS-CoV-2 Lineage 20I/501Y.V1 in a Nursing Home Underlines the Crucial Role of Vaccination in Both Residents and Staff. Vaccines (Basel). 2021 Jun 2;9(6):591. doi: 10.3390/vaccines9060591. PMID: 34199663; PMCID: PMC8228066.

vaccinated staff member of the nursing home was diagnosed with a SARS-CoV-2 infection. Following the outbreak investigation, a total of 70% (14/20) of residents aged 77-100 years were found positive. A phylogenetic analysis showed that the outbreak was caused by the SARS-CoV-2 variant of concern 202012/01. However, all but one of the positive subjects (13/14) were fully asymptomatic. The only symptomatic patient was a vaccinated 86-year-old female with a highly compromised health background and deceased approximately two weeks later. A subsequent serological investigation showed that the deceased patient was the only vaccinated subject that did not develop the anti-Spike protein antibody response. Although the available mRNA SARS-CoV-2 vaccine was not able to prevent several asymptomatic infections, it was able to avert most symptomatic disease cases caused by the SARS-CoV-2 variant of concern 202012/01.

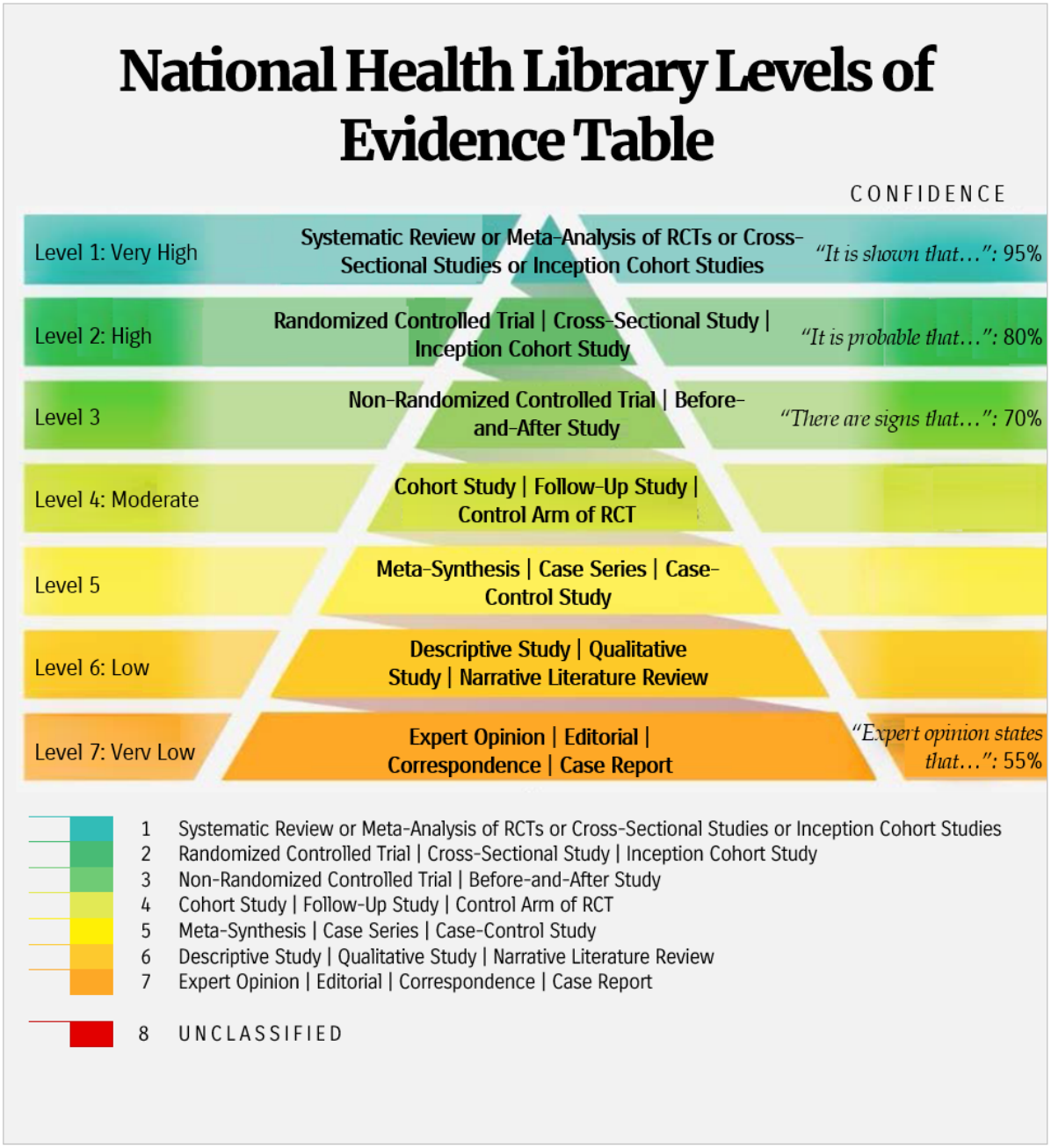
The following PICO(T) was used as a basis for the evidence summary:

	Healthcare workers
	COVID-19 vaccination
	No vaccination
	SARS-CoV-2 transmission, infection (asymptomatic and symptomatic), severe disease, death.

The following search strategy was used:

1 exp Coronavirinae/ 66981
2 coronavirus disease 2019/ 154274
3 coronavirus.ab,ti. 71806
4 "corona virus".ab,ti. 2500
5 (Wuhan adj3 virus).ab,ti. 134
6 ("2019-nCoV" or "2019 ncov").ab,ti. 1406
7 "severe acute respiratory syndrome coronavirus 2".ab,ti. 16546
8 ("2019" and (new or novel) and coronavirus).ab,ti. 12038
9 (covid19 or "covid 19").ab,ti. 160843
10 (delta and variant).ab,ti. 1684
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 214798
12 exp vaccination/ 185759
13 exp vaccine/ 356466
14 "vaccin*".ab,ti. 395574
15 ("Pfizer BNT162b2" or "Moderna mRNA-1273" or "Covaxin BBV152").ab,ti. 49
16 (pfizer or moderna or janssen or covaxin).ab,ti. 14862
17 12 or 13 or 14 or 15 or 16 527261
18 exp virus transmission/ 74072
19 ((transmission or transmit* or dispers* or spread*) adj3 (virus* or viral or disease* or infection*)).ab,ti. 136960
20 18 or 19 191979
21 11 and 17 and 20 3129
22 mortality/ or hospital mortality/ or mortality rate/ 912704
23 death/ 277121
24 clinical outcome/ 200528
25 hospitalization/ 427545
26 (mortality or death or hospitali*).ab,ti. 2429701
27 ((treatment or patient or disease) adj1 outcomes).ab,ti. 125317
28 (severe adj1 (disease or illness)).ab,ti. 39478
29 ((ICU or "intensive care" or "critical care") adj2 (admitted or admission*)).ab,ti. 45651
30 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 3130025
31 21 and 30 1082
32 limit 31 to yr="2021" 515

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



† Brendan Leen, Area Library Manager, HSE South [Author, Editor]; Isabelle Delaunois Librarian, University Hospital Limerick [Author]; Emma Quinn , Librarian, St. Luke's General Hospital, Kilkenny [Author]; Siobhan McCarthy, Information Specialist, Health Intelligence Unit, Strategic Planning and Transformation [Author, Editor]; NIAC Sub-Group Contributors: Philippa White, Peter O'Reilly, Margaret Brennan and Oisin Hennigan.