

Literature screening report

COVID-19 vaccines and post-vaccination data: Literature update (9)

<i>Report submission date:</i>	30.09.2021
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Abstract

This report addresses the most relevant data on COVID-19 vaccines literature as of 27 September 2021. The current report addresses vaccine effectiveness against the Delta (B.1.617.2) variant, methodological issues in assessing vaccine effectiveness, an in-depth overview of both mRNA vaccines (Pfizer-BioNTech and Moderna), protection of booster doses against COVID-19 infections, the effects of vaccination on transmissibility of SARS-CoV-2, the characteristics of breakthrough infections, and maternal vaccinations. To conclude, the report highlights the latest SARS-CoV-2 vaccine development information on COVID-19 vaccine candidates.

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Preamble

A large number of scientific publications become available on a daily basis, reflecting the rapid development of knowledge and progress of science on COVID-19 related issues. Leading authorities should base decisions or policies on this knowledge; hence they need to master the actual state of this knowledge. Due to the large number of publications shared daily, decision makers heavily depend on accurate summaries of these publications, in the different public health domains. Therefore, the authors of this report were mandated by the Swiss School of Public Health plus (SSPH+), upon request of the Federal Office of Public Health (FOPH), to inform the FOPH on recent findings from the literature.

Background

At the start of 2021, vaccination rollouts demonstrated high vaccine effectiveness against the original SARS-CoV-2 strain; however, concerns about vaccine immunity waning and vaccine effectiveness against variants of concern (VOC), particularly the Delta (B.1.167.2) strain, long-term immunogenicity, and viral transmissibility arise. The latest data has shown COVID-19 vaccines to be safe and highly effective against severe COVID-19 infection, hospitalizations, and deaths. This can be exemplified in a case example from Singapore, a country that has 82% of its population fully vaccinated; of the ~11,000 new infections registered over the last four weeks, 98% of cases were asymptomatic or mild¹. Despite COVID-19 vaccines demonstrating satisfactory effectiveness against severe COVID-19 infection, hospitalization, and deaths, a small difference in the effectiveness between the two mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna) have been reported, especially against the Delta variant. Multiple studies, including the latest effectiveness study on mRNA COVID-19 vaccine among U.S. health care personnel², have consistently reported higher effectiveness for participants vaccinated with the mRNA-1273 vaccine (Moderna).

Although rare, vaccine breakthrough cases are expected to be reported in the real-world setting, especially now with the rise of the Delta variant worldwide. Reporting breakthrough infections and studying its characteristics such as the clinical outcomes, transmission, and viral kinetics of those infections provide epidemiologists, scientists and public health professionals crucial information that can help mitigate the ongoing pandemic. Reports on breakthrough infections have emphasized how sub-populations such as immunocompromised, older adults, and individuals with multiple underlying medical conditions are most at risk of serious illness³. As a result, multiple countries have begun administering booster doses to those vulnerable groups while other countries have expanded their booster dose campaign to the general population.

As WHO EUL approved vaccines continue to be administered throughout the world, the scientific community continues to develop and test the efficacy, safety, tolerability, and immunogenicity of numerous COVID-19 vaccine candidates.

This report thus focuses on published studies that covered the questions/points below.

¹ Update on local COVID-19 situation (19 September 2021). *Ministry of Health Singapore*. [https://www.moh.gov.sg/news-highlights/details/update-on-local-covid-19-situation-\(19-sep-2021\)](https://www.moh.gov.sg/news-highlights/details/update-on-local-covid-19-situation-(19-sep-2021)) [accessed 23 September 2021].

² Effectiveness of mRNA Covid-19 Vaccine among U.S. Health Care Personnel. *The New England Journal of Medicine*. https://www.nejm.org/doi/full/10.1056/NEJMoa2106599?query=featured_home

³ Risk of severe breakthrough Covid-19 higher for seniors and people with underlying conditions. *CNN Health*. <https://edition.cnn.com/2021/09/08/health/severe-breakthrough-cases-cdc-studies/index.html>

Questions addressed

- What is the effectiveness of vaccines against the Delta variant (B.1.617.2)?
 - What are the latest updates on the Pfizer-BioNTech and Moderna vaccines and how do they compare?
 - What are some characteristics of SARS-CoV-2 breakthrough infections?
 - What do we know about the protection of booster doses against COVID-19 infections?
 - What are the latest updates regarding pregnancy and maternal COVID-19 vaccination?
 - What is the status of SARS-CoV-2 vaccine candidates?
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Methodology

The current report screened the databases of PubMed, Embase, medRxiv, bioRxiv, SSRN, Cochrane, and clinical trial databases such as ClinicalTrials and WHO Trial registry for vaccine-related literature as of 30 September 2021. We focused on studies that would help to discuss the points raised above. For more information on the methodology, please refer to previous reports.

Results and Findings

What is the effectiveness of vaccines against the Delta variant (B.1.617.2)?

Summary:

Given the rise of the more infectious and transmissible Delta variant (B.1.617.2) throughout the world⁴ and reports of vaccine immunity waning over time⁵, it is important to continuously track real-world vaccine effectiveness, particularly to determine the vaccine-induced protection against severe disease, hospitalization, and death. Initial real-world observational studies demonstrated that all six WHO EUL authorised vaccines (BNT162b2/Comirnaty [Pfizer-BioNTech]; mRNA-1273 /Spikevax [Moderna]; Vaxzevria/ ChAdOx1 nCoV-19/ AZD1222/ Covishield [AstraZeneca]; Johnson & Johnson Covid-19 vaccine [Janssen]; BBIBP-CorV [Sinopharm]; CoronaVac [Sinovac]) demonstrated similar effectiveness in real-world settings to their respective phase III clinical trials and further efficacy studies⁶. Both mRNA vaccines demonstrated slightly reduced real-life effectiveness than their respective clinical data efficacy⁷, fluctuating at around **90%** effectiveness⁸. Both AstraZeneca's ChAdOx1 nCoV-19 and Janssen's Johnson & Johnson Covid-19 vaccine demonstrate similar vaccine effectiveness to their efficacy trials, **85%**⁹ and **69%**¹⁰, respectively, while Sinovac's CoronaVac fared better in real-world settings than reported in its efficacy data¹¹. Little data on Sinopharm's BBIBP-CorV vaccine effectiveness has been published thus far.

The Center for Disease Control and Prevention (CDC) reported that prior to the Delta variant's predominance, unvaccinated individuals were infected at **11.1 (95% CI, 7.8 – 15.8)** times the rate of vaccinated individuals; post-Delta variant predominance, the risk of infection for unvaccinated

⁴ Tracking of variants. *GISAID*. <https://www.gisaid.org/hcov19-variants/>

⁵ COVID vaccine immunity is waning — how much does that matter? *Nature*. <https://www.nature.com/articles/d41586-021-02532-4>

⁶ COVID-19 vaccines in the WHO's Emergency Use Listing EUL: Report (4). *Federal Office of Public Health*. <https://www.bag.admin.ch/bag/en/home/suche.html#vaccine%20reports>

⁷ 94.5% for BNT162b2/ Comirnaty. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *New England Journal of Medicine*. <https://doi.org/10.1056/NEJMoa2034577>; 94.1% for mRNA-1273/ Spikevax efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *New England Journal of Medicine*. <https://doi.org/10.1056/NEJMoa2035389>

⁸ Coronavirus disease 2019 (COVID-19) mRNA vaccine effectiveness in asymptomatic healthcare workers. *Infection Control & Hospital Epidemiology*. <https://doi.org/10.1017/ice.2021.287>

⁹ An observational cohort study on the incidence of SARS-CoV-2 infection and B.1.1.7 variant infection in healthcare workers by antibody and vaccination status. *Clinical Infectious Diseases*. <https://doi.org/10.1093/cid/ciab608>

¹⁰ Effectiveness of the Single-Dose Ad26.COVS.S COVID Vaccine. *medRxiv*. <https://doi.org/10.1101/2021.09.10.21263385>

¹¹ Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. *New England Journal of Medicine*. <https://doi.org/10.1056/NEJMoa2107715>

individuals reduced to **4.6 (2.5 – 8.5)** times the rate of those vaccinated¹². Recently published data on vaccine effectiveness have demonstrated vaccine protection waning against SARS-CoV-2 (asymptomatic or symptomatic) infection over time^{13,14}. Despite reports of reduced effectiveness against SARS-CoV-2 infection with the circulating Delta variant, **vaccine effectiveness remains high against severe infection, hospitalization, and death for all vaccines**. The latest data on vaccine effectiveness against the Delta variant is summarised below.

Results:

mRNA vaccines: Prior to the Delta variant's predominance throughout the globe, mRNA vaccine effectiveness had an estimated range of **86% to 94%** effectiveness mark in the US (1-3) and between **89% to 95%** in several countries including the UK, Israel, Canada, and Western Europe (4-8). Since the Delta variant took over as the dominant strain, various studies reported reductions in vaccine effectiveness estimates throughout the world. For example, a study conducted by the CDC investigated mRNA vaccine effectiveness against SARS-CoV-2 infection observed that age-adjusted vaccine effectiveness declined from **91.8%** in May (pre-Delta variant predominance) to **75%** in July (Delta variant predominance)(2). These findings are consistent with another US study that demonstrated reductions in vaccine effectiveness against infection from April (**BNT162b2: 86.1%; mRNA-1273: 93.3%**) to July (**BNT162b2: 76%; mRNA-1273: 86.3%**) (3). Further US- (9) and UK-based (10) studies corroborated the above-mentioned findings where reductions in effectiveness were most pronounced in older adults (≥ 65 years) and individuals with underlying comorbidities. Interestingly, a UK study reported that there was no evidence of reduced effectiveness in the Delta-dominant period when compared to the Alpha-dominant period (Alpha: **78%**; Delta: **80%**; $p=0.5$) **80%** for the Pfizer vaccine (11), while a US-veterans study reported an increase in mRNA vaccine effectiveness: from **84.1% (95% CI, 74.1-90.2)** in February-June to **89.3% (95% CI, 80.1-94.3)** in July-August (2, 9, 11-13). Despite contradicting effectiveness estimates against SARS-CoV-2 infection, mRNA vaccines have been demonstrated to maintain high effectiveness rates against SARS-CoV-2 hospitalization and ICU admission (2, 9, 11-13). A CDC study demonstrated sustained mRNA vaccine effectiveness against hospitalization over a 24-week period from March until July 2021 [VE 2-12 weeks after second dose= **86% (95% CI, 82-90)**; VE 12-24 weeks after second dose= **84% (95% CI, 77-90)**; $p=0.854$] (14). Vaccine effectiveness against hospitalization was **87% (95% CI, 83-90)** during the pre-Delta variant months (March-May) and **84% (95% CI, 79-89)**, during the Delta-predominant

¹² Of those vaccinated, 92% received either Pfizer/ BioNTech or Moderna. The remainder (8%) received the Janssen (Johnson & Johnson) vaccine mRNA vaccine. Covid-19: Unvaccinated face 11 times risk of death from delta variant, CDC data show. BMJ. <https://www.bmj.com/content/374/bmj.n2282.long>; Monitoring Incidence of COVID-19 Cases, Hospitalizations, and Deaths, by Vaccination Status — 13 U.S. Jurisdictions, April 4–July 17, 2021. *Morbidity & Mortality Weekly Report*. <https://www.cdc.gov/mmwr/volumes/70/wr/mm7037e1.htm>

¹³ Durability analysis of the highly effective BNT162b2 vaccine against COVID-19. *medRxiv*. <https://www.medrxiv.org/content/10.1101/2021.09.04.21263115v1>

¹⁴ Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. *medRxiv*. <https://www.medrxiv.org/content/10.1101/2021.08.06.21261707v3>

months (June-July). The authors additionally reported sustained, albeit lower, vaccine immunity in older (≥ 65 years; numerical data not reported, only graphical) immunocompromised individuals [**63% (95% CI, 44-76)**](14). Other studies provide evidence that mRNA vaccine effectiveness was consistently lower in individuals aged 65 and above than younger adults (typically 18-64 years) (9, 10); vaccine effectiveness against hospitalizations among adults aged ≥ 65 years was **79.8% (95% CI, 67.7-87.4)** than adults aged 18-64 (**95.1% (95% CI, 89.1-97.8)**)(15).

AstraZeneca: In general, AstraZeneca's ChadOx1 nCoV-12/ Vaxzevria demonstrates lower vaccine effectiveness than both mRNA vaccines (10, 11). Recently published vaccine effectiveness data have demonstrated varied results. Since the Delta variant became the predominant strain in the UK, the Office of National Statistics Covid-19 Infection Survey reported that effectiveness against infection had decreased from **79% (95% CI, 56-90)** in the Alpha-dominant period to **67% (95% CI, 62-71)** in the Delta-dominant period; this reduction however, was not significant ($p=0.23$) (11). A Scottish study (REACT-SCOT case control study) reported that vaccine effectiveness did not vary over calendar time: vaccine effectiveness in June-July 2021 was similar to that of March-April (13). In the Delta-predominant period, vaccine effectiveness was calculated to be **91% (95% CI, 86-95)** against severe COVID-19 illness and **88% (95% CI, 85-90)** against hospitalization or death due to COVID-19. The study additionally reported that vaccine efficacy decreases rapidly over the first two months after the second dose, but stabilised over time (13). Lastly, the ChAdOx1 nCoV-19/ Vaxzevria demonstrates higher vaccine effectiveness in younger than older age groups, higher effectiveness against the Alpha than the Delta variant, and higher effectiveness against severe illness than symptomatic infection (10).

Johnson & Johnson: Ad26.COV2.S vaccine effectiveness has been reported to be high and sustained over time: effectiveness was reported to be **78% (95% CI, 73-82)** against SARS-CoV-2 infection and **85% (95% CI, 73-91)** against hospitalizations among U.S. states with high Delta variant incidence during the months of June and July (16). Interestingly, another U.S. study conducted prior to the Delta variant's predominance (surveillance period: 1 January to 22 June) reported lower AD26.COV2.S effectiveness rates compared to the above-mentioned study: **68% (95% CI, 50-79)** against SARS-CoV-2 hospitalization and **73% (95% CI, 59-82)** against SARS-CoV-2 infection leading to an emergency department or urgent care visit (17). These pre-Delta findings, however, should be interpreted with caution due to small number of observations.

Inactivated virus vaccines (Sinopharm and Sinovac):

As of 27 September, little data has been published on either Sinopharm's BBIBP-CorV or Sinovac's CoronaVac's effectiveness against the Delta variant. A study conducted in Jiangsu, China analysed

the effect of inactivated virus vaccines against the B.1.617 strain and concluded that a single dose did not offer clinically meaningful protection against severe illness, while two doses provided an adjusted risk reduction of **88% (95% CI, 55-98)** in developing severe SARS-CoV-2 illness (18). The study did not specify which inactivated COVID-19 vaccines were used.

No real-world studies have thus far been published in English on Sinopharm's vaccine effectiveness (19), while two studies analysed CoronaVac's vaccine effectiveness against the B.1.617.2 strain. In Guangzhou, China, full-dose vaccine effectiveness was estimated to be **58% (95% CI, 15-81)** against SARS-CoV-2 infection and **70.2% (95% CI, 29.6-89.3)** against moderate COVID-19 disease (20), and in Guangdong province, China, CoronaVac's adjusted vaccine effective was estimated to be **69.5% (95% CI, 42.8-96.3)** against COVID-19 pneumonia and **100%** against severe/ critical illness (21). The majority of CoronaVac's effectiveness studies were about the wild-type strain (22, 23) or the Gamma (P.1) variant (24, 25) [see COVID-19 vaccines and post-vaccination data: Literature Update (8) [30.08.2021] for further information¹⁵]. Moreover, some studies assessed the CoronaVac's safety and efficacy upon the administration of booster doses (26) and heterologous booster doses (27-29). The administration of a third CoronaVac booster dose, 6 months or more after the second dose, effectively increased neutralizing antibody levels [GMT increased to **137.9 (95% CI, 99.9-190.4)** from **4.1 (95%CI, 3.3-5.2)**] against SARS-CoV-2 (26). Lastly, one study reported that the administration of a Vaxzevria booster shot to fully vaccinated CoronaVac individuals yielded comparable antibody levels [**797 U/mL (95% CI, 598.7-1062)**] to individuals who received two doses of Vaxzevria [**818 U/mL (95% CI, 662.5-1010)**] (29), while another study demonstrated that the AZD1222 booster shot (administered 1-2 months after the second CoronaVac shot) was nine-fold greater (**7,947 U/mL**) than that of fully vaccinated AZD1222 individuals (28).

What are the latest updates on the Pfizer-BioNTech and Moderna vaccines and how do they compare?

Summary: Following reports by Pfizer-BioNTech and Moderna that protection from their COVID-19 vaccines wanes over time, scientists and public health officials are following the latest updates regarding both vaccines' immunogenicity, duration of protection, and incidences of breakthrough infection. Pfizer-BioNTech confirmed that their vaccine's protection declined six to eight months after the administration of their vaccine's second dose, falling from an estimated effectiveness of **96.2%**

¹⁵ COVID-19 vaccines and post-vaccination dates; as of 08/30/2021. Federal Office of Public Health.
<https://www.bag.admin.ch/bag/de/home/suche.html#literature%20update%208>

one week after full inoculation to **83.7%** four months later¹⁶. Conversely, Moderna presented Phase III data in early August that the vaccine's efficacy remains durable (**93%**) six months after the second dose¹⁷. However, recently published data reported vaccinated individuals (median ≤ 8 months) had lower risks of [**36% (95% CI, 17-52 incidence rate reduction)**] developing breakthrough infections than those vaccinated more than a year ago (median ≥ 13 months)¹⁸, underpinning the need for a possible third booster dose among the general population (see booster dose section below). Recent studies have observed that Moderna's vaccine protection may provide longer immunity and protection against SARS-CoV-2 infection than Pfizer-BioNTech's BNT162b2. This section summarises the latest data on both Pfizer-BioNTech and Moderna's vaccines, keeping in mind that comparison across vaccines, particularly across populations, is subject to sources of confounding bias.

Results:

Immunogenicity

A Belgian study compared the neutralization level after two doses of either Pfizer-BioNTech's BNT162b2 or Moderna's mRNA-1273 vaccine and observed that the mRNA-1273 vaccine produced significantly **higher humoral immunogenicity** compared to the BNT162b2 vaccine (30). Further research however needs to be conducted to correlate humoral immunity to duration of protection, risk of transmission, and breakthrough infection. Moderna's higher neutralization levels could be attributed to higher doses of mRNA (100 ug) encapsulated within the mRNA-1273 vaccine than the BNT162b2 vaccine (30 ug) or longer intervals between the first and second shots (Moderna: 28 days; Pfizer-BioNTech: 21 days) (3).

Breakthrough infections

A study conducted across five U.S. states reported that Moderna's mRNA-1273 vaccine demonstrated a two-fold risk reduction against breakthrough infection compared to BNT162b2 (3). Within the state of Florida, risk of a breakthrough infection occurring was 60% lower for mRNA-1273 vaccine recipients than BNT162b2 recipients within the Delta-predominant period in July (3).

Real-world effectiveness

Recently published mRNA vaccine data have demonstrated varied results in relation to both Pfizer-BioNTech and Moderna vaccine effectiveness. A study that was conducted in five U.S. states over the month of July (period of high Delta variant prevalence) demonstrated that the BNT162b2 vaccine

¹⁶ Pfizer and Moderna say Covid vaccine protection wanes over time. *Financial Times*. <https://www.ft.com/content/8d42600f-7da3-452a-a7ab-22735c6f73c7>

¹⁷ Moderna reports second quarter fiscal year 2021 financial results and provides business updates. *Moderna*.

<https://investors.modernatx.com/news-releases/news-release-details/moderna-reports-second-quarter-fiscal-year-2021-financial>

¹⁸ Moderna Highlights New Clinical Data on its COVID-19 Vaccine. *Moderna*. <https://investors.modernatx.com/news-releases/news-release-details/moderna-highlights-new-clinical-data-its-covid-19-vaccine>

had an effectiveness of **42% (95% CI, 13-62)** against B.1.617.2 infection (corroborating Israeli vaccine data (31)), while the Moderna vaccine had an effectiveness of **76% (95% CI, 58-87)** (3). The authors concluded that both vaccines' reduced effectiveness could be due to "waning immunity over time" or the "dynamic landscape of SARS-CoV-2 variants". Other studies also demonstrated lower BNT162b2 vaccine effectiveness when compared to Moderna's mRNA-1273 vaccine: adjusted vaccine effectiveness against COVID-19 related hospitalization over a six-month period (1 February to 6 August) was **91.6% (95% CI, 83.5-95.7)** for mRNA-1273 and **83.4% (95% CI, 74-89.4)** for BNT162b2 (15), while another study observed that (>120 days after the second dose) the Moderna vaccine was **92% (95% CI, 87-96)** effective at preventing hospitalization, while the Pfizer-BioNTech vaccine was only **77% (95% CI, 67-84)** effective (32). Other US-based studies report that two doses of either the mRNA-1273 or BNT162b2 vaccine provide similar effectiveness among ≥ 50 year old adults [effectiveness against hospitalization: **87% Pfizer-BioNTech; 91% Moderna**] (17) and nursing home residents [effectiveness against infection: **52.4% Pfizer-BioNTech; 50.6% Moderna**] (9) during the Delta variant period. Lastly, vaccine induced immunity against symptomatic B.1.617.2 COVID-19 infection waned more for the Pfizer-BioNTech vaccine (from **92.4%** one week after the administration of the second dose to **80.3% (95% CI, 79.9-80.6)** 10-14 weeks after the second dose than the Moderna vaccine (from **95.2%** to **90.3% (95% CI, 67.2-97.1)**)(10) .

What are some characteristics of SARS-CoV-2 vaccine breakthrough infections?

Summary:

COVID-19 vaccines are very effective at preventing infections, serious illnesses, hospitalizations, and death; however, since they are not 100% effective at preventing infection, some fully vaccinated individuals can still develop COVID-19. Although rare, these breakthrough infections have been reported in partially and fully vaccinated individuals and have risen in number, especially with the emergence of the Delta variant. In order to fully assess and control the ongoing COVID-19 pandemic, information on the characteristics of breakthrough infections such as clinical outcomes, transmission, and viral kinetics is essential. Overall, the incidence of severe or critical COVID-19 illness and the durations of both infectious virus shedding and symptoms are significantly reduced in vaccinated individuals. According to an analysis of UK data from National Immunisation Management Service (NIMS) and the Coronavirus Clinical Information Network (COCIN) between December 2020 and July 2021, 84% of hospitalized patients with COVID-19 had

not received a COVID-19 vaccine, 13% had received their first vaccine, and 3% their second¹⁹. Additionally, some data indicates that vaccination shortens the duration of time of high transmission potential and minimizes symptom duration²⁰.

Results:

Clinical Outcomes:

A study identifying patients admitted to the hospital with SARS-CoV-2 from real-world data collected by the Yale New Haven System from 23 March to 1 July 2021, identified a total of 969 patients with confirmed positive PCR test for SARS-CoV-2 (33). Out of the total cases, **18%** (172 patients) had received at least one dose of a COVID-19 vaccine (BNT162b2, mRNA-1273, or Ad.26.COVS.2.S) at the time of admission to the hospital. From those patients, **54 were fully vaccinated** and were evaluated for illness severity. Among the fully vaccinated patients, **46%** (25 patients) were **asymptomatic**, **7%** (4 patients) had **mild disease**, **20%** (11 patients) had **moderate disease**, and **26%** (14 patients) had **severe or critical illness**. Out of the 14 patients with severe or critical illness, four required intensive care, one required mechanical ventilation, and three died (33).

Another study assessing the rate of symptomatic infection and serious illness among breakthrough infections from 12 February to 29 July 2021 from the Washoe Health Country District health database, identified a total of 6399 COVID-19 cases of which 338 (**5.3%**) were classified as breakthrough infections (34). Out of the breakthrough infections, **85.5%** were **symptomatic**, **5%** required **hospitalization**, and **zero Covid deaths** were reported. Overall, the rate of breakthrough infections was more than **18-fold lower** than the rate of infections among unvaccinated individuals (34).

Another similar study aiming to determine risk factors and outcomes associated with breakthrough infections in the national COVID-19 database in Qatar from 23 December 2020 to 28 March 2021, detected 456 breakthrough infections among which **60.7%** were males, and more than 1 comorbid conditions were present in **61.2%** of the vaccinated persons (35). Severe disease was recorded in **10.5%** of persons with breakthrough infections and factors associated with severe disease or death included **increasing age** and **presence of symptoms at baseline**. Overall, fully vaccinated people who developed a breakthrough infection were significantly less likely to experience severe disease or death compared with matched unvaccinated people who developed infection (35).

Transmission:

¹⁹ Covid-19: How is vaccination affecting hospital admissions and deaths?. *BMJ*. <https://www.bmj.com/content/374/bmj.n2306>

²⁰ Longitudinal analysis of SARS-CoV-2 vaccine breakthrough infections reveal limited infectious virus shedding and restricted tissue distribution. *medRxiv*. <https://www.medrxiv.org/content/10.1101/2021.08.30.21262701v1>

A cohort study analysing the transmission risk by vaccination status between September 2020 and August 2021, observed that the household secondary attack rate for fully vaccinated contacts exposed to Delta was **19.7%** (95% CI, 11.6-31.3), compared with **35.7%** (95% CI, 16.4-61.2) in the unvaccinated (36). When analysing the transmission pattern between vaccinated participants, the results demonstrated that **one third** of infections in Delta-exposed contacts arose from fully vaccinated index cases and one-half of infected contacts were also fully vaccinated. Additionally, in the Delta-exposed contacts, one third of the reported infections came from fully vaccinated index cases (36).

Another study investigating whether vaccination would reduce transmission in the household setting in the context of breakthrough infections in England, identified that 96,898 secondary cases out of 960,765 household contacts (**10.1%**) were reported in households where the index case was not vaccinated before testing positive (37). Additionally, there were 196 secondary cases in 3,424 contacts (**5.72%**) where the index case received the ChAdOx1 nCoV-19 vaccine 21 days or more before testing positive, and 371 secondary cases in 5,939 contacts (**6.25%**) where the index case received the BNT162b2 vaccine 21 days or more before testing positive. The unadjusted odds ratio for being a secondary case if the index case was vaccinated with ChAdOx1 nCoV-19 21 days or more before testing positive (vs. index case not vaccinated) was **0.55** (95% CI, 0.46-0.67), and **0.57** (95% CI, 0.49-0.65) for BNT162b2. Overall, the results show that contacts of vaccinated cases have lower odds of being secondary cases if the index case was vaccinated 14 days or more before testing positive after controlling for calendar week, and that 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 (37).

Another study evaluated data from 194,362 household members of 144,525 health care workers who had been employed during March 2020 through November 2020 (38). From the results, COVID-19 cases were less common among household members of vaccinated health care 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 health care worker's second dose, the rate in household members was lower still (2.98 cases per 100 person-years). Relative to the period before each health care worker was vaccinated, the hazard ratio for a household member to become infected was **0.70** (95% CI, 0.63- 0.78) for the period beginning 14 days after the first dose and **0.46** (95% CI, 0.30-0.70) for the period beginning 14 days after the second dose. Overall, the evidence from the study suggested that vaccination may reduce transmission as vaccinated healthcare workers

were associated with a decrease in documented cases of COVID-19 among their household members (38).

Viral Kinetics:

Besides analysing the secondary attack rates and transmission patterns in vaccinated participants, a few studies have tried studying the viral dynamics and infectious shedding of breakthrough infections. This was the case of the UK study on community transmission and viral load kinetics (36). When comparing the viral loads of vaccinated and unvaccinated individuals, the peak viral load was similar in vaccinated and unvaccinated individuals with Delta variant infection; however, vaccinated Delta cases had a significantly **faster viral load decline** than unvaccinated Alpha or Delta cases. Despite the reduction of Delta infections and changes in viral kinetics through COVID-19 vaccinations, **fully vaccinated individuals with breakthrough infections still demonstrated peak viral loads similar to unvaccinated cases and efficiently transmitted the SARS-CoV-2 virus in a household setting, including to fully vaccinated contacts** (36).

Another study examining the viral dynamics and infectious virus shedding in adults infected with SARS-CoV-2 at varying stages of vaccination, observed that the duration of both infectious virus shedding, and symptoms were significantly reduced in vaccinated individuals compared to unvaccinated individuals. Additionally, the study also observed that in some breakthrough infections (2 patients), viral RNA was detectable in the saliva for 5 to 10 days while remaining undetectable or detectable at very low level in nasal swabs (39).

What do we know about the protection of booster doses against COVID-19 infections?

Summary:

With the emergence of new highly infectious variants of concerns such as the Delta variant and the reported waning vaccine-elicited immunity^{21,22}, many countries have started the administration of booster doses. Since its administration in Israel, the United States, the UAE, and many more, data on the immunogenicity, tolerability, and safety of the booster doses has become available for many COVID-19 vaccines such as BNT162b2, mRNA1273, ChAdOx1 nCov-19, Janssen, and CoronaVac.

²¹ Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel. *medRxiv*.

<https://www.medrxiv.org/content/10.1101/2021.08.24.21262423v1>

²² Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary study. *medRxiv*.

<https://www.medrxiv.org/content/10.1101/2021.07.29.21261317v1>

Overall, the different booster shots have proven to increase the neutralizing titers against SARS-CoV-2 and its different variants and to show consistent tolerability. Nevertheless, data on the protection of booster doses against COVID-19 was not available before publishing the data on BNT162b2 in ≥60-years-old individuals in Israel²³. The study showed promising results as the administration of the BNT162b2 booster dose was estimated to possibly bring the vaccine efficacy, in booster recipients, to approximately 95%, a value similar to the original vaccine efficacy reported against the Alpha variant.

Results:

BNT162b2:

Results from Israeli data on the administration of a third (booster) dose of BNT162b2 in persons aged 60 years of age or older who had the full jab of BNT162b2 at least 5 months earlier showed promising results in lowering the rates of confirmed COVID-19 and severe illnesses (40). According to the study, 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, 10.4-12.3)** and with an absolute between-group difference in the rate of confirmed infection of **86.6 infections per 100,000 person-days**. Regarding severe illnesses, the booster dose group also had a lower rate of severe illness than the non-booster group by a **factor of 19.5 (95% CI, 12.9-29.5)** and with an absolute between-group difference in the rate of severe illness of **7.5 cases per 100,000 person-days** (40). Additionally, the booster group reported having a lower rate of confirmed infection than the non-booster group by a **factor of 7 to 20** on each day during the period from 12 to 25 days after the receipt of the booster dose (40). Overall, the results suggest that the administration of a booster dose in an older population (60 years and older) could possibly bring the vaccine efficacy among booster recipients back to a similar value reported in the original 95% vaccine efficacy (40). Results from Israeli data on the administration of a third (booster) dose of BNT162b2 in persons aged 60 years of age or older who had the full jab of BNT162b2 at least 5 months earlier showed promising results in lowering the rates of confirmed COVID-19 and severe illnesses (40). According to the study, 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, 10.4-12.3)** with an absolute between-group difference in the rate of confirmed infection of **86.6 infections per 100,000 person-days**. Regarding severe illnesses, the booster dose group also had a lower rate of severe illness than the non-booster group by a **factor of 19.5 (95% CI, 12.9-29.5)** and with an absolute in between-group difference rate of **7.5 cases per 100,000 person-days** (40).

²³ Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. *NEJM*.

<https://www.nejm.org/doi/full/10.1056/NEJMoa2114255>

Other COVID-19 vaccines:

Although many other COVID-19 vaccines have on-going clinical trials on booster doses with preliminary results on the immunogenicity and tolerability of their booster doses, there is currently no available data on the protection of those doses against COVID-19. Any new results will be added in the upcoming reports as data becomes available.

What are the latest updates regarding pregnancy and maternal COVID-19 vaccination?

Summary: Compared to non-pregnant persons, pregnant persons that become infected with SARS-CoV-2 are at an increased risk of developing a severe COVID-19 infection leading to hospitalization and ICU admission^{24,25}, increased rates of pre-term birth²⁶ and COVID-19 related death²⁷. Additionally, there have been reports of increasing COVID-19 infection severity and hospitalizations in pregnancy cases with the Delta (B.1.617.2) variant surge²⁸. The U.S. state of Mississippi reported that at least eight unvaccinated women had died of COVID-19 related complications within a period of two months from 25 July to 18 September, possibly related to the rise in the Delta variant predominance²⁹. Many countries are endorsing pregnant women to get vaccinated, however, because pregnant and lactating women were excluded from participating in clinical trials, concerns are raised regarding the vaccine's safety and efficacy on pregnant persons. Thus far, data remains limited on the vaccine's safety and efficacy in pregnancy, however studies have demonstrated that vaccinating pregnant mothers is safe and highly effective (41). As stated by Shimabukuro et al.'s (2021) study, "more longitudinal follow-up, including follow-up of large numbers of women vaccinated earlier in pregnancy, is necessary to inform maternal, pregnancy, and infant outcomes" (p. 2273)³⁰.

²⁴ COVID-19 in pregnancy: What we know from the first year of the pandemic. *Biochimica et Biophysica Acta (BBA) – Molecular Basis of Disease*. <https://www.sciencedirect.com/science/article/pii/S0925443921001812?via%3Dihub>

²⁵ mRNA Covid-19 Vaccines in Pregnant Women. *The New England Journal of Medicine*.
https://www.nejm.org/doi/full/10.1056/NEJMe2107070?query=recirc_curatedRelated_article

²⁶ Pregnancy and birth outcomes after SARS-CoV-2 vaccination in pregnancy. *American Journal of Obstetrics & Gynecology: Maternal-Fetal Medicine*. [https://www.ajogfm.org/article/S2589-9333\(21\)00162-2/fulltext](https://www.ajogfm.org/article/S2589-9333(21)00162-2/fulltext)

²⁷ Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status — United States, January 22–October 3, 2020. *Morbidity & Mortality Weekly Report*.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7643892/>

²⁸ Increasing severity of COVID-19 in pregnancy with Delta (B.1.617.2) variant surge. *American Journal of Obstetrics and Gynecology*. [https://www.ajog.org/article/S0002-9378\(21\)01005-X/pdf](https://www.ajog.org/article/S0002-9378(21)01005-X/pdf)

²⁹ Mississippi says Covid-19 deaths in pregnant women are rising -- and it's pleading with them to get vaccinated. *CNN Health*.
<https://edition.cnn.com/2021/09/17/health/mississippi-pregnant-women-covid-vaccine/index.html>

³⁰ Preliminary findings of mRNA COVID-19 vaccine safety in pregnant persons. *The New England Journal of Medicine*.
<https://www.nejm.org/doi/full/10.1056/nejmoa2104983>

Results:

Safety

A rapid systematic review evaluated the safety of COVAX listed COVID-19 vaccines and found no evidence of pregnancy-associated safety concerns for any of the vaccines (Novavax, Sanofi/ GSK, Clover, Johnson & Johnson, Moderna, Pfizer-BioNTech, CureVac and AstraZeneca) (42). Another study analysed self-reported postvaccination adverse events among pregnant persons (43): **9.4% of all 827 completed pregnancies** were preterm births, **3.2%** of neonates were small for their gestational age, and were 46 reports of spontaneous abortions. No neonatal deaths were reported (43). The authors stated that the calculated proportions of self-reported adverse events in persons vaccinated against COVID-19 were **similar to adverse events reported among pregnant women before the COVID-19 pandemic** (43), while another study reported that the odds of being vaccinated against COVID-19 **did not increase a woman's chances of having a spontaneous abortion** (44). The above mentioned findings are additionally corroborated by a longitudinal CDC study (45). Overall, all WHO EUL approved vaccines are safe for adults including those with pre-existing conditions including, diabetes, asthma, auto-immune disorders, and chronic infections (46).

Effectiveness

An Israeli study conducted from December 2020 to June 2021 confirmed that BNT162b2 vaccine effectiveness was not lower among pregnant woman than among the general population: effectiveness against symptomatic SARS-CoV-2 infection and hospitalization 7-56 days after the second dose among pregnant women was **97% (CI, 91-100)** and **89% (95% CI, 43-100)**, respectively (47). mRNA vaccines were reported to generate similar humoral immunity in pregnant and lactating women, with immunogenicity and reactogenicity similar to that observed in nonpregnant women (48). Additionally, studies have reported vaccine induced SARS-CoV-2 binding and neutralizing antibodies are able to be transmitted from vaccinated mothers to their babies via passive transplacental transfer or through breastmilk (49). The transfer of maternal antibodies could provide beneficial infant protection against SARS-CoV-2 infection, however further studies are needed to confirm immunogenicity level (50).

What is the status of SARS-CoV-2 vaccine candidates?

Summary:

Apart from the 6 WHO EUL approved vaccines, numerous vaccine candidates such as Novavax, Sputnik V, CureVac, Clover COVID-19 vaccine, and ZyCoV-D have shown promising results in terms of their immunogenicity, tolerability, and efficacy. A short summary of the results and news on new and ongoing clinical trials is found down below.

Results:

Novavax:

Novavax's recombinant protein vaccine (NVX-CoV2373) has not yet been authorised by WHO EUL or other authorising countries. Following the status of COVID-19 vaccines within WHO EUL/ PQ evaluation process, Novavax's rolling application has been accepted for review as of 19 August by the WHO³¹. The European Medicines Agency (EMA) is also reviewing Novavax's rolling application³². On 8 September, Novavax announced the enrolment of the first participants in a Phase 1/2 study that combines Novavax' seasonal Influenza and COVID-19 vaccine. The clinical trial combines NVX-CoV2373 and NanoFlu and will evaluate the safety, tolerability, and immune response to this combination vaccine³³. Additionally, on 16 September, Novavax announced its participation in an expanded Phase 2 clinical trial (Com-COV3) that will evaluate, in adolescents, the potential for combined regimens that mix vaccines from different manufacturers. Novavax is also participating in the (Com-COV2) which evaluates the same outcomes in adults³⁴.

Sputnik V:

The Russian vaccine Sputnik V has been approved for administration in multiple countries such as Russia, Argentina, India, and Brazil; however, the vaccine is still awaiting WHO EUL and EMA approval. Russia first applied for WHO EUL approval in February, but due to ongoing inspections

- ³¹ Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process. *World Health Organization*. https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_19August2021.pdf
- ³² EMA starts rolling review of Novavax's COVID-19 vaccine (NVX-CoV2373). *European Medicines Agency*. <https://www.ema.europa.eu/en/news/ema-starts-rolling-review-novavaxs-covid-19-vaccine-nvx-cov2373>
- ³³ Novavax Initiates Phase 1/2 Clinical Trial of Combination Vaccine for COVID-19 and Seasonal Influenza. *Novavax*. <https://ir.novavax.com/2021-09-08-Novavax-Initiates-Phase-1-2-Clinical-Trial-of-Combination-Vaccine-for-COVID-19-and-Seasonal-Influenza>
- ³⁴ Novavax to Participate in University of Oxford Com-COV3 Study Comparing Mixed COVID-19 Vaccine Schedule in Adolescents. *Novavax*. <https://ir.novavax.com/2021-09-16-Novavax-to-Participate-in-University-of-Oxford-Com-COV3-Study-Comparing-Mixed-COVID-19-Vaccine-Schedule-in-Adolescents>

carried out at the manufacturing plants, and incomplete data from the vaccine's manufacturers, Sputnik V has not yet been approved by WHO EUL³⁵.

According to a new case-control study assessing the vaccine effectiveness against referral to hospital and severe lung injury associated with COVID-19, the vaccine effectiveness against referral to hospital was **81% (95% CI, 68-88)** for complete vaccination while the effect of partial vaccination were not statistically significant (51). In terms of vaccine protective effect against lung injury, an increase in protective effect was reported from **54% (95% CI, 59-60)** effectiveness against any sign of lung injury to **76% (95% CI, 59-86)** effectiveness against more than 50% lung involvement (51).

In terms of immunogenicity, a study exploring the immunity and the ability of Sputnik V to elicit antibody response against SARS-CoV-2 reported an increase in the anti-RBD IgG levels in naïve vaccine recipients after the second vaccine dose. Despite antibody levels being detected in naïve populations, B cell and antibody response to Sputnik V were heavily dependent on whether the vaccinee was previously infected or not where the plasmablast, RBD-specific MBCs, SARS-CoV-2-specific MBC-derived ASC response, and humoral responses were more prominent in the recovered group of vaccinees than in the naïve group (52). Another study aiming to establish changes in the level of antibodies to SARS-CoV-2 during immunization with Sputnik V found that the level of IgM did not change from the 17th to the 38th day after immunization with the first jab of the vaccine; however, by the 30th day, a decrease in IgM was observed. Regarding the IgG, a significant increase after immunization with the second dose was observed and by the 51st day 100% of participants reported seroconversion (53). Overall, 90% of the cases lead to the formation of sufficiently high level of antibodies against SARS-CoV-2 (53). Finally, a study evaluating the immunoglobulin (Ig) G antibody response against NP and RBD protein of SARS-CoV-2 before and after receiving the Sputnik V vaccine, demonstrated that 2 doses of the Sputnik V vaccine triggered antibody response in all study individuals, although the second Sputnik V dose had no impact of IgG response for those seropositive for SARS-CoV-2 antigens before vaccination (54).

CureVac:

Prior clinical trial results demonstrated that CureVac, an mRNA-based COVID-19 vaccine encapsulated in lipid nanoparticle, had a lower vaccine efficacy than other mRNA-based COVID-19 approved vaccines such as the BNT162b2 and mRNA-1273. A new study on the efficacy and safety of the of CVnCoV was published on 27 August 2021 reporting an overall vaccine efficacy of **48.2% (95% CI, 31.0-61.4)** against SARS-CoV-2 infections (55). Although the efficacy against the

³⁵ Sputnik V: WHO suspends approval process for COVID vaccine due to 'manufacturing' concerns. *Euronews.next*.
<https://www.euronews.com/next/2021/09/16/sputnik-v-who-suspends-approval-process-for-covid-vaccine-due-to-manufacturing-concerns>

infection was below 50%, the vaccine efficacy against moderate-to-severe COVID-19 was higher with a reported efficacy of **70.7% (95% CI, 42.5-86.1)**. The efficacy in participants aged 18-60 years was **52.5% (95% CI, 36.2-64.8)** while the one for participants aged 65 and over was inconclusive due to the too few cases that occurred (55). The vaccine efficacy against variants of concerns such as the Alpha (**55%; 95% CI: 24-74**), Gamma (**67%; 95% CI: 30-85**), Lambda (**53%; 95% CI: 8-76**) was comparable with the overall efficacy, except for the variant Mu where an efficacy of **42% (95% CI, -25-73)** was reported (55). As for the safety of the vaccine, solicited adverse events were mostly systemic with **27.1%** of CVnCOv recipients reporting grade 3 events. The most reported systemic reactions were **fatigue** and **headache**, and the most frequently reported local reaction was **injection site pain**. Overall, the vaccine demonstrated an acceptable safety profile (55). As for the safety of the vaccine, solicited adverse events were mostly systemic with **542/2002** CVnCOv recipients reporting grade 3 events. Prior clinical trial results demonstrated that CureVac, an mRNA-based COVID-19 vaccine encapsulated in lipid nanoparticle, had a lower vaccine efficacy than other mRNA-based COVID-19 approved vaccines such as the BNT162b2 and mRNA-1273. A new study on the efficacy and safety of the of CVnCoV was published on 27 August 2021 reporting an overall vaccine efficacy of **48.2% (95% CI, 31.0-61.4)** against SARS-CoV-2 infections (55). Although the efficacy against the infection was below 50%, the vaccine efficacy against moderate-to-severe COVID-19 was higher with a reported efficacy of **70.7% (95% CI, 42.5-86.1)**. The efficacy in participants aged 18-60 years was **52.5% (95% CI, 36.2-64.8)** while the one for participants aged 65 and over was precluding due to the too few cases that occurred (55). The vaccine efficacy against variants of concerns such as the Alpha (**55%; 95% CI: 24-74**), Gamma (**67%; 95% CI: 30-85**), Lambda (**53%; 95% CI: 8-76**) was comparable with the overall efficacy, except for the variant Mu where an efficacy of **42% (95% CI, -25-73)** was reported (55). As for the safety of the vaccine, solicited adverse events were mostly systemic with **27.1%** of CVnCOv recipients reporting grade 3 events. The most reported systemic reactions were **fatigue** and **headache**, and the most frequently reported local reaction was **injection site pain**. Overall, the vaccine demonstrated an acceptable safety profile (55). As for the safety of the vaccine, solicited adverse events were mostly systemic with **542/2002** CVnCOv recipients reporting grade 3 events.

SCB COVID-19:

Previous studies on the safety and immunogenicity four weeks after two doses of the Clover COVID-19 vaccine candidate, SCB-2019, a stabilized pre-fusion form of the SARS-CoV-2 S-protein (S-trimer) were reported. Recently, a study analysing the persistence of antibodies up to 6 months after vaccination, and cross-neutralization titers against three variants of concerns was published (56). From the results, titers waned from their peak at day 36-50, however, the IgG

antibodies, ACE2-competitive binding antibodies, and neutralizing antibodies against the wild-type SARS-CoV-2 persisted 25-35% of their observed peak levels at day 184. Regarding neutralizing antibodies against variants of concerns (i.e. Alpha, Beta, and Gamma), an increase in neutralizing titers against variants was observed in day 36 sera (56).

ZyCoV-D:

India has recently approved a new COVID-19 vaccine that uses circular strands of DNA named ZyCoV-D. The new DNA vaccine is administered into the skin without an injection and had been found to be 67% protective against symptomatic COVID-19 in clinical trials (57). Despite its injection-free administration, the vaccine requires a minimum of three doses to achieve its initial efficacy. The DNA vaccine was developed by Indian pharmaceutical firm Zydus Cadila, headquartered in Ahmedabad and was authorized on 20 August for people aged 12 and older (57). India has recently approved a new COVID-19 vaccine that uses circular strands of DNA names ZyCoV-D. The new DNA vaccine is administered into the skin without an injection and had been found to be 67% protective against symptomatic COVID-19 in clinical trials (57).

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