Literature screening report

COVID-19 vaccines and post-vaccination data: literature update (8)

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Abstract

This report addresses the most relevant data on COVID-19 vaccines literature as of 27 August, 2021. The current report addresses vaccine effectiveness against SARS-CoV-2 infection, focusing in particular, on vaccine effectiveness against variants, vaccine duration of protection, virus transmissibility and shedding post vaccination, the administration of booster doses, and the importance of children and adolescent's timely vaccination. Lastly, the report highlights the latest updates regarding 'new' SARS-CoV-2 vaccines.

Content

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

Due to the global spread of the variants of concern (VOC), particularly the more infectious and transmissible Delta variant (B.1.167.2), the epidemiological situation continues to evolve despite increasing vaccination rates. Vaccination rollouts at the start of 2021 demonstrated high vaccine effectiveness against the original SARS-CoV-2 strain, however reductions in neutralization capacities, and therefore vaccine effectiveness, were subsequently reported with the rise of VOCs around the world. As the B.1.167.2 strain becomes the dominant variant worldwide, questions concerning vaccine effectiveness, long-term immunogenicity and viral transmissibility arise. In order to mitigate the current epidemiological situation, Israel has begun to vaccinate children under the age of 12 years and to administer booster doses to immunocompromised individuals and persons over the age of 30 (including pregnant women) that were immunized more than five months ago[1,2]. The United Arab Emirates also began to vaccinate children (3-17 years)[3] and to administer booster shots to Sinopharm recipients six months after their two-dose regimen[4], while some cantons in Switzerland have authorised the administration of third booster shots to highly immunosuppressed individuals[5,6]. In the meantime, new data from clinical trials are published for new vaccine candidates. This report thus focuses on published studies that covered the following questions/points:

Questions addressed

- What is the efficacy or effectiveness of vaccines against SARS-CoV-2 infection, particularly in relation to variants of concern?
- What is the effectiveness of vaccines against the Delta variant (B.1.617.2) in terms of hospitalisations and deaths?
- What is the reported duration of protection of the approved vaccines?

[1] From Israel to Britain, which countries are planning to give COVID-19 vaccine booster shots. *Firstpost.* https://www.firstpost.com/health/from-israel-to-britain-which-countries-are-planning-to-give-covid-19-vaccine-booster-shots-9859111.html

[2] Third dose of the COVID-19 Vaccine. *Ministry of Health Israel.* https://govextra.gov.il/ministry-of-health/covid19-vaccine/en-covid-19-vaccine-3rd-dose/

[3] Sinopharm and Pfizer-BioNTech vaccines are available for citizens and residents for free. *Department of Health: Abu Dhabi Public Health Centre.* https://www.doh.gov.ae/en/covid-19/national-vaccination

[4] MoHAP provides Pfizer-BioNTech vaccine to 12-15 age group, announces availability of Sinopharm booster shot. *Ministry of Health & Prevention.* https://www.mohap.gov.ae/en/MediaCenter/News/Pages/2930.aspx

[5] FAQ on vaccination against COVID-19. *Republique et Canton de Genève*. https://www.ge.ch/en/getting-vaccinated-against-covid-19/faq-vaccination-against-covid-19

[6] Info on third vaccination. *Corona Impfzentrum Basel-Stadt.* https://www.coronaimpfzentrumbasel.ch/drittimpfung/

- What is known about virus transmissibility and shedding in breakthrough infections?
- Should we start administering booster doses to the vaccinated population?
- What is the efficacy, immunogenicity, and safety of the mRNA vaccines approved for children?
- What is the status of new SARS-CoV-2 vaccines?

Methodology

The current report screened the databases of PubMed, Embase, medRxiv, bioRxiv, Cochrane, and clinical trial databases such as ClinicalTrials and WHO Trial registry for vaccine-related literature as of 27 August, 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 SARS-CoV infection, particularly in relation to variants of concern?

Introduction:

As phase III COVID-19 vaccine trials confirmed vaccine efficacy and safety for all six World Health Organization (WHO) Emergency Use Listing (EUL) vaccines, and as the share of fully vaccinated people begin to slowly increase across countries, it is important to assess vaccine effectiveness in real-world conditions, especially in relation to evolving variants of concern (VOC). The first SARS-CoV-2 mutation (the Alpha variant; B.1.1.7) was the predominant strain throughout Switzerland from March to June 2021, leading to a 50% increase in transmission rates (1). By the end of June, the Delta variant (B.1.617.2) replaced the Alpha variant as the new dominant strain and accounts for more than 90% of the cases within Switzerland since mid-July (2). The circulation of both Beta (B.1.513) and Gamma (P.1) variants have thus far been rare, maintaining a constant circulation frequency of less than 1% within Switzerland (2). The information below provides the latest updates and data on vaccine effectiveness against SARS-CoV-2 infection (both asymptomatic and symptomatic – refer to *page 8* for effectiveness against severe COVID-19 infection and

hospitalisation) in regard to the four circulating strains within Switzerland: Alpha (B.1.1.7), Beta (1.351), Gamma (P.1) and Delta (1.617.2).

Results summary:

Despite demonstrating reduced neutralization capacities and effectiveness in relation to the wild-type SARS-CoV-2 strain, both Pfizer-BioNTech and Moderna's mRNA vaccines provide adequate protection (most studies reported the estimated effectiveness to be above the WHO minimum efficacy threshold of 50% - see results below) against the Alpha, Beta and Delta variants (see references below). The exception is in Israel, where the BNT162b2 vaccine demonstrated an estimated effectiveness against SARS-CoV-2 infection between the period of 20 June and 17 July 2021 to be **39%** (**95% CI, 9-59**) (3). It is still uncertain why Israel demonstrates lower BNT126b2 effectiveness compared to other countries. Vaccine effectiveness are regulated by a variety of factors, including demographic, host, and viral variant, at the individual and population level (4), which could explain effectiveness differences at the country or regional level. Few studies have analysed the effectiveness of the mRNA vaccines against the Gamma variant; more data is needed to confirm the mRNA's vaccines effectiveness against the P.1 strain. Similar to the mRNA vaccines, AstraZeneca's viral vector vaccine provides similar effectiveness against the B.1.1.7 strain as to the wild type (5). The vaccine additionally provides protection against the Delta variant, although at reduced levels (5, 6), and demonstrates significantly reduced neutralization capacities against the B.1.351 variant (7, 8). The Johnson & Johnson vaccine demonstrated reduced neutralization capacities against the Alpha, Beta, Gamma, and Delta strains when compared to wild type (see results below); the vaccine neutralized the Delta variant at greater capacities than the B.1.351 and P.1 strains (9). Few studies have been published on Sinopharm's BBIBP-CorV real-world effectiveness; one Bahraini study confirmed that the inactivated vaccine provides partial protection against SARS-CoV-2 infection (10). CoronaVac has been demonstrated to provide protection (although at reduced levels when compared to wild type) against the Gamma variant (11-13) and the Delta variant (14). Further studies are needed to confirm CoronaVac's effectiveness against the Alpha, Beta, and Delta variants.

Results:

Early test-negative case-control studies conducted between December 2020 and March 2021 (15, 16) demonstrated Pfizer- BioNTech's BNT162b2/Comirnaty and Moderna's mRNA-1273/Spikevax's real-world effectiveness (**94.6%; 95% CI, 61.0-99.2),** and **100%**, respectively) to be similar to their efficacy in phase III clinical trials [**94.6%** Comirnaty (17); **94.1%** Spikevax (18)]. Regarding the non-Swiss authorized vaccines, effectiveness estimates for AstraZeneca's ChAdOx1 nCoV-19/ AZD1222/ Covishield [85%; 0.15 (0.08-0.26)] and Janssen's Johnson & Johnson COVID-19 vaccine **(76.7%;**

95% CI, 30.3-95.3) (19) are also comparable to their efficacy estimates in phase III trials (20-22). In a mass-vaccination Chilean setting (approximately 10.2 million persons), Sinovac/ CoronaVac's effectiveness **(65.9%; 95% CI, 65.2-66.6)** proved higher than its efficacy estimates (23). To our knowledge, few studies have been published on Sinopharm's BBIBP-CorV real-world effectiveness. While no study has thus far reported numerical effectiveness data, one study in Bahrain confirms that the Sinopharm vaccine provides partial protection against SARS-CoV-2 infection (10).

Ongoing clinical trials and observational studies, however, have demonstrated reduced vaccine efficacy and effectiveness capacity against COVID-19 variants compared to wild type. The data is summarised below:

Alpha (B.1.1.7) & Beta (B.1.351) variant

BNT162b2: Observational studies in England (6, 24), Scotland (5), Qatar (25), and Canada (26) corroborate that BNT162b2 provides comparable protection levels against the Alpha variant to those observed in clinical trials and the wild-type strain (24, 25). A prospective cohort study (15,000 participants) in the United Kingdom (UK) demonstrated two doses of BNT162b2 to be only **86%** effective against both asymptomatic and symptomatic infection (27). This observational study was conducted when the dominant variant of circulation was B.1.1.7, and although the vaccine's neutralization capacity was not specifically tested against the B.1.1.7 variant, it could explain BNT162b2's reduced effectiveness compared to prior reported data. Nevertheless, another negative-test, case-control study that specifically tested against the B.1.1.7 strain in the UK reported that BNT1262b had an overall effectiveness of **93.7% (95% CI, 91.6 to 95.3)** (6). Compared to the Alpha variant, the vaccine demonstrates reduced effectiveness against B.1.351 infection **(75.0%; 95% CI, 70.5 to 78.9)**; the vaccine however, still provides adequate protection against severe infection with the B.1.351 strain (25).

mRNA-1273: A laboratory study established that Moderna's mRNA-1273/ Spikevax vaccine induces similar neutralizing antibodies against the B.1.1.7 strain when compared to the wild type and has a reduced (yet still potent) neutralizing capacity against the B.1.351 strain (7). A real-life test-negative, case-control study following mass vaccination campaigns in Qatar demonstrated similar results to the laboratory study. Estimated vaccine effectiveness against (asymptomatic or symptomatic) infection with the B.1.1.7 variant was **88.1% (95% CI, 83.7-91.5)** and **100% (95% CI, 91.8-100)** two weeks after the first and second dose, respectively (28). Vaccine effectiveness against the Beta variant was robust yet slightly reduced when compared to the Alpha variant, demonstrating an effectiveness of **61.3% (95% CI, 56.5-65.5)** and **96.4% (95% CI, 91.9-98.7)** two weeks after the first and second dose, respectively (28). The authors concluded that the mRNA-1273 vaccine is highly effective against B.1.1.7 and B.1.351 infections.

ChAdOx1-nCoV: Vaccine efficacy against primary symptomatic B.1.1.7 disease (**74.6%; 95% CI, 41.6%-88.9)** is similar to that of the wild type (29). A cohort analysis in Scotland confirmed ChAdOx1-nCoV efficacy estimates, reporting a vaccine effectiveness of **73% (95% CI, 66-78)** (5). Similar to Pfizer- BioNTech and Moderna's vaccines, AstraZeneca's ChAdOx1-nCoV has a reduced neutralization capacity against the B.1.351 variant (7). Unlike the mRNA vaccines however, a two-dose regimen of ChAdOx1-nCoV in a laboratory study did not provide protection against the B.1.351 variant **(10.4%; 95% CI, -76.8-54.8)** (8). Further studies are needed to validate ChAdOx1-nCoV real-world effectiveness against the Beta variant.

Johnson & Johnson: In a laboratory study, the Ad26.COV2.S COVID-19 vaccine demonstrated similar neutralization capacities when compared to wild type for the B.1.1.7 strain and a 3.6-fold reduction for the B.1.351 strain (9). To our knowledge, no study has thus far been published on the vaccine's effectiveness against the Alpha and Beta variants.

Sinopharm: To our knowledge, no study has thus far been published on the vaccine's effectiveness against VOCs.

CoronaVac: To our knowledge, no study has thus far been published on the vaccine's effectiveness against the Alpha and Beta variants.

Gamma (P.1)

BNT162b2: Despite reduced neutralization capacity when compared to the Alpha variant (30), the BNT152b2 vaccine effectively neutralizes the P.1 strain in serum samples (31, 32).

mRNA01273: No studies have thus far been published on the vaccine's effectiveness against the Gamma variant (4).

ChAdOx1-nCoV: AstraZeneca reports that the ChAdOx1-nCoV vaccine has a similar neutralization capacity against P.1 as seen with B.1.1.7 and an enhanced neutralization capacity when compared to B.1.351. Geometric mean neutralization titres were **reduced 2.6-fold** against P.1 when compared to wild type (33, 34).

Johnson & Johnson: The Ad26.COV2.S COVID-19 vaccine shows a **3.4-fold reduction** in neutralization sensitivity when compared to wild type (9). To our knowledge, no further studies have been published on the vaccine's effectiveness against the Alpha and Beta variants.

CoronaVac: Case control studies in Brazil have demonstrated CoronaVac's effectiveness against the P.1 variant [ranging from **49.4%** (11) to **51.8%** (13)]. A further test-negative control study in adults aged ≥70 years demonstrated adjusted vaccine effectiveness against symptomatic COVID-19 to be **24.7% (95% CI, 14.7-33.4)** at 0-13 days after the first dose and **46.8% (95% CI, 38.7-53.8)** at ≥14 after the second dose (12).

Delta (B.1.617.2)

BNT162b2: Effectiveness studies in Canada (35), Scotland (5), England (6, 36), and Israel (3) have reported reduced vaccine effectiveness against the Delta variant compared to all prior viral strains. Scotland and England reported similar in country effectiveness estimates against B.1.617.2 infection: **79% (95% CI, 75-82)** and **79% (95% CI, 78-80)**, respectively. Results from another test-negative, case-control study in the UK demonstrated that effectiveness against the Delta variant was **88% (95% CI, 85.3-90.1)** (6). In Alberta, Canada vaccine effectiveness against symptomatic B.1.617.2 infection was **85% (95% CI, 78-89)** (35). However, Canada did not differentiate vaccine effectiveness between BNT162-b2, mRNA-1273, and ChAdOx1-nCoV. Interestingly, data from Israel reports much lower vaccine effectiveness compared to other countries: vaccine efficacy reportedly fell from **94%** to **64%** after the Delta strain became the dominant variant in the country (37), while vaccine effectiveness is reported to be **39% (95% CI, 9-59)** against SARS-CoV-2 infection and **40.5% (95% CI, 8.7-61.2)** for symptomatic cases (3). As of 27 August, it is still uncertain why Israel demonstrates lower BNT126b2 effectiveness compared to other countries (2). Interestingly, estimates from the UK's Real-time Assessment of Community Transmission-1 (REACT-1) adjusted vaccine effectiveness from May to July 2021 were lower than prior UK estimates **(49%; 95% CI, 22-67)** (38), but were consistent with data from Israel. Lower recent vaccine effectiveness in Israel and the UK could be related to decreasing long-term vaccine immunogenicity (2), although no studies have confirmed this yet.

mRNA-1273: On 24 August, the Centers for Disease Control and Prevention (CDC) reported a decline in mRNA vaccine effectiveness from **91% (95% CI, 81-96)** during the months preceding the Delta predominance to **66% (95% CI, 26-84)** (39). Unfortunately, the CDC did not disaggregate vaccine effectiveness data between the BNT162b2 and mRNA-1273 vaccines. In June, Moderna stated that preliminary neutralization trials showed modest reductions (**2.1-fold**) in neutralizing titres against the Delta variant and that further studies are being conducted (40). Another sera neutralization study confirmed Moderna's claim by demonstrating that the mRNA-1273 vaccine had **1.5-fold reduced** binding to B.1.617.2 when compared to the original strain of the virus, concluding that the vaccine provides sufficient protection against the highly infectious delta variant, although further studies are needed to clarify its full effectiveness (41). A large community-based survey in the UK reported that one dose of the mRNA-1273 vaccine (due to data availability, the authors could only test the effectiveness of a single mRNA-1273 dose) provided similar or greater protection compared to a single dose of BNT162b2 or ChAdOx1 against the delta variant (42). A possible confounding factor could be driven by age – mRNA-1273 recipients were on average younger than BNT162b2 and ChAdOx1 recipients (42) and vaccine estimates have been observed to be lower in older compared to younger individuals after a single dose (43).

ChAdOx1-nCoV: After the administration of two doses, vaccine effectiveness ranged from **59.8% (95% CI, 28.9-77.3)** (24) to **67% (95% CI, 61.3-71.8)** (6) following observational studies in England. A test-negative analysis that estimated vaccine effectiveness in preventing RT-PCR-confirmed SARS-CoV-2 B.1.167.2 infection in Scotland corroborated the English results, providing **60% (95% CI, 53-66)** protection (5).

Johnson & Johnson: In a preprint published by Janssen, the single-shot vaccine demonstrated a **1.6-fold** reduction in neutralization sensitivity against the Delta variant when compared to the original SARS-CoV-2 variant (9). The Ad26.COV2.S COVID-19 vaccine neutralizes the Delta variant at greater capacities than the B.1.351 and P.1 strains (see *Beta* and *Gamma* sections above). No efficacy or real-life effectiveness studies have been conducted thus far (9).

CoronaVac: Vaccine effectiveness observed two weeks after the second dose Guangzhou, China was estimated at **58% (95% CI, 15-81)** against SARS-CoV-2 infection and **70.2% (95% CI, 29.6-89.3)** against moderate COVID-19 disease (14).

Studies quantifying the effectiveness of vaccines against asymptomatic and symptomatic B.1.617.2 infection are ongoing.

What is the effectiveness of vaccines against the Delta variant (B.1.617.2) in terms of hospitalisations and deaths?

Summary:

As countries began vaccinating individuals in early 2021, case numbers, hospitalisations and death rates have decreased[7]. However, the global spread of VOCs has led to reduced vaccine effectiveness against asymptomatic and symptomatic SARS-CoV-2 infection, particularly with the B.1.167.2 strain (Delta variant). The burden of severe COVID-19 infections and hospitalisations on health care systems has been drastic; preventing COVID-19 related death and severe infections has been one of the major factors guiding vaccine development and rollout[8]. It is concerning that many countries are now reaching vaccine saturation without having reached herd immunity[9], and as a consequence, hospitalisation rates are increasing. While vaccines are not able to fully curb infections against

[7] Vaccines are curbing COVID: Data from Israel show drop in infections. *Nature.* https://www.nature.com/articles/d41586-021-00316-4

[8] Evaluation of COVID-19 vaccine effectiveness. *World Health Organization*. https://apps.who.int/iris/rest/bitstreams/1337417/retrieve

[9] COVID-19 herd immunity? It's not going to happen, so what next?. *The Conversation*. https://theconversation.com/covid-19-herd-immunity-its-not-going-to-happen-so-what-next-165471

variants, reports have demonstrated that full immunization against SARS-CoV-2 effectively prevent severe infections, hospitalisations, and death[10], helping prevent the further collapse of health systems around the world.

Results:

Pre-Delta:

Early vaccination data from Israel demonstrated that case numbers and hospitalisations significantly decreased two months after the start of their vaccination campaign. Their Ministry of Health reported an approximate 77% drop in cases, a 45% drop in positive test percentage, a 68% drop in hospitalisations, and a 67% drop in severe hospitalisations when compared to peak values (44). Data published four months after the start of their vaccination rollout confirmed BNT162b2 effectiveness across all age groups (≥16 years) in preventing COVID-19 related hospitalisations (**97.2%; 95% CI, 96.8-97.5**), severe disease (**97.5%; 95% CI, 97.1-97.8**) and death (**96.7%; 95% CI, 96.0-97.3**), including those caused by the B.1.1.7 SARS-CoV-2 strain (45). A Canadian study (43) corroborates the data from Israel: mRNA vaccine effectiveness against hospital admission or death observed 7 days or more after the first and second doses were **70% (95% CI, 60-77)** and **98% (95% CI, 88-100)**. The study did not differentiate between the two mRNA vaccines.

Delta:

Despite the Delta variant's higher infectivity, potency, and transmissibility, vaccination protection against severe B.1.167.2 infection is high (2). As of 6 August, the Delta variant accounted for approximately 99% of cases in the UK (46), yet hospital admissions of fully vaccinated individuals decreased significantly from January to August 2021 and 97% of the hospitalized cases were willingly unvaccinated individuals (46). Data published by Public Health England reported that two doses of BNT162b2 or ChAdOx1-nCoV provided **96% (95% CI, 86-99)** and **92% (95% CI, 75-97)** vaccine effectiveness against hospitalisation, respectively (47). Although recent published data from Israel demonstrated reduced vaccine effectiveness against asymptomatic and symptomatic B.1.617.2 SARS-CoV-2 infection, the BNT162b2 and mRNA-1273 vaccines still provide high effectiveness against COVID-19 hospitalisation **(88%; 95% CI, 78.9-93.2)** and severe[11] COVID-19 (**91.4%; 95% CI, 82.5-95.7**) (3). Another retrospective cohort study conducted in Southern California, reported a vaccine effectiveness against hospitalization for Delta of **93% (95% CI, 84-96)** for all ages (48).

A test-negative case control study in China estimated CoronaVac's effectiveness against severe B.1.617.2 disease to be **100%** - the authors mentioned however that the results may be

[10] Confirmed cases of COVID-19 variants identified in UK. *Public Health England*. https://www.gov.uk/government/news/confirmed-cases-of-covid-19-variants-identified-in-uk

[11] Including severe, critical and death.

overestimated due to their small sample size (14). While no further studies have been published on CoronaVac's effectiveness against the Delta variant, CoronaVac provided **56%** and **61%** protection against the P.1 (Gamma) SARS-CoV-2-related hospitalisations and deaths in individuals aged 70 years and above in Brazil (12).

What is the reported duration of protection of the approved vaccines?

Summary:

Since the approval and administration of COVID-19 vaccines, limited data on the duration of protection of the WHO EUL approved vaccines has become available; however, few studies on the persistence of antibodies, humoral, and cellular immune responses have demonstrated that vaccine induced antibodies appears to last up to 6 to 8 months after full vaccine coverage[12,13,14]. A similar duration of antibodies was reported in the convalescent sera of unvaccinated COVID-19 patients[15]. Nonetheless, conclusive data and further studies that evaluate the immune persistence of approved vaccines are greatly needed.

Results:

mRNA Vaccines:

A study that measured the SARS-CoV-2 specific antibody, memory B cell, and memory T cell responses through 6 months post-vaccination in a group of healthy subjects who received both does of mRNA vaccine demonstrated that mRNA vaccines induced **durable immune memory to SARS-CoV-2 through 6 months post-vaccination** (49). The analyses revealed that although circulating antibody levels declined in some individuals, the memory B cell response were robustly induced for at least 6 months after receiving the full mRNA vaccines (49). Additionally, the mRNA vaccination generated highly mutated memory B cells that were capable of cross-binding to B.1.1.7 (Alpha), B.1.351 (Beta), and B.1.617.2 (Delta) (49).

BNT162b2:

[12] Antibody Persistence through 6 Months after the Second Dose of mRNA-1273 Vaccine for Covid-19. *The New England Journal of Medicine.* https://www.nejm.org/doi/full/10.1056/nejmc2103916

[13] Durable Humoral and Cellular Immune Responses 8 Months after Ad26.COV2.S Vaccination. *The New England Journal of Medicine.* https://www.nejm.org/doi/full/10.1056/NEJMc2108829

[14] A booster dose is immunogenic and will be needed for older adults who have completed two dose vaccination with CoronaVac: a randomized, double-blind, placebo-controlled, phase 1/2 clinical trial. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.08.03.21261544v1

[15] Evolution of antibody immunity to SARS-CoV-2. *Nature.* https://www.nature.com/articles/s41586-021-03207-w

Limited data regarding the duration of protection of the Pfizer-BioNTech (BNT162b2) vaccine exists; however, a retrospective cohort study performed in a large state-mandated health care organization in Israel determined that the median time between the second dose and breakthrough was **146 days (IQR, 121-167)** (50). To better understand the waning protection, a study conducted in Israel analysed the data of more than 1.3 million individuals that received their vaccines between January and April 2021 to assess the correlation between time-from-vaccine and incidence of breakthrough infection. From the results, early vaccinees were found to have a statistically significant **53% (95% CI, 40-68)** increased risk for breakthrough infection than late vaccinees (51). Additionally, individuals vaccinated in January 2021 had a **2.26-fold (95% CI, 1.80-3.01) increased risk** for breakthrough infection compared to individuals vaccinated in April 2021 (51). In another retrospective cohort study performed in the Unites States from December 2020 to August 2021, the effectiveness against infections declined from **88% (95% CI, 86-89)** during the first month of full vaccination to **47% (95% CI, 43-51)** after 5 months and more (48).

mRNA1273:

Results regarding the duration of protection for the mRNA-1273 vaccine demonstrate that antibodies persisted approximately **6 months** after receiving the second dose. At **day 209**, antibody activity remained high in all age groups after the second dose of mRNA-1273 vaccine. The geometric mean endpoint titers (GMT) remained the highest in the 18-55 age group **(92451; 95% CI, 57148-149562)** compared to the 56-70 age group **(62424; 95% CI, 36765-105990)** and the 71 years of age or older group **(49373; 95% CI, 25171-96849)** (52). Results regarding the duration of protection for the mRNA-1273 vaccine demonstrate that antibodies persisted approximately **6 months** after receiving the second dose. At **day 209**, antibody activity remained high in all age groups after the second dose of mRNA-1273 vaccine. The geometric mean endpoint titers (GMT) remained the highest in the 18-55 age group **(92451; 95% CI, 57148-149562)** compared to the 56-70 age group **(62424, 95% CI 36765-105990)** and the 71 years of age or older group **(49373; 95% CI, 25171-96849)** (52).

ChAdOx1 nCoV-19:

The immune response remained elevated from the baseline for at least one year following single dose. After a single dose of the ChAdOx1 vaccine, the antibody response declined within one year, but remained above the baseline levels. Compared to the antibody level peak at day 28, the geometric mean antibody levels were halved by day 180 **(GMR 0.54; 95% CI, 0.47-0.61)** and by day 320 the GMR were **0.30 (95% CI, 0.24-0.39**) (53). In terms of the cellular immune response, at day 182 after the first dose, the cellular immune response had a median of **237 SFUx10^6 PBMC**

(IQR, 109-520) (53). Regarding individuals administered the second dose with longer intervals between doses, the antibody levels remained significantly higher in the group with 15–25 week interval **(median 1240; IQR, 432-2002**) compared with the 8-12 week interval **(278; IQR, 166-499)** six months after administration of the second dose (53).

Ad26.COV2.S:

As for the humoral and cellular immune response of Ad26.COV2.S (Janssen) vaccine, a durable response was reported up to **8 months** after the single dose vaccine. Antibody responses were detected in all vaccine recipients on **day 239**, but a **reduction by a factor of 1.8** between peak response (day 71) and day 239 in the median neutralizing antibody titers was reported (54).

Sinovac/CoronaVac:

The immunogenicity of CoronaVac was reported to declines to below the seropositive cut-off, **6 months** after the two priming doses, highlighting the possible need of a booster dose in older populations (55).

What is known about virus transmissibility and shedding in breakthrough infections?

Summary:

Beyond the effectiveness of COVID-19 against infection, the virus transmissibility and shedding in breakthrough infections remains crucial information for governments to assess possible implementation of future policies that can better control the ongoing pandemic. While it might be hard to infer infectiousness, many studies use the SARS-CoV-2 PCR cycle threshold (Ct) values of 25-30 or lower as an indicator of the presence of infectious SARS-CoV-2 and, therefore, are able to infer the infectiousness, transmissibility, and virus shedding in infected individuals. Studies conducted before the highly transmissible Delta variant demonstrate that infectivity and transmission was significantly reduced in vaccinated cases as vaccinated people who got infected were up to 40% to 78% less likely to spread the virus to household members than unvaccinated people[16,17,18]. However, with Delta becoming the prevalent variant worldwide, key

[16] Effect of Vaccination on Household Transmission of SARS-CoV-2 in England. *New England Journal of Medicine*. https://www.nejm.org/doi/10.1056/NEJMc2107717

[17] Impact of BNT162b2 vaccination and isolation on SARS-CoV-2 transmission in Israeli households: an observational study. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.07.12.21260377v1.full-text

[18] Vaccination with BNT162b2 reduces transmission of SARS-CoV-2 to household contacts. *medRxiv.* *https://www.medrxiv.org/content/10.1101/2021.07.13.21260393v1.full-text*

questions regarding its infectiousness and transmission in vaccinated population remained. Recently, studies comparing Ct values in vaccinated and unvaccinated individuals detected no significant difference in Ct values by vaccination status, suggesting that vaccinated individuals who became infected with the Delta variant may have the potential to transmit SARS-CoV-2 to others[19] [20]. Nevertheless, a study conducted in Singapore reported that although the Ct values were similar in both vaccinated and unvaccinated groups, viral loads decreased faster in vaccinated individuals[21]. Additionally, another study demonstrated lower probability of infectious virus detection in vaccinated individuals[22].

Results:

Pre-Delta:

Prior to the predominant Delta variant, the vaccine effectiveness against infectiousness given infections for the BNT162b2 vaccine was calculated to be **41.3% (95% CI, 9.5-73.0)**, while the vaccine effectiveness against transmission which combines the reduction in risk of infection and risk of infectiousness given infection, was calculated to be **88.5% (95% CI, 82.3-94.8)** (56).

Delta:

When the Delta variant was prevalent, various preprints looking at the Ct value in vaccinated and unvaccinated individuals discovered **similar Ct values** in both groups. In a study conducted in Wisconsin, USA, the Ct values of 719 people between 29 June and 31 July was analysed. It was discovered that **90%** of the 122 coronavirus samples sequenced were the Delta variant. After isolating specimens with Ct <25, the researchers found that both vaccinated and unvaccinated persons shed infectious virus regardless of vaccination status (57). Similar results were discovered in a study performed in Singapore whose objective was to study if vaccination altered virological and serological kinetics in breakthrough infections. When analysing the virological kinetics of infected individuals, the initial median Ct value between unvaccinated **(18.8; 95% CI, 14.9-22.7)** and vaccinated patients **(19.2; 95% CI, 15.2-22.2)** did not greatly differ; however, vaccinated patients had a faster rate of increase in Ct value over time compared with unvaccinated individuals, suggesting a faster viral load decline (58).

[19] Shedding of Infectious SARS-CoV-2 Despite Vaccination when the Delta Variant is Prevalent – Wisconsin, July 2021. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.07.31.21261387v3.full

[20] Delta variants of SARS-CoV-2 cause significantly increased vaccine breakthrough COVID-19 cases in Houston, Texas. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.07.19.21260808v2.full-text

[21] Virological and serological kinetics of SARS-CoV-2 Delta variants vaccine-breakthrough infections: a multi-center cohort study. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.07.28.21261295v1

[22] Virological characteristics of SARS-CoV-2 vaccine breakthrough infections in health care workers. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.08.20.21262158v1.full.pdf+html

What is known about administering booster doses to the vaccinated population?

Summary:

Multiple countries have engaged in the conversation regarding the administration of booster doses after the Ministry of Health of Israel released raw data on vaccinations and infections from December 2020 to July 2021 and estimated that vaccine protection against both infection and severe disease had dropped from above 90% in the early months to around 40% by late June[23]. Countries such as France, Germany, and UK are planning on administering a third dose of mRNA vaccines to the immunosuppressed populations at the beginning of Autumn, while the U.S., Israel, and Switzerland already started their administration after studies revealed that these populations demonstrated to generate low antibody levels and poor humoral response after receiving one or two doses of mRNA vaccines[24]. Results on the immunogenicity and safety of third doses in immunocompromised patients showed that a homologous or even heterologous third booster dose significantly improved their immune response and even provided some neutralizing antibodies against variants of concern such as Delta.

Other countries such as UAE and China also started to ponder on the administration of booster doses to individuals that received the Sinopharm vaccine after results on the effectiveness of Sinopharm were well below the expected range, especially in older adults. China is planning on using the domestically produced mRNA and protein vaccines as boosters for its inactivated-virus vaccine, while the United Arab Emirates (UAE) has started the administration of booster doses of either Sinopharm or Pfizer-BioNTech to anyone vaccinated more than 6 months[25].

As of right now, third booster doses have not been recommended or approved for administration for the overall population (12 years old and over) apart from Israel who started administering third doses to those over 30 years old[26], and the UAE who started offering booster shots to anyone

[23] *Ministry of Health of Israel*. https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_two-dose-vaccination-data.pdf

[24] Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. *JAMA.* https://jamanetwork.com/journals/jama/fullarticle/2779852

[25] COVID vaccine boosters: the most important questions. *Nature.* https://www.nature.com/articles/d41586-021-02158-6#ref-CR5

[26] Third dose of the COVID-19 Vaccine. *Ministry of Health Israel.* *https://govextra.gov.il/ministry-of-health/covid19-vaccine/en-covid-19-vaccine-3rd-dose/*

who received their immunization six or more months ago[27]. Nevertheless, ongoing trials performed by Pfizer-BioNTech[28] and Moderna Inc.[29] are testing the tolerability and immunogenicity of their booster doses and have demonstrated, in their preliminary results, that the booster doses have consistent tolerability and elicit high neutralizing titers against variants of concerns. Additionally, clinical trials evaluating the administration of heterologous booster doses (Sinopharm/BNT162b2) are ongoing.

Although countries with no supply constraints are considering or have started administering a third boost dose, ethical concerns regarding third dose administration remain an issue, especially in lower-income countries where only ~1.1% of the populations have received their first jab[30]. Furthermore, the World Health Organization has called for a moratorium on COVID-19 boosters until the end of next month, with the aim of ensuring that at least 10% of the worldwide population is vaccinated[31].

Results:

Immunosuppressed Individuals:

The prevalence of anti-SARS-Cov-2 antibodies after the homologous third booster dose of the BNT162b2 vaccine in solid-organ transplant recipients increased from **41% (95% CI, 37-46)** after the second dose to **68% (95% CI, 63-73)** 4 weeks after the third dose (59). Additionally, among 232 patients who were seronegative before the third dose, **45%** turned positive after the third dose and no serious adverse events or acute rejection was observed (59). Nevertheless, the seroconversion rate remained low in patients taking immunosuppressant drugs. Similarly, **49%** solid-organ transplant recipients that received the homologous third boosted dose of the mRNA1273 vaccine showed antibody greater than 50 AU/mL after the third dose (60). Additionally, **81.3%** of patients with a weak response after the second dose were more likely to develop antibody response compared to **27.4%** of patients that did not develop a response after the second dose (60). No severe adverse events were observed after the third dose.

[27] MoHAP provides Pfizer-BioNTech vaccine to 12-15 age group, announces availability of Sinopharm booster shot. *Ministry of Health & Prevention.* https://www.mohap.gov.ae/en/MediaCenter/News/Pages/2930.aspx

[28] Pfizer and BioNTech Provide Update on Booster Program in Light of the Delta-Variant NEW YORK and MAINZ, GERMANY, July 8, 2021. *Pfizer N Biotech Press Release.* https://cdn.pfizer.com/pfizercom/2021-07/Delta_Variant_Study_Press_Statement_Final_7.8.21.pdf

[29] Moderna Announces Positive Initial Booster Data Against SARS-CoV-2 Variants of Concern. *Moderna Inc. Press Release.* https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-positive-initial-booster-data-against-sars-cov

[30] If we're not careful, booster vaccines could end up giving the coronavirus a boost. The sooner we start using booster jabs, the more likely it is that we will need them. *The Telegraph.* *https://www.telegraph.co.uk/global-health/science-and-disease/not-careful-booster-vaccines-could-end-giving-coronavirus-boost/*

[31] The WHO is right to call a temporary halt to COVID vaccine boosters. *Nature.* https://www.nature.com/articles/d41586-021-02219-w

In regards of the third dose providing neutralizing antibodies against variants of concerns in solid-organ transplant recipients, there was a **significant increase in median pseudo-neutralization of all variants** in some patients. However, these results were significantly lower than that of healthy control groups after receiving two doses of mRNA-based vaccines (61). Additionally, only **6%** of the patients had pseudo-neutralization for the Delta variant (61).

General Population:

Regarding the administration of booster doses to the overall population, ongoing trials performed by Pfizer-BioNTech and Moderna Inc, show promising results. A third booster dose of ChAdOx1 also showed promising results as the booster shot, given at least 6 months after the second dose, elicited robust immune response even against variants of concerns.

BNT162b2:

Initial data for BNT162b2 booster shot demonstrates that administration of the third dose 8 to 9 months after the second dose has consistent tolerability and high immunogenicity against wild type, Beta variant, and Delta variant (62-64).

mRNA1273/mRNA1273.351:

Preliminary data on the safety and immunogenicity for the booster shot against SARS-CoV-2 variants of concerns (mRNA-1273 & mRNA-1273.351) showed to be promising. In terms of safety, the most common solicited local adverse events were injection-site pain **(68.4% for mRNA-1273.351, 90% for mRNA-1273)**, fatigue **(36.8% for mRNA-1273.351, 70% for mRNA-1273)**, headache **(36.8% for mRNA1273.351, 55.0% for mRNA-1273)**, myalgia **(31.6% for mRNA-1273.351, 45.0% for mRNA-1273)**, and arthralgia **(21.1% for mRNA-1273, 50.0% for mRNA-1273)** (65). As for the immunogenicity, the booster doses (mRNA-1273 or mRNA-1273.351) increased neutralizing antibody titers and resulted in the detection of robust neutralization titers against both wild and variant viruses (65).

ChAdOx1:

Antibody levels after the third homologous dose of ChAdOx1 resulted to be significantly higher than after a second dose where the median tIgG EU after the second dose were **1792 (IQR, 899-4634)** and after the third dose were **3746 (IQR, 2047-6420)** (53). Neutralizing antibody titers against the Alpha (B.1.1.7), Beta (B.1.351), and Delta (B.1.617.2) variants were also higher in individuals administered the third dose. As for the spike specific cellular immune responses, the median response in individuals who received the third dose increased from **200 SFUx10^6 PBMC**

(IQR, 127-389) after the second dose to **399 SFUx10^6 PBMC (IQR, 314-662)** after the third one (53).

What is the efficacy, immunogenicity, and safety of the mRNA vaccines approved for children?

Summary:

With Switzerland clearing the Pfizer-BioNTech[32] and Moderna[33] vaccine for use on teenagers aged 12 and above on 4 June and 9 August 2021, respectively, concerns on the efficacy, immunogenicity, and safety of those vaccines in children rise. During phase III trials, both vaccines have shown to be efficacious, immunogenic, and safe with comparable results in immune response and safety in teenagers aged 12 to 17 years old to those aged 18 to 25 years.

Although children below the age group of 12 to 17 years old are excluded from the current vaccine roll-out, ongoing studies performed by Pfizer-BioNTech and Moderna are testing the safety, efficacy, and immunogenicity of their vaccines in children aged 6 months to 11 years old.

Results:

The BNT162b2 mRNA vaccine (Pfizer-BioNTech) demonstrated an efficacy of **75% (95% CI, 7.6-95.5)** after one dose and an efficacy of **100%** after the second dose in adolescents aged 12 to 15 years old (66). On the other hand, the mRNA1273 vaccine (Moderna) demonstrated a similar efficacy after one dose **(92.7%)** and second dose **(93.3%)** in adolescents aged 12 to 17 years old (67).

In terms of the humoral response elicited by the mRNA vaccines in adolescents, adolescents aged 12 to 15 years old administered with BNT162b2 reported a robust immune response with **1283 GMN_{50}** neutralizing antibodies one month after the second dose (66). As for the mRNA1273 vaccine, adolescents aged 12 to 17 years of age responded with a slightly higher number of neutralizing antibodies **(1401.7 GMN_{50})** and with a **98.8%** positive serological response (67).

[32] Pfizer/BioNTech COVID-19 vaccine approved for young people in Switzerland. *Swissmedic*. https://www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/covid-19-impfstoff-pfizer-biontech-fuer-jugendliche.html

[33] Swissmedic approves the extension of the indication for the Spikevax vaccine to people aged 12 to 17. *Swissmedic*. https://www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/indikationserweiterung-spikevax-impfstoff.html

Both mRNA vaccines have demonstrated to be safe in the 12 years old and above age group. Nevertheless, local and systemic events were reported in both groups – which were generally mild to moderate. In the 12 to 15 year old participants administered the BNT162b2 vaccine, adverse events were reported in **6%** and severe adverse events were only reported in **0.6%** of the participants (66). Injection-site pain **(86%)**, fatigue **(66%)**, and headache **(65%)** were the most common mild-to-moderate events reported (66). As for the participants that received the mRNA1273 vaccine, similar results were demonstrated. The most common solicited adverse events reported in adolescents aged 12 to 17 years old were injection-site pain **(92.4%)**, headache **(70.2%)**, and fatigue **(67.8%)** (67). Although both vaccines have demonstrated to be safe, very few reports of acute myocarditis and pericarditis have been reported in children aged 16 to 17 with an adjusted risk ratio for myocarditis/pericarditis events in children and young adults between 16 and 24 years of age of **0.94 (95% CI, 0.59-1.52)** (68).

What is the status of new SARS-CoV-2 vaccines?

Summary:

Apart from the 6 WHO EUL approved vaccines, numerous vaccine candidates such as Sputnik V, Novavax, Ad5-nCov, Covaxin, and Abdala/Soberana have shown promising results in terms of their immunogenicity, tolerability, and efficacy. A short summary of the results is found down below.

Results:

Sputnik V:

Results on the immunogenicity elicited by the first dose of the Sputnik V vaccine are promising. After the first dose of Sputnik V, **94%** of seronegative participants developed SARS-CoV-2 IgG response with a geometric mean titer of **244 (95% CI, 180-328)** (69). A small difference was observed in different age groups, with participants younger than 60 years old showing a **96%** seroconversion after the first dose and participants older than 60 showing a seroconversion of **89%** after the first dose (69). After the second dose was administered, **100%** participants showed seroconversion with a **GMT of 2148 (95% CI, 1742-2649)** (69). Neutralizing antibodies were detected in **90%** of the naïve population, after the first dose (69).

Additionally, in a study analysing the neutralizing activity of sera from Sputnik V vaccinated people against variants of concerns, no significant differences were observed in neutralizing activity against B.1.1.7, B.1.617.3 and the wild type and local genetic lineages (70). About 3.1-

folds decrease against B.1.351, 2.8-folds decrease against B.1.351, P.1, and 2.5-folds decrease against the B.1.617.2 in the neutralizing activity were observed (70).

The results of a study examining the longitudinal antibody response and viral neutralizing capacity against variants of concern in volunteers up to 6 months after receiving the Sputnik V vaccine, indicated that while the anti-spike IgG levels significantly waned over time, neutralizing antibodies against the first-wave lineages of SARS-CoV-2 and variants of concern increased within 4 months of vaccination (71). Serum samples collected 42 days after vaccination showed a **2.5- and 5.1-fold decrease** in neutralizing activity against the Alpha and Delta variants, respectively. Additionally, the samples were less effective at neutralizing the Beta and Gamma variants **(19.2- and 13.8-fold reduction, respectively)**. Furthermore, serum samples collected 120 days after vaccination showed a further decrease in neutralizing activity against the Alpha, Beta, Gamma, and Delta variants **(2.9-, 9.7-, 4.2-, 3.4-fold decrease)** (71). However, the neutralizing potency index (calculated by dividing the neutralizing titer of each sample by its respective IgG anti-spike concentration (IU/mL)) values were reported to increase over time, suggesting the maturation of antibody response in Sputnik V vaccinated participants (71).

Novavax:

Data from an ongoing phase 2 trial assessing the 2 dose Novavax COVID-19 vaccine showed that a 6-month booster dose, in observed participants, significantly improved antibody titers with a 4.6-fold increase in functional antibody titers and provided hope of benefit against the Delta variant (B1.617.2) (72).

Ad5-nCov:

In a randomised phase 1 clinical trial for the safety, tolerability and immunogenicity of the Ad5-nCoV COVID-19 vaccines in adults, the Ad5-nCoV vaccine was administered via intramuscular injection, aerosol inhalation, or both. From the results, the aerosolised vaccines were well tolerated without causing any vaccine related serious adverse events, and the two doses of the aerosolised vaccine elicited neutralising antibody response, similar to the one dose of intramuscular injection (73). Additionally, an aerosolised booster vaccination at 28 days after the first intramuscular injection induced strong IgG and neutralising responses (73).

CureVac:

No further studies after the preliminary results of phase 2b/3 trials of the COVID-19 vaccines candidate CVnCoV (CureVac) were found with new relevant data.

Covaxin:

Covaxin is an Indian developed and manufactured COVID-19 vaccine that uses a whole-virion inactivated vero cell derived platform technology. The vaccine is currently undergoing its phase 3 efficacy trial. Preliminary results from a cross-sectional coronavirus vaccine-induced antibody titre study after the first dose of ChadOx1-nCOV and BBV-152(Covaxin), assessed the the anti-spike binding antibody at four timepoints between 21 days or more after the first dose to 6 months after the second dose (74). The responder rate and median rise in anti-spike antibody was reported as **43% and 6 AU/mL** in participants who received the Covaxin vaccine and showed seroposivity to anti-spike antibody 21 days or more after the first dose. **31.2%** of Covaxin receipients reported adverse events (74).

Abdala/Soberana:

The Abdala vaccine (three dose vaccine), and the Soberana vaccine (Soberana 01, Soberna 02, and Soberana Plus) are COVID-19 vaccines produced in Cuba by BioCubaFarma. The vaccines use a SARS-CoV-2 spike protein conjugated chemically to meningococcal B or tetanus toxoid or Aluminum. The Centre for State Control of Medicines, Equipment and Medical Devices reported for the Abdala vaccine to be 92% efficacious after the administration of its three doses (75). Additionally, the administration of Soberana2 combined with a booster vaccine called Soberana Plus were reported to be 91% effective, as reported by the centre (75).

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