

Literature screening report

COVID-19 vaccines and post-vaccination data: Literature update (13)

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Abstract

This report addresses the most relevant data on COVID-19 vaccines literature as of 28 January 2022. The current report addresses the latest data on the newly identified variant of concern (VOC) Omicron, vaccine effectiveness, booster doses, children vaccination, and new 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 long-term vaccine immunogenicity and vaccine effectiveness against variants of concern (VOC), particularly the Delta (B.1.617.2) variant and the recently identified Omicron (B.1.1.529) strain, arise.

The Omicron strain encompasses several mutations that evade vaccine-induced immunity given that all manufactured vaccines express the ancestral SARS-CoV-2 Spike (S) glycoprotein (the S glycoprotein, in addition to its antigenic domains and epitopes generate neutralizing antibodies against SARS-CoV-2 infection).¹ As a result, immune responses against the Omicron variant are weaker when compared to past VOCs,² leading to the rapid increase and dissemination of breakthrough and reinfection cases throughout Switzerland and Europe.³

Despite SARS-CoV-2 incidences in Switzerland being the highest they have ever been throughout this pandemic, “the number of hospitalizations relative to the confirmed cases have been falling steadily since mid-October 2021”⁴, demonstrating the protective effects of vaccines against severe SARS-CoV-2 cases. Additionally, the basic reproduction number (R_0) has dropped from an estimated value of **1.6** in late December 2021 to **1.19 (95% CI, 0.98-1.4)** by 25 January 2022⁵, indicating that Switzerland may have already reached the peak of the Omicron wave or will reach it soon⁶. Switzerland is currently monitoring a subtype of the Omicron VOC, BA.2, a strain that is currently on the rise and is harder to distinguish through PCR tests. The BA.2 strain’s frequency is still rare in Switzerland, however it already accounts

¹ SARS-COV-2 vaccines based on the Spike glycoprotein and implications of new viral variants. *Frontiers in Immunology*. <https://www.frontiersin.org/articles/10.3389/fimmu.2021.701501/full>

² [https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964\(21\)00379-0/fulltext](https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00379-0/fulltext)

³ Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nature*. <https://doi.org/10.1038/s41586-021-04389-z>

⁴ Scientific update of 25 January 2022. *Swiss National COVID-19 Science Task Force*. <https://scienctaskforce.ch/en/scientific-update-of-25-january-2022/>

⁵ Scientific update of 25 January 2022. *Swiss National COVID-19 Science Task Force*. <https://scienctaskforce.ch/en/scientific-update-of-25-january-2022/>

⁶ Coronavirus: the situation in Switzerland. *SwissInfo* https://www.swissinfo.ch/eng/covid-19_coronavirus--the-situation-in-switzerland/45592192?utm_campaign=teaser-in-channel&utm_source=swissinfoch&utm_content=o&utm_medium=display

for over 50% of sequenced cases in Denmark, India and the Philippines⁷. Thus far, little is known about BA.2's immune evasion, transmissibility, and virulence.

Despite reports of immune escape, a third dose of COVID-19 vaccines has demonstrated to provide adequate protection against serious illness and hospitalizations. Various western countries throughout the world are currently administering the third booster dose to its populations and Israel has begun to administer a fourth dose to persons above the age of 60 years and to health-care workers.⁸

Nevertheless, the WHO is calling for countries to re-evaluate their strategies to keep administering booster doses every time a new variant emerges and instead should focus on “producing new vaccines that work better against transmission of emerging variants”.⁹ These new vaccines should “elicit immune responses that are broad, strong, and long lasting in order to reduce the need for successive booster doses”.¹⁰

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 provides an in-depth summary of the latest published data regarding COVID-19 vaccine immunogenicity and effectiveness, particularly against the Omicron variant. Our report covers the following questions/points:

Questions addressed

- How does the Omicron variant affect COVID-19 vaccines?
- What is the latest information regarding vaccine effectiveness?
- What is the latest data on COVID-19 booster doses?
- What are the latest updates regarding COVID-19 vaccines in children?
- What is the status of SARS-CoV-2 vaccine candidates?

⁷ Scientific update of 25 January 2022. *Swiss National COVID-19 Science Task Force*. <https://scienctaskforce.ch/en/scientific-update-of-25-january-2022/>

⁸ Fourth dose of COVID-19 vaccines in Israel. *The Lancet – Respiratory Medicine*. [https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(22\)00010-8/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00010-8/fulltext)

⁹ COVID-19: Focus should be on new vaccines rather than boosters, says WHO. *BMJ*. <https://www.bmj.com/content/376/bmj.o108>

¹⁰ COVID-19: Focus should be on new vaccines rather than boosters, says WHO. *BMJ*. <https://www.bmj.com/content/376/bmj.o108>

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 28 January 2022. We focused on studies that would help to discuss the points raised above. For more information on the methodology, please refer to previous reports¹¹.

Results and Findings

How does the Omicron variant affect COVID-19 vaccines?

Summary:

Since the Omicron variant's (B.1.1.529) identification in early November 2021, and its recognition by the WHO's Technical Advisory Group on 26 November 2021 as a variant of concern (VOC), Omicron cases have soared worldwide and is on the way to becoming the dominant variant across the globe.¹² The Omicron variant is characterised by its high (30-40) number of mutations in the virus spike (S) glycoprotein,¹³ leading to higher affinities to the binding angiotensin-converting enzyme 2 (ACE-2) domain of the SARS-CoV-2 virus,^{14,15} and potential evasions of vaccine-induced immunity.^{16,17} While certain data and knowledge (i.e. real world vaccine effectiveness & transmissibility) regarding the

¹¹ COVID-19 vaccines: efficacy and safety (Literature Review 1). Swiss School of Public Health.

https://www.bag.admin.ch/dam/bag/de/dokumente/mt/k-und-i/aktuelle-ausbrueche-pandemien/2019-nCoV/Literaturrecherchen/literaturrecherchen_covid-19-impfstoffe_20210209.pdf.download.pdf/20210209_Literaturrecherchen_Covid-19-Impfstoffe_EN.pdf

¹² Weekly epidemiological update on COVID-19 – 11 January 2022. World Health Organization.

<https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---11-january-2022>

¹³ In comparison to 7-10 mutations in the other VOCs; Neutralization and Stability of SARS-CoV-2 Omicron variant. medRxiv.

<https://www.biorxiv.org/content/10.1101/2021.12.16.472934v1.full>

¹⁴ The Omicron variant increases the interaction of SARS-CoV-2 spike glycoprotein with ACE2. bioRxiv.

<https://www.biorxiv.org/content/10.1101/2021.12.06.471377v2>

¹⁵ Structural insights of SARS-CoV-2 spike protein from Delta and Omicron variants. bioRxiv.

<https://www.biorxiv.org/content/10.1101/2021.12.08.471777v1>

¹⁶ Reduced neutralization of SARS-CoV Omicron B.1.1.529 variant by post-immunization serum. medRxiv.

<https://www.medrxiv.org/content/10.1101/2021.12.10.21267534v1>

¹⁷ Reduced neutralization of SARS-CoV Omicron B.1.1.529 variant by post-immunization serum. medRxiv.

<https://www.medrxiv.org/content/10.1101/2021.12.10.21267534v1>

Omicron strain need further clarification and analysis, recently published studies have confirmed that although vaccine-induced immune responses against Omicron is substantially lower than that of the ancestral wild type (Wuhan) strain,¹⁸ and the Alpha, Beta and Delta VOCs,¹⁹ neutralizing antibody responses remain protective among boosted (three vaccine doses)^{20,21} individuals or in previous SARS-CoV-2 infected persons who are double vaccinated.²² This decrease in antibody efficacy explains the rapid increase and dissemination of breakthrough and reinfection cases.²³ Omicron's considerable immune evasion and community spread (even among vaccinated or recovered individuals²⁴) is causing a shift away from the Delta VOC predominance.^{25,26,27} The number of Omicron infections have already surpassed the number of Delta infections in Switzerland; 90% of sequenced SARS-CoV-2 cases were caused by the B.1.1.529 strain.²⁸

Results:

Immunogenicity:

Since Omicron's recognition as a VOC in late November 2021, various immunological studies have confirmed the B.1.1.529 strain's ability to escape both convalescent and vaccine-induced immunity. A preliminary literature review outlined that the neutralizing potency of all eight WHO-approved COVID-19 vaccines and the Sputnik V vaccine is substantially reduced against the Omicron variant (1); BNT162b2-double-vaccinated individuals demonstrated **15- to 127-fold** reductions in neutralization capacities, while the neutralizing potency among those vaccinated with mRNA-1273 and BBIBP-CorV decreased by **factors of 9-122 and 12-20**, respectively (1). Serum samples from BNT162b2 (obtained 1 month post second dose), mRNA-1273 (obtained 4-6 months post second

¹⁸ Reduced neutralization of SARS-CoV Omicron B.1.1.529 variant by post-immunization serum. *medRxiv*.

<https://www.medrxiv.org/content/10.1101/2021.12.10.21267534v1>

¹⁹ SARS-CoV-2 Omicron Variant neutralization in serum from vaccinated and convalescent persons. *New England Journal of Medicine*. https://www.nejm.org/doi/full/10.1056/NEJMc2119236?query=featured_home

²⁰ Variable loss of antibody potency against SARS-CoV-2 B.1.1.529 (Omicron). *medRxiv*.

<https://www.biorxiv.org/content/10.1101/2021.12.19.473354v1>

²¹ Neutralization and Stability of SARS-CoV-2 Omicron variant. *medRxiv*.

<https://www.biorxiv.org/content/10.1101/2021.12.16.472934v1.full>

²² Imprinted SARS-CoV-2-specific memory lymphocytes define hybrid immunity. *medRxiv*.

<https://www.medrxiv.org/content/10.1101/2022.01.12.22269192v1>

²³ Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nature*. <https://doi.org/10.1038/s41586-021-04389-z>

²⁴ Evidence of early community transmission of Omicron (B.1.1.529) in Delhi – a city with very high seropositivity and past-exposure! *medRxiv*. <https://www.medrxiv.org/content/10.1101/2022.01.10.22269041v1.full-text>

²⁵ The spread of SARS-CoV-2 variant Omicron with the doubling time of 2.0–3.3 days can be explained by immune evasion. *medRxiv*.

<https://www.medrxiv.org/content/10.1101/2021.12.08.21267494v2>

²⁶ Evidence of early community transmission of Omicron (B.1.1.529) in Delhi- A city with very high seropositivity and past-exposure!. *medRxiv*.

<https://www.medrxiv.org/content/10.1101/2022.01.10.22269041v1>

²⁷ A Quick Displacement of the SARS-CoV-2 variant Delta with Omicron: Unprecedented Spike in COVID-19 Cases Associated with Fewer Admissions and Comparable Upper Respiratory Viral Loads. *medRxiv*.

<https://www.medrxiv.org/content/10.1101/2022.01.26.22269927v1>

²⁸ Scientific update of 25 January 2022. *Swiss National COVID-19 Science Task Force*. <https://scienctaskforce.ch/en/scientific-update-of-25-january-2022/>

dose) or ChAdOx1 nCoV-19 (obtained 1 month post second dose) vaccinated individuals demonstrated significantly lower neutralization capacities against the Omicron variant than when compared with the Alpha, Beta, or Delta variants (2). Likewise, serum samples from either Alpha-, Beta-, or Delta-recovered individuals were not able to effectively neutralize the Omicron variant (all samples were below the IC_{50} cut off; apart from one Beta-convalescent and one Delta-convalescent sample (2). Serum samples obtained from SARS-CoV-2 recovered and vaccinated individuals effectively neutralized the Omicron variant ($IC_{50} \sim 256$), although to a lesser extent than the Delta variant ($IC_{50} \sim 1024$) (2). A similar study demonstrated that neutralizing activity against the B.1.1.529 strain dropped **23- and 42-fold** among BNT162b2 and 42 mRNA-1273 vaccinated individuals, respectively, relative to the ancestral wild type (WT) strain (3). The mRNA vaccines' neutralizing potency increased against the Omicron variant when boosted, nevertheless, they still demonstrated a **7.5- and 16.7-fold** drop (for BNT162b2 and mRNA-1273, respectively) when compared to WT (3). The long-term effects of waning immunity are also evident against the Omicron VOC; sera collected five months post either BNT162b2 or ChAdOx1 nCoV-19 two-dose vaccination could not detect any neutralization activity against the Omicron variant (4). Another immunogenicity study confirmed that BNT162b2-derived antibody responses against Omicron SARS-CoV-2 pseudoviruses were lower relative to WT and Delta strains throughout all measurement time points (7- and 210-days post second dose, and 7- and 28-days post third dose) (5). It must be noted that pseudotyped viruses are more sensitive to neutralization than live viruses (6); the study's results may thus be an overestimation of BNT162b2's neutralization capacity of the Omicron variant and should be interpreted with caution. A study that compared both pseudo and live virus neutralization assays observed that geometric mean neutralization titres (GMT) against Omicron pseudovirus were **22.8-fold lower** than the Wuhan WT pseudovirus while neutralizing GMTs against live B.1.1.529 were **61.3-fold lower** compared to the WT reference, when vaccinated with BNT162b2 (21-days post full vaccination) (7). To contrast Omicron's results with previous VOCs, neutralization titres against Beta and Delta pseudoviruses were **reduced by 6.7-fold (GMT of 24)** and **2.2-fold (GMT of 73)**, respectively, when compared to the Wuhan pseudovirus (7). When triple vaccinated, GMTs against live B.1.1.529 strains were only **3.4-fold lower** when compared to WT neutralization assays from fully BNT162b2-vaccinated individuals' sera samples (7), indicating that while two doses of the BNT162b2 mRNA vaccine may not effectively protect against Omicron infection, three doses boosted neutralization capacities against Omicron to "robust levels" (7). Studies have been demonstrating that longer intervals between mRNA vaccination doses (i.e. ≥ 40 days) improves immunogenicity against the Delta variant (i.e. **GMT=54.6** [spike antibody concentration: **1697 U/mL**] when dosing interval was 18-28 days vs. **GMT=230.8** [spike antibody concentration: **2476 U/mL**] when dosing interval was between 42-49 days) (8). While further research is needed to confirm this with the Omicron VOC (8, 9), a preprint

study observed that plasma from individuals who received a long-dose interval regimen (16 weeks) of the BNT162b2 vaccine were better able to neutralize the Omicron variant compared to individuals who received a 4-week interval regimen (10).

Breakthrough Infections:

Numerous preliminary studies show early evidence that Omicron breakthrough infections occur at increased rates in comparison to Alpha or Delta variants, which may suggest high transmissibility and decreased vaccine effectiveness against the newest variant of concern (11-13). However, studies also consistently demonstrated that hospitalization, disease severity, and overall disease outcomes are less severe for Omicron-associated infections compared with other circulating variants.

In a cohort study investigating risk of hospitalization or death in Long-Term Care Facility (LTCF) residents who tested positive for SARS-CoV-2 in England between 01 September 2021 and 17 January 2022, results largely agreed with other preliminary studies on the decreased severity of Omicron. Among 1241 LTCF residents infected during the Omicron-period, **4.01% (95% CI, 2.87-5.59)** were hospitalized compared with **10.08% hospitalizations (95% CI, 8.13-14.29)** in 398 LTCF residents infected during the pre-Omicron period (14). This reduction in risk of hospitalization was similar for all LTCF residents regardless of vaccine received (AstraZeneca, ChAdOx1, Pfizer) or unvaccinated status. Moreover, within 28 days following infection; the authors found reduced risk of death during the predominance of the Omicron variant with **1.1 deaths/1000 person-days (95% CI, 0.6-2.2)** compared to **3.8 deaths/1000 person-days (95% CI, 2.8-5.2)** during the pre-Omicron period (14). When restricting analyses to sequenced or spike-gene status confirmed/probable subsets of Delta or Omicron infections, results of the main study were further supported. Subset analyses also demonstrated that Omicron infections are associated with substantially reduced disease severity and death compared with previous variants.

A study in Thailand examining binding antibody responses and neutralization of SAR-CoV-2 variants using sera from COVID patients vaccinated with CoronaVac, COVID naïve individuals vaccinated with CoronaVac, and individuals who received AZD1222 (Oxford-AstraZeneca) as a booster dose provide some insight regarding Omicron breakthrough infections. Results showed that sera from patients with vaccine-induced immunity and breakthrough infections had reduced neutralizing activity against Omicron with neutralizing potency **11.7-fold less** than that for wild-type, and **7.9-fold less** than that for Delta (15). Decreased antibody neutralization may allude to immune escape of the Omicron variant in breakthrough cases. A decrease in neutralization against Omicron was also found in a study conducted in South Africa using sera from persons vaccinated with BNT162b2 and previously infected with COVID as well as vaccinated persons without history of infection. Similar to the study in Thailand, results from this South African investigation showed a **22-fold escape** from

vaccine elicited neutralization of Omicron (16). Here, the authors suggest that partial escape of the Omicron may be a factor to the variant's milder breakthrough infections in terms of hospitalization (length of stay, requirement for extensive medical interventions, and death).

Transmission:

While much is still unknown about the transmissibility of the Omicron variant, rapid increases in COVID-19 cases around the world confirm that the Omicron VOC is partially able to evade vaccine-derived immunity and demonstrates higher person-to-person transmissibility (17). Infection rates in South Africa, the first country to report the B.1.1.529 strain to the WHO (24 November 2021), increased substantially, faster than any previous SARS-CoV-2 waves in the country (16). A South African lab group measured Omicron's exponential growth in the Gauteng Province from 8 November to 5 December 2021, observed that the Omicron VOC demonstrated a doubling time of **3.38 (95% CI, 3.18-3.61) days** (18). Data collected over a four week period from early to late November 2022 revealed even shorter doubling times in Australia (**3.0 days**), New York state (**2.5 days**), Denmark (**2.0 days**), and the United Kingdom (UK; **2.4 days**) (19). By 22 December 2021, Omicron cases were doubling every **1-2 days** in the UK (20). Omicron's increased transmissibility rate is explained by its numerous spike protein mutations; the NY501Y mutation enhanced the strain's ACE-2 binding affinity, which in combination with waning immunity, leads to greater numbers of case infections and transmissions (17). Nevertheless, boosted individuals demonstrate reduced transmissions rates (particularly when their contacts are also boosted) compared to non-boosted individuals; for example, a Norway contact tracing investigation reported a **59% confirmed secondary attack rate** of Omicron cases among fully vaccinated individuals (21) while an Israeli study only reported a **2% infection rate among primary contacts** (of which 88% were triple-vaccinated and 91% wore masks) (22).

Effectiveness:

As COVID-19 continues to surge worldwide throughout the Winter season, the Omicron VOC has been identified to be the cause of the majority of cases in many countries. Current literature shows that vaccine effectiveness (VE) against the latest VOC is significantly lower than that against earlier VOCs such as Beta and Delta.

Using Danish nationwide databases from 20 November 2021 to 12 December 2021, preliminary studies conducted in Denmark investigating effectiveness of BNT162b2 or mRNA-1273 against Omicron infection show that VE was **55.2% (95% CI, 23.5- 73.7%)** for BNT162b2 and **36.7% (95% CI: -69.9-76.4%)** for mRNA-1273 in the first month after primary vaccination (23). However, these results were found to be significantly lower compared with Delta infection and declined rapidly over time. Evidence of low VE mRNA-1273 against Omicron were further corroborated by a study

conducted in the United States which evidenced that VE against Omicron infection was **30.4% (95% CI, 5.0-49.0)** at 14-90 days after complete vaccination and declined quickly thereafter (24).

Despite results of low effectiveness against infection with the Omicron variant, there is also evidence that vaccination protects against severe disease outcomes. In the Sisonke phase 3B Ad.26.COV2.S vaccine trial conducted in South Africa among health care workers, the authors show that although rates of Omicron breakthrough infections were higher compared with Delta, disease was less severe overall. Among a total of 40,538 breakthrough infections detected during the period of study (17 February 2021 to 15 December 2021), it was found that **Omicron daily infections were three times the peak observed during predominance of the Delta variant** (12). Of the 1,914 breakthrough infection-related hospitalizations identified, **408 hospitalizations occurred during Omicron** study period in comparison with **77 during the Beta period** and **1,429 during the Delta period** (12). Patients with Omicron were also found to require significantly less intensive care and intense respiratory support than patients infected with Beta or Delta variants (12). Among hospitalized HCWs, **3% required intensive care** during the Omicron period compared with **7% during Delta** and **16% during Beta** study periods (12). Finally, the length of hospital stay was significantly lower with Omicron cases (**median length of 3 days**) compared with Beta and Delta cases (**median length of 5-6 days**) (12).

Overall, early studies show that effectiveness of vaccines against infection with the Omicron variant are significantly lower in comparison with other VOCs. However, there is also substantial evidence that vaccines protect against hospitalization, extensive medical treatment, and mortality (25-27). A review of reported studies investigating VE against Omicron emphasized that while current literature shows lower effectiveness of primary and booster vaccinations against Omicron infection, VE are still within FDA criteria for reduction of symptomatic infections (28). Further, the study reiterated that vaccination offers considerable protection against severe disease outcomes for Omicron in comparison with other VOCs. As new information is discovered about Omicron, additional studies are needed to truly understand the pathogenicity of the variant in order to guide decision making about vaccination campaigns and other health measures.

Booster:

The new variant of concern Omicron (B.1.1529) has raised many concerns amongst the scientific community as numerous studies demonstrated the decrease in neutralizing capacity against the variant of concern. Nevertheless, studies analyzing the effects of booster doses against the Omicron variant are showing that a third homologous or even heterologous booster dose significantly increases the neutralizing antibodies compared to the primary vaccination schedule. This increase in neutralizing antibodies can be noted in studies evaluating the third dose of the BNT162b2 booster

against Omicron. This is the case of the following studies. In the first study conducted by Furukawa and colleagues, the induction of neutralizing antibodies against Omicron after two or three doses of the BNT162b2 vaccine in recipients of different ages was investigated (29). Based on the results, the booster vaccination effectively increased the neutralizing antibody titers against the wild type, Delta, and Omicron variants. In the younger age group, the neutralizing antibodies increased by **41-fold** (95% CI, 30-56), while in the middle-aged and older groups, the increase was of **43-fold** (95% CI, 32-58) and **27-fold** (95% CI, 20-36), respectively (29). Another similar study also evaluating the neutralization capacity of the BNT162b2 booster dose against Omicron, found that the third booster vaccination induced a robust increase in anti-spike antibodies and cross-reactivity with Omicron (30).

Similar outcomes regarding the Omicron variant can be noted in other booster doses such as mRNA1273 and BBIBP-CorV. For instance, a study evaluating the Omicron neutralization by serum samples of participants who received a third mRNA1273 homologous booster dose observed that a booster dose of 50 µg of the mRNA-1273 vaccine increased the geometric mean titers by **20-fold** against the Omicron variant (31). Although an increase in neutralizing antibodies against Omicron was noted in boosted participants, these titers were **2.9 times lower** than those against the wild type. Additionally, the neutralization titers against Omicron 6 months after the third dose were **6.3 times lower** than the peak titers assessed 1 month after receiving the booster injection, but remained detectable in all participants (31). Overall, the results showed that booster dose was associated with an increase in neutralizing antibodies, substantially reducing the risk of breakthrough infections. In another study analyzing the neutralizing sensitivity of the BBIBP-CorV homologous booster against the Omicron variant, the results demonstrated that, although the booster dose increased the neutralizing antibodies against the Omicron variant, the vaccine-induced immunity was more likely escaped by Omicron than other variants of concern (32). Based on the results, the neutralizing antibodies increased to **285.6 pVNT**, **215.7 pVNT**, **250.8 pVNT**, and **48.73 pVNT** against the wild type, Beta, Delta, and Omicron variants 14 days after receiving the homologous booster dose (32).

Similar results have also been noted in heterologous booster doses. A study including six vaccination combinations (four homologous primary-booster combinations including mRNA-1273 (Moderna, two doses of 100-µg) followed by boosting with 100-µg or 50-µg mRNA-1273, Ad26.COVS (Janssen, one dose of 5×10^{10} virus particles) followed by the same dose of Ad25.COVS and BNT162b2 (Pfizer-BioNTech, two doses of 30-µg) followed by 30-µg of BNT162b2; and two heterologous primary-booster combinations: BNT162b2 followed by Ad26.COVS and Ad26.COVS followed by BNT162b2) assessed the homologous and heterologous capacity to neutralize the wild type and Omicron variant (33). Based on the results of the study, the booster dose increased the geometric mean titers (GMTs) in most combinations to above **1000** against the wild type and above **250** against Omicron; however, the GMTs were **2.3 to 7.5-fold lower** against Omicron than the wild type (33).

Out of all combinations, the homologous prime-boost Ad26.COV2.S had the lowest neutralizing antibodies on day 29 after the booster against both the wild type and Omicron variant (33). Another study evaluating the neutralizing antibodies of heterologous booster doses concluded similar results as the previous study. The study tested for neutralizing antibodies against the wild type and Omicron variant in participants aged 30 years and over who previously received two doses of an inactivated COVID-19 vaccine and were administered a third dose of the BNT162b2 vaccine (34). Based on the results, a third heterologous booster dose of BNT162b2 substantially increased antibody titers by boosting the neutralizing titers by **at least 27-fold** against the wild type and by **at least 14-fold** against the Omicron variant (34). Overall, heterologous booster doses have shown to increase the neutralizing capacity against the Omicron variant when compared to non-boosted groups.

On top of increasing the immune response against Omicron, booster doses have also shown to restore and increase the reported waning effectiveness. In this matched test-negative case-control study conducted in individuals vaccinated with a mRNA booster dose, the effectiveness of mRNA boosters was analyzed against Delta and Omicron infections as well as COVID-related hospitalization and COVID-19 related deaths due to the Omicron variant (25). Based on the results, the vaccine effectiveness against Delta infection was **77%** (95% CI, 75-79), **62%** (95% CI, 59-65) against Omicron infection, **91%** (95% CI, 85-94) against Omicron COVID-19 related hospitalization, and **96%** (95% CI, 91-98) against Omicron COVID-19 related deaths (25). Overall, the administration of an mRNA booster dose continued to protection against infections, hospitalization, and death caused by the Omicron variant (25).

What is the latest information regarding vaccine effectiveness?

Summary:

Numerous studies regarding the effectiveness of leading first-generation SARS-CoV-2 vaccines continually demonstrate positive evidence against reducing any SARS-CoV-2 infections, symptomatic COVID-19, severe cases, hospitalization, and death even amidst circulation of variants.^{29,30,31} Although we are currently in an Omicron dominant period of the pandemic, Delta remains a large public health concern especially when considering waning immunity, breakthrough infections, and the immune comprised (i.e., the elderly population). New studies support previous data that mRNA-based vaccines are highly effective against infection with Delta and associated hospitalizations, and advocate for booster doses and prioritization of older populations. Furthermore, literature regarding vaccine effectiveness of inactivated viral vaccines continue to be published at a slower rate compared to mRNA and adenovirus-vector vaccines. While studies have shown comparable effectiveness of inactivated vaccines to its other vaccine counterparts, mRNA vaccines still demonstrate higher VE overall and slower rates of waning immunity.^{32,33}

Results:

In a meta-analysis conducted in October 2021 to assess the overall effectiveness of mRNA-1273 vaccination against the Delta variant, researchers found that the full-dose of mRNA-1273 still confers considerable protection against infection from Delta albeit lower than the reported efficacy from phase 3 randomized trials. From the five studies included in the review, pooled vaccine effectiveness of mRNA-1273 against the Delta variant was **66% (95% CI, 65.0–67.0)** ≥21 days after the first dose and **91% (95% CI, 84.0–95.0)** ≥14 days after the second dose (35). Although this systematic review and meta-analysis was limited due to its inclusion and exclusion factors, findings are still relevant in supporting the continued relevance of vaccines and administration of booster doses.

²⁹ Early effectiveness of BNT162b2 Covid-19 vaccine in preventing SARS-CoV-2 infection in healthcare personnel in six Israeli hospitals (CoVEHPI). *Vaccine*. <https://www.sciencedirect.com/science/article/pii/S0264410X21015802?via%3Dihub>

³⁰ Comparative Effectiveness of Coronavirus Vaccine in Preventing Breakthrough Infections among Vaccinated Persons Infected with Delta and Alpha Variants. *CDC*. https://wwwnc.cdc.gov/eid/article/28/2/21-1789_article

³¹ Vaccination Induces Stronger Spike Immunity and Better Protection Against SARS-CoV-2 Infection in COVID-19 Recovered Subjects than in Naïve Individuals. SSRN Preprint. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4000583

³² SARS-CoV-2 Reinfection Rate and Estimated Effectiveness of the Inactivated Whole Virion Vaccine BBV152 Against Reinfection Among Health Care Workers in New Delhi, India. *JAMA*. <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2787712>

³³ Waning antibody levels after COVID-19 vaccination with mRNA Comirnaty and inactivated CoronaVac vaccines in blood donors, Hong Kong, April 2020 to October 2021. *Eurosurveillance*. https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2022.27.2.2101197#html_fulltext

A study in Slovenia investigating the effectiveness of vaccines authorized in the country (BNT162b2, mRNA-1273, ChAdOx1n CoV-19, and Ad26.COV2-S) against severe COVID-19 disease was conducted during the predominance of the Delta variant in October 2021. Using national surveillance data from all hospitals in Slovenia as well as national registry databases, the authors found that vaccines were highly effective against hospitalizations with VE for full vaccination status at **86% (95% CI, 79.0–90.0)** for ages 18-49, **89% (95% CI, 85.0–91.0)** for 50-64, and **77% (95% CI, 74.0–81.0)** for ≥ 65 year-olds (36). However, among individuals who received mRNA-based vaccines, waning immunity was observed especially among individuals ≥ 65 year-old wherein **VE decreased from 93% (95% CI, 88.0–96.0) ≤ 3 months after vaccination to 43% (95% CI, 30.0–54.0) ≥ 6 months after vaccination** (36).

Substantial decrease of vaccine effectiveness among the elderly population are corroborated by other studies investigating COVID-19 outbreaks in long-term care facilities (LTCFs). In a national French survey of LTCFs conducted from March to April 2021, researchers found that despite full vaccination with BNT162b2, VE is low overall but confers strong protection against severe disease and mortality. Of 27 LTCFs participating in the study, the COVID-19 mean attack rate among residents fully vaccinated with BNT162b2 was **18.0% (95% CI, 12.8-23.2)** compared with **27.5% (95% CI, 16.3-38.7)** among unvaccinated individuals (**RR 4.17, 95% CI, 2.43-7.17**) (37). Development of severe cases occurred in **55.3%** of unvaccinated LTCF residents versus **22.9%** of vaccinated residents. Mortality was also higher among unvaccinated residents at **26.3%** and **6.5%** in vaccinated residents (**RR 5.11, 95% CI, 2.49-10.5**) (37). Overall, the estimated VE of BNT162b2 against infection was **34.5% (95% CI, 18.5-47.3)**, **58.6% (95% CI, 43.8-69.6)** against severe disease, and **75.2% (95% CI, 54.6-86.4)** against death (37). Another study conducted in Ireland among nursing home residents vaccinated with BNT162b2 also showed evidence of diminished protection from COVID-19. Based on analyses of Serum Nucleocapsid and Anti-Spike Receptor Binding Domain (RBD) antibodies; researchers found a sharp decline in antibody levels among fully vaccinated, COVID-19 naïve residents (**632.5 U/mL; IQR: 170-1848 U/mL at 5 weeks to 133 U/mL; IQR: 54-337 U/mL at 6 months**) as well as fully vaccinated residents with history of previous infection (**22,451 U/mL; IQR: 14,021-25,000 U/mL at weeks to 6332 U/mL; IQR: 3372-9667 U/mL at 6 months**) (38).

Another study conducted in France using data from the French National Health Data System (which is also linked to the COVID-19 vaccination database) estimated the effectiveness of mRNA-based vaccines in 1.4 million individuals ≥ 75 years old. In this 1:2 cohort study comparing vaccinated and unvaccinated individuals, researchers found an **86% risk reduction (Adjusted HR: 0.14; 95% CI, 0.11-0.17)** of hospitalization from day 7 after second dose of mRNA vaccination among persons aged 75 and older (39). Likewise, a case-control study in Lebanon comparing the effectiveness of Pfizer-

BioNTech against hospitalizations among fully and partially vaccinated individuals ≥ 75 years old showed a VE of **82% (95% CI, 69.0-90.0)** for those fully vaccinated and 53% (95% CI, 23.0-71.00) for those partially vaccinated (≥ 14 days of first or within 14 days of second dose) (40).

As for inactivated and viral vector vaccines, a longitudinal study investigating the influence of age on Vaxzevria and CoronaVac effectiveness conducted in Brazil show that overall VE progressively decreases with age. Among persons < 60 years fully vaccinated with Vaxzevria, VE against death was **96.5% (95% CI, 82.1-99.3)** compared with **68.5% (95% CI, 40.0-83.4)** in those ≥ 90 years (41). Effectiveness against death was even lower among individuals fully vaccinated with CoronaVac, VE was **84.8% (95% CI, 77.1-89.9)** in those < 60 years, **63.5% (95% CI, 58.7-67.7)** for those aged 80-89 years and **48.6% (95% CI, 35.0-59.3)** for individuals aged ≥ 90 years (41). With multiple studies reporting on the diminished protection of vaccines among the elderly, there is sustained evidence that prioritization of primary vaccination and booster doses for this subpopulation is essential.

Other studies investigating inactivated and viral vector vaccines have shown comparative effectiveness to its other vaccine counterparts. A historical cohort study conducted in Iran analyzing the effectiveness of BBIBP-CorV, ChAdOx1-S/nCoV-19, rAd26-rAd5, and BIV1-CovIran demonstrated a significant reduction in infection, hospitalization, and mortality. Among fully vaccinated individuals aged at least 18 years in Southern Iran, VE against infection was **79.9% (95% CI, 79.4-80.4)** for BBIBP-CorV and **84.4% (95% CI, 83.5-85.3)** for ChAdOx1-S/nCoV-19 (42). Further, VE against hospitalization was **71.9% (95% CI, 70.7-73.1)** and **81.5% (95% CI, 79.5-83.4)** for full immunization with BBIBP-CorV and ChAdOx1-S/nCoV-19 respectively (42). Notable reduction in mortality among fully vaccinated individuals was also calculated, with a VE of **86.1% (95% CI, 84.1-88.0%)** for BBIBP-CorV and **91.8% (95% CI, 88.2-95.4)** for ChAdOx1-S/nCoV-19 (42). However, the effectiveness of BBIBP-CorV demonstrated in Iran is contradicted by a study in Bahrain. In this observational analytical study of one “extensive multiplexed Bahraini family” (N=56) authors showed that the Sinopharm vaccine was unable to prevent against COVID-19 infection, but does provide protection against severe disease and reduces mortality (43). Additional studies are required to validate the results of Sinopharm’s “partial protection” since this study was limited to one family in Bahrain.

What is the latest data on COVID-19 booster doses?

Summary:

COVID-19 vaccines have played a major role in mitigating severe disease and death during the ongoing COVID-19 pandemic. Nevertheless, the effectiveness and the protection these vaccines grant has waned over the course of their initial administration. Based on numerous studies evaluating the immunogenicity, protection, and effectiveness of booster doses, the results have demonstrated that the third homologous or heterologous dose has improved the immune response and therefore the protection against SARS-CoV-2.³⁴ Recent studies continue to emphasize that a third homologous dose of BNT162b2,^{35,36,37} Ad26.COVS (Janssen),³⁸ and CoronaVac³⁹ provide a **higher immune response than the previous second doses**. Additionally, heterologous boosters have also shown to provide higher immune responses than the previous two doses, especially when mixing any COVID-19 vaccine platform with an mRNA vaccine.^{40,41} As a matter of fact, Switzerland approved on 27 December 2021 the booster dose with the COVID-19 vaccine Janssen and the administration of mixed vaccination.⁴² Although booster doses have demonstrated to increase the levels of neutralizing antibodies against multiple variants of concern (Alpha, Beta, Gamma, Delta, and Omicron) and provide a higher protection against infections, hospitalizations, and deaths, multiple international organizations continue to advocate for the global prioritization of the first and second doses over boosters.⁴³ While the debate on booster doses continues, countries such as Israel begun vaccinating

- ³⁴ Effects of BNT162b2 Covid-19 Vaccine Booster in Long-Term Care Facilities in Israel. *The New England Journal of Medicine*. <https://www.nejm.org/doi/full/10.1056/NEJMc2117385>
- ³⁵ Association of a Third Dose of BNT162b2 Vaccine with Incidence of SARS-CoV-2 Infection Among Health Care Workers in Israel. *JAMA*. <https://jamanetwork.com/journals/jama/fullarticle/2788104>
- ³⁶ Third Dose of BNT162b2 Vaccine Results in Very High Levels of Neutralizing Antibodies against SARS-CoV-2; Results of a Prospective Study in 150 Health Professionals in Greece. *American Journal of Hematology*. <https://onlinelibrary.wiley.com/doi/10.1002/ajh.26468>
- ³⁷ Serological response to COVID-19 Comirnaty booster vaccine, London, United Kingdom, September to December 2021. *Eurosurveillance*. <https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2022.27.1.2101114>
- ³⁸ Immunogenicity and Reactogenicity of Vaccine Booster after Ad26.COVS Priming. *The New England Journal of Medicine*. <https://www.nejm.org/doi/full/10.1056/NEJMoa2116747>
- ³⁹ Immunogenicity and safety of a third dose of CoronaVac, and immune persistence of a two-dose schedule, in health adults: interim results from two single-centre, double-blind, randomised, placebo-controlled phase 2 clinical trials. *The Lancet Infectious Diseases*. [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(21\)00681-2/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00681-2/fulltext)
- ⁴⁰ Immunogenicity of a third dose viral-vectored COVID-19 vaccine after receiving two-dose inactivated vaccines in health adults. *Vaccine*. <https://www.sciencedirect.com/science/article/pii/S0264410X21015607?via%3Dihub>
- ⁴¹ The immunogenicity against variants of concern and reactogenicity of four COVID-19 booster vaccinations following CoronaVac or ChAdOx1 nCoV-19 primary series. *medRxiv*. <https://www.medrxiv.org/content/10.1101/2021.11.29.21266947v2>
- ⁴² Swissmedic approves booster dose with the COVID-19 vaccine from Janssen-Cilag AG. *Swissmedic*. Accessed on: 24 January 2022. <https://www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/booster-janssen-cilag-genehmigt.html>
- ⁴³ Prioritise first doses of COVID-19 vaccines over boosters, say WHO experts. *GAVI – The Vaccine Alliance*. Accessed on: 21 January 2022. <https://www.gavi.org/vaccineswork/prioritise-first-doses-covid-19-vaccines-over-boosters-say-who-experts>

citizen aged 60 years and over and health-care workers with the fourth dose of a COVID-19 amid the rapid spread of Omicron and the increasing spike of COVID-19 infections.⁴⁴

Results:

Immunogenicity:

A third dose of a COVID-19 vaccine has proven to significantly increase the immune response, antibody levels, and neutralizing capacity against the wild type and variants of concern. This has been the case with the majority of COVID-19 vaccine platform. Recent studies on the BNT162b2 vaccine concur with these findings. For instance, a study conducted in Greece aiming to evaluate the neutralizing antibodies produced by a third dose of BNT162b2 in healthy adults found that the percent inhibition of neutralizing antibodies was the greatest after receiving the booster dose (44). Based on the results, one month after the booster dose the median inhibition percentage was **97.6%** (mean 95.9%); the highest when compared to the first and second dose (44). Another study conducted in London aimed to evaluate the serological response to COVID-19 BNT162b2 booster vaccine in adults aged 50 years and older who received the extended dose interval of the mRNA1273 (mRNA1272-extended) or BNT162b2 (BNT162b2-extended) primary vaccination schedule (received their second dose over 21 days), and participants who received the normal BNT162b2 interval dose (BNT162b2-control) (45). Based on the study's results, the antibody geometric titers (GMT) were the highest at 2-4 weeks in the BNT162b2-control participants with a GMT of **18104** (95% CI, 13911-23560), followed by the BNT162b2-extended participants (**GMT 13980** [95% CI, 11902-16421]), and the mRNA1273-extended participants (**GMT 10799** [95% CI, 8510-13704]) (45). The highest post-booster increase in GMT was observed in the BNT162b2-control participants with a **76.3-fold increase**, followed by the mRNA1273-extended with a **57.2-fold increase**, and the BNT162b2-extended with a **15.9-fold increase** (45). Overall, the BNT162b2 booster dose increased the geometric mean titers in all of the groups.

Until now, the majority of studies analyzing the immunogenicity of booster doses were conducted using the mRNA platform mainly focusing on the third dose of a BNT162b2 dose; however, more and more studies have begun analyzing the effects of a third dose of other COVID-19 platforms. Recently, results on the immunogenicity of a booster dose of the Ad26.COVS.2.S (Janssen), NVX-CoV2373 (Novavax), BBV152 (Covaxin), and CoronaVac vaccine have become available. A single-blind, multicenter, randomized, controlled trial involving health care workers who received the Ad26.COVS.2.S vaccine assessed the immunogenicity and reactogenicity of receiving a homologous

⁴⁴ Fourth dose of COVID-19 vaccines in Israel. *The Lancet – Respiratory Medicine*.

[https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(22\)00010-8/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00010-8/fulltext)

or heterologous booster vaccination (46). Based on the results, participants who received the homologous Ad26.COVS booster vaccination had more binding anti-S IgG antibodies than those who did not receive a booster (**beta coefficient: 0.64** [98.3% CI, 0.41-0.81]). Similarly, participants who received the heterologous BNT162b2 booster vaccine (**beta coefficient: 0.73** [98.3% CI, 0.57-0.90]) and the heterologous mRNA1273 booster vaccine (**beta coefficient: 0.94** [98.3% CI, 0.85-1.12]) had more binding antibodies than those who only received one dose of Ad26.COVS (46). Additionally, the neutralizing antibody levels after the booster were assessed. The results showed that the heterologous mRNA-based booster vaccinations increased the neutralizing antibody levels to a greater extent than the homologous Ad26.COVS booster (46). Overall, the homologous and heterologous boosters led to an increase in binding and neutralizing antibodies, but the increase was higher in participants who received the mRNA heterologous booster dose.

A phase 2 randomized placebo-controlled trial on the booster dose of the NVX-CoV2373 vaccine aimed to analyze the immunogenicity and safety of the homologous booster in healthy adults aged 18 to 84 years of age approximately 6 months following their primary vaccination schedule (47). Based on the results, the serum IgG geometric mean titers (GMTs) following the booster dose for the wild type increased around **4.7-fold** (from **43,905 EU** 14 days after the second dose to **204,367 EU** 28 days after the booster) (47). As for the neutralizing antibodies, a similar increase following the booster was reported with an increase of around **4.1-fold** in GMTs (from 1470 14 days after the second dose and 6023 28 days after the booster) (47). When analyzing the binding inhibition activity against various variants, a **54.4-fold** (wild type), **21.9-fold** (Alpha), **24.5-fold** (Beta), **24.4-fold** (Delta), and **20.1-fold** (Omicron) **increase** in titers was reported 28 days after the booster in comparison to 14 days after the second dose (47). Overall, the administration of a homologous NVX-CoV2373 booster dose approximately 6 months following the primary vaccination enhanced the immune response of participants while proving to be safe and tolerable.

A similar study was conducted with the BBV152 (Covaxin) homologous booster dose. Based on the results from the 184 healthy adults who received the homologous booster 6 months after the second dose, the geometric mean titres increased to **746.6** PRNT₅₀ (95% CI, 514.9-1081) four weeks after the booster vaccination compared with **100.7** PRNT₅₀ (95% CI, 43.6-232.6) in the placebo group (47). As for the neutralizing antibodies against variants of concerns, the GMTs increased **32.6-fold** against the Alpha, **161.0-fold** against the Beta, **264.7-fold** against the Delta, and **174.2-fold** against the Delta plus variants when boosted with the homologous vaccine (47). Overall, the homologous BBV152 booster increased the neutralizing capacity against the wild type and variants of interest, all while remaining safe and tolerable in participants.

Finally, during a phase 2 clinical trial evaluating the immunogenicity and safety of a third homologous CoronaVac dose in healthy adults aged 18 years and older, the results showed that the administration of the homologous booster 8 months after the second dose effectively increased the concentration of antibodies against SARS-CoV-2 (48).

Efficacy/Effectiveness:

Although the effects of a booster dose continue to be evaluated and analyzed, a third COVID-19 vaccine dose has demonstrated to increase the protection and restore the waning immunity against SARS-CoV-2 and its variants of concerns as well as its effectiveness. With the aim of assessing the effects of a booster dose of the mRNA vaccine BNT161b2 on the acquisition of SARS-CoV-2 infection, Spitzer and colleagues provided a booster vaccine dose to a cohort of health care workers who had completed the 2-dose vaccination series of BNT162b2 (49). A total of 1928 health care workers were included in the study, of which only 1650 received a booster dose (49). After obtaining PCR tests before and after the booster dose, the incidence of infection was **116 per 100,000 person-day** prior to the booster dose and **12.8 per 100,000 person-day** after the booster dose (49). Based on those results, an estimated relative reduction of **93% (hazard ratio: 0.07 [95% CI, 0.02-0.2])** was calculated. Overall, the booster vaccine dose demonstrated to reduce the risk of symptomatic and asymptomatic infection.

Another study estimating the effectiveness of the BNT162b2 and mRNA1273 COVID-19 booster vaccines against COVID-19 related symptoms, hospitalizations, and death in adults in England provides evidence that the booster vaccine dose significantly increased the protection against mild and severe disease irrespective of the primary course (50). For this test-negative case-control study a total of 343,955 positive adult cases between 13 September to 5 December 2021 were included in the analysis (50). Based on the results, in individuals aged 18 to 49 years where the primary course was the ChAdOx1-S vaccine, the effectiveness against symptomatic disease peaked at day 14-35 days after the BNT162b2 booster at **89.6%** (95% CI, 88.6-90.4) and **95.3%** (95% CI, 91.8-97.3) after the mRNA1273 booster (50). In individuals where the BNT162b2 vaccine was the primary course, the vaccine effectiveness 14-35 days after the BNT162b2 booster was **82.8%** (95% CI, 81.8-83.7) and **90.9%** (95% CI, 84.5-94.7) 14-35 days after the mRNA1273 booster (50). As for individuals aged 50 years and over, the vaccine effectiveness was similar as the estimated one for individuals aged 18 through 49. When estimating the vaccine effectiveness against hospitalizations and deaths, high levels of protection were also seen. In individuals aged 50 years and over, the vaccine effectiveness 14-35 days after the BNT162b2 booster dose was **99.2%** (95% CI, 98.6-99.5) where the primary course was ChAdOX1-S and **98.6%** (95% CI, 98.0-99.0) where the BNT162b2 was used as the primary course (50). In younger individuals who received the primary course with ChadOx1-S, the

vaccine effectiveness against hospitalizations was **97.5%** (93.3-99.1) and **98.8%** (95% CI, 97.2-99.5) where the BNT162b2 was the primary course (50). Regarding the estimated vaccine effectiveness against deaths in individuals aged 50 years and older, the vaccine effectiveness 14-34 days after the BNT162b2 booster dose was **97.8%** (95% CI, 94.4-99.1) after a ChAdOx1-S primary course and **98.7%** (95% CI, 97.4-99.4) after the BNT162b2 primary course (50).

Heterologous:

Multiple studies examining the immunogenicity and safety of heterologous booster doses have concluded that the administration of a heterologous booster dose was safe, well tolerated, and led to a higher immune response than most homologous booster doses. A recent study conducted in Chile, a country that started inoculating a high percentage of the target population with homologous and heterologous booster schemes, aimed to compare the immunogenicity of the humoral response elicited by the CoronaVac vaccine in combination with homologous or heterologous boosters (51). A total of 44 individuals who were previously vaccinated with two doses of CoronaVac received, around 180 days after the second dose, a booster dose of either the ChAdOx1, BNT162b2, or CoronaVac vaccine. Based on the results, the CoronaVac booster vaccine induced a higher antibody production than the second dose, but to a lesser extent than the other booster doses (51). The CoronaVac booster had a **9.8-fold increase** in antibody production, the ChAdOx1 booster had a **12.4-fold increase** in antibody production, and the BNT162b2 booster had a **11.2-fold increase** in antibody production (51). Additionally, when analyzing the duration of the antibody response following the booster dose, the homologous booster group showed signs of immunological waning 100 days following the booster dose, while the immune response of the heterologous booster groups remained high through the 100 days of investigation (51). Overall, this study demonstrated that the response induced by CoronaVac can be greatly potentiated with a heterologous booster dose of either BNT162b2 or ChAdOx1 vaccines.

Another study evaluating homologous and heterologous booster vaccination in persons who receive the full COVID-19 vaccine regimen demonstrated promising results in terms of reactogenicity and immunogenicity (52). This phase 1/2 clinical trial included healthy adults who had received a COVID-19 vaccine available under EUA (BNT162b2, mRNA-1273, and Ad26.COV2.S.) at least 12 weeks earlier and boosted them with either a homologous booster dose or a heterologous booster dose from the three EUA vaccines. In total 458 participants were enrolled in the study and assigned to the nine different combinations. Based on results, the reactogenicity for the heterologous schedules was similar to the one reported for the primary series where injection site pain, malaise, headache, and myalgia were the main side effects reported in more than half the participants (52). In regards of the immunogenicity elicited by the booster doses, the booster vaccines **increased** the neutralizing activity

by **4- to 73-fold** and binding antibody titers **increased 5- to 55-fold** for all combinations, where the greatest increase was observed in for those who received BNT162b2 and mRNA-1273 boost after an Ad26.COVS.S primary vaccination (52). Homologous booster **increased** neutralizing antibody titers **4- to 20-fold** whereas the heterologous boost **increased** titers **6- to 73-fold** (52). When comparing the different combinations of COVID-19 vaccine booster doses, major differences can be noted. For participants who initially received the completed Pfizer and BioNTech COVID-19 vaccine schedule, receiving a booster dose of Moderna, Pfizer and BioNTech, and Janssen led to an **increase** of IgG binding antibodies of **17-, 15-, and 6-fold**, respectively (52). As for participants who initially received the completed Moderna COVID-19 vaccine schedule, receiving a booster dose of Pfizer and BioNTech, Moderna, and Janssen led to an **increase** of IgG binding antibodies of **10-, 8-, and 5-fold**, respectively (52). Finally, participants who initially received the Janssen COVID-19 vaccine schedule and then received a booster dose of Moderna, Pfizer and BioNTech, and Janssen led to an **increase** of IgG binding antibody of **55-, 34-, and 5-fold**, respectively (52). Overall, the homologous and heterologous booster vaccinations were well-tolerated and immunogenic.

Fourth Dose:

While the duration of protection of the booster doses remains relatively unknown, countries such as Israel begun vaccinating citizen aged 60 years and over and health-care workers with the fourth dose of a COVID-19, on 2 January 2022, amid the rapid spread of Omicron and the increasing spike of COVID-19 infections (53). Based on the results of a study analysing the antibody response of a fourth messenger RNA COVID-19 vaccine in immunocompromised patients (Kidney Transplant Recipients), a fourth dose produced satisfactory antibody response in recipients who had an inadequate response after the 3 previous doses (54). Although the fourth dose of BNT162b2 has shown to raise COVID-19 antibody levels higher than after the third dose, numerous breakthrough infections with the Omicron variant continue to be reported in Israel leading to multiple experts to believe that the fourth dose might 'not be good enough' against the Omicron variant (55).

What are the latest updates regarding COVID-19 vaccines in children?

Summary:

As many countries have moved to adolescent and child vaccination in their vaccination schemes, child vaccination rates are increasing globally and more new literature regarding safety and effectiveness has been published. While the wealth of this data is regarding the BN16b2 Comirnaty vaccine, as it is the most widely used vaccine option for children, new literature regarding other vaccines such as mRNA-1273 (Moderna) and BBIBP-CorV (Sinopharm) are also available in this report. In general, these safety and effectiveness studies show promising results, with high effectiveness against several outcomes regarding COVID-19, and low rates of adverse events.^{45,46} Studies which focus on safety in younger children (5-11 years of age) show similarly low rates of serious/systemic adverse events,⁴⁷ similar to that which has been seen in older adolescents. Specific case studies of some of the more concerning rare adverse events, such as multi-inflammatory syndrome in children (MIS-C)^{48,49} and myocarditis^{50,51} can also be found below. Overall, these events are occurring at low rates in the vaccinated child population and are considered rare adverse events without clear association to vaccination. Furthermore, these conditions are often mild, and self-resolving, or easily resolved with swift and appropriate care. As the Omicron variant of concern (VOC) continues to dominate global SARS-CoV-2-caused infection, some literature has been published regarding the effectiveness of the BNT162b2 and mRNA-1273 vaccines against Omicron in children and adolescents, specifically. These studies fall in line with observed neutralization rates in vaccinated adults- participants with 2 doses of a vaccine show weakened neutralizing ability

⁴⁵ Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents. *New England Journal of Medicine*.

<https://doi.org/10.1056/NEJMoa2109522>.

⁴⁶ Safety and immunogenicity of the BBIBP-CorV vaccine in adolescents aged 12-17 years in Thai population, prospective cohort study. *medRxiv*. <https://doi.org/10.1101/2022.01.07.22268883>.

⁴⁷ COVID-19 Vaccine Safety in Children Aged 5-11 Years - United States, November 3-December 19, 2021. *MMWR Morbidity and mortality weekly report*. <https://doi.org/10.15585/mmwr.mm705152a1>.

⁴⁸ Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) Aged 12–20 Years in the United States Who Received COVID-19 Vaccine, December 2020 through August 2021. *medRxiv*. <https://doi.org/10.1101/2022.01.03.22268681>.

⁴⁹ Multisystemic inflammatory syndrome following COVID-19 mRNA vaccine in children: a national post-authorization pharmacovigilance study. *medRxiv*. <https://doi.org/10.1101/2022.01.17.22269263>.

⁵⁰ Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. *New England Journal of Medicine*. <https://doi.org/10.1056/NEJMoa2110737>.

⁵¹ Comparisons of the risk of myopericarditis between COVID-19 patients and individuals receiving COVID-19 vaccines: a population-based study. *medRxiv*. <https://doi.org/10.1101/2021.12.13.21267730>

against Omicron when compared to their ability to neutralize wild-type SARS-CoV-2, which suggests a strongly weakened effectiveness of vaccines against Omicron in children and adolescents.^{52,53}

Results

Safety and Effectiveness:

In the United States, growing vaccination campaigns for children and adolescents have created a large body of vaccinated individuals to survey for potential adverse events. The US vaccine safety reporting system, VAERS, processed reports of adverse events in children aged 5-11 vaccinated with the BNT162b2 Comirnaty vaccine between November and December 2021. Out of 4,249 reports, **4,149 (97.6%)** were for non-serious adverse events. These events were typically associated with vaccine administration itself- local tenderness at injection site. 100 (2.4%) of these reports were for serious events, and the most common of these was fever (29%). There were **11** verified reports of myocarditis (56). Another reporting system called V-Safe surveying a large cohort of 29,899 children who received both doses of the BNT162b2 vaccine observed adverse events after vaccination and showed that fever and other systemic reactions was more frequently reported after the second dose than the first dose. The most frequent reactions observed were injection site pain, fatigue, and headache (56).

A study observing a mass vaccination campaign of South Korean 12th graders observed participants who received 1 or 2 doses of the BNT162b2 vaccine for adverse events. In this group, **0.29%** of participants reported any adverse event after their first dose, while **0.61%** reported any adverse event after their second dose. **0.01%** of total reports of events were considered serious adverse events, in both single and double-vaccinated respondents. The most common serious adverse event was myocarditis, with a rate of **4.3 cases per 100,000 (95%CI, 2.6-6.7)** among those who had received both doses. There were no deaths observed in this study. In general, these statistics fall in line with those observed in Israel, where a majority of child COVID-19 vaccination safety studies originate. This study also observed vaccine effectiveness against SARS-CoV-2 infection in this group. Vaccine effectiveness against infection at 14 days post first dose was seen to be **91.1% (95% CI, 89.6-92.5)**. VE against infection at 14 days post second dose was **99.1% (95% CI, 98.8-99.5)**. However, these statistics reflect vaccine effectiveness against the Delta variant.⁽⁵⁷⁾ Under the PROTECT study, a prospective cohort study of 243 adolescents (age 12-17) in Arizona, US had participants complete weekly SARS-CoV-2 testing for 19 weeks beginning in July 2021 in to assess vaccine effectiveness.

⁵² Loss of Pfizer (BNT162b2) Vaccine-Induced Antibody Responses Against the SARS-CoV-2 Omicron Variant in Adolescents and Adults. SSRN. <https://ssrn.com/abstract=4010891>

⁵³ mRNA-1273 Vaccine-elicited Neutralization of SARS-CoV-2 Omicron in Adolescents and Children. medRxiv. <https://doi.org/10.1101/2022.01.24.22269666>.

This study reports an estimated adjusted vaccine effectiveness of **92% (95% CI, 79-97)** from July to December in this cohort. This time period includes the period of time where Delta became the predominant variant of concern, corroborating findings from the previous study showing the strong effectiveness of this vaccine against the Delta variant in adolescents (58).

A matched case-control study from Israel utilized a large, centralized health database to evaluate the duration of protection provided by the BNT162b2 vaccine among adolescents, using two outcomes: documented SARS-CoV-2 infection, and symptomatic infection. In adolescents aged 12-16, the study found that vaccine effectiveness against breakthrough infection reduced to **75% (95% CI: 71%, 79%)** after 90-149 days from administration of a second dose and was reduced to **58% (95% CI: 52%, 64%)** 150-180 days after the second dose. Vaccine effectiveness against symptomatic infection was **78% (95% CI: 73%, 82%)** after 90-140 days since receipt of a second dose and **65% (95% CI: 58%, 71%)** after 150-180 days since receipt of a second dose. These statistics fall in line with the trend of waning vaccine duration over time seen in adults (59).

A test-negative case-control study of 31 hospitals across 23 states in the US assessed the effectiveness of the BNT162b2 vaccine against hospitalization and severe Covid-19 among adolescents aged 12-18 by comparing hospitalization outcomes against vaccination status. These results showed that the effectiveness of the vaccine against hospitalization was **94% (95% CI, 90-96)**. Vaccine effectiveness against requiring ICU services was **98% (95% CI, 93-99)**, and vaccine effectiveness against requiring life support was **98% (95% CI, 92-100)**. Other interesting findings from this study were that only 2 case patients had been fully vaccinated out of 180 case patients who were admitted to the ICU. All of the 13 patients who received extracorporeal membrane oxygenation (ECMO), and the 7 who died, were unvaccinated (60).

A test-negative case-control study design was used to assess BNT162b2 vaccine effectiveness against multi-system inflammatory syndrome (MIS-C) in adolescents aged 12-18 at 24 hospitals across 20 states in the US from July to December 2021. The study sample included 102 MIS-C case patients and 181 controls, which included both test-negative and syndrome-negative hospitalized patients. In this sample, the estimated effectiveness of both doses of the BNT162b2 vaccine in protecting against MIS-C was **91% (95% CI, 78-97)**. All the 38 case patients who required life supporting aid, such as ventilation or ECMO, were unvaccinated. These results add to the body of evidence supporting the effectiveness and importance of vaccination with BNT162b2 in preventing adverse outcomes related to COVID-19 (61).

In addition to the information being added to the considerable library on vaccination with BNT162b2 in adolescents, studies on other vaccines have added value to discussions on safety and effectiveness of these less utilized platforms. A phase 2/3 placebo controlled clinical trial was

conducted to evaluate the safety and immunogenicity of the mRNA-1273 vaccine in healthy adolescents between 12 and 17 years of age. Particular focus was made on comparing the strength of the immune response of adolescents as compared to that in young adults (18 to 25 years of age). Out of a total 3732 participants, 2489 received the mRNA-1273 vaccine. The most common adverse reactions were injection-site pain (92.4% after second dose), headache (70.2% after second dose), and fatigue (67.8% after second dose). These same adverse events were also observed in the placebo group, though at much lower frequency. No serious adverse events of interest (such as MIS-C, myocarditis) were reported in this group. The geometric mean titer ratio (GMT ratio) comparing the immune response of this group to that of adults was **1.08 (95% CI, 0.94-1.24)**, showing the strength and acceptability of immune response among adolescents. Additionally, there were zero cases of COVID-19 in the mRNA-1273 group within 14 days of administration, as opposed to 4 cases in the placebo. This trial provides evidence for the acceptability of this vaccine for this age group with respect to safety, immunogenicity, and effectiveness (62).

A prospective cohort study in Thailand examined the immunogenicity and safety of the BBIBP-CorV (Sinopharm) vaccine in healthy individuals aged 12-17 and compared these results against those of an 18-30 age cohort. This study examined the anti-RBD concentration in participants 4 weeks after completion of the vaccination (2 doses). Additionally this study collected any reports of adverse events. Results showed that after 4 weeks, anti-RBD levels in the adolescent cohort was **102.9 BAU/ml (95% CI, 91.0-116.4)**. The geometric mean ratio (GMR) of this result against that of the adult group was **2.79 (95% CI, 2.25-3.46)**. This result suggests the superiority of the immune response in the adolescent cohort in comparison to adults. The study also found that reactogenicity and rates of adverse events were lower in the adolescent group. Altogether, these results further suggest that the BBIBP-CorV vaccine is safe and effective to use in adolescents, as it is in adults.(63) A similar study was done assessing the immunogenicity and safety of the BBV152 (Covaxin) vaccine. An open-label, age de-escalated phase 2/3 study was done across six hospitals in India assessing the safety, immunogenicity and reactogenicity of the BBV152 (Covaxin) vaccine in children from ages 2 to 18. This study found that the vaccine fostered no significant difference in reactogenicity profiles between children and adults. There were no serious adverse events or deaths during the study. Reactions were limited to local reactions, and these mainly consisted of injection-site pain (35% after first dose, 25% after second dose). Seroconversion, as measured by plaque reduction neutralization test (PRNT) achieved high levels in all child sub-groups by 4 weeks post-second vaccination. The PRNT GMT ratio of **1.76 (95% CI, 1.32-2.33)**, comparing the GMT of all child sub-groups to that of adults, shows a superior antibody response in children (64).

Adverse events:

Much attention has been paid to the potential for adverse effects which may differ between adolescents/children and adults, making this group a particular concern for regulatory bodies. Multi-system inflammatory syndrome in children (MIS-C) is one of the main rare adverse events which has received great focus. US study conducted through the Vaccine Adverse Event Reporting System (VAERS) was used to identify cases of MIS-C in adolescents who were vaccinated in the early stages of the US vaccination scheme, This investigation aimed to describe the phenomenon of MIS-C after COVID-19 vaccination, while also factoring in previous/ current SARS-CoV-2 infection. Out of 62 potential reports, 21 verified cases of MIS-C after vaccination were identified. Of the 21 adolescents with MIS-C, 15 (**71%**) had evidence of SARS-CoV-2 infection. Of these 15 cases, 47% (7) were aged 12-15, 33% (5) were aged 16-17, 20% (3) were aged 18-20. **66%** of these patients had only received one dose of the vaccine. The remaining 6 cases had no evidence of SARS-CoV-2 infection. All patients observed in this study showed clinical improvement, did not have major complications beyond MIS-C, and were sent home without incident. During the duration of this study, 21,335,331 people aged 12-20 received one or more doses of a SARS-CoV-2 vaccine, making the reported rate of MIS-C in this study **1.0 cases per million people** with one or more dose. The rate for those without evidence of SARS-CoV-2 infection was 0.3 cases per million vaccinated people.(65) The French national agency for Medicines and Health Products Safety (ANSM) conducted a pharmacovigilance survey to assess the rates of multi-inflammatory syndrome in children (MIS-C) among vaccinated French adolescents between 12 and 17. Out of 4,079,324 children who received both doses of an mRNA vaccine, there were 9 who had cases of MIS-C. This corresponds to a national reporting rate of **1.1 (95%CI, 0.5, 2.1)** per 1,000,000 mRNA doses. For those participants without evidence of previous infection, this rate drops to **0.7 (95% CI, 0.3, 1.6)** per 1,000,000 mRNA doses. The observed rate of MIS-C was significantly higher for adolescent males than adolescent females (66).

Another outcome which was observed by this study was the MIS-C rate attributable to SARS-CoV-2 infection, a distinction which is potentially important to make for the purpose of risk-benefit analysis. This rate was **113.3 (95%CI, 94.7, 134.6) per 1,000,000** among same age group. These findings provide further reinforcement for increasing child vaccination efforts, as the benefits of child vaccination appear to outweigh potential risks.

Another potential adverse outcome that has been identified is aseptic meningitis. for A study from South Korea presented a case of a previously healthy 18-year-old male who presented to the hospital with a headache which had lasted for 2 days. In taking the patient's medical history, he revealed that he had received his second dose of the BNT162b2 Comirnaty vaccine 3 weeks prior.

Nasopharyngeal swab testing for SARS-CoV-2 was negative, and the patient was treated with antibiotics and mannitol for suspected bacterial or viral meningitis. As cerebrospinal fluid culture results did not show bacterial growth, the vancomycin was discontinued, but the mannitol treatment was sustained. On day 4, the patient began to show improvement and by day 5, he was discharged. The patient was tested for a host of other possible causes of meningitis, bacterial and viral, but no other plausible cause was found. This case should be added to a body of evidence composed of case studies of rare cases of meningitis after vaccine administration, which could point towards some association between the two. Overall, meningitis after vaccine administration is exceedingly rare (67).

Myocarditis:

A rare yet distinct concern regarding adverse outcomes in adolescents specifically is myocarditis, as previous literature has shown that myocarditis is more common in certain demographics, typically younger males. The largest healthcare database in Israel was used to investigate the association between the onset of myocarditis and the receipt of at least one dose of the BNT162b2 Comirnaty vaccine. The study was limited to subjects ages 16 and older. Among 2.5 million people who met this criterion, 54 cases met the diagnostic criteria for myocarditis. The estimated rate of myocarditis was **2.13 (95% CI, 1.56-2.70)** cases per 100,000 people. This rate was highest among the demographic of males between ages of 16 and 29. Out of the confirmed cases of myocarditis, **76%** were “mild”, and 22% were “intermediate” in severity. Out of the whole cohort, there was one death after discharge from hospital, which was of an unknown cause. (68) Like with the case of MIS-C, studies have also focused on the distinction between the risk of myocarditis associated with vaccination vs that associated with COVID-19 infection. A population based cohort study of adults (not adolescents; for the purpose of organization, this study has been included in this sub-section) was used to evaluate the effect of either COVID-19 positivity or SARS-CoV-2 vaccination on rates of myocarditis reports in the population. Out of 11441 Patients who tested positive for COVID-19, 4 had myocarditis, making a rate of **350 per million (95% CI, 140-900)**. This rate is higher than what existed in this population before the pandemic. Compared to these figures, the rates of myocarditis among vaccinated subjects were lower- **8.6 per million (95% CI, 6.4-11.6)**. These rates are comparable to those seen among vaccinated people in other countries such as the United States and the United Kingdom (69).

More case studies regarding vaccinated individuals who presented with myocarditis some time after vaccination have been made available. This case study describes the case of an otherwise healthy 17-year-old male who presented to the hospital with chest pain and fever. He had received the first dose of the Comirnaty vaccine 10 days prior to symptom onset. Testing and diagnostics showed that

he was negative for SARS-CoV-2, but showed elevated troponin levels, and further tests confirmed the diagnosis of myocarditis. The patient was discharged with prescribed medical therapies of ACE-inhibitors, colchicine, and ibuprofen. Although the patient also appeared to have suffered from a COVID-like illness the week before his vaccination, which was confirmed by nucleocapsid antibody testing, this is considered unlikely to be the cause of the myocarditis due to the timing of the event. This case study lends more evidence to the trend of the rare yet seemingly persistent side effect of myocarditis being more common in young adult and adolescent males (70). Following this trend, a collection of 7 case studies of myocarditis diagnoses reported on their characteristic. All patients in this sample were young, previously health males, ranging in age from 14 to 19. All patients in this sample presented to the hospital with chest pain within 4 days after receipt of the second dose of the Pfizer-BioNTech vaccine. Negative SARS-CoV-2 tests ruled out active COVID-19 as a cause of the myocarditis in all cases, as well. 6 of the 7 had negative nucleocapsid antibody results, which also ruled out previous SARS-CoV-2 as a cause for these patients. All patients also had elevated troponin levels. After treatment, all patients resolved their conditions without incident. While these case studies do not offer any substantial evidence to draw a link between SARS-CoV-2 vaccination and myocarditis, it offers evidence that regulatory bodies should be aware of this potential rare side effect. Another study reported on 2 case studies of patients who presented with acute myocarditis within 3 days of receiving an mRNA-based SARS-CoV-2 vaccine, either the BNT162b2 (Pfizer) vaccine or the mRNA-1273 (Moderna) vaccine. Both patients fit the recently defined profile of those who appear to be more at risk of myocarditis- young, previously healthy males. Neither patient had a history of prior COVID-19 infection and tested negative for current infection during their stay. Both patients recovered quickly after appropriate treatment, and were discharged without incident (71).

Omicron

A study comparing humoral immune responses to BNT162b2 vaccination between adolescents and adults looked at neutralizing antibody response against a panel of VOCs, including the most recent and dominant variant Omicron. This study found that overall adolescent participants who received two doses of the Pfizer vaccine had stronger immune responses than adults did. Both adolescents and adults showed moderate decline in humoral response against some variants, however none as great as that against the Omicron variant. In both adolescents and adults, the reduction of effectiveness against Omicron was **3-4-fold** when compared to wild-type variants. In adolescents, vaccinees showed a median IgG binding titer of **10038 (range 4549-16000)** against other variants of concern, but a titer of only **3340 (range 1541-6615)** against Omicron, in those who even showed any neutralizing ability. Only **3 out of 15** adolescents showed detectable titers, showing that

neutralization is mainly failing against Omicron. GMT for adolescents against wild-type variants was **329 (range from 94-1096)**, whereas against Omicron this figure dropped to **39 (25-64)**. This study further suggests breakthrough potential of Omicron in adults and adolescents, pointing towards a need for booster doses for children and adolescents as well as adults (72). A study utilizing samples of adults, adolescents (12-17) and children (6-12) from three separate cohorts of a Coronavirus Efficacy (COVE) trial assessed neutralization activity of the mRNA-1273 vaccine against Omicron in children and adolescents in comparison to that of adults. The study found that in adolescents (12-17), the GMT was **11.8-fold lower** against Omicron than against an older variant (D614G). In children, the GMT was **reduced 22.1-fold**. Both the studies on the adolescent cohort and the child cohort showed a stronger immunogenic response than the adult cohort. This study confirms the well-established effect of stronger immunogenic responses among younger age groups, but also lends more evidence to the strongly reduced effectiveness of a double-dose vaccine regimen against Omicron (73).

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

Summary:

Apart from the 8 WHO EUL approved vaccines, numerous vaccine candidates such as Sputnik V, SANOFI, Clover/ SCB-2019, CHO Cell/ NVSI-06-07, CureVac, SOBERANA/ ABDALA, MVC-COV1901, Ad5-nCoV/ CanSino, and ZF2001 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:

Sputnik/ Sputnik Light:

With the emergence of the newest variant Omicron (B.1.1.529) and the reported decrease in neutralization of COVID-19 vaccines against the Omicron variant, a study aimed to analyze the neutralization of RBD-specific IgG antibody in the sera samples of individuals vaccinated with the Sputnik V 6 to 12 months ago and revaccinated with the Sputnik Light booster dose 2 to 3 months ago (74). Based on the results, a decrease of **9.62-folds** in neutralizing antibodies against the Omicron variant was observed in the overall participants, in comparison with the wild type (74). When analyzing the sera of people who received the Sputnik Light booster, a smaller decrease of **7.13-folds** in neutralizing antibodies against Omicron was observed compared to the wild type (74). Notably, the highest decrease in neutralization was observed in participants who received their Sputnik V vaccination 6 to 12 months ago with a decrease of **11.76-folds** in neutralizing antibodies against Omicron compared to the wild type. Overall, the data shows that 2 to 3 months after receiving the booster dose Sputnik Light induced a higher neutralizing antibody response against the Omicron variant with the lowest reported decrease in neutralization response.

Another study also aimed to analyzing the neutralizing activity of the sera of individuals who were vaccinated with two doses of the Sputnik V or BNT162b2. A total of 31 samples from individuals vaccinated with Sputnik V and 51 samples from individuals vaccinated with BNT162b2 with no history of COVID-19 were obtained (75). Based on the results, the decrease in the neutralizing antibody level to the Omicron variant in comparison to the wild type in the Sputnik V vaccinated sera was **8.1-folds** (GMT 58.5 vs 7.2) and **21.4-folds** in the sera of individuals vaccinated with BNT162b2 (GMT 72.7 vs. 3.4) (75).

SANOFI:

Sanofi Pasteur and GSK's COVID-19 vaccine uses a two dose adjuvanted recombinant protein-based platform to combat SARS-CoV-2. With the satisfactory phase 2 clinical trial results of the vaccine showing strong rates of neutralizing antibody response of **95% to 100%** seroconversion following a second injection in all age groups (18 to 95 years old) (76), the vaccine moved to its phase 3.⁵⁴ In addition to being tested as a primary vaccine, the vaccine is also being tested as a booster regardless of the primary vaccine received (mRNA or adenovirus vector-based vaccines). On 15 December, Sanofi Pasteur and GSK announced positive preliminary booster data for the COVID-19 vaccine candidate while continuing their ongoing phase 3 clinical trial (77). Based on the press release, the booster data showed that neutralizing antibodies increased across all primary vaccines received in a **9- to 43-fold range** for all age groups (77). Additionally, the booster dose demonstrated to be safe and well tolerated within the participants (77). The companies continue to evaluate the data of its ongoing clinical trials and intends to file booster data with the regulatory authorities as soon as the Phase 3 results are available and made public (77).

Clover/ SCB-2019:

Clover Biopharmaceuticals' COVID-19 vaccine candidate uses the Trimer-Tag technology platform (a stabilized trimeric antigen of the S-protein based on the original strain of SARS-CoV-2 virus) and the CpG1018 and Alum adjuvant to combat the SARS-CoV-2 virus. During its phase 2/3 clinical trial, the vaccine achieved primary efficacy endpoint and secondary efficacy endpoints by demonstrating a **100%** efficacy against severe COVID-19, **100%** efficacy against hospitalizations due to COVID-19, **84% efficacy** against moderate-to-severe COVID-19, and **67.2%** efficacy against COVID-19 of any severity caused by any strain of SARS-CoV-2⁵⁵. Additionally, the vaccine demonstrated a **79%** efficacy against COVID-19 of any severity caused by the Delta variant. In addition to its ongoing clinical trial in adults, the company will start a Phase 2/3 clinical trial to assess the reactogenicity, safety, and immunogenicity of the SCB-2019 COVID-19 vaccine in children below 18 years of age⁵⁶.

⁵⁴ Phase 3 Clinical Trial for COVID-19 Recombinant Protein Vaccine Candidate. [Press Release] Sanofi Pasteur. Accessed on: 19 January 2022. <https://www.sanofi.com/en/our-covid-19-vaccine-candidates/phase-3-clinical-trial-for-COVID19-recombinant-protein-vaccine-candidate>.

⁵⁵ SCB-2019 (CpG1018/Alum) COVID-19 Vaccine Candidate: SPECTRA Phase 2/3 Clinical Trial Results. Clover Biopharmaceuticals. Accessed on: 19 January 2022. https://www.cloverbiopharma.com/upload/pdf/SPECTRA-Data-Presentation_2021.09.22_FINAL_EN.pdf

⁵⁶ Safety and Immunogenicity of SCB-2019 in Children <18 Years of Age. ClinicalTrials.gov <https://clinicaltrials.gov/ct2/show/NCT05193279?term=Safety+and+Immunogenicity+of+SCB-2019+in+Children+%3C18+Years+of+Age&draw=2&rank=1>

Recently, a study aiming to compare the immunogenicity of the SCB-2019 COVID-19 vaccine against 4 approved vaccines (mRNA-1273, BNT162b2, ChAdOx1 nCoV-19, and Ad.26COV2.S) demonstrated that the SCB-2019 COVID-19 vaccine had an immune response against the Alpha and Delta variant comparable to the other COVID-19 approved vaccines (78). The sera from 100 participants of Clover's SPECTRA phase 2/3 clinical trial were selected and tested for RBD binding IgG antibodies and compared to the sera of individuals who received 4 different COVID-19 vaccines (78). Based on the results, the geometric mean concentration (GMC) of Clover vaccine recipients following 2 doses was **1010 BAU/mL** (95% CI, 752-1355) compared with the GMC following 2 doses of the mRNA-1273 (**5530 BAU/mL** [95% CI, 4007–7633]), BNT162b2 (**2667 BAU/mL** [95% CI, 2071–3425]), and ChAdOx1 nCoV-19 (**196 BAU/mL** [95% CI, 141–273]) and after 1 dose of Ad.26COV2.s (**61 BAU/mL** [95% CI, 37–101]) (78). When analysing the RBD IgG GMC of the SCB-2019 COVID-19 vaccine against different variants across age groups, participants aged 18 to 60 years of age had a S-protein GMC of **700 BAU/mL (511-961)** against the Alpha variant and a GMC of **248 BAU/mL (95% CI, 187-329)** against the Delta variant (78). As for participants aged over 60 years old, a S-protein GMC of **345 BAU/mL (95% CI, 153-779)** against the Alpha variant and a GMC of **129 BAU/mL (95% CI, 55-307)** against the Delta variant was reported (78).

CHO Cell/ NVSI-06-07:

The NVSI-06-07 (CHO cells) vaccine is a second-generation recombinant protein-based booster COVID-19 vaccine produced by Sinopharm. Earlier in December, the vaccine was approved for emergency use as a booster in the United Arab Emirates⁵⁷ and following its administration to individuals double vaccinated with the inactivated vaccine BBIBP-CorV, results on its safety and immunogenicity were subsequently published. The phase 2 randomized, double-blinded, controlled clinical trial was conducted in healthy adults (aged ≥18) who received the BBIBP-CorV vaccine in the United Arab Emirates. Based on the results, the heterologous administration of the NVSI-06-07 booster vaccine led to significantly higher seroconversion and RBD-specific IgG antibodies than in the individuals who received the homologous booster dose (BBIBP-CorV) (79). In homologous BBIBP-CorV booster group, the seroconversion rates were **59-92%** (95%CI, 53-52%-66-08%), **36-80%** (30-81%-43-11%) and **81-75%** (76-41%-86-31%) in the 1-3-month, 4-6-month and ≥6-month boosting-interval groups, respectively on day 28 post-boosting (79). For participants in the heterologous NVSI-06-07 booster group, the seroconversion rates were **90-63%** (95%CI, 86-37%-93-90%), **89-96%** (85-54%-93-40%) and **97-52%** (94-68%-99-08%), respectively (79) on day 28 post-

⁵⁷ Sinopharm protein-based booster stronger against Omicron than earlier shot. [Press Release] Reuters. Accessed on: 20 January 2022. <https://www.reuters.com/business/healthcare-pharmaceuticals/sinopharm-protein-based-booster-stronger-against-omicron-than-earlier-shot-study-2022-01-07/>

boosting. Regarding the neutralizing geometric titers (GMT), the homologous booster increased the baseline neutralizing GMTs by **7.08-fold** (95% CI, 5.91-8.48), **4.20-fold** (95% CI, 3.57-4.94), and **16.78-fold** (95% CI, 13.51-20.83) in the three groups, respectively at day 28 post-boost (79). As for the heterologous booster, the GMT increased by **21.01-fold** (95%CI, 18.01-24.52), **23.10-fold** (19.44-27.44) and **63.85-fold** (52.15-78.18), respectively on day 28 post-boost (79). Additionally, the sera of both homologous and heterologous recipients were analysed against the Omicron variant to determine the neutralization capacity. Based on those results, the neutralizing antibody GMT against Omicron was significantly reduced by **11.32-folds** compared to the wild type in homologous recipients and reduced by **6.62-folds** compared to the wild type in heterologous recipients (79). Furthermore, the neutralizing antibody GMT against Omicron elicited by the heterologous booster was **292.53** (95% CI, 22.81-384.07) (79). Overall, the results demonstrate that the administration of the heterologous booster NVSI-06-07 in recipients previously vaccinated with BBIBP-Corv led to higher seroconversion, neutralizing antibodies against the wild type and the Omicron variant.

CureVac:

After withdrawal of the first-generation COVID-19 vaccines, no further data on CureVac's second-generation vaccines are available by the time of writing this report.

SOBERANA/ABDALA:

Two of Cuba's biggest pharmaceutical institutes, Finlay Institute and CIGB (Centro de Ingeniería Genética y Biotecnología), have developed and tested two primary COVID-19 vaccines (SOBERANA 02 and ABDALA) and one booster dose (SOBERANA Plus). Thus far, both vaccines and booster dose have shown to elicit satisfactory antibody levels and be highly effective against SARS-CoV-2 infections. A recent study analyzing the safety and immunogenicity of the SOBERANA 02 vaccine and the SOBERANA Plus booster found that the two doses of SOBERANA 02 were well tolerate, safe and immunogenic in adults, while the heterologous combination with a third dose of SOBERANA Plus increased the neutralizing antibodies in recipients (80). A total of 810 healthy adults were included in the Phase 2b clinical trial. Based on the results of the immune response, on day 14 following the administration of the first dose of the SOBERANA 02 vaccines, participants had a **≥4-fold increase** in anti-RBD IgG concentration (20%) compared to the placebo group (80). After receiving the second dose a concentration of **76.3%** (26.5 AU/mL) was observed while a concentration of **96.8%** (median 122.2 AU/mL) was observed in individuals who received the booster dose (80). Overall, a **4.6-fold increase** in RBD IgG concentration after the third dose compared to a

2.4-fold increase in RBD IgG concentration after the second dose was observed. Additionally, a neutralization assay against the Alpha, Delta, and Beta variants was performed. Based on those results, the neutralizing geometric mean titer (GMT) was **364** (95% CI 305-435) against the wild type and **339** (95% CI, 277-414), **156.7** (95% CI, 123-201) and **51.4** (95% CI 31-85) against the Alpha, Delta and Beta variants, respectively (80).

Regarding Cuba's second COVID-19 vaccine, ABDALA, the results of the Phase 1/2 clinical trial were recently made available to the public. The study aimed to evaluate the safety and immunogenicity of the recombinant spike protein vaccine administered intramuscularly in different strengths and vaccination schedules (81). The subjects aged 19 to 80 years old of the clinical trial were divided into three different groups, placebo, 25µg and 50µg vaccine dose and then evaluated for safety and immunogenicity (81). Based on the results, the ADBALA vaccine against SARS-CoV-2 was safe, well tolerated and induced humoral immune responses against SARS-CoV-2 in the **50µg group**.

MVC-COV1901:

MVC-COV1901 is a vaccine candidate based on a recombinant protein platform containing pre-fusion-stabilized spike protein S-2P adjuvanted with CpG 1018 and aluminum. In a phase 1 trial, the vaccine candidate showed to be tolerated with a good safety profile in health adults aged 20-49 years. Recently, results of a phase 2 clinical trial evaluating the safety, tolerability, and immunogenicity of the MVC-COV1901 were published in the Lancet Respiratory Medicine Journal.⁵⁸ Recently, studies on the administration of a homologous or heterologous booster dose of the MVC-COV1901 vaccines have been made available. One of the studies is an extension to the phase 1 clinical trial study where a booster dose of the MVC-COV1901 vaccines is administered 180 days following the second dose (82). A total of 45 healthy adults from 20 to 49 years of age received the booster dose and were evaluated for reactogenicity and immunogenicity. Based on the results, the adverse reactions after the booster dose were mostly mild and comparable to the first two doses. As for the neutralizing antibodies, the levels remained detectable on day 209 at **59.4, 79.4, and 113.2 IU/mL** for the low dose (LD), middle dose (MD), and high dose (HD) groups, respectively (82). Four weeks after the administration of the booster dose, the neutralizing titers increased to **1719.6, 818.3, and 1345.6 IU/mL** for the low dose, middle dose, and high dose groups, respectively (82). Additionally, the booster dose was tested against the Omicron variant. Based on the results, the serum samples from day 237 of the middle dose and the high dose had neutralizing levels **8.7- and 6.4-fold lower** for the

⁵⁸ Safety and immunogenicity of CpG 1018 and aluminum hydroxide-adjuvanted SARS-CoV-2 S-2P protein vaccine MVC-COV1901: interim results of a large-scale, double-blind, randomized, placebo-controlled phase 2 trial in Taiwan. *The Lancet Respiratory Medicine*. [https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(21\)00402-1/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00402-1/fulltext)

Omicron variant compared to the wild type but remained above the lower limit of detection (82). Overall, the study demonstrates that the MVC-COV1901 booster dose was safe and well tolerated all while eliciting antibodies.

Another study evaluating the safety and immunogenicity of the administration of a heterologous booster dose in participants who previously received two doses of the ChAdOx1 nCoV-19 vaccine was recently made available. The MVC-COV1901 booster dose was administered at 12 to 24 weeks after the two doses of the ChAdOx1 nCoV-19 vaccine in a total of 201 participants (83). Based on the results, at one month after the MVC-COV1901 booster dose, the anti-spike IgG levels increased to **724.9 BAU/mL** or to an almost **14-fold increase** compared to the levels on the day of the booster (83). The neutralizing antibody titer also increased after the administration of the booster from **59.0 IU/mL** at the time of the booster to **385.4 IU/mL** at one month after the booster (83). The neutralizing ability against the Omicron variant was also tested using the serum of 30 participants. In individuals only vaccinated with two doses of the ChAdOx1 nCoV-19 vaccine, the neutralizing levels against Omicron were reduced by **7.3-fold** when compared with the wild type (83). As for individuals who received the heterologous booster, about **90%** of the individuals had detectable neutralizing titers with a **5.7-fold increase** in geometric mean titers against the Omicron variant compared to individuals who were not boosted (83). Additionally, the injection of the third shot was generally safe with no major adverse effects.

Ad5V-nCoV/ CanSino:

The Ad5-nCoV COVID-19 vaccine is a single-dose adenovirus type 5 (Ad5) vectored vaccine expressing the SARS-CoV-2 spike protein. Previously in phase 1 and 2 studies, the vaccine candidate showed to be well-tolerated and immunogenic (84). During a double-blind, randomized, phase 3, clinical trial the efficacy, safety, and immunogenicity of a single dose in adults 18 years and older was evaluated. Based on the results, one dose of the Ad5-nCoV showed an efficacy against symptomatic PCR-confirmed COVID-19 infections 28 days or more post-vaccination of overall **57.5%** (95% CI, 39.7 -70.0) (84). When stratifying by age groups, participants aged 18-44 years demonstrated an efficacy of **60.9%** (95%CI, 39.0-75.0) against symptomatic infections, **62.2%** (24.0-81.2) in participants aged 45-59 years, and **17.5%** (95% CI, -127.6-70.1) in participants aged 60 years and over 28 days after vaccination (84). Additionally, the vaccine efficacy against severe disease in participants 60 years and older beginning 14 days after immunization was estimated at **90.1%** (95% CI, 22.3-98.7) (84). In terms of safety, the primary safety analysis demonstrated that the vaccine had no significant difference in the incidence of serious adverse events or medically attended adverse events between the Ad5-nCoV recipients and the placebo recipients (84). Out of the solicited systemic

adverse events reported, headache was the most commonly reported adverse events (84). Overall, the one dose Ad5V-nCoV vaccine was safe and showed to be relatively efficacious in healthy adults aged 18 years and older.

ZF2001:

The ZF2001 COVID-19 vaccine candidate is an adjuvanted protein subunit COVID-19 vaccine developed by Anhui Zhifei Longcom in collaboration with the Institute of Microbiology at the Chinese Academy of Sciences currently undergoing Phase 3 clinical trials. Recently, a study analyzing the binding and neutralizing antibodies elicited by three doses (two priming doses and one booster dose) of the vaccine ZF2001 was published (85). The serum samples from ZF2001 recipients were grouped into two groups based on the interval between the second and third dose (short-interval: received second dose 1 month after the first dose and the third dose 1 month after the second one; prolonged-interval: received second dose 1 month after the first dose and the third dose 4 months after second dose). Based on the results, the decrease in the titers of antibodies binding to the Omicron variant were greater in the serum from both ZF2001 groups than in those from the inactivated vaccine or convalescent group; nevertheless, the antibodies in the serum samples from the inactivated-vaccine and ZF2001 groups remained effective in the neutralization against the Omicron variant (85). Regarding the neutralization capacity against the omicron variant, the titers against Omicron **decreased** by a **factor of 10.6** in the short-interval ZF2001 group, and by a **factor of 3.1** in the prolonged-interval ZF2001 group compared to the wild type (85). Overall, the longer interval between the second priming dose of vaccine and the booster dose (prolonged interval: received second dose 1 month after the first dose and the third dose 4 months after second dose) appears to induce higher neutralizing antibodies titers against all variants tested.

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