

Literature screening report

COVID-19 vaccines and post-vaccination data: Literature update (11)

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<i>Responsible author:</i> <small>*Authors contributed equally</small>	Sabina Rodriguez Velásquez* ^{A,B} Gabriela Guizzo Dri* ^{A,B} Camille Beatrice Gaza Valera* ^{A,B}
<i>Co-authors:</i>	Muaamar Al Gobari ^{B,C} Sara Botero-Mesa ^{A,B} Olivia Keiser ^A
<i>Affiliation:</i>	^A Institute of Global Health, University of Geneva, Switzerland ^B Association Actions en Santé Publique (ASP) & The GRAPH Network, ^C Department of Occupational and Environmental Health, Center for Primary Care and Public Health (Unisanté), University of Lausanne, Epalinges-Lausanne, Switzerland.
<i>Coordination contact:</i>	Jorgen Bauwens (SSPH+)

Abstract

This report addresses the most relevant data on COVID-19 vaccines literature as of 26 November 2021. The current report addresses the latest data on the new WHO EUL approved vaccine COVAXIN/BBV152, vaccine effectiveness its waning immunity and duration of protection, the vaccine-induced humoral, cellular, and neutralizing response of the Chinese inactivated vaccines, breakthrough infections, virus transmissibility, vaccine booster doses, COVID-19 vaccines in children, COVID-19 vaccine safety and myocarditis. To conclude, the report highlights the latest SARS-CoV-2 vaccine development information on COVID-19 vaccine candidates.

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Preamble

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

Background

At the start of 2021, vaccination rollouts demonstrated high vaccine effectiveness against the original SARS-CoV-2 strain; however, concerns about vaccine immunity waning and vaccine effectiveness against variants of concern (VOC), particularly the Delta (B.1.167.2) strain, long-term immunogenicity, and viral transmissibility arise.

The Delta 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 Delta variant are decreased by a factor of 4 when compared to the original wild-type strain².

Despite recent reports of waning vaccine immunity, the latest data continues to demonstrate that COVID-19 vaccines are highly effective against symptomatic and severe COVID-19 infection, hospitalizations, and deaths. A real-life observational study conducted in Israel demonstrated the effect of mass vaccination on COVID-19 mortality by reporting that vaccines prevented 4,750 deaths between March and June 2021 in individuals over 70 years of age³. Nevertheless, a third dose of COVID-19 vaccines has demonstrated to boost up the waning immunity and provide a high protection against the illness, hospitalizations, and the more infectious variants such as the Delta. Multiple countries, including Switzerland, have now expanded their vaccination mandate to allow the general population to receive their third booster dose.

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

This report thus focuses on published studies that covered the following questions/points:

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- 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 Vaccination after prior COVID-19 infection: Implications for dose sparing and booster shots. *EBioMedicine*.
[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 How many lives do COVID vaccines save? Evidence from Israel. *medRxiv*.
<https://www.medrxiv.org/content/10.1101/2021.10.27.21265591v1.full-text>

Questions addressed

- What is known about the newly WHO EUL approved vaccine COVAXIN/BBV152?
 - What are the latest updates regarding vaccine waning immunity and duration of protection?
 - What are the latest updates regarding vaccine immunogenicity for Sinopharm's BBIBP-CorV and Sinovac's CoronaVac?
 - What are the latest updates on breakthrough infections?
 - What are the latest updates on virus transmissibility in fully vaccinated individuals?
 - What is the latest data on COVID-19 booster doses?
 - What are the latest updates regarding COVID-19 vaccines in children?
 - What are the latest updates on vaccine safety?
 - What is the status of SARS-CoV-2 vaccine candidates?
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Methodology

The current report screened the databases of PubMed, Embase, medRxiv, bioRxiv, SSRN, Cochrane, and clinical trial databases such as ClinicalTrials and WHO Trial registry for vaccine-related literature as of 26 November 2021. We focused on studies that would help to discuss the points raised above. For more information on the methodology, please refer to previous reports⁴.

⁴ 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

Results and Findings

What is known about the newly WHO EUL approved vaccine COVAXIN/BBV152?

Summary:

On 3 November 2021, the WHO issued an emergency listing for COVAXIN/BBV152 (India's first indigenous COVID-19 vaccine manufactured and developed by Bharat Biotech) by adding it to its validated portfolio of vaccines against SARS-CoV-2⁵. The COVAXIN (BBV152) vaccine is a two-dose vaccination regimen given 28 days apart developed using whole-virion inactivated Vero cell platform technology. Overall, the vaccine has demonstrated promising safety data without any reactogenicity while inducing a robust immunogenicity and achieving good levels of efficacy and effectiveness against COVID-19.

Results:

Efficacy:

Based on the phase 1/2 clinical trial results, the vaccine generated adequate safety data without any reactogenicity, led to tolerable safety outcomes, induced neutralizing antibody titers against two divergent SARS-CoV-2 strains, and enhanced humoral and cell-mediated immune responses (1, 2). During the randomized, double-blinded, placebo-controlled, multicentre phase 3 clinical trial, the efficacy, safety, and immunogenicity of COVAXIN was evaluated in individuals aged 18 years and older (3). Based on those results, the vaccine demonstrated **77.8%** vaccine efficacy against symptomatic COVID-19 disease, **93.4%** efficacy against severe symptomatic COVID-19 disease, and **63.6%** efficacy protection against asymptomatic COVID-19 disease (3). When adjusting for age, the efficacy against symptomatic COVID-19 disease was **79.4%** (95% CI, 66.0-88.2) for participants younger than 60 years and **66.2%** (95% CI, 33.8-84.0) in older participants (3). Additionally, the vaccine demonstrated an efficacy of **65.2%** (95% CI, 33.1-83.0) protection against the Delta (B.1.617.2) variant and **90.1%** (95% CI, 30.4-99.8) against the Kappa (B.1.617.1) variant. (3).

Safety & Adverse Events:

Based on the phase 3 clinical trial results, the inactivated vaccine COVAXIN had a good reactogenicity profile with similar proportions of participants reporting solicited, unsolicited, and

⁵ WHO issues emergency use listing for eighth COVID-19 vaccine. *WHO News*. <https://www.who.int/news/item/03-11-2021-who-issues-emergency-use-listing-for-eighth-covid-19-vaccine>

serious adverse events and adverse events of special interest in the vaccine and placebo groups (3). A total of 0.3% of participants who received the COVAXIN vaccine reported serious adverse events of which one case of immune thrombocytopenic purpura 39 days after the second dose in a vaccine recipient who was SARS-CoV-2-seropositive at baseline (3). The most frequent solicited systemic adverse event overall was **headache**, followed by **pyrexia** (fever), **fatigue**, and **myalgia**, but occurred in less than 1% of participants in either group (3). Overall, the vaccine was safe and demonstrated to be well tolerated in participants.

Immunogenicity:

Based on the phase 3 clinical trials for the COVAXIN vaccine, the COVID-19 vaccine demonstrated to elicit robust immune response in participants. A day 56, the SARS-CoV-2 neutralizing antibodies for all lots was **125.6 Geometric Mean Titer (GMT)** (95% CI, 111.2-141.8), the S1 protein-binding IgG at day 56 for all lots was **9742 GMT** (95% CI, 8949-10606), the RBD-binding IgG at day 56 for all lots was **4124 GMT** (3731-4557), and the N protein-binding IgG at day 56 for all lots was **4161 GMT** (3736-4633). Another study aiming to determine the magnitude, quality, and persistence of cellular and humoral memory responses up to 6 months demonstrated that the inactivated virus vaccine COVAXIN induces robust immune memory to SARS-CoV-2 and variants of concern, which persist for at least 6 months after vaccination (4).

Effectiveness:

When analysing real world effectiveness data, one study conducted in India among people aged 45 years old and over during April to June 2021 estimated COVAXIN (BBV152) to have an effectiveness of **52.0%** (95% CI, 39.0-63.0) for partially vaccinated individuals and **83.0%** (95% CI, 73.0-89.0) for fully vaccinated individuals against symptomatic COVID-19 disease (5). Another study estimating the effectiveness of COVAXIN and AZD1222 against severe COVID-19 among individuals aged 45 years old and over, estimated a vaccine effectiveness of **69%** (95% CI, 54-79) against severe COVID-19 for COVAXIN and **80%** (95% CI, 73-86) for AZD1222 (6). Vaccine effectiveness against the Delta variant and sub-lineages was **64%** (95% CI: 40%-79%) for full dose of COVAXIN against severe COVID-19 and **81%** (95% CI, 71-88) for full dose of AZD1222 (6). Finally, a test-negative, case-control study evaluating the effectiveness of the COVAXIN vaccine among employees of a hospital in New Delhi, India, between April 15 and May 15, 2021, estimated an adjusted effectiveness against symptomatic COVID-19 after two doses administered at least 14 days before testing of **50%** (95% CI, 33-62) (7). The adjusted effectiveness of two doses administered at least 28 days before testing was **46%** (95% CI, 22-62), and at least 42 days before testing was **57%** (95% CI, 21-76) (7).

What are the latest updates regarding vaccine waning immunity and duration of protection?

Summary:

Numerous studies regarding the effectiveness of leading first-generation SARS-CoV-2 vaccines continually show positive evidence against reducing any SARS-CoV-2 infections, symptomatic COVID-19, severe cases, hospitalization, and death even amidst circulation of variants^{6,7}. Evidence from a living systematic review coordinated by the European Centre for Disease and Prevention and Control (ECDC) particularly demonstrate that authorized vaccines within the European Union are effective with respect to the Delta variant. Based on the literature screened by the ECDC from 01 January to 25 August 2021, pooled vaccine effectiveness (PVE) of studies indicate that prevention of severe cases was **93.8%** (95% CI, 83.0-98.0), prevention of hospitalization at **90.9%** (95% CI, 84.5-94.7), with PVE against symptomatic and asymptomatic infection was at **75.7%** (95% CI, 69.3-80.8) and **63.1%** (95% CI, 40.9-76.9) respectively, and PVE against any infection was **66.9%** (95% CI, 58.4-73.6) (8). Despite these reassuring results; however, duration of protection and waning immunity are key topics as cases begin to surge once more and the issue of booster dose administration are debated worldwide. Current literature describes various decline in effectiveness among all vaccine types during follow-up studies, but also illustrate evidence of continued protection against severe disease and risk of death.

Results:

Pfizer, Moderna, Janssen

Israel's mass vaccination campaign utilizing Pfizer's BNT162b2 vaccine during December 2020 initially characterized it as a successful country in containing the COVID-19 outbreak overwhelming the globe. However, a spike in cases during the summer months of 2021 and dominance of the Delta variant hinted at waning immunity of vaccines. In a study published in the New England Medical Journal, data of all Israeli residents who completed the Pfizer vaccine regimen before June 2021 were analyzed in order to assess COVID-19 infection and severe disease progression along varying time periods. Overall results of this national study illustrated that for all age groups, immunity waned months after receiving the second dose. For instance, evidence showed the within

⁶ SARS-CoV-2 variants and effectiveness of vaccines: A review of current evidence. *Epidemiology & Infection*. <https://www.cambridge.org/core/journals/epidemiology-and-infection/article/sarscov2-variants-and-effectiveness-of-vaccines-a-review-of-current-evidence/39243FCC3CED73D5F1D94E497F8823D3>

⁷ Effectiveness and safety of SARS-CoV-2 vaccine in real-world studies: A systematic review and meta-analysis. *Infectious Diseases of Poverty*. <https://idpjournal.biomedcentral.com/articles/10.1186/s40249-021-00915-3>

the oldest age groups (60 years and older), the infection rate ratio (**1.6; 95% CI, 1.3 to 2.0**) was higher among individuals vaccinated in January 2021 in comparison to individuals within the same age group, but vaccinated in March 2021 (9). In terms of severe disease progression among the oldest age groups; the rate ratio (**1.8, 95% CI; 1.1 to 2.9**) was higher among those vaccinated in the first months of eligibility for the vaccine campaign versus those vaccinated in March 2021 (9). Suggestive evidence of Pfizer's waning immunity are further corroborated by studies conducted in the United States regarding effectiveness of mRNA vaccines. Among US veterans, an investigation of vaccine effectiveness against infection (VE-I) and death (VE-D) showed that from February to October 2021 VE-I declined (**87.9% to 48.1%**) for all vaccine types studied (Pfizer, Moderna, as well as the viral vector vaccine, Janssen) even after adjusting for age, sex, and comorbidities (10). With regard to the two mRNA vaccine types; Pfizer had a sharper decline in VE-I **from 86.9% (95% CI: 86.5% to 87.3%)** in March 2021 to **43.3% (95% CI: 41.9% to 44.6%)** in September 2021 compared with Moderna's VE-I of **89.2% (95% CI: 88.8% to 89.6%)** in March to **58.0% (95% CI: 56.9% to 59.1%)** in September (10). Alternatively, Janssen had the largest decline in VE-I overall from **86.4% (95% CI: 85.2% to 87.6%)** to **13.1% (95% CI: 9.2% to 16.8%)** (10). Despite evidence of decreased VE-I; all vaccines remained protective against death; VE-D for any vaccine was **71.6% (95% CI: 68.6% to 74.2%)** for those in the oldest age groups (≥ 65 years) and **81.7% (95% CI: 75.7% to 86.2%)** for individuals < 65 years (10). By vaccine type; VE-D from July to October was **84.3%** for Pfizer, **81.5%** for Moderna, and **73.0%** for Janssen for individuals < 65 years, while VE-D for those ≥ 65 years was **70.1%** for Pfizer, **75.5%** for Moderna, and **52.2%** for Janssen (10). Similar results for Pfizer, Moderna, and Janssen were obtained for studies conducted in the US Coast Guard personnel from May to August 2021 as well as a 9-month surveillance study in the State of North Carolina (11, 12).

Persistence of Immune Protection

Despite evidence of waning immunity of vaccines, studies have also illustrated persistent immune-protection through investigating level of neutralizing antibodies, specialized memory cells. One such study was conducted in Italy wherein they depict decrease in antibody titre among BNT162b2 vaccinated individuals, but also an increase in memory T-cells – such as memory CD8+ T-cells – over time, which suggest long-lived immune response against COVID-19 infection, allowing for protection despite inadequate production of antibodies (13). In a similar study investigating BNT162b2 among fully vaccinated Italian health care workers (HCWs), it was again found that SARS-CoV-2 specific antibodies decline after vaccination; however, similar to the study by Claudia Rossi and colleagues, Terreri et. al illustrated that in fact, memory B cells persist increase over time. Further, in breakthrough infections among HCWs, they found that memory B cells illicit rapid

immune response by triggering memory B cell differentiation and generation of IgA for mucosal protection (14).

What are the latest updates regarding vaccine immunogenicity for Sinopharm's BBIBP-CorV and Sinovac's CoronaVac?

Summary:

China's BBIBP-CorV and CoronaVac vaccines have been crucial in accelerating the vaccination rollout across the world, particularly in middle-income countries such as Peru, Brazil, Morocco, Egypt, Turkey, and Pakistan⁸. However, studies over the past couple of months have demonstrated that the Chinese inactivated vaccines wane rapidly, faster than its mRNA or adenoviral counterparts, particularly in older populations⁹. The World Health Organization's Strategic Advisory Group of Experts on Immunization (SAGE) advised in early October that "an additional (third) dose of the homologous vaccine should be offered to persons aged 60 and above as part of an extended primary series" and that "the use of a heterologous platforms vaccine for the additional dose may also be considered"¹⁰. Consequently, countries that initially began vaccinating with BBIBP-CorV or CoronaVac are now providing other alternatives¹¹. Both inactivated vaccines may trigger less of an immune response against SARS-CoV-2 because its platform provokes an immune response against many viral proteins relative to mRNA or viral-vector vaccines, which are specifically targeted to the S protein¹². Despite Sinopharm and Sinovac's vaccines being among the most widely delivered and administered vaccines, relatively few real-life vaccine effectiveness studies have been published thus far, and the majority of published data centre around neutralizing antibody, humoral or cellular responses. Measures of all three, anti-SARS-CoV-2 antibody,

⁸ COVID-19 vaccines for low- and middle-income countries. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7989148/>

⁹ China's COVID vaccines have been crucial – now immunity is waning. *Nature News*. <https://www.nature.com/articles/d41586-021-02796-w>

¹⁰ Highlights from the meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization [4-7 October 2021]. *Weekly Epidemiological Record*. https://cdn.who.int/media/docs/default-source/immunization/sage/2021/october/sage_oct2021_meetinghighlights.pdf

¹¹ China's COVID vaccines have been crucial – now immunity is waning. *Nature News*. <https://www.nature.com/articles/d41586-021-02796-w>

¹² China's COVID vaccines have been crucial – now immunity is waning. *Nature News*. <https://www.nature.com/articles/d41586-021-02796-w>

humoral or cellular responses have been demonstrated to effectively predict vaccine protection^{13,14}.
These data are summarised below.

Results:

Inactivated vaccine-elicited antibody levels decline rapidly over time

A Thai study evaluated CoronaVac's ability to neutralize various strains of SARS-CoV-2 among 207 recruited healthcare workers (HCW) (15). Two to three weeks after full two-dose immunization, the proportion of participants who were seropositive against the Wild-type strain was **61.1% (91/149)**. Ten to twelve weeks post two-dose administration, this proportion fell to **50% (28/56)**. Likewise, the proportion of HCWs who were seropositive against the Alpha and Delta strains fell from **35.6% (53/149)** and **8.7% (13/149)** 2-3 weeks post immunization to **17.9% (10/56)** and **1.8% (1/56)** 10-12 weeks post immunization, respectively (16). While the mean neutralizing rate against SARS-CoV-2 Wild-type did not differ at 2-3 weeks post two-dose immunization (**49.3%; 95% CI, 44.9–53.6**) and 10-12 weeks post two-dose immunization (**48.0%; 95% CI, 39.9–56.1**), neutralizing rates declined significantly over that time period for both the Alpha (**2-3 weeks: 40.9%; 10-12 weeks: 21.8%**) and Delta variants (**2-3 weeks: 10.8%; 10-12 weeks: 1.0%**) (16). A Turkish study corroborates the Thai study's data: 45 days post second-dose immunization, anti-S1 antibodies decreased significantly in CoronaVac vaccinated individuals (17). To compare, anti-S1 antibodies did not decrease in SARS-CoV-2 convalescent patients over time (17). Likewise, a Chinese study demonstrated that BBIBP-CorV- or CoronaVac-elicited antibody levels were significantly lower 42 days or more post two-dose vaccine administration relative to 0-20 days ($P<0.05$) and 21-31 days ($P<0.05$) (18). Given inactivated vaccines rapid decline in antibody levels over time, booster doses are recommended to maintain adequate protection against SARS-CoV-2 infection (15, 19) [See *Booster Dose section*].

Effect of age on vaccine immunogenicity

Neutralizing antibodies are sustained for longer duration periods in younger individuals relative to older populations (20, 21); mean anti-IgG level in individuals over the age of 42 years were significantly lower than that of younger participants (18). Older individuals demonstrate significantly lower antibody levels than younger individuals at any point in time (18, 22).

¹³ Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nature Medicine*.
<https://www.nature.com/articles/s41591-021-01540-1>

¹⁴ Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. *Science*.
<https://pubmed.ncbi.nlm.nih.gov/34812653/>

Effect of sex on vaccine immunogenicity

While sex (female, male) was not associated with anti-Immunoglobulin M (IgM) and anti-Immunoglobulin G (IgG) levels post full inactivated anti-SARS-CoV-2 inoculation in Shenzhen China [97 participants; June-July 2021] (18), the female sex was associated with higher neutralizing antibody titres after 2-doses of CoronaVac when compared to males in in Tangerang, Indonesia [350 participants; February-May 2021] (23), Belem, Brazil [358 participants; March-April 2021], (22) and Turkey [1,053 participants] (24).

CoronaVac

In Thailand, seropositivity rate for total antibodies against the receptor-binding domain (RBD) epitope were **67%** (Geometric mean concentration (GMC); **1.98 U/mL**) 21 days after one dose and **100% (92.9 U/mL)** one month after the second dose of CoronaVac (19). Immunoglobulin G (IgG) seroconversion rates were **1%** after one dose and **62.8%** after two doses of CoronaVac (19). While antibody responses were comparable to SARS-CoV-2 convalescent plasma up until 3 months, CoronaVac elicited antibodies waned rapidly after 3 months post two-dose vaccination (19). Another study also reported that CoronaVac-elicited antibody titres were lower than plasma titres of SARS-CoV-2 convalescent individuals (25). Lastly, a serological study that evaluated factors affecting CoronaVac-elicited antibody response reported total antibody responses against RBD were significantly lower in smokers (**27.5% had antibody titres >250 U/mL**) than non-smokers (**72.5% had antibody titres >250 U/mL**). Furthermore, although not significant ($P=0.316$), high BMI individuals ($BMI \geq 30$; obese) demonstrated lower antibody titres at greater frequencies than individuals within the average (19-24.9) BMI range (25).

Comparing CoronaVac with other vaccines

A Hong Kong study compared CoronaVac's vaccine immunogenicity to Pfizer-BioNTech's BNT162b2 vaccine. While both vaccines were immunogenic in the sample population, two doses of CoronaVac demonstrated lower surrogate neutralizing antibody (sNAb) levels (**94.4%** vs. **100%**, respectively; $P < 0.001$), and **11-fold lower** levels of anti-spike Immunoglobulin G (IgG) (**1,005.2 AU/ mL** vs. **11,572.6 AU/ mL**, respectively; $P < 0.001$) than the BNT162b2 vaccine (26). Serological data obtained 12 weeks post full immunization demonstrated that while there was no difference in anti-spike IgG positivity rate for both vaccines (**98.5% in CoronaVac and 99% in BNT162b2**), waning of IgG and sNAb levels were observed for both vaccines. Although the CoronaVac vaccine demonstrated a smaller percentage decline (**-64.6%**) of IgG levels at 12 weeks compared to BNT162b2 (**-72%**; $P < 0.001$), CoronaVac's anti-spike IgG levels remained **11-fold lower (253.60 AU/ mL** vs. **2,840.25 AU/ mL**, respectively; $P < 0.001$) and demonstrated larger declines in sNAbs

(-28.3% in CoronaVac vs. -2.3% in BNT162b2; $P < 0.001$) (20). Another Hong Kong serological study reported that “vaccination with BNT162b2 induces stronger humoral responses than CoronaVac” (21), corroborating the aforementioned data. Interestingly, CoronaVac elicited higher CD4+ and CD8+ T cell responses than BNT162b2 (21). Studies have reported that sustained T cell immunity effectively reduce the rates of severe SARS-CoV-2 infection (27). Lastly, a Thai study confirmed that one month after the second dose, CoronaVac-elicited antibodies against RBD were lower (GMC: 92.9 U/mL; 95%, 82.2-105.0) than antibodies induced by Pfizer-BioNTech’s BNT162b2 vaccine (GMC: 1,108 U/mL; 95%, 1,049-1170) (19).

Comparing BBIBP-CorV with other vaccines

A Bangladeshi study compared vaccine immunogenicity between mRNA-1273, AZD1222, and BBIBP-CorV among 120 participants aged between 60 and 72 years (28). Anti S1 RBD IgG levels were highest in the mRNA-1273 recipients (**577.1 ± 44.33 AU/ml; $P < 0.05$**). Immunoglobulin G levels were also significantly higher for AZD1222 recipients (**308.5 ± 37.91 AU/ml**) relative to BBIBP-CorV recipients (**257.5 ± 32.75 AU/ml**) (28). The authors did not compare vaccine immunogenicity over time. Similarly, a Mongolian study compared 196 plasma specimens (collected from the 3 to 7 July 2021: Alpha variant dominant period) across four anti-SARS-CoV-2 vaccines: Pfizer/BioNTech (BNT162b2), AstraZeneca (ChAdOx1-S), Sputnik V (Gam-COVID-Vac) and Sinopharm (BBIBP-CorV) (29). The authors measured antibody blocking of angiotensin-converting enzyme 2 (ACE2) host receptor protein binding to SARS-CoV-2 RBD and found that both BBIBP-CorV and Gam-COVID-Vac vaccines generate lower RBD-ACE2 blocking activity than the BNT162b2 or ChAdOx1-S vaccines (29). Among the four analysed vaccines, BBIBP-CorV demonstrated the lowest percentage of ACE2 blocking against the Alpha, Beta, Gamma and Delta variants (29).

Intradermal inoculation: preliminary study

Given reports of inactivated vaccines’ rapidly decreasing antibody levels, particularly among elderly individuals (20, 21), a preliminary study assessed the effect of intradermal inoculation on NAb and IgG anti-S/N antibody levels over a period of 180 days (30). None of the 20 participants that were intradermally immunized developed any serious adverse reactions, although all participants developed skin redness on the inoculation site. A single intradermal injection with an inactivated vaccine elicited a sustained high anti-SARS-CoV-2 immunological response over a period of 6 months. The authors did not specify which of the two Chinese-produced vaccines were used. Further studies, especially with larger samples sizes, are needed to validate this preliminary’s studies results.

What are the latest updates on breakthrough infections?

Summary:

While all WHO EUL authorised vaccines have demonstrated to be effective against severe SARS-CoV-2 infections and hospitalization, the combined effects of low vaccination rates¹⁵, waning vaccine immunity, and the emergence of the Delta variant has led to increased cases of SARS-CoV-2 breakthrough infections, raising concerns among the general population and further contributing to vaccine hesitancy. However, breakthrough cases, including those of the Delta strain, are clinically milder¹⁶, are more likely to recover swiftly from illness than unvaccinated persons^{17,18}, and are less likely to infect others^{19,20}. Of the few breakthrough cases that require hospitalization, patients often have comorbidities or are immunocompromised^{21,22}. However, it must be mentioned that SARS-CoV-2 reinfection post natural infection and two-dose immunization can occur²³. Nevertheless, given the possibility of developing breakthrough infections, however small, studies recommend continuing the implementation of social distancing and non-pharmaceutical measures in order to mitigate the pandemic effects. The latest data on SARS-CoV-2 breakthrough infections are summarised below.

Results:

A community-based UK study quantified the number of SARS-CoV-2 breakthrough infections using self-reported data from the *COVID Symptom Study* mobile phone app and identified potential risk factors for post-vaccination SARS-CoV-2 infection (31). Between 8 December 2020 and 4 July 2021, 971,594 individuals reported having received a dose on the *COVID Symptom Study* app, of which **0.2%** ($n=2,370$) tested positive for SARS-CoV-2. The authors reported that age and post-vaccination infection (adjusted for BMI and sex) were inversely correlated; the odds ratio of developing a

¹⁵ Community-level evidence for SARS-CoV-2 vaccine protection of unvaccinated individuals. *Nature Medicine*.
<https://www.nature.com/articles/s41591-021-01407-5>

¹⁶ Vaccination after prior COVID-19 infection: Implications for dose sparing and booster shots. *EBioMedicine*.
[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)

¹⁷ Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: A retrospective cohort study. *The Lancet*. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(21\)02183-8/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02183-8/fulltext)

¹⁸ Understanding breakthrough infections following mRNA SARS-CoV-2 vaccination. *JAMA*.
<https://jamanetwork.com/journals/jama/fullarticle/2786040>

¹⁹ Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study. *bioRxiv*.
<https://www.medrxiv.org/content/10.1101/2021.07.28.21261295v1.full?origin=app>

²⁰ Understanding breakthrough infections following mRNA SARS-CoV-2 vaccination. *JAMA Network*.
<https://jamanetwork.com/journals/jama/fullarticle/2786040>

²¹ Understanding breakthrough infections following mRNA SARS-CoV-2 vaccination. *JAMA*.
<https://jamanetwork.com/journals/jama/fullarticle/2786040>

²² Association between mRNA vaccination and COVID-19 hospitalization and disease severity. *JAMA*.
<https://jamanetwork.com/journals/jama/fullarticle/2786039>

²³ SARS-CoV-2 vaccine breakthrough infection following a previous infection in a healthcare worker. *Journal of Infection*.
[https://www.journalofinfection.com/article/S0163-4453\(21\)00506-5/fulltext](https://www.journalofinfection.com/article/S0163-4453(21)00506-5/fulltext)

breakthrough infection was **0.93** per year increase in age (**95% CI, 0.92-0.95**) following full immunization against SARS-CoV-2 (31). Adjusting for age and sex, frailty in older adults (comorbidities such as kidney, heart, and lung disease) and low socio-economic status increased the odds of SARS-CoV-2 infection (OR: **1.93, 95% CI, 1.50-2.48** and OR: **1.11, 95% CI, 1.01-1.23**, respectively) after one dose. While the *COVID Symptom Study* reported quite a low percentage of breakthrough infections (possibly due to self-reported data), the Mayo Clinic, a non-profit American academic medical centre, identified **18% (n=1,120/ 6,161)** SARS-CoV-2 breakthrough infections in Florida from 3 January 2021 until 28 August 2021 (32). Interestingly, **97%** of the breakthrough cases occurred after 2 May 2021, corresponding to the emergence of the Delta variant circulation in Florida. Additionally, Prior to 2 May 2021, only **2.1%** of breakthrough infections resulted in hospitalizations; the percentage of hospitalized breakthrough infections rose to **19.1%** after 2 May 2021 (32). A similar study conducted in Alachua, Florida confirms the Mayo Clinic's results: the majority of breakthrough cases (**74.6%**) were Delta variant infections (33). Additionally, the authors reported that breakthrough infections typically occurred three months (104 ± 57.5 days) after full vaccination (33), demonstrating that breakthrough infections could be a combined outcome of waning vaccine immunity and the more virulent Delta variant. From a large SARS-CoV-2 Delta variant outbreak in Massachusetts, USA, **81% (n=918/1,128)** of cases were identified as breakthrough cases, of which **504 (55%)** received the Pfizer-BioNTech vaccine, **293 (32%)** received the Moderna vaccine, and **121 (13%)** received the Janssen vaccine (34). Sixteen SARS-CoV-2 primary/ secondary case pairs occurred in fully vaccinated individuals and the median time from vaccination completion to SARS-CoV-2 infection was **105 days** (range **15-326 days**) (34). A Vietnamese study analysed clinical features, viral evolution and antibody dynamics following a series of Delta variant breakthrough infections, which occurred among staff members of a hospital in Ho Chi Minh City (35). Seven to eight weeks after receiving the second dose of the Oxford-AstraZeneca vaccine, 69 (out of 866; 8%) staff tested positive for SARS-CoV-2; of the 69 infected, 60 participated in the clinical study, of which 13 were asymptomatic and 49 developed mild symptoms. Symptomatic patients demonstrated higher viral loads (median IQR: 16.5, equivalent to median \log_{10} viral load of 9.2 copies per mL) and prolonged PCR positivity than asymptomatic cases (median viral load IQR: 30.8, 4.7 \log_{10} copies per mL). Additionally, breakthrough infections were characterised by having low levels of neutralizing antibodies after vaccination (median % of NAb inhibition: 69.4) and at testing positive for SARS-CoV-2 (median % of NAb inhibition: 59.4) relative to control participants (median % of NAb inhibition after vaccination: 91.3; median % of NAb inhibition at 7-8 weeks uninfected control: 91.1) (35). The authors highlighted that “the absence of correlation between neutralizing antibody levels and peak viral loads suggested that vaccine might not lower the transmission potential of breakthrough infection cases” (36).

In a tertiary Dental Hospital in New Delhi, India, 355 healthcare workers (HCW) were fully vaccinated, of which 62.4% received Covishield and 37% received Covaxin; of the 355 fully immunised HCWs, **4.5%** experienced breakthrough infections (37). The breakthrough infection positivity rate was similar in both Covaxin and Covishield administered individuals. Interestingly, all breakthrough cases were symptomatic, however, all symptoms were mild, except for one, which required hospitalization. Approximately 63% of infected HCWs transmitted SARS-CoV-2 to their family members; the authors did not specify whether family members were vaccinated or not (37). An Israeli hospital (Sheba Medical Centre, Tel Aviv) reported a lower percentage of breakthrough infections (**2.6%; among 1,497 fully vaccinated healthcare workers, 39 breakthrough cases were detected**) among their HCWs (36) than the hospital in New Delhi. Additionally, no secondary infections were documented. All Israeli HCWs at the Sheba Medical Centre were vaccinated with Pfizer-BioNTech's BNT162b2/ Comirnaty vaccine. Given that BNT162b2/ Comirnaty demonstrates higher vaccine effectiveness rates compared to the Covishield or Covaxin vaccines (38), a lower percentage of breakthrough infections among BNT162b2 vaccines is unsurprising. Among the 39 individuals who tested positive for SARS-CoV-2, **33.3%** were asymptomatic and **19%** reported having long COVID-19 symptoms six weeks post-infection (39). **Seventy-four per cent** of the breakthrough infection cases demonstrated a high viral load (Ct value <30). Similarly, another Israeli study analysed viral loads of Delta variant breakthrough infections using reverse transcription quantitative polymerase chain reaction (RT-qPCR) test measurements (40). Within an average of two months of full vaccination, the BNT162b2 vaccine reduces breakthrough infection viral loads by a magnitude of **10 (95% CI, 4-30)**, however, this effect begins to diminish three months post vaccination and disappears after six months. Nevertheless, the authors demonstrated that booster doses restored reduced viral loads in breakthrough infections (40).

Findings from a systematic review and meta-analysis that analysed SARS-CoV-2 transmission data between October 2020 and June 2021, have demonstrated that the household is a major site of SARS-CoV-2 transmission, representing a secondary attack rate of **18.9%** (95% CI, 16.2-22.0) (39). The study did not assess whether contacts were vaccinated or not, however a German study reported significant reductions in transmission rates among vaccinated contacts than unvaccinated contacts (41). Additionally, a Scottish study published in the *New England Journal of Medicine* demonstrated that unvaccinated household members of unvaccinated healthcare workers have a hazard ratio of **0.7** (95% CI, 0.63-0.78) to become infected when compared to their vaccinated HCW counterparts (42).

Following vaccine effectiveness results, a Qatari study reported that Moderna's mRNA-1273 vaccine prevents more breakthrough infections than Pfizer-BioNTech's BNT162b2 vaccine (43). Breakthrough infection incidence rates were **2.25 (95% CI, 2.11-2.41)** and **3.25 (95% CI, 3.07-3.43)**

per 10,000 persons-weeks for the mRNA-1273 and BNT162b2 vaccines, respectively (43). In line with the aforementioned studies, the majority of breakthrough infections occurred during the Delta-predominant period (43). Lastly, a study (pre-print) in Bahrain analysed vaccine effectiveness against breakthrough infections and reported that individuals who were vaccinated with Pfizer-BioNTech's BNT162b2 vaccine were less likely to develop post-vaccination infections (OR: 0.44), hospitalizations (OR: 0.13), ICU admissions (OR: 0.04) and deaths (OR: 0.15) compared to persons vaccinated with Sinopharm's BBIBP-CorV vaccine (44).

What are the latest updates on virus transmissibility in fully vaccinated individuals?

Summary:

Despite breakthrough infection concerns, little is still known about vaccine effectiveness in preventing secondary SARS-CoV-2 transmission²⁴. Pre-Delta, vaccines successfully reduced viral loads²⁵, preventing transmission despite infection, however recent reports that vaccinated and unvaccinated individuals demonstrate similar viral loads when infected with the Delta strain^{26,27} has raised the question whether vaccines are still able to effectively prevent SARS-CoV-2 transmission. A recently published study further confirmed SARS-CoV-2 transmissibility and contagiousness are associated with viral load, regardless of vaccination or symptomatic status²⁸. Even in this case, vaccinated individuals demonstrate faster declines in viral load than unvaccinated individuals²⁹, therefore leading to a reduced transmission timeframe to infect others³⁰. Recently published studies have demonstrated that full vaccination against COVID-19 reduces the risk of transmission, even when infected with the

²⁴ Higher vaccination rate predicts reduction in SARS-CoV-2 transmission across the United States. *medRxiv*.

<https://www.medrxiv.org/content/10.1101/2021.11.14.21266325v1.full-text>

²⁵ The impact of SARS-CoV-2 vaccination on Alpha & Delta variant transmission. *medRxiv*.

<https://www.medrxiv.org/content/10.1101/2021.09.28.21264260v2>

²⁶ Outbreak of SARS-CoV-2 infections, including COVID-19 vaccine breakthrough infections, associated with large public gatherings – Barnstable County, Massachusetts, July 2021. *Morbidity and Mortality Weekly Report*.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8367314/>

²⁷ Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. *Nature Medicine*.

<https://www.nature.com/articles/s41591-021-01548-7>

²⁸ Isolation of 4000 SARS-CoV-2 shows that contagiousness is associated with viral load, not vaccine or symptomatic status. *Emerging Microbes & Infections*. <https://www.tandfonline.com/doi/full/10.1080/22221751.2021.2008776>

²⁹ Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study. *bioRxiv*.

<https://www.medrxiv.org/content/10.1101/2021.07.28.21261295v1.full?origin=app>

³⁰ Understanding breakthrough infections following mRNA SARS-CoV-2 vaccination. *JAMA Network*.

<https://jamanetwork.com/journals/jama/fullarticle/2786040>

Delta variant^{31,32} and that populations with “higher percentages of fully vaccinated individuals report fewer COVID-19 cases among unvaccinated persons³³. Given this is a rising topic, further studies are needed to confirm current findings.

Results:

A UK study that analysed transmission risk by vaccination status for household contacts exposed to SARS-CoV-2 Delta cases, reported that secondary attack rates (SAR) were lower (but not significantly) in vaccinated household contacts (**25%; 95% CI, 18-33**) than in unvaccinated contacts (**38%, 95% CI, 24-53**) (45). Likewise, the SAR in household contacts exposed to fully vaccinated index cases was **25% (95% CI, 15-35)**, which was similar to the SAR of those exposed to unvaccinated index cases (**23%; 95% CI, 15-31**), demonstrating that vaccination³⁴ unfortunately does not prevent transmission in a household setting (45). A pre-print that compared RT-PCR Ct data from fully vaccinated and unvaccinated individuals corroborate the UK study’s findings: **68% of fully vaccinated individuals** demonstrated low cycle threshold (Ct) values (<25)³⁵ in comparison with **63% of unvaccinated individuals** (46). The authors recommend getting tested regularly, regardless of vaccination status, particularly when symptomatic or after exposure to a suspected or confirmed COVID-19 case. Additionally, the authors stressed the continuation of non-pharmaceutical measures as an important factor in mitigating SARS-CoV-2 transmission (46). Another study that assessed the transmission potential during a SARS-CoV-2 Delta outbreak in a prison setting over the months of July and August 2021 found no differences in RT-PCR positivity, Ct values, or durations of viral culture positivity between unvaccinated and fully vaccinated individuals (47). When comparing across vaccines, the authors observed that individuals who received the Moderna vaccine demonstrated shorter culture positivity durations relative to Pfizer-BioNTech or Janssen vaccine recipients, although these results are confounded by the fact that the Moderna vaccine was administered more recently than the other vaccines, which were administered earlier in 2021 (47).

While the results of the aforementioned studies report minimal vaccine effectiveness in reducing secondary attack rates particularly in breakthrough infections, other publications demonstrate

³¹ Vaccine effectiveness against SARS-CoV-2 transmission to household contacts during dominance of Delta variant (B.1.617.2), the Netherlands, August to September 2021. *Eurosurveillance*.
<https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.44.2100977>

³² What is the vaccine effect on reducing transmission in the context of the SARS-CoV-2 delta variant. *The Lancet Infectious Diseases*. <https://www.sciencedirect.com/science/article/pii/S1473309921006903?via%3Dihub>

³³ Higher vaccination rate predicts reduction in SARS-CoV-2 transmission across the United States. *medRxiv*.
<https://www.medrxiv.org/content/10.1101/2021.11.14.21266325v1.full-text>

³⁴ Individuals were vaccinated with either Comirnaty/ BNT162b2 or the Vaxzevria/ ChAdOx1 nCoV19; one individual was vaccinated with the inactivated whole-virion vaccine CoronaVac.

³⁵ RT-PCR values of less than 25 typically infer SARS-CoV-2 transmission (shedding of virus).
Source: Shedding of infectious SARS-CoV-2 despite vaccination. *medRxiv*.
<https://www.medrxiv.org/content/10.1101/2021.07.31.21261387v6.full-text>

otherwise. A study in Cologne, Germany assessed transmission rates between vaccinated³⁶ and unvaccinated individuals and their close contacts, and determined that of the 979 close contacts of SARS-CoV positive vaccinated index cases, **10.1%** ($n=99$) became infected in comparison to **37.8%** ($n=303$) of the 802 contacts of unvaccinated SARS-CoV-2 cases (41). Additionally, binary logistic regression demonstrated that close contacts were **79% less likely to be infected** if the index source [individual] was vaccinated than unvaccinated. Contrary to previous reports that vaccinated and unvaccinated individuals demonstrate and shed similar viral loads when infected with SARS-CoV2 (particularly with the Delta strain) (46), the Ct values were significantly ($P<0.001$) higher in vaccinated breakthrough cases (**29.5 ± 7.5**) than in unvaccinated individuals (**25.7 ± 6.6**) (41). Among the index cases' (regardless of vaccination status) contact cases, contacts that were subsequently infected were significantly less likely to be fully vaccinated ($P<0.001$). Similarly, a Dutch study observed that vaccine effectiveness against transmission from a vaccinated index case to an unvaccinated contact is **63%** (95% CI, 46-75), significantly higher when compared to the effectiveness of transmitting the Delta strain to a vaccinated contact (**40%; 95% CI, 20-54**) (48). The transmission data was extracted from individuals vaccinated with Comirnaty (BNT162b2), Spikevax (mRNA-1273), Vaxzevria (ChAdOx1 nCoV-19), and COVID-19 vaccine Janssen (Ad26.COV2-S). In a separate interview, the author of the Dutch paper, Brechje de Gier, specified that it should be remembered that the data only reveals the effect of transmission following a breakthrough infection, the actual effectiveness against transmission is even higher than 63%, since vaccinated people are already partially immune against infection (49). **Despite plentiful evidence that COVID-19 vaccines reduce SARS-CoV-2 shedding and transmission relative to unvaccinated individuals, SARS-CoV-2 transmission between two fully vaccinated individuals can still occur (34, 50, 51), thus, it is crucial to maintain masking and physical distancing measures in place.**

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

Summary:

As the evidence on the waning immunity of COVID-19 vaccines continues to grow and breakthrough infections increase, multiple countries have taken measures into their hands and have expanded their recommendations for booster doses to not only include immunocompromised patients and public health professionals but to include all adults who received their second dose at least six months ago.

³⁶ The authors did not specify which vaccines data were analysed, however Cologne, Germany vaccinated their population with Comirnaty (BNT162b2), Spikevax (mRNA-1273), Vaxzevria (ChAdOx1 nCoV-19), and COVID-19 vaccine Janssen (Ad26.COV2-S).

Many countries such as the United Kingdom, Norway³⁷, and the United States³⁸ have expanded their recommendations to include all adults ages 18 years and older. On 23 November, Switzerland joined the other countries in approving the booster doses to its general population by approving the extension of the Pfizer-BioNTech booster dose to everyone aged 16 years and over³⁹. Amounting evidence on the efficacy and effectiveness of booster doses highlight the immunological benefits of COVID-19 vaccine boosters as they restore the serum neutralization activity that has waned after the initial two-dose vaccination and provide high protection against the disease, all while remaining safe⁴⁰. Nevertheless, inherent ethical concerns about selected countries delivering third doses while low-and middle-income countries remain under vaccinated exist. Details on the newest data regarding efficacy, safety, effectiveness, and vaccine induced immunity are reported below.

Results:

Efficacy:

On 19 November, Pfizer published data on the efficacy and safety of BNT162b2 booster doses based on 10,000 participants 16 years of age or older who completed a two-dose series of BNT162b2 (52). The relative efficacy of the booster dose against symptomatic COVID-19 was included in the report. Based on the 2-month interim results, the relative vaccine efficacy of the booster dose in participants without evidence of prior infection was **95.3%** (95% CI, 89.5-98.3) and the relative vaccine efficacy in participants with or without evidence of prior infection was **94.6%** (95% CI, 88.5-97.9) (52). When evaluating the relative efficacy of the booster doses by age group, a relative efficacy of **96.5%** (95% CI, 89.3-99.3) for participants aged 16-55 years of age and a relative efficacy of **93.1%** (95% CI, 78.4-98.6) for participants aged over 55 years of age was estimated against symptomatic COVID-19 (52). Overall, high relative efficacy in the booster group compared to the boosted group was observed with the multiple subgroup analyses showing that the efficacy was consistent irrespective of age, sex, race, ethnicity, and comorbid conditions.

Safety & Adverse Events:

On 19 November, Pfizer published data on the efficacy and safety of BNT162b2 booster doses based on 10,000 participants 16 years of age or older who completed a two-dose series of BNT162b2 (52). The safety evaluations of adverse events and reactogenicity were included in the report. Based on

³⁷ Norway offers booster shot to everyone over the age of 18. *abc News*. Accessed on: 23.11.2021.

<https://abcnews.go.com/Health/wireStory/norway-offers-booster-shot-age-18-81128007>

³⁸ CDC Expands Eligibility for COVID-19 Booster Shots to All Adults. *CDC*. <https://www.cdc.gov/media/releases/2021/s1119-booster-shots.html>

³⁹ COVID-19 vaccine from Pfizer-BioNTech: Swissmedic approves the extension of the booster dose to everyone aged 16 years and over. *Swissmedic*. Accessed on: 23.11.2021. <https://www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/covid-19-impfstoff-pfizer-biontech-boosterdosis.html>

⁴⁰ Boosting immunity to COVID-19 vaccines. *Nature Medicine*. <https://www.nature.com/articles/s41591-021-01560-x#ref-CR2>

the 2-month interim results, a total of **25.0%** of participants reported at least one adverse event from the day of administration up to one month afterwards (52). A total of **6.6%** of participants reported grade 3 or higher reactogenicity events while **0.7%** reported local reactions and **5.9%** reported systemic events (52). Out of the local reactions reported, the most frequent were injection site pain, injection site redness, and injection site swelling. As for the systemic events, the most frequently reported events were fatigue, muscle pain, and fever. Only **0.3%** of participants reported serious adverse events from the booster vaccination and no cases of myocarditis or pericarditis were observed (52). Overall, the booster vaccine demonstrated to be safe and well tolerated.

Effectiveness:

A test-negative case-control study estimated the vaccine effectiveness of the booster dose BNT162b2 in individuals aged over 50 years and older who received the ChAdOx1-S or BNT162b2 as their primary, two-dose vaccines (53). A total of 271,747 tests results from the National Immunization Management system were obtained and used to estimate the effectiveness of the BNT162b2 booster vaccination against symptomatic COVID-19. Based on the results, the vaccine effectiveness of a BNT162b2 booster dose relative to those that had received only two doses was **87.4%** (95% CI, 84.9-89.4) in individuals who received the first 2-doses of ChAdOx1-S and **84.4%** (95% CI, 82.8-85.8) in individuals who received the first 2-doses of BNT162b2 (53). When estimating the vaccine effectiveness against symptomatic COVID-19 of unvaccinated individuals and individuals who received the booster dose from 14 days after vaccination, an absolute effectiveness of **93.1%** (95% CI, 91.7-94.3) after receiving ChAdOx1-S as the primary course and **94.0%** (95% CI 93.4-94.6) after receiving BNT162b2 as the primary course were estimated (53). Overall, the BNT162b2 booster dose provided a significant increase in the protection against symptomatic COVID-19 in individuals who received the primary course of either BNT162b2 or ChAdOx1-S in adults aged 50 years and older.

Immunity:

mRNA vaccines:

To evaluate and assess the anti-spike IgG antibody titers before and after receiving a booster dose of BNT162b2 in adults aged 60 years and older, an Israeli study collected serum blood samples from adults aged 60 years and over who received their third dose of the BNT162b2 and evaluated the IgG values before and 10 to 19 days after the third dose (54). A total of 97 participants were included in the study. Based on the results, **97%** of the participants were seropositive before receiving the booster dose, however all participants become seropositive after the booster shot and an increase from a median of **440 AU/mL** (IQR, 294-923) to **25,468 AU/mL** (IQR, 14,203-36,618) was noted after the administration of the third dose (54). Overall, the study found that a third dose in adults aged 60 years

and older was associated with a significant increase in IgG titers after 10 to 19 days and no major adverse events.

Inactivated vaccines:

A study including more than 500 individuals and evaluating the antibody immunity to SARS-CoV-2 elicited by a third dose of the inactivated vaccine BBIBP-CorV was recently published (55). The kinetics of RBD antibodies, neutralizing antibodies, and RBD-specific memory B cells against the wild type and the SARS-CoV-2 Beta, Delta, and Lambda variants was analysed and compared to the immune response of individuals that only received two doses of the vaccine. Based on the results, the mean IgG values of individuals receiving a third dose **increased 8.0-fold** compared with those before third vaccination and **1.4-fold** compared with those after second vaccination (55). Additionally, when trying to evaluate the neutralizing and binding of antibodies against variants of concern, the plasma inhibitions against the wild-type, Beta, Delta, and Lambda after the third vaccination were significantly increased to **94.6%**, **71.6%**, **83.4%**, and **89.0%** within 2 weeks, respectively (55). Overall, a third dose of the inactivated vaccine significantly increased and elicited a robust immune response in recipients against the wild type and Beta, Delta, and Lambda variants of SARS-CoV-2.

Another study and evaluating the antibody immunity to SARS-CoV-2 elicited by a third dose of the inactivated vaccine CoronaVac demonstrated that a booster dose of the CoronaVac vaccine increased the levels of neutralizing antibodies against SARS-CoV-2 (56). A total of 129 healthy adults aged 18 years and over who previously received their complete CoronaVac vaccination were included in the study and received a third dose of CoronaVac. Based on the results, a decrease in the levels of anti-SARS-CoV-2 antibodies neutralizing capacities five months after the second dose was observed (**GMU 39.0**; 95% CI, 32.4-47.0); however, an **increase** of up to **12 times** was observed at four weeks after receiving the booster dose (**GMU 499.4**; 95% CI, 370.0-673.0) (56). Overall, the results support the notion that a booster dose of the SARS-CoV-2 inactivated vaccine increased the levels of neutralizing antibodies.

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

Summary:

After an evaluation of the scientific evidence regarding the vaccination of children aged 5 to 11 years with BNT162b2, the FDA authorized, on 29 October 2021, the emergency use of the Pfizer-BioNTech vaccine for prevention of COVID-19 to include children 5 through 11 years of age⁴¹. On the following

⁴¹ FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Children 5 through 11 Years of Age. *FDA*. <https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age>

week, the CDC expanded their vaccine recommendations to include children in this age group, officially commencing the administration of the two 10- μ g dose BNT162b2 vaccine in children all over the United States⁴². The decision was based on the preliminary results made available by Pfizer-BioNTech, now published in the New England Journal of Medicine⁴³. The study reported that the two 10- μ g dose BNT162b2 vaccine in children (5-11) was found to be safe, immunogenic, and efficacious. In the previous three months, other countries such as Chile, China, Cuba, and the United Arab Emirates (UAE) started inoculating children younger than 12 years old with various COVID-19 vaccines. For instances, UAE started administering the Sinopharm COVID-19 vaccine to children aged 3 to 17 years during the beginning of August⁴⁴ and has recently approved the BNT162b2 vaccine for children aged 5 to 11 years. On 18 and 19 of November, Switzerland received the application for the extension of the mRNA-1273 COVID-19 vaccine to children aged 6 to 11 years old⁴⁵, as well as the application for the extension of the BNT162b2 COVID-19 vaccine to children aged 5 to 11 years old⁴⁶.

Results:

Children aged 5-11 years old:

On 9 November results from a randomized, placebo-controlled, phase 1/2/3 study evaluating the safety, immunogenicity, and efficacy of its 10- μ g dose COVID-19 vaccine in healthy children (5 to 11 years old) was published in the New England Journal of Medicine (57). Based on the results from the phase 2/3 clinical trial, the vaccine was well tolerated and demonstrated a favorable safety profile (57). In terms of immunogenicity, the neutralizing geometric mean titers (GMTs) observed at 1 month after the second dose was **1197.6** (95% CI: 1106.1-1296.6) for the overall children aged 5 to 11 years old. For children 5 through 6 years, 7 through 8 years, and 9 through 11 years, the neutralizing GMTs was **1164.1, 1236.1, and 1191.5**, respectively (57). Overall, children developed a robust neutralizing antibody response. Additionally, the two-dose BNT162b2 vaccine administer 3 weeks apart to children aged 5 to 11 years old elicited high neutralizing titers to both the wild-type virus and

⁴² CDC Recommends Pediatric COVID-19 Vaccine for Children 5 to 11 Years. *CDC*.

<https://www.cdc.gov/media/releases/2021/s1102-PediatricCOVID-19Vaccine.html>

⁴³ Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. *NEJM*.

<https://www.nejm.org/doi/full/10.1056/NEJMoa2116298>

⁴⁴ UAE rolls out Sinopharm COVID-19 vaccine to children aged 3-17. [Press Release] *Reuters*.

<https://www.reuters.com/world/middle-east/uae-rolls-out-sinopharm-covid-19-vaccine-children-aged-3-17-2021-08-02/>

⁴⁵ COVID-19 vaccine for children aged 6 to 11: Moderna submits application for indication extension. *Swissmedic*. Accessed on: 20.11.2021. <https://www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/moderna-indikationserweiterung-covid-19-impfstoff-kinder-6-11-jahren.html>

⁴⁶ Pfizer applies for indication extension of COVID-19 vaccine to children aged 5 to 11. *Swissmedic*. Accessed on: 20.11.2021. <https://www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/pfizer-indikationserweiterung-covid-19-impfstoff-kinder-5-11-jahren.html>

the Delta variant (57). Finally, the observed vaccine efficacy against confirmed COVID-19 at least 7 days after dose 2 in children (5-11 years old) without prior evidence of SARS-CoV-2 infection was **90.7%** (95% CI: 67.7-98.3) (57). Overall, the 10-µg BNT162b2 vaccine in children aged 5 to 11 years old demonstrated to be well tolerated, to elicit robust immune response, and to have a high efficacy.

What are the latest updates on COVID-19 vaccine safety?

Summary:

As countries continue to promote COVID-19 vaccination and expand their vaccine platform to include younger individuals and introduce booster doses, many people continue to be hesitant toward receiving their COVID-19 vaccine, mainly due to safety concerns. As proven through rigorous testing in clinical trials, all the WHO EUL COVID-19 vaccines have shown to be safe and well tolerate. Nevertheless, concerns revolving the reporting of rare adverse events in vaccinees such as thrombosis or myocarditis exist. Although the number of reported cases of myocarditis after receiving an mRNA vaccine are relatively low and very rare, multiple countries such as Germany, France, Finland, Sweden, Denmark, and Norway have restricted the use of the Moderna COVID-19 vaccine in younger people due to slightly higher than expected occurrence of myocardial inflammation in male adolescents and younger adults⁴⁷. After more than 11 million dose of mRNA COVID-19 vaccines administered in Switzerland by 3 November 2021, only 199 potential cases of vaccine-associated myocarditis or pericarditis have been reported to Swissmedic⁴⁸ making the benefits of COVID-19 mRNA vaccination, such as the prevention of hospitalizations, outweigh the risk of vaccine-associated myocarditis⁴⁹. A more detailed account of vaccine safety and myocarditis reports can be read down below.

Results:

Overall vaccine safety:

⁴⁷ Germany, France Restrict Moderna's Covid Vaccine For Under-30s Over Rare Heart Risk—Despite Surging Cases. *Forbes*. <https://www.forbes.com/sites/roberthart/2021/11/10/germany-france-restrict-modernas-covid-vaccine-for-under-30s-over-rare-heart-risk-despite-surging-cases/?sh=43616e292a8a>

⁴⁸ Reports of suspected adverse reactions to COVID-19 vaccines in Switzerland – update. *Swissmedic*. <https://www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/covid-19-vaccines-safety-update-8.html>

⁴⁹ The very low risk of myocarditis and pericarditis after mRNA COVID-19 vaccination should not discourage vaccination. <https://smw.ch/article/doi/smw.2021.w30087>

The risk of developing an adverse reaction to the two vaccines distributed in Switzerland (Pfizer-BioNTech/Comirnaty or Moderna/ Spikevax) are incredibly small. As of 3 November, a total of 11,137,489 vaccine doses have been administered in Switzerland with less than 0.09% of these vaccine administrations resulting in adverse reactions, of which 65.5% were non-serious cases (58). In very rare cases (0.03%), severe side effects may occur. These severe side effects are mostly allergic reactions and are easy to treat. It is common however, for individuals to develop mild side effects after receiving the first or second dose of the vaccine. Side effects typically last 24-48 hours and include pain or redness at the injection site, muscle & joint pain, headache, and fever. Redness and swelling of the vaccination arm, one-week post-vaccination is common, particularly for Moderna's Spikevax vaccine. Nevertheless, the reactions are harmless, short-lived, and do not lead to any long-term consequences. Other adverse events such as cutaneous reactions or allergic and anaphylactic reactions have been reported and may occur. Although COVID-19 vaccines can be reported to develop allergic and anaphylactic reactions, especially after the administration of mRNA vaccines and in people with previous allergies, the cutaneous reactions remain at a low rate and the cases are quickly resolved and benign (59).

Myocarditis:

Many studies trying to investigate the incidence of and risk for myocarditis and pericarditis following COVID-19 vaccines, have discovered that mRNA vaccines were significantly associated with increased risk for myocarditis among younger males, compared to other COVID-19 vaccines, ages, and sex. Nevertheless, reported cases remain relatively low and very rare. Based on the Moderna global safety database, among approximately 151.1 million mRNA-1273 vaccine recipients a total of **1,439 cases of myocarditis or pericarditis** were reported up until 30 September 2021, leading to a reporting rate among all vaccinees of **0.95 cases per 100,000 vaccine recipients** – lower than the expected rate from the reference population of 2.12 cases per 100,000 vaccinees (60). When stratifying the data by sex and age, the highest observed rates were identified in males aged 39 years old and younger, particularly those aged 18 through 24 years (7.40 cases per 100,000 vaccinees) while the rate ratio for males and females aged less than 18 years was **1.05 (95% CI: 0.52-2.13)** and **0.21 (95% CI, 0.04-0.94)**, respectively (60). Overall, myocarditis accounted for 0.4% of adverse events reported to the Moderna global safety database after receiving the mRNA-1273 vaccine.

During a study designed to investigate the incidence rate of and risk of myocarditis and pericarditis following COVID-19 vaccination in the United States and using the Vaccine Adverse Events Reporting System (VAERS) from 11 December 2020 to 13 August 2021, an incidence rate for myocarditis of **5.98 (95% CI = 5.73–6.24)** cases per million doses administered was calculated (61). When stratifying

by age, a higher incidence was observed in adolescents after the administration of the second dose of COVID-19 mRNA vaccines. Overall, reporting odds ratio for myocarditis of **2.91 (95% CI, 2.21–3.83)** for the BNT162b2 vaccine, **5.37 (95% CI, 4.10–7.04)** for mRNA-1273, and **1.39 (95% CI, 0.99–1.97)** for Ad26.COV2.S were estimated when compared to all other vaccines from VAERS.

Based on data from a systematic review of reports of myocarditis and pericarditis following mRNA COVID-19 vaccines from the UK, Europe, and the US, multiple reports indicate that younger vaccinees more frequently reported myocarditis and pericarditis following mRNA COVID-19 vaccines compared to older vaccinees (62). Overall, a total of **435** reports of myocarditis and **327** reports of pericarditis cases were reported to UK's Yellow Card scheme up to 20 October 2021, **1,936** reports of myocarditis and **1,271** reports of pericarditis were submitted to VAERS in the US up to 21 October 2021, and **2,924** report of myocarditis and **1,855** reports of pericarditis have been submitted to EudraVigilance up to 21 October 2021 (62). Out of all the reported cases of myocarditis/pericarditis, **73.3%** of the reports were reported after the administration of the BNT162b vaccine with males representing **74.9%** of the reports for myocarditis and **56.9%** for pericarditis and the majority being under 40 years old (62). All the reported cases were characterized with mild courses and followed by full recovery, in most cases.

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

Summary:

Apart from the 8 WHO EUL approved vaccines, numerous vaccine candidates such as Novavax, Sputnik V, CureVac, SOBERANA, V-01, and MVC-COV1901 have shown promising results in terms of their immunogenicity, tolerability, and efficacy. A short summary of the results and news on new and ongoing clinical trials is found down below.

Results:

Novavax:

In the month of November, Novavax has made significant progress in filing for emergency use authorization across multiple countries and authorizing authorities. Thus far, the company has filed

for provisional authorization of its COVID-19 vaccine in the United Kingdom⁵⁰, Australia⁵¹, Canada⁵², and New Zealand⁵³ while also being granted the emergency use administration in Indonesia⁵⁴. Additionally, Novavax completed the submission to WHO of all the modules required for the regulatory evaluation of the NVX-CoV2373 COVID-19 vaccine⁵⁵.

Sputnik/ Sputnik Light

An observational study in the Republic of Belarus was conducted from January to August 2021 to assess the safety and epidemiological efficacy of the Gam-COVID-Vac (Sputnik V) vaccine (63). Based on the results, Sputnik V was well tolerated with the majority of adverse reactions being reported as mild (**91.4%**; 95% CI, 91.2-91.6) and moderate (**8.6%**; 95% CI, 8.6-8.8) (63). As for the estimated vaccine efficacy, the epidemiological efficacy of the Sputnik V vaccine was reported as **96.3%** with a efficacy index of 26.7 (63).

To address the evident shortage of licensed COVID-19 vaccines across nations, Sputnik Light - a new single-dose vaccine based on the adenovirus vaccine Sputnik V - was developed only using the adenovirus type 26 (rAd26) vector that carries the gene for SARS-CoV-2 spike S glycoprotein. An open and non-randomized phase 1/2 clinical trial was performed to evaluate the safety, tolerability, and immunogenicity of the single-dose vaccine in healthy adult (64). A total of 110 participants were enrolled in the study and received the single dose of Sputnik Light. Based on the safety results, **67.2%** of participants reported solicited adverse reactions of which 66.4% were classified as mild (64). Only **5.5%** of participants reported moderate adverse events and no serious adverse events were reported. The most frequent solicited systemic reaction was flu-like syndrome (65.5%) while other solicited systemic adverse events included fatigue (5.5%), headache (4.5%), muscle and joint pain (4.5%), hyperthermia (4.5%), chills (4.5%), decreased appetite (3.6%), rash (2.7%), hidrosis (2.7%), and dizziness (1.8%) (64). Regarding immunogenicity, all participants

- ⁵⁰ Novavax Files for Authorization of its COVID-19 Vaccine in the United Kingdom. [Press Release] - Novavax. <https://ir.novavax.com/2021-10-27-Novavax-Files-for-Authorization-of-its-COVID-19-Vaccine-in-the-United-Kingdom>
- ⁵¹ Novavax Files for Provisional Approval of its COVID-19 Vaccine in Australia. [Press Release] - Novavax. <https://ir.novavax.com/2021-10-29-Novavax-Files-for-Provisional-Approval-of-its-COVID-19-Vaccine-in-Australia>.
- ⁵² Novavax Files for COVID-19 Vaccine Authorization with Health Canada and Completes Submission for Rolling Review to European Medicines Agency. [Press Release] - Novavax. <https://ir.novavax.com/2021-11-01-Novavax-Files-for-COVID-19-Vaccine-Authorization-with-Health-Canada-and-Completes-Submission-for-Rolling-Review-to-European-Medicines-Agency>
- ⁵³ Novavax Files for Authorization of its COVID-19 Vaccine in New Zealand. [Press Release] - Novavax. <https://ir.novavax.com/2021-11-03-Novavax-Files-COVID-19-Vaccine-for-Provisional-Approval-in-New-Zealand>
- ⁵⁴ Novavax and Serum Institute of India Receives Emergency Use Authorization for COVID-19 Vaccine in Indonesia. [Press Release] - Novavax. <https://ir.novavax.com/2021-11-01-Novavax-and-Serum-Institute-of-India-Receive-Emergency-Use-Authorization-for-COVID-19-Vaccine-in-Indonesia>
- ⁵⁵ Novavax Files COVID-19 Vaccine for Emergency Use Listing with World Health Organization. [Press Release] - Novavax. <https://ir.novavax.com/2021-11-04-Novavax-Files-COVID-19-Vaccine-for-Emergency-Use-Listing-with-World-Health-Organization>

resulted in increased RBD-specific IgG reaching the highest levels on day 28 (GMT 2395), and day 42 (GMT 2285) and no significant correlation between the RBD-specific IgG response and age of vaccinees was detected (64). As for neutralizing antibodies, vaccination with Sputnik Light in the seroconversion of **92.8%** seropositive recipients, and **58.3%** seronegative recipients (64). When evaluating the neutralizing capacity of Sputnik Light against the variants of concern Alpha (B.1.1.7) and Beta (B.1.351) a 1.1 and 1.99-fold decrease in virus neutralization was noted against the Alpha and Beta variant, respectively (64). Overall, the single-dose COVID-19 vaccine Sputnik Light has a good safety profile and induces a strong humoral and cellular immune response.

CureVac:

Earlier in the month of October, CureVac announced their strategic decision to withdraw their first generation COVID-19 vaccine candidate, CVnCoV, from the current approval process with the European Medicines Agency (EMA) to re-allocate and accelerate the development of their second generation COVID-19 vaccine candidate, CV2CoV, in collaboration with GSK⁵⁶. On 18 November 2021, the biopharmaceutical company announced preclinical results of their second-generation vaccine candidate CV2CoV⁵⁷. The newly published data, in the journal Nature, demonstrated that the second-generation vaccine candidate induced substantially higher binding and neutralizing antibodies, memory B cell responses, and T cell responses as compared to the previous vaccine candidate CVnCoV when administered to nonhuman primates (65). Overall, the data demonstrated that the new vaccine candidate with optimization of non-coding regions greatly improved the immunogenicity and protective efficacy in nonhuman primates. On 23 November, after the company's decision to cease the activities on the CVnCoV candidate vaccine, results on the efficacy and safety of the CVnCoV vaccine were made available to the public and published in The Lancet Infectious Diseases⁵⁸. Based on the results from the phase 2b/3 clinical trial conducted in ten countries in Europe and Latin America, an overall efficacy against symptomatic COVID-19 of **48.2%** (95% CI, 31-61.4) was calculated (66). The vaccine efficacy against moderate-to-severe COVID-19 was **70.7%** (95% CI, 42.5-86.1), while the vaccine efficacy against symptomatic disease in

⁵⁶ CureVac to Shift Focus of COVID-19 Vaccine Development to Second-Generation mRNA Technology. [Press Release]. CureVac. <https://www.curevac.com/en/2021/10/12/curevac-to-shift-focus-of-covid-19-vaccine-development-to-second-generation-mrna-technology/>

⁵⁷ CureVac Published in Nature Preclinical Data of Second-Generation COVID-19 Candidate, CV2CoV, Demonstrating Comparable Antibody Levels to Licensed mRNA Vaccine. [Press Release] CureVac. <https://www.curevac.com/en/2021/11/18/curevac-publishes-in-nature-preclinical-data-of-second-generation-covid-19-candidate-cv2cov-demonstrating-comparable-antibody-levels-to-licensed-mrna-vaccine/>

⁵⁸ Efficacy and safety of the CVnCoV SARS-CoV-2 mRNA vaccine candidate in ten countries in Europe and Latin America (HERALD): a randomised, observer-blind, placebo-controlled, phase 2b/3 trial. *The Lancet Infectious Diseases*. [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(21\)00677-0/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00677-0/fulltext)

participants aged 18-60 years was **52.5%** (95% CI, 36.2-64.8) (66). In terms of safety and tolerability, the vaccine demonstrated an acceptable safety profile.

SOBERANA 02/Plus:

SOBERANA 02, a Cuban produced and manufactured vaccine, is a two-dose COVID-19 conjugate vaccine based on SARS-CoV-2 recombinant RBD conjugated to tetanus toxoid, while the SOBERANA Plus is a dimeric-RBD that is used as a third dose. During a phase 1/2 clinical trials, the safety, reactogenicity, and immunogenicity of SOBERANA 02 and the homologous or heterologous (with SOBERANA Plus) third doses were evaluated (67). Based on the results, no serious adverse events or deaths were reported with majority of adverse events being classified as mild. The most frequent solicited adverse event was pain at the injection site, followed by headaches (67). After the second dose of both formulations of SOBERANA 02, the vaccine induced seroconversion in over **75%** participants. Regarding the third dose, the homologous booster dose induced seroconversion in **85.7%** participants, while the heterologous booster dose (SOBERANA Plus) led to **100%** seroconversion (67). Overall, the SOBERANA 02 COVID-19 vaccine was safe, well tolerated, and immunogenic in adults aged 19-80 years, while the application of a heterologous scheme with SOBERANA Plus increased the immune response and led to a robust memory cell response (67).

After the promising results of the phase 1/2 clinical trials for SOBERANA 02 and SOBERANA Plus, a randomized, double-blind, placebo-controlled, phase 3 trial was performed to evaluate the efficacy and safety of the Cuban vaccines (68). A total of 44031 participants aged 19-80 years were enrolled in the study and assigned to three groups to test the 1) two doses SOBERANA 02, 2) two doses SOBERANA 02 and third homologous dose, or 3) two doses SOBERANA 02 and third heterologous dose of SOBERANA Plus. Based on the results, the two-dose and three-dose homologous and heterologous vaccine schedules were safe. In terms of efficacy, an efficacy of **71.0%** (95% CI, 58.9-79.1) against symptomatic COVID-19, an efficacy of **63.0%** against severe COVID-19, and an efficacy of **59.0%** against COVID-19 death, after receiving the two doses of SOBERANA 02, were calculated (68). When adjusting for age, the two-dose vaccine had an efficacy of **68.0%** (95% CI, 55.1-77.9) for participants aged 19 to 64 years and an efficacy of **85.0%** (95% CI, 48.8-95.4) for participants aged over 65 years (68). As for the three-dose heterologous vaccine, an efficacy of **92.4%** (95% CI, 86.9-95.6) against symptomatic COVID-19 and an efficacy of **100%** against COVID-19 deaths were calculated. Overall, the SOBERANA 02 conjugate vaccine and the SOBERANA Plus reported to be safe and efficacious vaccine to prevent symptomatic COVID-19 in the adult population aged 19-80 years.

V01:

The V-01 vaccine is a two-dose recombinant fusion protein vaccine against COVID-19 developed and manufactured in China by the Institute of Biophysics under the Chinese Academy of Sciences and Livzon Pharmaceutical Group Inc. After satisfactory preliminary results from the phase 1/2 demonstrating a favourable safety and immunogenicity profile in 1060 adult participants, the study on a homologous booster dose was conducted (69). A total of 43 eligible participants who previously received the two-dose regimen took part in the study. Based on the results, the third dose significantly boosted the effects of humoral immune response in participants for both the wild type and variants of concerns. A **60.4-fold increase** in younger adults and a **53.6-fold increase** in older adults in neutralizing titres against SARS-CoV-2 after receiving the third dose was observed (69). Additionally, after receiving the booster dose, an increase in neutralizing titres against variants of concerns was observed from day 28 post the second vaccination to day 14 post booster vaccination with GMTs of **206** (95% CI, 163-259) versus **607** (95% CI, 478-771) for Alpha strain, **54** (95% CI, 38-77) versus **329** (95% CI, 255-425) for Beta strain, and **219** (95% CI, 157-306) versus **647** (95% CI, 484-865) for Delta strain (69). Overall, the V-01 booster vaccine reported to be safe, well-tolerated, elicited a robust immune response against the wild-type and variants strains of SARS-CoV-2.

MVC-COV1901:

MVC-COV1901 is a new 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 Journal⁵⁹. A total of 3844 participants, screened between 30 December 2020 and 2 April 2021, took part in the study. Based on the safety data, **no vaccine-related serious adverse events were recorded**, and the most common solicited adverse events were pain at the injection site (71.2%), malaise (36.0%), and fatigue (29.7%) (70). Regarding the wild-type SARS-CoV-2 neutralizing antibody, at 28 days after the second dose of MVC-COV1901, the GMT was **662.3** (95% CI, 628.7-697.8; 408.5 IU/mL), the GMT ratio was **163.2**, and the seroconversion rate was **99.8%** (95% CI, 99.2-100) (70). Overall,

⁵⁹ 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)

the MVC-COV1901 vaccine candidate reported to have a good safety profile and elicits promising immunogenicity responses.

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