Literature screening report

COVID-19 vaccines and post-vaccination data: Literature update (14)

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Abstract

This report addresses the most relevant data on COVID-19 vaccines literature as of 24 February 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.

Content

Preamble

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

Background

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 recently identified Omicron (B.1.1.529) strain and its subvariant BA.2, 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 the steady increase in the incidence of SARS-CoV-2 throughout Switzerland until the end of January 2022, the number of confirmed cases has decreased over the course of the last few weeks, suggesting the end of the Omicron peak in the country. Based on the confirmed cases, hospitalizations, and deaths reported by the Swiss National COVID-19 Science Task

[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

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

Force over the last 14 days, the number of confirmed cases decreased at a rate of **-19 (95% CI, -7 to -30) per week**, hospitalizations fell at a rate of **-21% (95% CI, -12 to -29) per week**, and deaths decreased at a rate of **-18% (95% CI, 9 to -38) per week**.[4] Although the Omicron subtype BA.1 remains the dominant strain in Switzerland, its frequency has decreased to **69%** while the BA.2 strain's frequency increased to **31%**.[5] As of right now, information regarding BA.2's immune evasion, transmissibility, and virulence remains scarce; however, Danish researchers have recently found that the BA.2 subvariant appears to be **30% more transmissible** than BA.1.[6]

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 many countries such as Israel have begun to administer a fourth dose to persons above the age of 60 years and to health-care workers.[7] Additionally, an Israeli government advisory panel has recently recommended offering a fourth COVID-19 vaccine dose to all adults who have received their third dose or have recovered from illness at least five months ago; however, the implementation of such measures remains subject to approval by the ministry's director-general.[8] While the interest of implementing a fourth increases in multiple countries, the WHO is calling for nations 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]

[4] Overview and evolution of the situation, 28 February 2022. *Swiss National COVID-19 Science Task Force.* https://sciencetaskforce.ch/en/overview-and-evolution-of-the-situation-28-february-2022/

[5] Overview and evolution of the situation, 28 February 2022. *Swiss National COVID-19 Science Task Force.* https://sciencetaskforce.ch/en/overview-and-evolution-of-the-situation-28-february-2022/

[6] Transmission of SARS-CoV-2 Omicron VOC subvariants BA.1 and BA.2: Evidence from Danish Households. *medRxiv*. https://www.medrxiv.org/content/10.1101/2022.01.28.22270044v1

[7] 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

[8] Israel mulls offering 4th COVID vaccine dose to all adults. *Reuters.* https://www.reuters.com/business/healthcare-pharmaceuticals/israel-mulls-offering-4th-covid-vaccine-dose-all-adults-2022-01-25/

[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

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 effectiveness and booster doses, particularly against the Omicron variant. Our report covers the following questions/points:

Questions addressed

- To what extent do COVID-19 vaccines protect against the Omicron variant (B.1.1.529)?
- To what extent do booster doses protect against SARS-CoV-2 and Omicron?
- To what extent does a fourth booster dose protect against SARS-CoV-2 and Omicron?
- What are the latest findings regarding transmission dynamics for the Omicron variant?
- What are the latest findings regarding COVID-19 vaccines in children?
- What is the status of SARS-CoV-2 vaccine candidates?

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 24 February 2022. We focused on studies that would help to discuss the points raised above. For more information on the methodology, please refer to previous reports[11].

[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

Results and Findings

To what extent do COVID-19 vaccines protect against the Omicron variant (B.1.1.529)?

Summary:

The variant of concern (VOC), Omicron continues to be responsible for the majority of COVID-19 cases in numerous countries around the globe. While preliminary studies regarding the protective elements of vaccination effectiveness (VE) against Omicron have been congruent thus far (ie; less severe disease manifestations and decreased hospitalization rates), knowledge gaps persist especially concerning the differences of VE against Omicron sub-lineages BA.1 and BA.2, immunogenicity, breakthrough infections, and VE of booster doses. A short summary of study results addressing these topics can be reviewed below.

Results:

Effectiveness

In the United Kingdom, the UK Health Security Agency (UKHSA) conducted a test-negative case control study of VE against BA.2 symptomatic disease compared to the BA.1 sub-lineage. Utilizing tests between 27 December 2021 and 21 January 2022, early analysis combining all vaccines (BNT162b2, mRNA-1273, and ChAdOx1) showed that VE against BA.1 symptomatic infection was **9% (95% CI, 7.0-10.0)** approximately 25+ weeks after completion of the primary vaccination doses (1). Alternatively, VE against BA.2 symptomatic infection appeared to be slightly higher at **13% (95% CI, -26.0-40.0)** 25+ weeks after completion of the primary vaccination doses (1). It should be noted that no statistical difference in VE against BA.1 and BA.2 infection was found — analyses will be repeated by the UKHSA. Nevertheless, these current VE estimates against BA.1 and BA.2 sub-lineages give a small insight of the true situation as well as contribute to decisions concerning booster doses and relaxation of public health measures. Future analyses should also investigate VE of each individual vaccine to determine which platforms offer the most protection.

Breakthrough Infections

In the United States, a study utilizing genome sequenced specimens from health institutions in the metropolitan area of Houston, Texas from 27 November 2021 through 05 January 2022 was conducted to assess the disease character of Omicron. Using the CDC definition for breakthrough infections (BTIs), researchers found that among 4468 total Omicron patients, **55.9% (2497/4468)** met

the criteria for BTI (2). With regard to primary vaccinations, **73% (1828/2497)** of patients who met the CDC definition of BTIs received full doses of BNT162b2, **22% (553/2497)** received a full dose of mRNA-1273, and **5% (115/2497)** received the Janssen vaccine (2). When considering other VOC, analyses showed that there were significantly higher percentage of patients with Omicron-associated BTIs compared with Alpha and Delta infections at **55.9%, 3.2%, and 24.3%,** respectively. Further, among individuals who received a third dose of BNT162b2 or mRNA-1273, the percentage of BTIs was lower at **15.9%** among the total number of patients with Omicron (2).

Immunogenicity

A narrative review was conducted on the immunogenicity and vaccine effectiveness of various vaccines against Omicron. Ultimately, 32 studies were included in this review, which utilized the databases MEDLINE (PubMed), Embase, BioRxiv and MedRxiv. The review mainly focused on 4 vaccines approved by the EMA and FDA- Pfizer, Moderna, Janssen, AstraZeneca (3). Through this review, researchers concluded that humoral immune evasion from Omicron is the main factor determining the progression of Omicron cases, in both vaccinated and recovered people. The review also found that Omicron is not capable of fully escaping cell-mediated immunity, which may contribute towards the clinical mildness that has been seen in most Omicron cases. Primary vaccination was universally seen to have a drastic decrease in protection against Omicron infections, which was marginally improved after receipt of a booster vaccine. The study also reaffirmed the importance and effectiveness against severe forms of Omicron infection. This narrative review did not extract any novel information different from that which has been reported in previous editions of this report; rather, the value of this study lies in proving the reproducibility of results regarding immunogenicity through a search method similar to that used to create this report (3).

Regarding the immunogenicity of vaccines against Omicron, there is added value to be found in studies considering the dual effect of vaccination and infection on humoral immune responses against Omicron. Such a study was conducted in Durban, South Africa to investigate whether convalescent sera of participants infected with Omicron had neutralizing capacity against the Delta variant, and how a person's vaccination status interacted with these elements (4). Overall, 23 participants infected with Omicron were enrolled in the study, 10 of which were breakthrough cases. These breakthrough cases were vaccinated with either Pfizer or Janssen. Samples were taken at multiple points starting from 5 days post-symptom onset to 23 days post symptom onset. Of the vaccinated participants, Omicron neutralization increased over time from a GMT of **28** to **378,** or **13.7-fold**. Unvaccinated participants also had an increased Omicron neutralization but only increased from **26** to **113**, or **4.4 -fold**. This finding points towards the importance of being vaccinated in maximizing acquired immunity against Omicron. Delta virus neutralization, meanwhile, increased **6.1-fold** in vaccinated participants,

but did not show a statistically significant increase in unvaccinated people. At follow-up, Delta neutralization was **2.1-fold** higher than Omicron neutralization at the same point. The study concluded that based on this information, Omicron re-infection is more likely than Delta re-infection in both Delta-infected people, and those who are infected with Omicron and vaccinated. This assertion makes sense considering the extreme speed and ease with which Omicron has come to dominate daily infection statistics (4).

To what extent do booster doses protect against SARS-CoV-2 and Omicron?

Summary:

Although COVID-19 mRNA vaccines provide protection against infection with SARS-CoV-2 and are highly effective against hospitalization, vaccine effectiveness has shown trends of decline after several months among fully vaccinated individuals. Due to this decline and new highly infectious variants of concern, a third booster dose has been recommended and administered in eligible individuals. By now, multiple studies assessing the effectiveness of booster doses against infection and hospitalization have demonstrated that a third dose significantly increase the waning effectiveness of vaccines and provides a higher protection against infection and hospitalizations caused by COVID-19 than two doses. Recent studies assessing the effectiveness of COVID-19 booster doses have added to the mounting evidence that booster doses are associated with a higher effectiveness and protection against infection, hospitalization, and Omicron derived infections; nevertheless, the duration of the protection granted by booster doses remains a topic of concern within the scientific community as limited literature exists on the topic. According to a few reports and studies assessing the immune response and vaccine effectiveness of booster doses over time, the immune response and vaccine effectiveness of individuals with a third COVID-19 vaccine dose has similarly waned over time.

Results:

Effectiveness

In a study of hospitalized adults, the receipt of two mRNA COVID-19 vaccine doses versus the receipt of a third dose was compared for vaccine effectiveness against hospitalization among adults with or without immunocompromising conditions (5). The study was conducted from 19 August to 15 December 2021, a Delta predominant period, in adults admitted to hospitals within the United States.

A total of 2,952 adults aged over 18 years of age with or without immunocompromised conditions were hospitalized at 21 U.S. hospitals (5). When assessing the effectiveness of mRNA vaccines in adults without immunocompromising conditions, a vaccine effectiveness (VE) against hospitalization of **97% (95% CI, 95-99)** was estimated in participants who received a third dose, while a VE of **82% (95% CI, 77-86)** was estimated among two-dose recipients (5). A higher VE against hospitalization was also reported in adults with immunocompromising conditions who received their third dose than adults with only two doses of the mRNA vaccines. The VE against hospitalization in the immunocompromised adults was **88% (95% CI, 81-93)** and **69% (95% CI, 57-78)** among individuals who received their third dose and individuals who received only two doses, respectively (5). Overall, the administration of a third COVID-19 mRNA vaccine dose as part of a primary series among immunocompromised adults, or as a booster dose among non-immunocompromised adults provided an increased protection against COVID-19 associate hospitalization.

An increase in the protection against COVID-19 was similarly reported in another study. In this retrospective study assessing the protective effect of the third BNT162b2 dose among health care workers in Israel, the rate of breakthrough infections among the participants who received three doses was **lower** than in participants who only received two doses (6). The data of 5,371 health care workers with their vaccination status was used in the study to assess the rate of breakthrough infection in two-dose or three-dose recipients. Based on the results, the booster recipients had a remarkably reduced infection risk in the 120 days after vaccination with a **0.7% breakthrough infection rate** and a relative risk of **30 (95% CI, 20-50)** compared to two-dose recipients with a **21% breakthrough infection rate** (6). A similar effectiveness was observed in all age groups, although the most distinctive protection was noted in adults older than 45 years of age, with a **30%** absolute risk reduction ($p < 0.001$) (6). Overall, the results highlight that a booster vaccination with BNT162b2 significantly improved protection against SARS-CoV-2 during the Delta variant surge.

Omicron

A follow-up study was conducted in Spain between 03 January 2022 and 06 February 2022 investigating the effectiveness of mRNA-based booster vaccination against infection during the Omicron predominant period. Using nationwide population registries, COVID-naïve individuals aged ≥40 years and fully vaccinated ≥3 months were included in the study and matched with controls of the same sex, age group, postal code, types of vaccine, time since primary vaccination, and number of previous tests. Statistical analyses showed that overall VE of a booster against Omicron was **51.3% (95% CI, 50.2-52.4)** 7 to 34 days after immunization (7). Alternatively, VE was **43.6% (95% CI, 40.0-47.1)** when booster doses were administered 6 months after primary vaccination, and **52.2% (95% CI, 51.0-53.3)** for longer intervals (7). Overall VE of boosters among individuals aged 60-79 were

found to be higher at **58.0% (95% CI, 55.8-60.4)** compared with **49.9% (95% CI, 48.6-51.3)** for those aged 40-59 (7). Among sexes, booster VE was found to be slightly higher for females compared with males **52.6% (95% CI, 51.1-54.1)** versus **49.8% (95% CI, 48.1-51.5)** (7). Vaccine specific effectiveness against Omicron was **52.5% (95% CI, 51.3, 53.7)** for mRNA-1273 boosters and **46.2% (95% CI, 43.5,-48.7)** for BNT162b2 boosters (7). Overall VE of boosters resulting from the Spanish study are corroborated by early estimates of booster effectiveness against Omicron sub-lineages BA.1 and BA.2 conducted by the UKHSA. Discussed in the previous section (Vaccine Effectiveness), the study also showed that pooled VE of boosters for all vaccines available in the UK was **63% (95% CI, 63.0-64.0)** against BA.1 and **70% (95% CI, 58.0-79.0)** against BA.2 (1).

A study conducted China based on serum samples collected within 2 months after receiving a third vaccination demonstrated positive cross-neutralization activity against Omicron. Among 200 study participants who all received homologous doses of inactivated vaccines, neutralization activity was found to be **95.5%** for the pseudotyped Omicron variant compared to **99.5%** for the prototype, and **98.5%** for the Delta variant (8). While geometric mean titers **(GMT) for Omicron was 49 and sustained immune levels for 2 months, GMT decreased by 4.9 and 3.0-fold** compared with the prototype and Delta variant GMT, which were 239 and 148 respectively (8).

Duration of protection

Although booster doses provide a higher increased protection against COVID-19 and the Omicron variant, some studies are reporting a waning in the vaccine-induced immunity and effectiveness of third COVID-19 vaccine doses few months following their administration. A study assessing the serological responses and six-month trajectories of mRNA vaccines in United Kingdom found that waning rates appear to be similar following two or three doses of the mRNA vaccines, suggesting that countries should optimize the timing of future COVID-19 vaccine doses (9). The study evaluated adults aged 50 years and older who were part of the CONSENSUS cohort[12] - a study comparing short versus longer interval vaccine schedules in older adults - and monitored their immune response and antibody waning over time (9). A total of 471 participants volunteered to provide serum samples for up to 14 weeks after their booster dose with BNT162nb2 or mRNA1273. Based on the results, the geometric mean levels (GMLs) peaked 2 to 4 weeks post booster and started waning from 5 to 9 weeks, for all participants regardless of their primary vaccine schedule and booster dose (9). By week 10 to 14, the GMLs had reduced to **65%** in BNT162b2-extended/BNT162b2 boosted individuals, **49%**

[12] Robust antibody responses in 70–80-year-olds 3 weeks after the first or second doses of Pfizer/BioNTech COVID-19 vaccine, United Kingdom, January to February 2021. *Eurosurveillance.* https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.12.2100329?crawler=true

in mRNA1273-extended/BNT162b2 boosted individuals and **40%** in BNT162b2/BNT162b2 boosted individuals in infection-naïve participants and by **48%** in mRNA1273-extended and BNT162b2 boosted individuals, **38%** in BNT162b2-extended and BNT162b2 boosted individuals and **18%** in BNT162b2 and BNT162b2 boosted individuals in previously infected participants (9). Overall, the results demonstrate that although a mRNA booster dose increased the serological response, waning was observed after 5 weeks. Data from the UK Health Security Agency COVID-19 vaccine surveillance report reported similar results regarding the waning of the immune response and vaccine effectiveness over time in individuals who received a third COVID-19 vaccine dose (10). According to the report, two to four weeks after a booster dose of either the BNT162b2 or mRNA1273 vaccine effectiveness against symptomatic disease ranged from around **60% to 75%**, dropping to **25% to 40%** from 15 or more weeks after the booster dose (10). In regard to vaccine effectiveness against hospitalization, the vaccine effectiveness in individuals who received a BNT162b2 booster (after either primary vaccination course), started at around **90%** dropping to around **75%** after 10 to 14 weeks post booster and for individuals who received the mRNA-1273 booster (after either primary vaccination course), the vaccine effectiveness against hospitalization was **90 to 95%** up to 9 weeks after vaccination (10). Finally, the vaccine effectiveness against mortality with Omicron for all vaccines combined in individuals aged 50 years and older was **95% (95% CI, 90-98)** (10).

To what extent does a fourth COVID-19 vaccine dose protect against SARS-CoV-2 and Omicron?

Summary:

With the new emerging evidence that the immunogenicity of boosted-individuals is waning over time, some countries and scientists have decided to administer and test the safety, immunogenicity, and effectiveness of a fourth COVID-19 vaccine dose. Although a fourth dose appears to lower the confirmed rate of infection and severe illness[13] and increase the neutralizing capacity against the Omicron variant[14], the duration of protection of the fourth dose remains poorly known, especially against variants of concerns such as Omicron.

Results:

[13] Protection by the 4th dose of BNT162b2 against Omicron in Israel. *medRxiv.* https://www.medrxiv.org/content/10.1101/2022.02.01.22270232v1

[14] 4th dose COVID-19 mRNA Vaccines' Immunogenicity & Efficacy Against Omicron VOC. *medRxiv.* https://www.medrxiv.org/content/10.1101/2022.02.15.22270948v1

Recently, scientists in Israel published preliminary results on the protection of the fourth dose of BNT162b2 against the Omicron variant in Israel. The first study compared the rate of confirmed COVID-19 and severe illnesses between individuals who received a fourth dose and those who only received three doses of the BNT162b2 vaccine (11). In this retrospective study, a total of 1,138,681 adults aged 60 years and older were included in the analysis. Based on the results, the rate of confirmed infection was lower in people who received the fourth dose than in people who only received three doses of the BNT162b2 vaccine by a factor of **2.0 (95% CI, 2.0-2.1)** while the rate against severe illness was lowered by a factor of **4.3 (95% CI, 2.4-7.6)** (11). In another study conducted in Israel, an open-label, nonrandomized, clinical trial assessing the safety and immunogenicity of a fourth dose of BNT162b2 or mRNA1273 showed evidence that a fourth dose of mRNA-based vaccines reestablish antibody titers to the peak of post-third dose levels. Among 1050 healthcare workers included in the trial, 154 received BNT162b2 and 120 received mRNA1273 as fourth doses and were compared to 426 age-matched controls. Analyses showed that participants had an estimated **9- to 10-fold increase in IgG and neutralizing titers after 2 weeks** of immunization regardless of the mRNA-based vaccine received as well as an **8-fold increase in Omicron neutralization**, which was comparable to the titers measured after immunization with the third dose (12). Consistent with current studies published regarding Omicron breakthrough infections, researchers found that while breakthrough infections after the fourth dose were common with high viral loads, disease presentation was mild in principle. Overall, the preliminary trial results demonstrated that efficacy against Omicron-associated infections was **30% (95%CI, -9%-55%)** and **11% (95%CI, -43%-43%)** for BNT162b2 and mRNA1273, respectively, while only **80% local and 40% systemic adverse reactions** were reported in the participants (12).

A fourth dose of the inactivated SARS-CoV-2 vaccines (SinoPharm) was also assessed in individuals previously vaccinated with SinoPharm (13). In this longitudinal clinical study, the safety and effectiveness of the fourth dose of inactivated SARS-CoV-2 vaccine was evaluated in a total of 38 health care workers previously investigated for their responses to the first three doses of the SinoPharm vaccine (13). While the immune response induced by the third dose of the inactivated vaccine waned rapidly over time, especially against the Omicron variant, a fourth dose recalled the waned immune response of participants. The fourth dose robustly recalled neutralizing antibody titers against the wild-type virus by **19-fold** as well as cross-reactive neutralizing antibody titers to Omicron by a **2.9-fold increase** (13). Although the fourth dose was safe and capable of recalling waned immunity response 6 months after the third dose, the peak of RBD neutralizing antibody level induced by the fourth dose was inferior to the peak after the third dose (13). Therefore, the data reveals that

updated vaccines with more diverse epitopes capable of inducing neutralizing antibodies against variants of concerns could be a possible future direction for boosters.

What are the latest findings regarding transmission dynamics for the Omicron variant?

Summary:

Latest findings regarding transmission dynamics for the Omicron variant mainly consist of new information on global transmission dynamics that provides a more complete picture of the mechanism of Omicron dominance. The obvious superiority of Omicron over Delta has been known, however the studies included in this section offer more information regarding serial intervals and secondary attack rates which give more specifics as to how this is happening. Another issue of concern in the topic of Omicron transmissibility is the differences between the BA.1 and BA.2 sub-lineages. Selected studies in this report show that the BA.2 variant is more infective than the BA.1 variant, shows the same clinical mildness, and that infection with BA.1 provides some immune protection against BA.2, especially among vaccinated people. This section of the report also covers the role of vaccination, even under conditions of reduced effectiveness, on shaping the Omicron transmission dynamics.

Results:

A study from the Netherlands was conducted to assess differences between serial intervals of the Omicron BA.1 variant and the Delta variant. (14) The Omicron variant was first identified in the Netherlands on 19 November 2021, so this study conducted from 13 December to 23 December was conducted entirely after the arrival of Omicron. This study included pairs of primary and secondary cases with serial intervals between 5 and 15 days, from a national database. Variant infection was confirmed with PCR tests focused on S-gene target failure (SGTF), used as a proxy for confirmation of the BA.1 variant. The mean serial interval for these Omicron cases was **0.2-0.6 days** shorter than for non-Omicron cases. This study also found the incubation period of Omicron to be just **2.8 days**, compared **4 days** for non-Omicron cases. During the observation period, the proportion of SGTF-detected positive cases increased substantially from **9.0%** to **28.6%**, from one week to the next. With a highly vaccinated, small population, the Netherlands served as a case study for conditions where Omicron thrives as the main VOC. (14)

A study from Denmark focused on the BA.2 sub-lineage of Omicron that has dominated transmission in in the country. (15) Using Danish register data which links individuals to their households by their

ID number, this study linked the data with information on all antigen and RT-PCR test information and vaccination records, both from national databases. Primary cases were defined as the first individual tested positive for an Omicron variant in a household, Whole-genome sequencing was used to confirm variant status. With this design, this study estimated a secondary attack rate of **29%** for Omicron BA.1, and **39%** for Omicron BA.2 from the 8,541 primary cases and 5,702 secondary cases. BA.2 was associated with a higher odds of infection for unvaccinated people, with an odds ratio (OR) of 2.19 **(95% CI, 1.58-3.04**). Fully vaccinated, and boosted individuals also showed increased susceptibility of infection from BA.2. in comparison to BA.1. However, in cases of boosted and double-vaccinated primary cases, vaccination did appear to reduce transmissibility, with BA.2 having an **OR below 1**. (15)

Another study from Denmark investigated the rate of BA.2 re-infection cases within a short window of time after initial infections with BA.1 to infer information about the dynamics of acquired immunity from these two genetically similar sub-variants(16). Using a subset of samples from a potential pool of 1.8 million cases of infection between 22 November, 2021 and 11 February 2022, individuals with 2 positive test results between 20 and 60 days apart were identified. Whole-genome sequencing was used to confirm BA.1 or BA.2 status of these infections. From a total of **187** eligible re-infection cases, there were **47** instances of a BA.2 re-infection after BA.1 infection. The remaining cases (140) were from Delta to BA.2 reinfection. These 47 cases offered more insight as to the vaccination status of this group- 42 of them were not vaccinated **(89%)**, 3 of them were vaccinated twice **(6%),** and 2 people **(4%)** only received one dose of a vaccine. Additionally, in this group reinfection cases were all mild, with no need for hospitalization. Reinfection appeared to be more common in younger age groups, as the median age of the 47 cases was only **15 years,** and **70%** were under 20 years old(16).

A stochastic branching process model from New Zealand simulated the spread of COVID-19, factoring in unvaccinated, vaccinated and boosted people to model the potential for the start of local outbreaks. The model used vaccination status to calculate the likelihood of getting infected, or infecting someone else, with COVID-19. The model was applied to both the Delta and Omicron variants(17). This model output showed that regarding the Delta variant, a vaccinated traveler (not in quarantine) infected with COVID-19 was **9 times less** likely to seed an outbreak than an unvaccinated traveler with COVID-19. However, this disparity was not seen when the model was applied to the Omicron variant. There was not much difference between outbreaks seeded by vaccinated or unvaccinated people. This model showed that under conditions where Delta is dominant, unvaccinated people were responsible for **87%** of all infections. However, under the Omicron variant, this number dropped to **45%**, with vaccinated people making up **39%**, and boosted people being

responsible for **15%**. However, it was shown that only **3%** of infections occurred between 2 people who were both boosted. Using a total population vaccination rate of **78.7%** (corresponding to 90% vaccination for the eligible population), the model showed that vaccinated people are **1.9 times** more likely to be infected by an unvaccinated individual than a vaccinated individual, despite the vast disparity in numbers of both populations at a 90% effective vaccination rate(17).

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

Summary:

Latest findings regarding COVID-19 vaccination in children offer results on a few different aspects as described in more detail below. This report includes promising results from a clinical trial of an inactivated vaccine (CoronaVac) for use in children. As the scientific community awaits the results of more clinical trials on the safety and efficacy of non-mRNA vaccines on children, much has been published regarding the effectiveness of the established mRNA vaccines in children against Omicron. In general, the same trends of waning immune response have been seen in children and adolescents as has been seen in adults. As concerns about the safety and efficacy of vaccines in children persist, vaccination of very young children (under 5) remains a particular point of concern, due mainly to the lack of a strong body of evidence showing the safety and immunogenicity of COVID-19 vaccines in children. In the United States, the FDA stated it required more evidence on the Pfizer/BioNTech vaccine's suitability for children from age 6 months to 4 years, which prompted the roll out to be delayed by another 2 months.[15] More information regarding this issue is likely to be seen in the literature in the coming months.

Additionally, this report contains some updates regarding myocarditis risk and maternal vaccination safety, which can be found below.

Results

Effectiveness

An interim report from a phase 3 clinical trial of CoronaVac among children and adolescents in Chile reported safety and immunogenicity data. In a 4-week interval, participants aged 3-17 years received

[15] U.S. COVID vaccine for children under 5 delayed by at least 2 months. *Reuters.* https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-postpones-panel-meeting-discuss-pfizer-covid-vaccine-kids-under-5-2022-02-11/

two doses of the CoronaVac vaccine and were monitored for local and systemic adverse reactions(18). Blood samples were taken from 148 participants for immunity analyses. These preliminary results showed promisingly low levels of adverse events, with the primary adverse reaction reported being mild. No age group showed rates of systemic reactions at higher than **2.2%.** Systemic adverse events immediately after injection occurred in less than **1%** of participants in the 3-11 years age group. Additionally, adolescents appeared to have marginally higher rates of adverse events than children aged 3-11 years. 4 weeks post-vaccination, significant increases in total and neutralizing antibodies against SARS-CoV-2 were observed, and significant neutralizing capacity was observed in plasma from the 3-11 age group and the 12-17 age group. Significant T-cell activation was also observed 4 weeks after the second dose. Notably, a reduced neutralization response was observed against the Delta and Omicron variants, as compared to the D614G variant, which is expected of the Omicron variant, in particular. This study has added value in its inclusion of children as young as 3 years, a group for which there is little safety and immunogenicity data for most vaccines(18).

Myocarditis

A narrative review which used a combination of databases such as PubMed and reporting systems such as VAERS to search for and synthesize information regarding cardiovascular adverse events after vaccination (19). This review looked at a variety of potential adverse events, ranging from myocarditis and pericarditis to vaccine-induced thrombotic thrombocytopenia (VITT) and Takotsubo cardiomyopathy. Ultimately, the review concluded that the overall incidence rate for all the reported event was very rare. The review also asserts that adverse event reports from early in 2021 may have been influenced by the fact that only elderly and high-risk populations received the vaccine first. These populations already have a higher prevalence of some cardiac events such as arrythmia. Though the review found a consistently higher prevalence of VITT and myocarditis in younger populations, a causal relationship is unclear. The review concluded that the benefits of vaccination outweigh the risks.(19)

Another study on myocarditis, however, came to a differing conclusion than the previous one. A study in the US was conducted with 2 aims in mind: to stratify the existing myocarditis/pericarditis data in young populations by age and vaccination dose, and to conduct a risk benefit analysis to weigh the benefits of one or two doses of vaccines(20). As young males are more likely to suffer from myocarditis after vaccination, the results of this analysis mainly focus on this demographic. The total number of cases of either myocarditis or pericarditis was **253**, including 129 after the 1st dose

and 124 after the second dose. **86.9%** of these cases were hospitalized. Incidence rates per million after two doses in males aged 12-15 years was **162.2** while for males aged 16-17 years it was **93.** After conducting a risk-benefit analysis weighing myocarditis risk against COVID-19 hospitalization due to the Delta variant, the 2 dose vaccine schedule was not seen to be favorable for all demographics in the youth age group. (20).

Maternal Vaccination

A systematic review of literature regarding pregnant or lactating people who received one or more doses of a COVID-19 vaccine selected 23 studies (21).

Findings from these studies showed increased placental transfer ratios in cord blood were associated with an increased time interval between the first dose of the vaccine to delivery, suggesting that vaccination earlier in pregnancy may maximize the protection conferred to the fetus. Pregnant and lactating individuals appeared to experience adverse events at a rate consistent with the general population, with no increased risk of adverse outcomes specific to obstetrics or neonatology. In the one study that examined the effectiveness of covid vaccines in pregnancy, vaccinated pregnant patients were less likely to be infected than unvaccinated patients before delivery. This review provides reassuring evidence of the safety and immunogenicity of vaccination in pregnant and lactating people (21).

What are the latest updates on SARS-CoV-2 vaccine candidates?

Summary:

Although multiple COVID-19 vaccines currently exist in the market, the production of safe, efficient, and affordable COVID-19 vaccines in low- and middle-income countries is needed to stop the transmission of SARS-CoV-2. Currently, various countries are aiming to produce and develop their safe and effective vaccines. Apart from the 8 WHO EUL approved vaccines, numerous vaccine candidates such as Sputnik V, Clover/ SCB-2019, CHO Cell/ NVSI-06-07, CureVac, SOBERANA/ ABDALA, AD5-nCoV/ CanSino, AKS-425, NDV-HXP-S, and CoviVac have shown promising results in 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 V/ Sputnik Light:

Results on the neutralizing activity of vaccinated sera against Omicron have demonstrated that multiple COVID-19 vaccines have experienced a decrease in neutralization and effectiveness against this new variant of concern. A similar decrease has been noted in the neutralization capacity of the Russian COVID-19 vaccine, Sputnik V. A study evaluating the neutralizing activity of sera against Omicron (B.1.1.529) variant compared to the wild-type virus in individuals vaccinated with two doses of Sputnik V or BNT162b2. In this study, a total of 31 individuals vaccinated with two doses of Sputnik V and 51 samples from 17 individuals vaccinated with two doses of BNT162b2 were included in the analysis of neutralizing antibodies. Based on the results, the levels of IgG between the Sputnik V and BNT162b2 groups was comparable, although the IgG dynamic over time was different (22). In individuals who received the Sputnik V vaccine, the IgG levels remained stable over time, while the sample for BNT162b2 participants peaked in the second week following full vaccination and significantly decreased at 3 and 6 months timepoints (22). When analysing the neutralizing antibodies for Omicron, an **8.1-fold decrease** in neutralizing antibodies compared to the wild type for the Sputnik V vaccine and a **21.4-fold decrease** for the BNT162b2 vaccine was observed (22). After stratifying the results by time period after receiving the second dose of vaccines, a decrease in neutralizing antibodies for receiving the second dose of the Sputnik V vaccine less than 3 months ago of **7.6-fold** was reported leading to **80%** detectable IgG levels in the participants' samples (22). Samples from individuals vaccinated with the second dose of Sputnik V 3 to 6 months ago had a **8.8-fold decrease** in neutralizing antibodies with a total of **68.8%** of samples with detectable IgG levels (22). On the other hand, individuals who received the second dose of the BNT162b2 vaccine less than 2 weeks ago had a **20.3-fold decrease** in neutralizing antibodies for Omicron compared to the wild type, while 3 and 6 months after receiving the second dose had a **19- and 25.3-fold decrease** in neutralizing antibodies, respectively (22). Overall, the results showed that participants vaccinated with Sputnik V had a decrease in neutralizing antibodies; however, the IgG levels remained slightly higher in Sputnik V vaccinated individuals than participants vaccinated with BNT162b2 (22).

Clover/ SCB-2019

The SCB-2019 (CpG/Alum) is a two dose COVID-19 vaccine candidate developed by Clover Biopharmaceuticals that uses the Trimer-Tag technology platform. Recently, the company published promising preliminary results of its phase 2/3 trial on the efficacy of the adjuvanted subunit protein vaccine (23). The ongoing phase 2 and 3 double-blind, placebo-controlled trials was performed in healthy adults aged 18 years and older with a total of 30128 participants enrolled and assigned to

their first vaccinee. Based on the results, the vaccine efficacy against any severity COVID-19 was of **67.2% (95.72% CI, 54.3-76.8)**, **83.7% (97.86% CI, 55.9-95.4)** against moderate-to-severe COVID-19, and **100% (97.86% CI, 25.3-100)** against severe COVID-19 (23). All of the COVID-19 cases reported during the clinical trial were caused by virus variants, allowing for the calculation of efficacy against the Delta, Gamma, and Mu variants. The vaccine candidate was **78.7% (95% CI, 57.3-90.4)** efficacious against Delta, **91.8% (95% CI, 44.9-99.8)** for Gamma, and **58.6% (95% CI, 13.3-81.5)** for Mu (23). In regard to reactogenicity, no safety issues were reported in the follow-up period, although mild-to-moderate solicited local and systemic adverse events were reported in both groups (experimental and placebo) (23). Overall, two doses of the vaccine candidate SCB-2019 vaccine provided notable protection against COVID-19 and the Delta variant.

At the beginning of this year, Clove Biopharmaceutical announced the development of a universal COVID-19 vaccine booster plan to support the global use of its COVID-19 vaccine candidate SCB-2019 (CpG 1018/Alum) (24). Based on preliminary results, the vaccine candidate induced at least **3-fold higher neutralizing antibodies** compared to AstraZeneca's COVID-19 vaccine in people previously receiving two doses of AstraZeneca's vaccine (24). With the promising results, the regulatory submission for SCB-2019 are expected to include booster data and be completed in mid-2022 for the China NMPA, WHO, and EMA, with the product launch commencing thereafter (24).

CHO Cell/ NVSI-06-07

The NVSI-06-07 (CHO Cells) COVID-19 vaccine candidate is a recombinant protein vaccine that has previously shown promising results in its reactogenicity and efficacy against COVID-19. In a recent study evaluating the safety and efficacy of heterologous booster vaccination, the administration of a booster dose of NVSI-06-08 in BBIBP-CorV (SinoPharm) primed individuals demonstrated to be well tolerated and induce a strong humoral immunity in individuals previously vaccinated with SinoPharm (25). In this exploratory study, a total of five BBIBP-CorV-primed volunteers received the NVSI-06-08 booster dose to evaluate the safety and efficacy of this heterologous vaccination schedule. Based on the results, the homologous-vaccination group (received three doses of SinoPharm) had a geometric mean antibody titer (GMT) of **345.8 GMT**, whereas the heterologous-vaccination group who received the NVSI-06-08 vaccine as a booster had a GMT of **1133.6** (25). In other words, the heterologous vaccination had a **3.28-fold increase** in antibody titers. Although these results suggest that the NVSI-06-08 heterologous vaccination might induce a stronger humoral immunity, the study sample is quite small (only five participants) making the results hard generalize to the overall population; nevertheless, the results remain promising and encourage further investigation.

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

The SOBERANA 02 COVID-19 vaccine candidate is a recombinant RB protein conjugated to the tetanus toxoid. During Phase I and Phase IIa trials the safety, reactogenicity, and immunogenicity of the candidate vaccine was assessed in adults 19-59 years of age and compared in a three-dose homologous or heterologous schedule. After an interim analysis, the 25 µg dose and the heterologous schedule were selected to move forward. Recently, the preliminary result of the Phase IIb clinical trial evaluating the immunogenicity, safety and reactogenicity of the two dose SOBERANA 02 vaccine with a third heterologous dose of the SOBERANA Plus vaccine were made available (26). During the Phase IIb trial, a total of 948 individuals were recruited of which 810 were included in the study. While assessing the immune response of the participants, the proportion of participants with a **4-fold increase or higher** in anti-RBD IgG concentration was significantly different in the vaccine group (**20%**) and the placebo group (**3.8%**) after the first dose. This further increased to **76.3% (median 26.5 AU/mL)** after the second dose and to **96.8% (median 122.2 AU/mL)** after the third dose in the vaccine group (26). When evaluating the neutralizing antibodies after two and three doses, a statistically significant increase of **3.3-fold increase** (219.6 GMT; 95% CI, 179.5-268.8) was observed after the third heterologous dose in comparison to the second dose (26). An additional analysis of neutralization against SARS-CoV-2 variants was performed in 18 participants that completed the vaccination schedule. The geometric mean titer against Alpha, Delta, and Beta variants was **339 (95% CI, 277.3-414.4), 156.7 (95% CI, 1224.6-200.6), and 51.4 (95% CI 31.23-84.49)**, respectively (26). Regarding the safety and reactogenicity of the vaccine, the vaccine was well tolerated and safe in adults aged 19-80 years old (26).

Ad5V-nCoV/ Convidecia/ CanSino

The AD5-nCOV (Convidecia) vaccine is a single-dose viral vector COVID-19 vaccine developed by CanoSino Biologics. In phase 3 trials, the one-shot vaccine had an effectiveness of 57.5% in preventing symptomatic disease making the results fall behind other COVID-19 vaccines (27). Due to the increased infectivity and transmissibility of new variants of concerns, the current vaccines have led to lower vaccine protection encouraging multiple countries and governments to administer homologous and heterologous booster doses. A recently published study evaluating the safety and immunogenicity of the recombinant vaccine AD5-nCOV as a heterologous booster observed that

heterologous boosting with AD5-nCOV following the initial vaccination with CoronaVac was safe and even more immunogenic than the homologous boosting (28). In this phase 4 clinical trial, a total of 300 participants were enrolled and assigned to Group A (primed with two doses of CoronaVac and AD5-nCOV as booster), Group B (primed with two doses of CoronaVac and CoronaVac as booster), Group C (one dose of CoronaVac and second dose of AD5-nCOV), and Group D (two doses of CoronaVac). The preliminary safety results indicated that the **heterologous boosting with Convidecia** following one or two doses of CoronaVac was **safe**, despite the higher reactogenicity than the homologous boosting (28). When analysing the neutralizing antibody responses against the wild-type virus, the heterologous groups (Group A and C) had **higher neutralizing antibodies** than the homologous groups (Group B and D). The heterologous booster dose led to a geometric mean fold increase (GMFI) of **78.3** in neutralizing antibodies, while the homologous booster led to a GMFI of **15.2** (28). Similar results were seen in the two dose groups, where the heterologous doses led to a GMFI of **25.7** and the homologous doses led to a GMFI of **6.2** (28). In line with the results of the neutralizing antibody titers against the wild-type virus, the **heterologous booster doses elicited significantly higher RBD-binding IgG than homologous boosting** (28). Regarding the neutralizing antibody responses against the Delta variant, the neutralizing antibody GMTs against SARS-CoV-2 Delta variant were significantly increased at day 14 after the booster in all groups; nevertheless, the heterologous vaccination with Convidecia induced a significantly higher neutralizing antibody levels than homologous immunization with CoronaVac (28). In addition, the study quantified virus-specific T cell responses by measuring the secretion of interferon (IFN)-γ. An increased level of IFN- γ was observed across all treatment groups at 14 days after the booster doses. In Group A, participants had a median IFN-γ+ spot counts of **65 per 106 PBMCs** (IQR: 40-135) compared with a count of **60 per 106 PBMCs** (IQR: 20-170) in Group B (28). Overall, the administration of AD5-nCOV as a booster dose was safe and highly immunogenic when compared to the CoronaVac homologous administration.

AKS-452

The AKS-452 is a recombinant fusion protein COVID-19 subunit vaccine comprising an Fc fusion protein of the SARS-CoV-2 viral spike protein receptor binding domain. Recently, the phase I interim results of the clinical trial study aiming to evaluate the dose-finding and safety of the candidate vaccine were made available to the public (29). The phase I study was conducted in 60 healthy adults aged 18 to 65 years old and tested the administration of one or two doses 28 days apart of 22.5 µg, 45 µg, or 90 µg of the AKS-452 vaccine (total of six cohorts of 10 participants each) (29). Based on the safety assessment results, none of the participants in all six cohorts had adverse events higher or equal to grade 3 (29). As for the IgG titers and seroconversion rates, the 45 µg and 90 µg doses resulted in

the highest significant titers, while the administration of a second dose significantly increased the titers even more than the single-dose cohorts (29). The highest titers levels were registered 56 days after the administration of the doses. Overall, the safety assessment and the immunogenicity levels of the AKS-452 candidate vaccine were promising and favourable, allowing the AKS-452 COVID-19 vaccine candidate to move forward with its phase 2 initiation.

NDV-HXP-S

The NDV-HXP-S vaccine is a two-dose inactivated COVID-19 candidate vaccine that uses an egg-based Newcastle disease virus (NDV) expressing the spike protein of SARS-CoV-2 and in delivered intramuscularly. The candidate vaccine is currently produced and clinically developed in Vietnam, Thailand, and Brazil, while currently undergoing phase 1/2 clinical trials. Out of the multiple ongoing trials, two of the studies have made their interim results available to the public. The first results are based on the Phase 1/2 trial in Vietnam in which a total of 120 healthy adults aged 18 through 59 years of age were randomly assigned to one of five treatments (1 µg with or without CpG1018, 3 µg alone, 10 µg alone, or placebo) (30). The study aimed to assess the safety of the vaccine 56 days after vaccination and immunogenicity up to 14 days after the second vaccination. Based on the results, the most common solicited adverse events among the participants were all predominantly mild and included injection site pain or tenderness (<58%), fatigue or malaise (<22%), headache (<21%), and myalgia (<14%) (30). In terms of the immune response, the 10µg formulation group had the highest response, followed by 1 µg +CpG1018, 3 µg, and 1µg formulations (30). Fourteen days after the second vaccination, the geometric mean concentrations (GMC) of 50% neutralizing antibody against wild-type virus ranged from **56.07 IU/mL** for the 1 µg (95% CI, 37.01-84.94) to **246.19 IU/mL** for the 10 µg (95% CI, 151.97-398.82), with **84% to 96%** of vaccine groups attaining a ≥ 4-fold increase over baseline (30). In addition, the study assessed the live virus neutralization against the B.1.617.3 (Delta) variant and found that, although the neutralizing capacity was reduced, the results remained in line with the observations for vaccines currently used. After careful analysis of the results and since the 10 µg dose had potential impact on manufacturing capacity, the 3 µg dose was selected to advance to the phase 2 trial along with a 6 µg dose.

The second phase 1 clinical trial was performed in Mexico where a total of 91 volunteers received the NDV-HXP-S vaccine prime-boost regimens via intramuscular, intranasal, or internasal followed by intramuscular routes (31). The study aimed to assess the vaccine safety and immunogenicity of the different administration regimens. In the interim analysis, the vaccine was found to be safe and higher doses tested were found to be immunogenic when given intramuscularly or intranasally followed by intramuscular administration (31). Overall, the vaccine showed to be well tolerated and immunogenic, allowing it to move to further clinical trials.

CoviVac

The CoviVac COVID-19 vaccine is a two-dose inactivated whole virion candidate vaccine that has previously not shown allergenic properties in rodents and nonhumans primates in preclinical trials. The vaccine has moved towards clinically testing the vaccine in human participants during its ongoing Phase 1 and Phase 2 clinical trials. Recently, preliminary results of the phase 1/2 multicenter, randomized, double-blind, placebo-controlled study were published (32). The study was performed in healthy adults aged 18 to 60 years old where the safety of the vaccine was assessed in 398 volunteers while the immunogenicity was assessed in 167 volunteers. The CoviVac vaccine showed good tolerability and safety among the studied sample with no reported deaths, serious adverse events, or other significant safety issues (32). In terms of immunogenicity, the seroconversion rate in participants who were negative at screening was **86.9%** (32). Overall, the inactivated CoviVac showed good tolerability and safety.

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