Literature screening report

COVID-19 vaccines and post-vaccination data: Literature update (Updated Version 10)

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Abstract

This report addresses the most relevant data on COVID-19 vaccines literature as of 02 November 2021. The current report addresses the latest data on vaccine effectiveness and its duration of protection, the vaccine-induced humoral, cellular, and neutralizing response over time, the effects of vaccination on transmissibility of SARS-CoV-2, vaccine booster doses, reported cases of myocarditis, the Pfizer and BioNTech vaccine in children, and the concomitant administration of the COVID-19 and Flu vaccines. To conclude, the report highlights the latest SARS-CoV-2 vaccine development information on COVID-19 vaccine candidates.

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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.

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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.

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.

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:

Questions addressed

- What are the latest updates regarding vaccine effectiveness?
- What are the latest updates regarding vaccine waning immunity and duration of protection?
- What are the vaccine-induced humoral, cellular, and neutralizing antibody (NAb) responses over time for inactivated vaccines?
- What is known about virus transmissibility in fully vaccinated individuals?
- What is the latest data on COVID-19 vaccine booster doses?
- What is the latest information on myocarditis data?
- What are the latest updates regarding COVID-19 vaccines for children?
- What do we know about the concomitant administration of the COVID-19 and Flu vaccines?
- 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 29 October 2021. We focused on studies that would help to discuss the points raised above. For more information on the methodology, please refer to previous reports[1].

Results and Findings

What are the latest updates regarding vaccine effectiveness?

Summary:

Given the rise of the more infectious and transmissible Delta variant (B.1.617.2)[2] and reports of vaccine immunity waning over time[3], it is important to continuously track real-world vaccine effectiveness. Initial real-world observational studies demonstrated that all six WHO EUL authorised vaccines (BNT162b2/Comirnaty [Pfizer-BioNTech]/; mRNA-1273 /Spikevax [Moderna]; Vaxzevria/ ChAdOx1 nCoV-19/ AZD1222/ Covishield [AstraZeneca]; Johnson & Johnson Covid-19 vaccine [Janssen]; BBIBP-CorV [Sinopharm]; CoronaVac [Sinovac]) demonstrated similar effectiveness in real-world settings to their respective phase III clinical trials and further efficacy studies[4]. Both mRNA vaccines demonstrated slightly reduced real-life effectiveness than their respective clinical data efficacy[5], fluctuating at around **90%** effectiveness[6]. Both AstraZeneca's ChAdOx1 nCoV-19 and

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[1] 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

[2] Tracking of variants. *GISAID*. https://www.gisaid.org/hcov19-variants/

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

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

[5] 94.5% for BNT162b2/ Comirnaty. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *New England Journal of Medicine*. https://doi.org/10.1056/NEJMoa2034577; 94.1% for mRNA-1273/ Spikevax fficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *New England Journal of Medicine*. https://doi.org/10.1056/NEJMoa2035389

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

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Janssen's Johnson & Johnson Covid-19 vaccine demonstrate similar vaccine effectiveness to their efficacy trials, **85%**[7] and **69%**[8], respectively, while Sinovac's CoronaVac fared better in real-world settings than reported in its efficacy data[9]. Little data on Sinopharm's BBIBP-CorV vaccine effectiveness has been published thus far.

Both mRNA vaccines demonstrate reduced effectiveness levels over time, however, Moderna's mRNA-1273 vaccine has continued to demonstrate higher effectiveness levels[10] than Pfizer-BioNTech's BNT162b2 vaccine. The latest vaccine effectiveness data on AstraZeneca's ChadOx1 nCoV-19/Vaxzevria or Janssen vaccines Ad26.COV2.S corroborate previously reported data on vaccine effectiveness, although two recent studies observed large declines in Ad26.COV2.S's duration of protection over time. The latest data on vaccine effectiveness is summarised below.

Results:

mRNA vaccines: BNT162b2 (Pfizer-BioNTech) & mRNA-1273 (Moderna)

A study estimated vaccine effectiveness against SARS-CoV-2 infection in Belgium, controlling for previous infections, household exposure, and temporal trends. Among a working age-population, Pfizer-BioNTech's vaccine (BNT162b2) effectiveness **(74% (95% CI, 72-76))** was lower than Moderna's **(85% (95% CI, 80-90)** (1). The study's data was collected under a period of extensive testing in Belgium, which contributed to the capture of asymptomatic infections, however the authors decided not to distinguish between asymptomatic and symptomatic infection as symptoms might have appeared after the contact trace call (1). Past studies have reported lower vaccine effectiveness against asymptomatic infection than symptomatic infection (2, 3). Interim estimates of COVID-19 vaccine effectiveness in the U.S. between June and August 2021 also demonstrated that the Moderna vaccine provides higher effectiveness against hospitalization (**95%, (95% CI, 92-97**) than Pfizer-BioNTech's BNT162b2 vaccine **(80% (95% CI, 73-85)** (4).

Following Sheikh et al.'s (5) large-scale vaccine effectiveness against SARS-CoV-2 infection and hospitalization study in Scotland, BNT162b2 vaccine effectiveness against death was **95% (95% CI, 79-99)** for individuals aged between 40 and 59 years and **87% (95% CI, 77-93)** for those aged 60 years and above (6); Vaccine effectiveness against death from the Delta variant two or more weeks

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

[8] Effectiveness of the Single-Dose Ad26.COV2.S COVID Vaccine. *medRxiv.* https://doi.org/10.1101/2021.09.10.21263385

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

[10] 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

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after the second vaccine dose was **90% (95% CI, 83-94)** (6), while BNT162b2 vaccine effectiveness against the B.1.617.2 infection was **80% (95% CI, 77-83)** 14 or more days after second dose (7).

Another study evaluated the effectiveness of the mRNA-1273 (Moderna) vaccine among incarcerated men in the Sierra Conservation Center, U.S, after a Delta variant outbreak that began on 16 July. As of 15 August, the estimated vaccine effectiveness was **56.6% (95% CI, 42.0-67.5)** against infection and **84.2%** (95% CI, 56.4-94.3) against symptomatic infection (8). Despite the vaccine demonstrating overall lower effectiveness against infection than other studies, the reduced effectiveness could be an outcome by the congregate settings and the "protection against symptomatic illness remained robust" (8).

Lastly, the latest variant of concern, Mu, has been demonstrated to have a similar resistance against mRNA vaccines than the Delta variant's resistance against mRNA vaccines. Takuya Tada et al. (2021) state that the "Mu variant does not present any additional concerns over Delta with which it is nearly identical" (9). Tada's statement is corroborated by another study, which reported that the Moderna's (mRNA-1273) two-dose vaccine effectiveness was **86.7% (95% CI, 84.3-88.7)** against Delta infection and **90.4% (95% CI,73.9-96.5)** against Mu infection (10).

ChAdOx1 nCoV-12 (AstraZeneca)

The latest vaccine effectiveness data on AstraZeneca's ChadOx1 nCoV-19/Vaxzevria corroborate previously reported data on AstraZeneca's vaccine effectiveness (11). The latest publications over the month of October have reported AstraZeneca's ChAdOx1 nCoV-12 vaccine effectiveness against any SARS-CoV-2 infection to be **53% (95% CI, 12-84)** in Belgium over the months of January to June (7) and **67% (95% CI, 62-71)** against the Delta variant strain in the UK (7).

ChAdOx1 nCoV-12 vaccine effectiveness against death was **88% (95% CI, 76-93)** for individuals aged between 40 and 59 years and **90% (95% CI, 84-94)** for those aged 60 years and above (6); Vaccine effectiveness against death from the Delta variant two or more weeks after the second vaccine dose was **91% (95% CI, 83-94)** (6).

Ad26COV2.S (Janssen)

A test-negative design study was conducted in Mato-Grosso di Sul, Brazil between 25 June and 30 September (a period of high Gamma and Delta predominance) to estimate the vaccine effectiveness of Ad26.COV2.S against symptomatic COVID-19. Adjusted effectiveness, 28 days after the single dose, was **50.9% (95% CI, 35.5-63.0)** against symptomatic COVID-19, **72.9% (95% CI, 35.1-91.1)** against hospitalization, and **90.5% (95% CI, 31.5-99.6)** against COVID-19 related death (12). These results however should be interpreted with caution; the study was prone to residual confounding

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factors, potentially underestimating vaccine effectiveness estimates. Due to the short data collection period, the authors could not measure the waning of the vaccine's effectiveness. Two studies corroborate the Brazilian data: Janssen's Ad26COV2.S vaccine effectiveness had a peak[11] effectiveness against SARS-CoV-2 infection of **58% (95% CI, 51-65)**[12] in Puerto Rico (13) and an overall effectiveness of **61% (95% CI, 29-84)** in Belgium between the months of January and June (1). See *Vaccine Waning Immunity and Duration of Protection section* for more information on Janssen's vaccine effectiveness.

Inactivated vaccines (Sinopharm and SinoVac)

As of 29 October, no new data has been published on either Sinopharm's BBIBP-CorV or Sinovac's CoronaVac's effectiveness in real world settings over the month of October. Thus far, all October-published studies analysed humoral, cellular, and/ or neutralizing antibody (NAb) responses. Refer to *Humoral, Cellular, and NAb response for Inactivated Vaccines section* below for further information.

Regarding Jara et al.'s large scale effectiveness study of the CoronaVac vaccine in Chile (14)[13], published on 2 September in *The New England Journal of Medicine (NEJM),* three letters to the journal's editor were subsequently published (15). All three letters addressed data presented in Table 2 and Figure 2B of Jara et al.'s article, which demonstrated that partially immunized (1 dose) participants had higher hospitalization, ICU admission, and death incidences than unvaccinated participants, and asked for further clarifications for these results. The letters to the editor provide a few explanations including "reduced compliance with mask-wearing and reduction in social distancing after vaccination" and potential confounders with time-dependent variables (e.g., "A person's vaccination status may vary over time, so it is not possible to separate participants into groups according to vaccination status. Still, if one tries to do this, as the authors do, all the persons who become infected during the interval between receiving the first and second doses of vaccine will be labelled as partially vaccinated, which severely biases the incidence of infection in this group.") (15). Franz J. Onishi and Janaina M. Goto further state that "the number of person-days in the unvaccinated group was at least 3.5 times as large as the combined number in the other groups studied, which could lead to biases in the analysis of the results, even with the use of analytic tools" (15). The authors replied to the letters explaining that the surge in COVID-19 cases in Chile could be

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[11] The authors do not state during which month this peak occurred; however, data was collected from 15 December 2020 to 1 October 2021.

[12] Refer to the *Vaccine Waning Immunity & Duration of Protection* section for more information on this study.

[13] The authors reported an estimated vaccine effectiveness of **65.9%** for preventing COVID-19, **87.5%** for preventing hospitalization, **90.3%** for preventing ICU admission, and **86.3%** for preventing COVID-19 related death. https://www.nejm.org/doi/full/10.1056/NEJMoa2107715

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a result of a highly transmissible virus circulating in a partially immunized population in addition to increased mobility, behavioural changes and lifting COVID-19 restrictions. They further explain that Table 2 reported the crude, unadjusted incidence rates for symptomatic disease, hospitalizations, ICU admissions, and confirmed deaths, and a "simple examination of the crude incidence rates may be misleading", because Chile's vaccination campaign prioritized high-risk persons (i.e. older adults and persons with underlying conditions). The authors state that they adjusted the confounding variables accordingly (age, sex, region of residence, income, nationality, and underlying comorbidities) and that "Simpson's paradox[14] which shows that the marginal and conditional association measures often differ, can explain the observed differences in incidence rates between groups according to immunization status" (15).

Despite reports of reduced effectiveness against SARS-CoV-2 infection with the circulating Delta variant, **vaccine effectiveness remains high against severe infection, hospitalization, and death for all vaccines**.

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

Summary:

Given the latest reports that observed reductions in vaccine protection in Israel[15] and the U.S.[16,17], studies have tried to determine whether these reductions in vaccine effectiveness are due to the more infectious and transmissible Delta variant or due to waning vaccine immunity. While the above-mentioned vaccine effectiveness studies solely analysed vaccine effectiveness for a particular point in time, this section provides a more in-depth review of studies that particularly analysed vaccine duration of protection over time (3-12 months) while factoring in for different SARS-CoV-2 strains. Thus far, the majority of studies concluded that reductions in vaccine effectiveness are due to waning vaccine immunity over time, and that the emergence of the Delta variant could have acted as an exacerbating factor. Some studies, however, have demonstrated otherwise, concluding that declines in vaccine protection are due to emerging strains. Further

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[14] On Simpson's paradox and the sure-thing principle. *Journal of the American Statistical Association.* https://www.tandfonline.com/doi/abs/10.1080/01621459.1972.10482387

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

[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

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studies are needed to verify the reports on waning vaccine immunity in order to implement timely public health measures.

Results:

A retrospective cohort study, that included more than 3 million participants across the U.S., concluded that reductions in BNT162b2 effectiveness over time are primarily due to waning vaccine effectiveness rather than reduced vaccine protection against the more infectious Delta variant (16). This large-scale cohort study demonstrated that vaccine effectiveness against Delta infection was **93% (95% CI, 85-97)** one month after the second dose, and dropped to **53% (95% CI, 39-65)** four months after full vaccination. Likewise, vaccine effectiveness against other variants was **97% (95% CI, 95-99)** one month after full vaccination and consequently dropped to **67% (95% CI, 45-80)**. The authors underscore the importance of administering booster doses to restore initial high levels of vaccine protection (16).

Likewise, a UK study found that there was no evidence of reduced effectiveness in the B.1.617.2 period than in the B.1.1.7 period for both Pfizer and AstraZeneca after full vaccination, and thus the authors concluded that the observed reductions in vaccine effectiveness due to waning vaccine immunity over time (7); BNT162b2 vaccine effectiveness reduced over time from **85% (95% CI, 79-90)** 14 days after second dose to **75% (95% CI, 70-80)** 90 days after second dose (*P*=0.007), while AstraZeneca's vaccine (ChAdOx1 nCoV-19) vaccine effectiveness reduced from **72% (95% CI, 64-78)** at 14 days after second dose to **63% (95% CI, 53-71)** at 90 days after second dose, but there was no heterogeneity (*P*=0.14) (7).

In Qatar, Pfizer-BioNTech's vaccine reached a peak effectiveness against SARS-CoV-2 infection of **77.5% (95% CI, 76.4-78.6)** four months after the second dose, and gradually declined thereafter (post 2 months VE=**73.2%**; post 3 months VE=**69.6**%; post 4 months VE=**51.7**%) (17). After 5 months, vaccine effectiveness declined substantially to **22.5% (95% CI, 10.6-32.7)** and remained low throughout months 6 and 7 (**17.3-22.3%**) (17). Declines in vaccine immunity were larger for individuals above the age of 60 years compared to those under 60, and effectiveness against asymptomatic infection was lower than effectiveness against symptomatic infection, but both demonstrated similar declines in vaccine immunity (17).

In Minnesota, U.S., adjusted vaccine effectiveness against asymptomatic infection for the Moderna vaccine dropped from **91% (95% CI, 72-98)** in January-March, to **71% (95% CI, 53-83)** in April-May, to **63% (95% CI, 44-76)** in June-August (18). Unfortunately, this study did not assess the impact of timing from vaccination on effectiveness, and only assessed vaccine effectiveness in that point in time, and thus could not conclude whether reductions in vaccine effectiveness were due to

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the rise in Delta predominance throughout the country or waning vaccine immunity. In California, Moderna's mRNA-1273 vaccine effectiveness against Delta declined from **94.1% (95% CI, 90.5-96.3)** 14-60 days after vaccination to **80% (95% CI, 70.2-86.6)** 151-180 days after vaccination (10). The study observed declines in vaccine effectiveness against both Delta and non-Delta variants, however, waning was less pronounced for non-Delta viral specimens (10) suggesting that reductions in vaccine effectiveness could be an outcome of both lower protection against Delta and waning vaccine immunity over time.

Interestingly, a study conducted in New York, concluded that declines in vaccine effectiveness "may have been driven by factors other than waning" because vaccine effectiveness declines were "not offset in calendar time by approximately one-month" (19). From 1 May to 3 September in New York, BNT162b2's effectiveness declined from **93.6%** on 1 May to **65.8%** by 10 July, subsequently increasing to **69%** on 28 August. Moderna's mRNA1273 vaccine demonstrated a similar decline from **96.5%** to **77.2%** and subsequently increased to **78.5%** over those dates, respectively (19). Janssen's Ad26.COV2.S vaccine declined from **89.4%** (May) to **51.7%** (July) and increased substantially to **70.2%** in August (19).

In line with previous studies (20-23), BNT162b2's vaccine effectiveness declined more than the Moderna vaccine in Puerto Rico (four months after receiving the second dose, BNT162b2 VE declined **31%,** from **87% (95% CI, 85-89)** to **56% (95% CI, 53-59)**, while mRNA-1273 VE only declined **19%,** from **90% (95% CI, 88- 91)** to **71% (95% CI, 68-74**) (13). Janssen's Ad26.COV2.S vaccine also declined **31%**, from **58% (95% CI, 51- 65)** to **27% (95% CI, 17- 37)** (13). The authors concluded that the decrease in effectiveness was not due to the Delta variant (13).

A similar study that utilised U.S. Veterans Health Administration (VHA) data, observed large declines in vaccine protection over time for BNT162b2, mRNA-1273, and Ad26.COV2.S (24). The greater reduction in vaccine immunity, particularly when compared to the Puerto Rican study, could be due to the older sample population demographic (approximately 50% of the participants (*N*=301,861 out of 619,755) were aged 65 and above); past studies have reported larger declines in vaccine protection over time among older persons (≥65 years) than younger individuals (7, 10, 16, 25). From March to August, vaccine effectiveness dropped from **91% (95% CI, 91-92)** to **50% (95% CI, 47-52)** and **92% (95% CI, 92-93)** to **64% (95% CI,62-66)** for the BNT162b2 and mRNA-1273 vaccines, respectively (24). Despite evidence of waning vaccine immunity, both mRNA vaccines maintained adequate protection levels (above the WHO required minimum of 50% VE (26)). Janssen's Ad26.COV2.S demonstrated the largest decline from **88% (95% CI, 98-89)** to **3% (95% CI, -7–12)** (24). The authors did not provide an explanation for Janssen's extremely low effectiveness.

Lastly, studies have observed that China's inactivated vaccines wane rapidly over time, particularly when compared to its mRNA or adenovirus vaccine counterparts (27). Thus far, few studies have assessed the real-world duration of protection for Sinopharm's BBIBP-CorV or Sinovac's CoronaVac vaccines, and the majority focus on humoral, cellular, and/ or NAb levels over time (27). Refer to the *Humoral, Cellular, and NAb response for Inactivated Vaccines section* below for further information.

What are the vaccine-induced humoral, cellular, and neutralizing antibody (NAb) responses over time for inactivated vaccines?

Summary:

Both neutralizing antibodies and vaccine elicited humoral and cell-mediated response are associated with protection against symptomatic SARS-CoV-2 infection[18,19] and vaccine immunogenicity against SARS-CoV-2 were analysed extensively prior to the large-scale rollout of COVID-19 vaccines throughout the world. However, recent reports of waning vaccine immunity have returned the attention to immunogenicity and the durability of cellular, humoral, and antibody responses. mRNA antibody levels, a proxy for vaccine protection, have been demonstrated to sustain vaccine elicited humoral and cell-mediated immunity for at least six months after full (two-dose) immunization[20,21,22], even against variant strains[23]. While both AstraZeneca's and Janssen's vaccines generate robust immune responses, their vaccine induced levels of anti-SARS-CoV-2 receptor-binding domain (RBD) immunoglobulin G (IgG) are typically lower than the mRNA's vaccines[24,25]. Studies have observed that both Sinopharm's (BBIBP-CorV) and Sinovac's (CoronaVac) inactivated vaccines generate lower

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[18] Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nature Medicine.* https://www.nature.com/articles/s41591-021-01377-8

[19] Immune Correlates Analysis of the mRNA-1273 COVID-19 Vaccine Efficacy Trial. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.08.09.21261290v4

[20] Impact of circulating SARS-CoV-2 variants on mRNA vaccine-induced immunity. *Nature.* https://www.nature.com/articles/s41586-021-04085-y

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[22] Evidence of SARS-CoV-2-Specific Memory B Cells Six Months After Vaccination with the BNT162b2 mRNA Vaccine. *Frontiers in Immunology.* https://www.frontiersin.org/articles/10.3389/fimmu.2021.740708/full

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[25] Differential Kinetics of Immune Responses elicited by COVID-19 Vaccines. *The New England Journal of Medicine.* https://www.nejm.org/doi/10.1056/NEJMc2115596

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levels of neutralizing antibodies compared to mRNA or adenovirus vaccines, particularly over time[26]. However, while antibodies function similarly to T- and B-cell responses in vaccinated individuals[27], declines in antibody levels does not equate to similar declines in immune protection[28], T and B cells responses have been shown to provide more solid and sustained defence[29].

Results:

After a full-dose administration of the CoronaVac vaccine, most participants demonstrated a robust antibody response (with a variable Ig anti-RBD level, measured seven days after the second dose) (28). The authors found no difference in Ig anti-RBD levels at 7, 14, 21, and 28 days after the second dose and the antibody levels remained relatively stable for the next 49 days. Antibody responses were stronger in individuals who had previous SARS-CoV-2 infection and lower in individuals aged 40 years old and above (28). Interestingly, out of the 131 fully immunized participants, 9 developed breakthrough infections, of which all had similar levels of Ig anti-RBD than the non-infected participants **(>250 U/ml)**. All breakthrough infections were either asymptomatic or exhibited mild COVID-19 symptoms (28). Another study assessed the persistence of humoral and cellular immune responses for 12 months after two doses of CoronaVac in Beijing, China. CoronaVac-induced RBD-specific antibodies reach a maximum S/CO value of **11.26 (95% CI, 9.29-13.24)** with a seropositivity rate of **99%** (29). Three months post-second dose, the S/CO value reduced to **3.87 (95% CI, 2.85-4.90; with 92%** seropositivity). This antibody titre was sustained throughout the following 3 months (6 months after second dose S/CO value= **3.68 (95% CI, 2.43-4.94**) and reduced to **2.11 (95% CI, 1.50-2.72)** at month 12. GMT levels decreased gradually over the first three months after the second dose, but subsequently stabilised at approximately **4.1 (95% CI, 2.0-6.2)** for the following 9 months (29). RBD-specific CD4$^+$ T central memory (T$_{CM}$) and CD8$^+$ T effector memory (T$_{EM}$) cell levels followed a similar trajectory to the antibody and GMT titres, peaking at 3 months (**15.25%** and **12.14%**, respectively), declining over time and then stabilising towards 12 months (29). Fractions of CD4$^+$ T$_{EM}$ and CD8$^+$ T$_E$ cells increased over time and constituted up to about **7.51%** of total peripheral blood CD4$^+$ T cells and about **8.74%** of total peripheral blood CD8$^+$ T cells. CD4$^+$ T$_{CM}$, CD4$^+$ T$_{EM}$, CD8$^+$ T$_{EM}$ and CD8$^+$ T$_E$ cells that produce IL-2 rose from 1 to 6 months after the second dose and were maintained at a high level throughout 12 months (29), demonstrating that CoronaVac elicits durable SARS-CoV-2 specific memory for CD4$^+$ and CD8$^+$ T cells.

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26 China's COVID vaccines have been crucial – now immunity is waning. *Nature News.*
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27 Impact of circulating SARS-CoV-2 variants on mRNA vaccine-induced immunity. *Nature.*
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28 China's COVID vaccines have been crucial – now immunity is waning. *Nature News.*
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A immunogenicity comparison study demonstrated that CoronaVac induced lower anti-SARS-CoV-2 RBD IgG seroconversion rate (**75.6% (136-180)**) and lower geometric mean (GM) antibody levels (**12.7 BAU/mL**) than AstraZeneca's ChAdOx1 vaccine (**100% (180/180; 69.8 BAU/ mL)** after one dose (30). Two weeks after the second dose, both vaccines induced **100%** seroconversion, however CoronaVac's induced anti-SARS-CoV-2 RBD IgG levels continued to be lower than AstraZeneca's and decreased over time (2 weeks GM 164.4 BAU/ mL; 4 weeks GM 94.8 BAU/ mL; and 8-12 weeks GM 34.7 BAU/ mL) (30). Lastly, CoronaVac demonstrated higher GMT against the original Wuhan strains than against variants of concern (Alpha, Beta, and Delta).

Lastly, a Sri-Lankan study analysed the persistence of antibody and T cell responses to the BBIBP-CorV vaccine 12 weeks after receiving the second dose (31). Antibody responses declined in all age groups (20-39 years, 40-59 years, ≥60 years), particularly for individuals aged 60 and above, but T cells persisted (31).

What is known about virus transmissibility in fully vaccinated individuals?

Summary:

Although vaccination can prevent onward transmission by reducing the symptomatic and asymptomatic infections and by reducing the onward spread from infected individuals, previous studies have demonstrated that in vaccinated and unvaccinated infected individuals with the Delta variant the viral load was similar, suggesting that vaccinated people might be equally infectious[30]. On the other hand, other studies suggested that vaccinated people were less likely to spread the virus and the Delta variant as their levels of nasal virus dropped faster than unvaccinated infected people[31,32]. In order to characterize transmission dynamics and better understand the ongoing pandemic, more studies investigating the impact of vaccination on onward transmission of SARS-CoV-2 and its variants of concerns are needed. One of the first studies to investigate how well vaccines prevent the spread of the Delta variant analysed testing data from 139,164 close contacts of 97,716 people infected with SARS-CoV-2 between January and August 2021 in the United

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[30] Outbreak of SARS-CoV-2 Infectious, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings – Barnestable Country, Massachusetts, July 2021. *MMWR.* https://www.cdc.gov/mmwr/volumes/70/wr/mm7031e2.htm?s_cid=mm7031e2_w

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[32] REACT-I round 13 final report: exponential growth, high prevalence of SARS-CoV- and vaccine effectiveness associated with Delta variant in England during May to July 2021. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.09.02.21262979v1

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Kingdom[33]. The study reported that although vaccination reduced the transmission of Delta, by less than the Alpha variant, the impact of vaccination decreased over time. Another study investigating the association between COVID-19 immunity within families and the risk of infection in nonimmune family members found that as the number of immune family members increased, the risk of contracting COVID-19 decreased[34]. Overall, vaccination remains an important public health measure to control and prevent the further spread of SARS-CoV-2.

Results:

Results from a retrospective observational cohort study demonstrated that vaccination reduced transmission of Delta but that the impact of vaccination decreased over time. Using data of adults' contacts of symptomatic and asymptomatic SARS-CoV-2-infected adult index cases from the English contact testing data, the study aimed to investigate the associations between transmission and index case, the contact vaccination status in relations to the Alpha and Delta variants, and the time since second vaccination (32).

Onward Transmission:

Based on the study's results, **46%** of the contacts of unvaccinated index cases, **35%** and **26%** contacts of partially vaccinated cases (ChAdOx1 and BNT162b2, respectively), and **28%** (ChAdOx1) and **21%** (BNT162b2) contacts of fully vaccinated cases tested PCR-positive for COVID-19 (32). The Delta variant was associated with increased onward transmission, in comparison with the Alpha variant (32). Overall, vaccine-associated reductions in transmission post-second dose in index cases were reduced with Delta for BNT162b2 and ChAdOx1 by approximately 1.6-fold.

Vaccination in contacts:

PCR-positivity was the highest in unvaccinated contacts with **52%** of them being infected with COVID-19, followed by **32%** of them being partially vaccinated with ChAdOx1, **32%** partially vaccinated with BNT162b2, **22%** fully vaccinated with ChAdOx1, and **17%** fully vaccinated with BNT162b2 (32). Overall, more vaccinated contacts tested positive with Delta than with Alpha.

Duration of Protection and Transmission Reductions:

The rate of contacts testing PCR-positive increased **1.08-fold** (95%CI 1.05-1.11) for ChAdOx1 and **1.13-fold** (1.05-1.21) for BNT162b2 with no evidence of a difference between vaccines for each

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[33] The impact of SARS-CoV-2 vaccination on Alpha & Delta variants. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.09.28.21264260v2.full-text#ref-8

[34] Association Between Risk of COVID-19 Infectious in Nonimmune Individuals and COVID-19 in Their Family Members. *JAMA.* https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2785141

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doubling of weeks 14 days after the administration of the second vaccination in index cases (32). In terms of the duration of protection and its transmission reduction, for the Alpha variant, transmission was reduced by **68%** (95% CI: 52-79) 2 weeks post second-dose of BNT162b2 and then fell to **52%** (95% CI: 29-67%) by 12 weeks, while the transmission reduction for ChAdOx1 was **52%** (95% CI: 22-70%) at 2 weeks and **38%** (95% CI: −1-62%) at 12 weeks (32). As for the Delta variant, transmission was reduced by **50%** (35-61%) 2 weeks and **24%** (95% CI: 20-28%) 12 weeks, respectively, and **24%** (95% CI: 18-30%) and **2%** (95% CI: −2-6%) for ChAdOx1 (32).

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

Summary:

At the beginning of the month, the European Medicines Agency (EMA) concluded that an extra dose of the COVID-19 vaccines BNT162b2 and mRNA-1273 could be given to people with severely weakened immune systems, while booster doses could be considered at least 6 months after the second dose for people aged 18 years and older[35]. Additionally, the F.D.A. amended and expanded their booster dose recommendations for Moderna, Janssen, Pfizer and BioNTech, and heterologous booster doses[36]. As countries continue to administer booster doses to vulnerable populations and expand their booster platform to include the general population, more data on the protection granted by vaccine boosters against COVID-19 (especially for the BNT162b2 vaccine) has become available. Recently, Pfizer and BioNTech released preliminary results from the first randomized, controlled COVID-19 vaccine booster trial aiming to evaluate the efficacy and safety of a booster dose of the BNT162b2 vaccine in individuals aged 16 years and over who previously received the Pfizer and BioNTech COVID-19 vaccine[37]. Compared to individuals who did not receive a booster, individuals who received their BNT162b2 booster dose showed a relative efficacy of 95.6% against COVID-19 during a period when Delta was the prevalent strain across all age groups. Additionally, during multiple subgroup analyses, the efficacy demonstrated to be consistent irrespective of age, sex, race, ethnicity, or comorbid conditions.

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[35] Comirnaty and Spikevax: EMA recommendations on extra doses and boosters. *EMA.* https://www.ema.europa.eu/en/news/comirnaty-spikevax-ema-recommendations-extra-doses-boosters

[36] Coronavirus (COVID-19) Update: FDA Takes Additional Actions on the Use of Booster Dose for COVID-19 Vaccines. *FDA.* https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-additional-actions-use-booster-dose-covid-19-vaccines

[37] Pfizer and BioNTech Announce Phase 3 Trial Data Showing High Efficacy of a Booster Dose of their COVID-19 Vaccine. *[Press Release] Pfizer and BioNTech.* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-phase-3-trial-data-showing

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Previously, the Israeli Ministry of Health released results on the protection of the BNT162b2 vaccine booster against COVID-19 in individuals 60 years and older and demonstrated that the rate of confirmed infection was lower in the booster group than the non-booster group by a factor of 11.3 and the rate of severe illness was lower by a factor of 19.5[38]. Since Israel was one of the first countries to administer booster doses to its general population, due to multiple studies such as Goldberg et al.[39] demonstrating the waning immunity of the BNT162b2 across all age groups, the Israeli Ministry of Health was able to preliminary analyse the protection of BNT162b2 vaccine booster against COVID-19 across different age groups and recently made its results available in medRxiv. Overall, the results concur with the previous results for individuals aged 60 years and older in that confirmed and severe illness rates were lower in the booster group compared to the non-booster group across age groups[40]. Additionally, one of the first studies evaluating the effectiveness of the BNT162b2 booster dose in Israel demonstrated that the booster dose provided a high effectiveness against severe COVID-19 across age groups[41].

While homologous vaccine schedules used to be recommended for booster administration, the administration of booster doses was approved by the F.D.A. on 20 October 2021 as findings of a National Institutes of Health (NIH) study on heterologous booster vaccination demonstrated that heterologous booster vaccinations were well-tolerated and immunogenic in adults with a completed primary COVID-19 vaccine regimen[42]. Overall, the results demonstrated that heterologous boosters increased titers 6.2 to 76-fold while homologous boosters increased titers 4.2 to 20-fold[43].

Results:

Efficacy of BNT162b2 Vaccine Booster:

Based on Pfizer and BioNtech preliminary phase 3 trial results from a randomized, controlled COVID-19 vaccine booster trial, a 30-µg booster dose of the Pfizer-BioNTech COVID-19 Vaccine in individuals 16 years of age and older demonstrated a vaccine efficacy of **95.6% against disease**

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[38] Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. *The New England Journal of Medicine* https://www.nejm.org/doi/full/10.1056/NEJMoa2114255

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[42] F.D.A. to Allow 'Mix and Match' Approach for Covid Booster Shots. *The New York Times.* https://www.nytimes.com/2021/10/18/us/politics/fda-mix-and-match-boosters.html?referringSource=articleShare

[43] Heterologous SARS-CoV-2 Booster Vaccinations – Preliminary Report. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.10.10.21264827v2

during a period when the Delta strain was prevalent. Over 10,000 individuals participated in the trial and were randomized 1:1 to receive either a 30-µg booster dose (the same dosage strength as those in primary series) or placebo. The median time between second dose and administration of the booster dose or placebo was approximately 11 months. During the study, 5 cases of COVID-19 in the booster group, and 109 cases in the non-boosted group were reported leading to an observed relative vaccine efficacy of **95.6% (95% CI: 89.3, 98.6)**. The median age of participants was 53 years, with 55.5% of participants between 16 and 55 years, and 23.3% of participants 65 years and older. Multiple subgroup analyses were performed to evaluate the efficacy. Based on the results from those subgroup analyses, the efficacy remained consistent irrespective of age, sex, race, ethnicity, or comorbid conditions. Overall, the adverse event profile was generally consistent with other clinical safety data for the vaccine, with no safety concerns identified.

Protection of BNT162b2 Vaccine Booster against COVID-19:

Based on the preprint on the protection of BNT162b2 vaccine booster against COVID-19 across age groups, the results show that the rate of confirmed infection and severe illness were substantially lowered among those who received a booster dose across all age groups (33). Overall, the confirmed infection rates were approximately **10-fold lower** in the booster group compared to the non-booster group (ranging from **8.8-17.6** for ≥12 days post booster administration across the five different age groups) with a lower rate of **12.4-fold** (95% CI: 11.9-2.9) for people 60+ years of age, **12.2-fold** (95% CI: 11.4 to 13.1) for people aged 50-59, **9.7-fold** (95% CI, 9.2 to 10.4) for people aged 40-49, **8.8-fold** (95% CI, 8.2 to 9.5) for people aged 30-39, and **17.6-fold** (95% CI, 15.6 to 19.9) for people aged 16-29 (33). As for the protection against severe illness, the rates were **18.7-fold** (95% CI, 15.7-22.4) ≥12 days post booster administration for ages 60 and over, and **22-fold** (95% CI, 10.3-47.0) for ages 40-60 (33). In terms of COVID-19 associated death rates, for ages 60 and over, the rates were **14.7-fold** (95% CI, 9.4-23.1) ≥12 days post booster administration (33).

Effectiveness of BNT16b2 Booster Dose:

Based on the data repositories of Israel's health-care organisation, the effectiveness of a third dose of the BNT162b2 mRNA vaccine for preventing severe COVID-19 outcomes was estimated (34). A total of 728,321 individuals who received the booster dose were matched (1:1) to demographically and clinically similar controls who did not receive a third dose. The effectiveness of the third vaccine dose, compared with two doses only, was estimated to be **93%** (95% CI: 88–97) **against admission to hospital**, **92%** (95% CI: 82–97) **against severe disease**, and **81%** (95% CI: 59–97) **against COVID-19-related death** (34). The third booster also demonstrated to be effective within different age groups with an estimated **effectiveness against admission to hospital** of **70%** (95%

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CI: -70-100) **for individuals aged 16 to 39 years**, **92%** (95% CI: 83-97) **for individuals aged 40 to 69 years**, and **93%** (95% CI: 87-97) **for individuals aged 70 years and over** (34). Additionally, an estimated **effectiveness against severe COVID-19 disease** of **94%** (95% CI: 85-99) for **40 to 69 years** and **92%** (95% CI: 83-98) for **70 years and over** was calculated (34). Overall, the results suggest that a third dose of the BNT162b2 mRNA vaccine is effective in protecting individuals against severe COVID-19-related outcomes across age groups, compared to individuals who only received two doses.

Heterologous Booster Doses:

The study evaluating homologous and heterologous booster vaccination in persons who receive the full COVID-19 vaccine regimen demonstrated promising results in terms of reactogenicity and immunogenicity (35). This phase 1/2 clinical trial included healthy adults who had received a COVID-19 vaccine available under EUA (BNT162b2, mRNA-1273, and Ad26.COV2.S.) at least 12 weeks earlier and boosted them with either a homologous booster dose or a heterologous booster dose from the three EUA vaccines. In total 458 participants were enrolled in the study and assigned to the nine different combinations. Based on results, the reactogenicity for the heterologous schedules was similar to the one reported for the primary series where injection site pain, malaise, headache, and myalgia were the main side effects reported in more than half the participants (35). In regards of the immunogenicity elicited by the booster doses, the booster vaccines **increased** the neutralizing activity by **4.2 to 76-fold** and binding antibody titers **increased 4.6 to 56-fold** for all combinations, where the greatest increase was observed in for those who received BNT162b2 and mRNA-1273 boost after an Ad26.COV2.S primary vaccination (35). Homologous booster **increased** neutralizing antibody titers **4.2-20-fold** whereas the heterologous boost **increased** titers **6.2 to 76-fold** (35). When comparing the different combinations of COVID-19 vaccine booster doses, major differences can be noted. For participants who initially received the completed Pfizer and BioNTech COVID-19 vaccine schedule, receiving a booster dose of Moderna, Pfizer and BioNTech, and Janssen led to an **increase** of binding and neutralizing antibody assay of **17.3, 14.9, and 6.2-fold**, respectively (35). As for participants who initially received the completed Moderna COVID-19 vaccine schedule, receiving a booster dose of Pfizer and BioNTech, Moderna, and Janssen led to an **increase** of binding and neutralizing antibody assay of **9.7, 7.9, and 64.7-fold**, respectively (35). Finally, participants who initially received the Janssen COVID-19 vaccine schedule and then received a booster dose of Moderna, Pfizer and BioNTech, and Janssen led to an **increase** of binding and neutralizing antibody assay of **56.1, 32.8, and 4.8-fold**, respectively (35). Overall, the homologous and heterologous booster vaccinations were well-tolerated and immunogenic.

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What is the latest information on myocarditis data?

Summary:

Reports of myocarditis, pericarditis and myopericarditis cases post COVID-19 vaccinations, particularly in young and adolescent men, have raised some concerns regarding vaccine safety among the younger population. Past studies have confirmed that the benefits of preventing SARS-CoV-2 infection and COVID-19 related hospitalization outweigh the risks of developing myocarditis or other cardiovascular side effects after COVID-19 vaccination[44,45,46,47,48]. Despite the risk-benefit analyses, countries such as Sweden, Norway, and Finland have temporarily paused the administration of Moderna's Spikevax (previously mRNA-1273) to young men under 30 years of age, in early October, given the rare risk of developing myocarditis and pericarditis[49]. These decisions followed upon referral of a yet unpublished Nordic study[50] (involving data from Finland, Sweden, Norway and Denmark) that has been sent to the European Medicines Agency (EMA) for further assessment. Pfizer-BioNTech's mRNA vaccine (Comirnaty) will continue to be deployed in Sweden, Norway, and Finland; men that received Spikevax as their first dose will consequently receive Comirnaty as their second dose in Finland[51].

The results below outline the latest published studies that assessed myocarditis and pericarditis cases upon COVID-19 vaccination. Data continues to support the continuation of anti-SARS-CoV-2 vaccination despite the rare risks of heart inflammation; young males are 6[52] to 18[53] times more likely to develop myocarditis after SARS-CoV-2 infection than after COVID-19 vaccination.

[44] Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices – United States, June 2021. *CDC Morbidity and Mortality Weekly Report (MMWR)*. https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm?s_cid=mm7027e2_w

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[46] Vaccinating adolescents against SARS-CoV-2 in England: A risk-benefit analysis. *OSF Preprints.* https://osf.io/grzma/

[47] Safety of the BNT162b2 mRNA COVID-19 vaccine in a nationwide setting. *The New England Journal of Medicine.* https://www.nejm.org/doi/full/10.1056/nejmoa2110475

[48] Myopericarditis after messenger RNA Coronavirus Disease 2019 Vaccination in Adolescents 12 to 18 years of age. *The Journal of Pediatrics.* https://www.jpeds.com/article/S0022-3476(21)00736-8/fulltext

[49] COVID-19: Sweden, Norway, and Finland suspend use of Moderna vaccine in young people "as a precaution". *BMJ.* https://www.bmj.com/content/375/bmj.n2477

[50] Study unavailable online in English.

[51] COVID-19: Sweden, Norway, and Finland suspend use of Moderna vaccine in young people "as a precaution". *BMJ.* https://www.bmj.com/content/375/bmj.n2477

[52] Risk of Myocarditis from COVID-19 Infection in People Under Age 20: A Population-Based Analysis. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.07.23.21260998v1.full-text

[53] Safety of the BNT162b2 mRNA COVID-19 vaccine in a nationwide setting. *The New England Journal of Medicine.* https://www.nejm.org/doi/full/10.1056/nejmoa2110475

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Results:

Two studies from Israel, published this month in *The New England Journal of Medicine,* quantified the risk of myocarditis following vaccination with the BNT162b2/ Comirnaty vaccine. Both studies reported that the estimated incidence rate of developing cardiovascular complications following the Pfizer-BioNTech shot were low. The overall estimated incidence of developing myocarditis within 42 days upon receiving the first dose was **4.12 cases (95% CI, 2.99-5.26) per 100,000 vaccinated** persons for **males** and **0.23 cases (95% CI, 0-0.49) per 100,000 vaccinated** persons for **females** in a large Israeli health care organization (Clalit Health Services) (36). The other nationwide Israeli study (utilising Israeli Ministry of Health data) reported an estimated incidence of **3.19 cases (95% CI, 2.37-4.02) per 100,000 vaccinated** persons for **males** and **0.39 cases (95% CI, 0.10-0.68) per 100,000 vaccinated** persons for **females,** 21 days after the second dose (37). Most cases in both studies occurred in young males aged between 16 and 29 years [**10.69 cases per 100,000 persons** (95% CI, 6.93-14.46) (36) and **13.60 cases per 100,000 persons** (95% CI, 9.30-19.20) (37)], driving up the standardized incidence ratio for the male population. Men aged 30 and above had a standardized incidence ratio of **2.11 (95% CI, 1.19 to 3.04)** (36) and **2.90 (95% CI, 1.98 to 4.09)** (37) per 100,000 persons. The vast majority of myocarditis cases were mild and occurred after the administration of the second dose. Another large-scale U.S-based study reported lower myocarditis incidence rates than the Israeli data. Of the ~2.4 million participants (50.2% received mRNA-1273 and 50.0% received BNT162b2), the incidence of acute myocarditis was **5.8 cases per 1 million second dose administrations** (observed over a 10-day time-window) [**IRR = 2.7 (95% CI, 1.4-4.8)**] (38). All cases were among men aged between 20 and 32 years. The development of myocarditis and other heart inflammation cases are additionally influenced by other factors including geographical and sociodemographic settings, which may explain the calculated incidence differences between Israel and the U.S. Furthermore, incidence differences could arise due to variations in study methodologies (39).

In summary: Recently published studies corroborate previously reported myocarditis data (40). Developing myocarditis complications post-COVID-19 vaccination is rare. Most cases are mild and resolve rapidly upon a benign clinical course. Young males (16-29 years) have an increased risk of developing complications compared to older individuals and/or women/ girls. Despite this, the benefits of the COVID-19 vaccine greatly outweigh the risks, even for young and adolescent males.

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

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Summary:

Pfizer-BioNTech COVID-19 vaccine has been approved for 12–15-year-olds by both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in May 2021, while the Moderna COVID-19 vaccines was approved for the younger population later in the year. Since then, many controlled trials and studies have been conducted to further monitor the vaccine's safety and immunogenicity, however, vaccine effectiveness against COVID-19 in-real world setting for children remains limited. Recent results on the Pfizer and BioNTech COVID-19 vaccine estimated vaccine effectiveness against SARS-CoV-2 among children aged 12 to 15 years old in Israel. Based on the results, the vaccine was highly effective in this younger population. While the Pfizer and BioNTech and Moderna COVID-19 vaccines has been available for children 12-years and older, younger children have yet to be approved for the administration of the vaccines. This may soon change as both Pfizer and BioNTech and Moderna have shared promising preliminary results of their vaccines in children younger than 12 years old.

Results:

Vaccine Effectiveness:

A retrospective cohort study estimated vaccine effectiveness against SARS-CoV-2 infections among 12–15-year-old children and adolescents in Israel during the month of July. Adjusted vaccine effectiveness 8-28 days after receiving the second dose was **91.5%** (95% CI, 88.2-93.9) (41). Another Israeli study found that 7 to 21 days after the second dose, vaccine effectiveness against documented B.1.617.2 (Delta) SARS-CoV-2 infection and symptomatic COVID-19 was **90%** (95% CI, 88-92) and **93%** (95% CI, 88-97), respectively among adolescents between 12 and 18 years of age (42). The Israeli findings are consistent with a US-based study, in which adjusted vaccine effectiveness was **91%** (95% CI, 88-93) against SARS-CoV-2 infection and **81%** (95% CI, -55-98) against SARS-CoV-2 related hospitalizations among individuals aged between 12 and 15 years (43). The study only assessed 45 hospitalization cases, contributing to the wide confidence intervals. However, another test-negative, case-control study was conducted across 19 U.S. pediatric hospitals during 1 June and 30 September to assess the effectiveness of the Pfizer-BioNTech vaccine (BNT162b2) against hospitalization among children aged 12 to 18 years. The authors concluded that the vaccine provided a high level of protection against hospitalization (**93%** (95% CI,83-97)); of those hospitalized, 97% (n=173) were unvaccinated (44). For further data on vaccine effectiveness in children, please refer to August's COVID-19 vaccines and post-vaccination data literature update (11).

Preliminary results in children (5-11 / 6-11 years old):

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Pfizer and BioNTech has released preliminary results from its ongoing, randomized, placebo-controlled, phase 1/2/3 study evaluating the safety, immunogenicity, and efficacy of its 10-µg dose COVID-19 vaccine in healthy children (5 to 11 years old) (45). Based on the results from the phase 2/3 clinical trial, the vaccine was well tolerated and demonstrated a favorable safety profile (45). 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 (45)**.** 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 the Delta variant (45). 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) (45). 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 with to have a high efficacy.

Moderna announced positive preliminary results from its ongoing, randomized, placebo-controlled, phase 2/3 study of the COVID-19 vaccine in children aged 6 to 11 years old. Based on the results, the two 50-µg doses of mRNA-1273 were generally well tolerated and showed robust neutralizing antibody titers while meeting the primary immunogenicity endpoints (46). A total of 4,753 participants were enrolled in the clinical trial. The SARS-CoV-2-neutralizing antibody geometric mean ratio (GMR) comparing the response in children to young adults was **1.5 (95% CI: 1.3-1.8)** with a seroresponse of **99.3%** (46). Overall, these results demonstrate that the vaccine elicited a robust and strong immune response. The mRNA-1273 vaccine was well tolerated in children with the majority of adverse events being mild or moderate in severity and with the most solicited adverse events being fatigue, headache, fever, and injection site pain (46).

What do we know about the concomitant administration of the COVID-19 and Flu Vaccine?

Summary:

As the ongoing COVID-19 pandemic enters yet another Fall and Winter season, in the Northern hemisphere, concerns regarding the possible collapse of health care facilities due to influenza and COVID-19 arise among physicians and other health care experts. In order to lessen the possible burden on healthcare systems, the administration of both the COVID-19 vaccine and the influenza

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vaccine should be encouraged; however, data on the timely, efficient, and safe delivery of both vaccines remains limited. During the previous influenza season (2020/2021), international health agencies recommended for the influenza and COVID-19 vaccines to be administered separately with a 14-day interval between each in order to avoid inaccurate attribution of side effects to the newly approved COVID-19 vaccines[54]. This decision was mainly due to the lack of data on concomitant vaccination; however, results from a study evaluating the safety and immunogenicity of the concomitant administration of COVID-19 and influenza vaccines was recently published as a preprint on SSRN providing insight into this topic[55]. Based on the results, the concomitant vaccination raised no safety concerns and preserved the immune response to both vaccines, making this same-day administration a promising possibility. Other ongoing clinical trials are also assessing the concomitant administration of the Shingles and Influenza vaccine with the COVID-19 booster vaccine[56]. In addition to the concomitant administration of the influenza and COVID-19 vaccines, pharmaceutical companies such as Novavax have created a vaccine that combines the COVID-19 and seasonal influenza vaccine into one and have proceeded to initiate a phase 1/2 clinical trial[57].

Results:

In order to evaluate the safety and immunogenicity of concomitant administration of a COVID-19 vaccine (BNT162b2 and ChAdOx1) and influenza vaccine (aTIV, QIVc,QIVr), the ComFluCOV study, a randomized, controlled, phase IV trial with blinding, was conducted across the United Kingdom (47). A total of 679 participants were recruited and randomized into six different cohorts and in the placebo cohorts. The second dose of COVID-19 vaccine and influenza vaccine were administered on the same day in different arms. Based on the results, the concomitant vaccination raised no safety concerns (47). Most reactions were mild or moderate with rates of local and unsolicited systemic reactions very similar between the randomized groups. Only one serious adverse event resulting in hospitalization with severe headache was considered related to the trial intervention (47). In regards of the immunogenicity, the anti-S IgG geometric units (GMU) measured 21 days after receiving either ChAdOx1 or BNT162b2 were similar between those who received a concomitant vaccination or

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COVID-19 vaccine alone in all cohorts (47). As for the influenza vaccine, similar results were seen in all cohorts (47). Overall, the concomitant vaccination raised no safety concerns and preserved the immune response to both vaccines.

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

Summary:

Apart from the 6 WHO EUL approved vaccines, numerous vaccine candidates such as Novavax, Sputnik V, Ad5 vectored vaccine, CureVac, AS03, Valneva, and SOBERANA 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:

The NVX-CoV2373 is an adjuvanted, recombinant S protein nanoparticle vaccine that has previously reported an efficacy of 89.7% against SARS-CoV-2 infection in a phase 3, randomized controlled trial conducted in multiple sites in the United Kingdom[58]. Recently, new data on the results from another Novavax's phase 3 clinical trials conducted in the United States and Mexico were made available. The study had a total of 29,949 participants randomized between 27 December 2020 to 18 February 2021, of which 29,582 received one or more than one dose (48). Based on the results, a vaccine efficacy (VE) **of 90.4% (95% CI, 82.9-94.6)** against all COVID-19 was reported. All the moderate-to-severe cases occurred in placebo recipients, leading to a VE against severe Covid-19 of **100% (95% CI, 34.6-100)** (48). In terms of reactogenicity, the majority of solicited local and systemic adverse events were mild-to-moderate and transient. The most frequently reported solicited local adverse event were tenderness and injection site pain (48). Overall, the vaccine was well tolerated and demonstrated a high vaccine efficacy.

Despite Novavax's COVID-19 vaccine demonstrating a very high vaccine efficacy in clinical trials, the company is facing significant hurdles in proving manufacturing that meets regulators' quality standards[59]. These challenges have resulted in production delays and delayed regulatory authorization for its administration to the general population.

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Sputnik V:

The Sputnik V COVID-19 vaccine, also known as Gam-COVID-Vac, uses a heterologous recombinant adenovirus approach that combines the adenovirus 26 (Ad26) and adenovirus 5 (Ad5) and uses them as vectors for the expression of the SARS-CoV-2 spike protein. During its phase 3 trial results, the vaccine was reported to be 91.6% effective at preventing severe infection[60]. Although the vaccine has yet to be approved for use by the European Medicines Agency (EMA) or the World Health Organization (WHO), multiple countries have approved the vaccine from its administration. **No further and new relevant studies on the Gam-COVID-Vac vaccine were found**.

Ad5 Vectored Vaccine:

The Ad5-vectored COVID-19 vaccine is a replication defective Ad5 vectored vaccines that expresses the spike glycoprotein of SARS-CoV-2 and that is administered in two doses 56 days apart. Interim analysis from a phase 3 clinical trial demonstrated that the vaccine had an efficacy of 65.3% and 90.1% at preventing symptomatic and severe COVID-19, respectively. Recent results evaluating the safety and immunogenicity of the vaccine candidate with a homologous prime-boost regiment in 6 years old and above were published[61]. A total of 430 participants aged 6 and older were enrolled in the study. Overall, the Ad5-vectored COVID-19 vaccine was safe, tolerable, and induced significant RBD-specific antibodies which decreased with increasing age, with geometric mean titres **(GMTs) of 1037.5 in 6–17-year-olds, 647.2 in 18–55-year-olds, and 338.0 in 56 and older** (49). Pseudo virus neutralising antibodies showed a similar pattern. A single dose in children and adolescents induced higher antibody responses than that elicited by two doses in adults (49).

CureVac:

CureVac's COVID-19 vaccine (CVnCoV), an mRNA-based COVID-19 vaccine encapsulated in lipid nanoparticle, uses mRNA technology to encode for SARS-CoV-2 spike protein. Prior clinical trial results demonstrated that CureVac had a lower vaccine efficacy than other mRNA-based COVID-19 approved vaccines such as the BNT162b2 and mRNA-1273. Based on the company's phase 2b/3 clinical trial, the vaccine reported an efficacy of 53% against COVID-19 of any severity, an efficacy of 77% against moderate, and severe disease, and full protection against hospitalization or

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death[62]. **No further studies on the COVID-19 vaccines candidate CVnCoV (CureVac) were found with new relevant data**.

SOBERANA Vaccine:

FINLAY-FR-1 (SOBERANA 01) and FINLAY-FR-1A (SOBERANA Plus) are recombinant dimeric RBD vaccine candidates produced at the Finlay Vaccine Institute and Centre of Molecular Immunology in Havana, Cuba. Both vaccines are absorbed on alum while FINLAY-FR-1 also has an outer membrane vesicle from *Neisseria meningitidis* group B (OMVs) as adjuvant. The preliminary results of their phase I randomized, double-blind clinical trial aimed to analyze the vaccines' safety, reactogenicity, and immunogenicity in 60 participants randomly allocated to three groups: FINLAY-FR-1, FINLAY-FR-1A-25, and FINLAY-FR-1A-50[63]. All three groups received three doses. Based on the results regarding safety, adverse events were reported by 80% of participants with most of the adverse events being classified as mild (63.5%), solicited (58.8%), and local (61.8%) (50). Out of the adverse events, 69.4% had a causal association with vaccination where pain at the vaccination site was the predominantly reported. In regard to the immunogenicity, **after the third dose, anti-RBD seroconversion was 100%, 94.4%, and 90%** for the FINLAY-FR-1, FINLAY-1A-50, and FINLAY-1A25, respectively. The geometric mean neutralizing titers after the third dose rose significantly in the group vaccinated with FINLAY-FR-1 (50). Additionally, no differences were found between homologous or heterologous schedules. Overall, the vaccine candidates were safe and immunogenic, all while inducing live-virus neutralizing antibodies against SARS-CoV-2 (50).

CoV2 preS dTM-AS03 Vaccine:

A new vaccine candidate using a baculovirus expression vector system (BEVS) to express stabilised SARS-CoV-2 pre-fusion Spike (S) antigen (preS dTM) has been developed by Sanofi Pasteur in collaboration with GlaxoSmithKline. Recently, results from the phase 2 clinical aiming to evaluate the safety, reactogenicity, and immunogenicity of three optimised formulations of the vaccine candidate containing 5,10, or 15 µg of antigen, administered as two intramuscular injections 21 days apart were published as a preprint[64]. Overall, the vaccine candidate demonstrated an **acceptable**

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safety profile and robust immunogenicity in SARS-CoV-2 naïve adults, including 60 years and older (51). From the three formulations tested, a monovalent D614G and a bivalent D614G and Beta variant vaccine, will undergo efficacy evaluation in phase 3 trials (51).

<u>Valneva:</u>

The pharmaceutical company Valneva is currently working on their COVID-19 vaccine named VLA2001. The vaccine is a whole virus, inactivated, adjuvant vaccine candidate against COVID-19 that is established using a Vero-cell platform. In addition to its inactivated whole virus particle of SARS-CoV-2 with high S-protein density, VLA2001 contains a combination of adjuvant alum and CpG 1018. The vaccine has previously shown promising results and Valneva recently released preliminary results from their pivotal Phase 3 trial[65]. A total of 4,012 participants aged 18 years old and older across the United Kingdom participated in the study. According to the trial results, **VLA2001 demonstrated superiority against AZD1222 (ChAdOx1-S), in terms of geometric mean titer for neutralization antibodies (VLA2001 GMT: 803.5 (95% CI: 748.48-862.59) vs. AZD1222 GMT 576.6 (95 CI: 543.6-611.7))**, as well as non-inferiority in terms of seroconversion rates at two weeks after the second vaccination in adults aged 30 years and older. Overall, the vaccine candidate was generally well-tolerated and demonstrated a broad T-cell response in participants (52).

On top of their ongoing clinical trials, the company Valneva is preparing for trials in children (5-12 years of age) and a sponsored booster trial that will evaluate VLA2001's booster performance for people in need of a booster.

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