Literature screening report

COVID-19 vaccines in the WHO's Emergency Use Listing (EUL): report (2)

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Abstract

This report focuses on the World Health Organization's (WHO) Emergency Use Listing (EUL) of authorized vaccines as of August 16, 2021. Currently six vaccines are authorised for emergency use: BNT162b2/COMIRNATY (Pfizer-BioNTech, USA), Spikevax/Moderna COVID-19 Vaccine/ mRNA-1273 (Moderna, USA), Vaxzevria/ChAdOx1 nCoV-19/AZD1222/Covishield (AstraZeneca/Oxford, UK, India), Janssen Covid-19 vaccine/Johnson & Johnson (Janssen, USA), Sinopharm/BBIBP-CorV (China), and Sinovac/CoronaVac (China). This report provides a condensed summary concerning vaccine efficacy, safety, protection against variants, and further important information for each vaccine, in the form of a synoptic table. The information and data in this synoptic table was extracted from phase III clinical trials and, in some cases, from observational studies. This report particularly focuses on heterologous vaccination schedules (e.g., mixing ChAdOx1 and mRNA vaccines), Sinopharm/

BBIBP-CorV and Sinovac/ CoronaVac's inactivated vaccines, and provides the latest updates and information on children and adolescent vaccinations.

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

According to the current global data on vaccinations, only 31.2% of the world populations had received at least one dose of a marketed Covid-19 vaccine as of 16 August 2021[1]. To further accelerate vaccination coverage worldwide, the World Health Organization (WHO) via COVAX ensures the supply of Covid-19 vaccines to member states. The WHO regularly assesses unlicensed vaccines, therapeutics, and in vitro diagnostics to expedite the availability of these products in emergencies[2]. Covid-19 vaccines are not an exception; several are currently under evaluation for an Emergency Use Listing (EUL). Of those, six vaccines [namely, Pfizer-BioNTech, USA), Spikevax/Moderna COVID-19 Vaccine/ mRNA-1273 (Moderna, USA), Vaxzevria/ChAdOx1 nCoV-19/AZD1222/Covishield (AstraZeneca/Oxford, UK, India), Janssen Covid-19 vaccine/Johnson & Johnson (Janssen, USA), Sinopharm/BBIBP-CorV (China), and Sinovac/CoronaVac (China)] were assessed and granted an authorization by WHO as of July 15, 2021. Here, data from phase III clinical trials – and observational studies where necessary – for those EUL-accepted vaccines was summarized. Additionally, articles regarding the two Chinese inactivated virus vaccines (Sinopharm and CoronaVac), the immunogenicity and reactogenicity of heterologous vaccination schedules, and children and adolescent vaccination were prioritized during the literature search. Data regarding those highlighted topics can be found in the table below.

Methodology

We screened the data for the EUL-accepted vaccines as of August 16, 2021 from PubMed, Embase, medRxiv, bioRxiv, Cochrane, and clinical trials databases such as ClinicalTrials and WHO Trial Registry. The methods used were reported previously.

[1] https://ourworldindata.org/covid-vaccinations (accessed on 12.08.2021).
[2] https://www.who.int/teams/regulation-prequalification/eul/ (accessed on 12.08.2021).

Results

Data updated biweekly was synthesized in the synoptic table below. Phase III clinical trials and further literature are cited at the end of this report.

Heterologous prime-boost COVID-19 vaccination has become an international topic of interest as several countries changed their recommendations regarding the ChAdOx1 vaccine due to safety concerns[3]. Furthermore, heterologous schedules provide flexibility in vaccination programs in response to supply availability, making them a topic of interest in countries with scarce vaccine access and availability[3]. This had led numerous studies to analyse the immunogenicity and reactogenicity of heterologous vaccination schedules with most on-going studies and published articles on the combination of ChAdOx1 and mRNA vaccines (mainly ChAdOx1/BNT162b2 schedules). Based on the preliminary results, the mixing of vaccines triggers a robust immune response similar to – or even stronger than – homologous vaccination[4]. Additionally, the majority of adverse events reported after undergoing a heterologous vaccination schedule were mild to moderate with very few severe events reported[5]. For the combination of BNT162b2 and ChAdOx1 as the booster shot (BNT162b2/ChAdOx1), a less robust immune response in terms of IgG antibodies than the homologous vaccination (BNT162b2/BNT162b2) was reported; however, the homologous schedule had a slightly higher T-cell response than the homologous one[6]. Nevertheless, studies reporting real-world effectiveness and safety are still needed.

[3] Heterologous vaccine regimens against COVID-19. *The Lancet.* https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01442-2/fulltext#back-bib10

[4] Mix-and-match COVID vaccines: the case is growing, but questions remain. *Nature.* https://www.nature.com/articles/d41586-021-01805-2

[5] Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial. *The Lancet.* *https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01420-3/fulltext*

[6] Safety and immunogenicity report from the Com-COV study – A single-blind randomised non-inferiority trial comparing heterologous and homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine. *SSRN.* *https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3874014*

Both inactivated virus vaccines, Sinopharm/ BBIBP-CorV and CoronaVac, have recently received emergency use approval by the WHO[7]. Both vaccines pass the WHO's minimum vaccine efficacy threshold of 50% and provide upwards than 90% protection against severe COVID-19 infections[8,9]. Phase III clinical trials demonstrated that Sinopharm/ BBIBP-CorV and the Sinovac/ CoronaVac vaccine provided 72.8%[10] - 79%[11] and 50.7%[12] efficacy respectively, against symptomatic COVID-19 infection. These trials were conducted between July and December of 2020, a period prior to the delta (B.1.617.2) variant transmission. Further case control studies in Brazil (a setting of high P.1-variant transmission) confirm CoronaVac's effectiveness outside a clinical setting, which ranged from 49.4%[13] to 51.8% between February and March 2021[14]. In a real-world study including 10.2 million participants in Chile, CoronaVac had an adjusted vaccine effectiveness of 65.9%[15]. Follow-up studies demonstrated that antibody production after BBIBP-CorV or CoronaVac vaccination decreases with older age of the vaccinated person over time[16,17]. Although no studies have been released thus far concerning the safety and immunogenicity of booster shots for BBIBP-CorV, a CoronaVac booster dose was found to be safe and rapidly re-establish robust immune responses in individuals over the age of 60 years[18].

[7] Immunogenicity and safety of the CoronaVac inactivated vaccine in patients with autoimmune rheumatic diseases: A phase 4 trial. *Nature Medicine.* https://www.nature.com/articles/s41591-021-01469-5

[8] Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. *JAMA.* https://jamanetwork.com/journals/jama/fullarticle/2780562

[9] Efficacy and safety of a COVID-19 inactivated vaccine in healthcare professionals in Brazil: The PROFISCOV Study. *SSRN – Preprint.* https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3822780

[10] Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. *JAMA.* https://jamanetwork.com/journals/jama/fullarticle/2780562

[11] WHO approval of Chinese CoronaVac COVID vaccine will be crucial to curbing pandemic. *Nature*. https://www.nature.com/articles/d41586-021-01497-8

[12] Efficacy and safety of a COVID-19 inactivated vaccine in healthcare professionals in Brazil: The PROFISCOV Study. *SSRN – Preprint.* https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3822780

[13] Effectiveness of CoronaVac in the setting of high SARS-CoV-2 P.1 variant transmission in Brazil: A test-negative case-control study. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.04.07.21255081v1

[14] Performance of vaccination with CoronaVac in a cohort of healthcare workers (HCW) - preliminary report. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.04.12.21255308v1

[15] Effectiveness of an inactivated SARS-CoV-2 Vaccine in Chile. *The New England Journal of Medicine.* https://www.nejm.org/doi/full/10.1056/NEJMoa2107715?query=featured_home

[16] Virus neutralizing antibody responses after two doses of BBIBP-CorV (Sinopharm, Beijing CNBG) vaccine. *medRxiv*. https://www.medrxiv.org/content/10.1101/2021.07.15.21260362v1

[17] Effectiveness of the CoronaVac vaccine in the elderly population during a P.1 variant-associated epidemic of COVID-19 in Brazil: A test-negative case-control study. *medRxiv*. https://www.medrxiv.org/content/10.1101/2021.05.19.21257472v1

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

Clinical trials and studies are currently focusing on the safety and efficacy of vaccines on children and adolescents. WHO's Strategic Advisory Group of Experts (SAGE) has deemed the Pfizer/ BioNTech vaccine to be suitable for children aged 12 years and above and recommends children of high risk to be vaccinated[19]. The U.S. Food and Drug Administration (FDA) has authorized the administration of Pfizer/ BioNTech in children and adolescents aged from 12 through to 15 years of age in the United States and is currently assessing Moderna's emergency use application to vaccinate people under the age of 15[20]. Swissmedic authorised the use of Pfizer/ BioNTech vaccine in young individuals (12 to 15 years) in June[21], and has recently approved Moderna's Spikevax vaccine to be extended towards children and adolescents aged 12 to 17[22]. Both Pfizer/ BioNTech and Moderna's clinical trials demonstrated comparable safety and immune responses in children to those in young adults aged 18 to 25 years. Additionally, the Chinse vaccine CoronaVac showed, in its phase1/2 report, that the vaccine was well tolerated, safe and induced a humoral response in children aged 3 to 17 years of age[23]. Further vaccine trials concerning children and adolescents are ongoing.

[19] Covid-19 advice for the public: Getting vaccinated. *World Health Organization.* [accessed 12.08.21] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice

[20] Coronavirus (COVID-19) Update: FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Adolescents in Another Important Action in Fight Against Pandemic. *U.S. Food & Drug Administration*. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use

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

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

[23] Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00319-4/fulltext

Synoptic table about SARS-CoV-2 vaccines accepted in the WHO's Emergency Use Listing (as of August 16th, 2021)

	BNT162b2/ COMIRNATY (Pfizer-BioNTech, USA)	**Spikevax/ Moderna COVID-19 Vaccine/ mRNA-1273 (Moderna, USA)**	**Vaxzevria/ ChAdOx1 nCoV-19/ AZD1222/ Covishield (AstraZeneca/Oxford, UK, India)**	**Janssen COVID-19 vaccine/Johnson & Johnson (Janssen, USA)**	**Sinopharm/BBIBP-CorV, China**	**Sinovac CoronaVac, China**
GENERAL VACCINE INFORMATION						
Platform	mRNA-based vaccine	mRNA-based vaccine	Non-replicating vector-based vaccine	Non-replicating vector-based vaccine	Inactivated virus (Vero cell)	Inactivated virus (Vero cell)
Dose and frequency	2 doses, 21 days apart	2 doses, 28 days apart	2 doses, 4-12 weeks apart	1 dose, once	2 doses, 21 days apart	2 doses, 14 days apart
Target population	12 years old and over	12 years old and over	18 years old and over	18 years old and over	18 years old and over	18 years old and over
Storage conditions	2°C to 8 °C (for 1 month)	2°C to 8 °C (for 1 month)	2°C until 8 °C	2°C to 8 °C (for 3 months)	2°C until 8 °C	2°C until 8 °C
Approving authorities	FDA, EMA, WHO EUL, and list of countries (including Switzerland)	FDA, EMA, WHO EUL, and list of countries (including Switzerland)	FDA (ongoing), EMA, WHO EUL, and list of countries (Switzerland is ongoing too)	FDA, EMA, WHO EUL, and list of countries (including Switzerland)	WHO EUL, and list of 55 countries (e.g., Argentina, Bahrain, Brazil, China, Indonesia, United Arab Emirates, Zimbabwe)	WHO EUL, and list of 33 countries (e.g., Albania, Chile, Egypt, Hong Kong, Malaysia, Tunisia, Turkey, Ukraine)

PHASE III TRIALS RESULTS						
Number of participants (vaccine/ placebo)	43,448 (21,720/ 21,728)[1]	30,420 (15,210/15,210)[2]	17,178 (8597/8581)[3]	39,321 (19,630/19,691)[4]	26,917 (13,459/13458); or 26,914 (13,465/13,458)[5]	9,823 (4,953/4,870)[6]
Total COVID-19 cases (vaccine/ control)	170(8/162)[1]	196 (11/185)[2]	332 (84/248)[3]	464 (116/348)[4]	121(26/95) or 116(21/95)[5]	253(85/168)[6]
Efficacy estimates in Phase III trials[i]	Starting from 7 days after 2nd dose: **95.0%** (95% CI, 90.3 to 97.6) in population without prior SARS-CoV-2 infection. Efficacy of **94.6%** (95% CI, 89.9 to 97.3) in population with or without prior infection. **100%** among adolescents (12-15 years old).[1]	After a median follow-up of less than 63 days: Efficacy of **94.1%** (95% CI, 89.3 to 96.8; P<0.001). **100%** among adolescents (12 to <18 years old).[2]	14 days and more, participants with two standard doses: efficacy was **63·1%** (95% CI 51.8 to 71.7) while those with first low dose and standard 2nd dose the efficacy was **80.7%** (95% CI 62.1 to 90.2). Pooled analysis efficacy was **66.7%** (95% CI 57.4 to 74.0). For any nucleic acid amplification test-	VE against moderate-severe-critical Covid-19 was **66.9%** (95% CI 59.0 to 73.4) after 14 days post vaccine administration, and **66.1%** (95% CI 55.0 to 89.1) after 28 days. VE against severe-critical COVID-19 cases was **76.7%** (95% CI 54.6 to 89.1) after 14 days and **85.4%**	After 14 days, efficacy against symptomatic cases was **72.8%** (95% CI 58.1 to 82.4; in WIV04 vaccine) or **78.1%** (95% CI 64.8 to 86.3; in HBO2 vaccine).[5]	After 14 days, efficacy against symptomatic cases was **50.7%** (95% CI 35.9 to 0-62.0).[6]

[i] Phase III trials were conducted between 27 July and 14 November 2020 for BNT162b2/ COMIRNATY, 27 July and 23 October 2020 for Spikevax/ Moderna, 23 April and 6 December 2020 for Vaxzevria/ ChAdOx1 nCoV-19/ AZD1222/ Covishield, 21 September 2020 and 22 January 2021 for Janssen Covid-19 vaccine/ Johnson & Johnson, 16 July and 20 December 2020 for Sinopharm/ BBIB-CorV, and 21 July and 16 December 2020 for the Sinovac/ CoronaVac vaccine. All trials were conducted prior to the transmission of the more contagious variant strains, particularly the delta variant (B.1.617.2). Studies are currently ongoing to determine the effectiveness of the vaccines against the delta variant. This will be covered in the next synoptic table report.

			positive swab: efficacy was 54.1% (95% CI 44.7 to 61.9).[3]	(95% CI 54.2 to 96.9) after 28 days.[4]		
EFFICACY						
Efficacy of single doses	52% (95% CI 29.5 to 68.4; starting at 12 days) or 82.2% (75.1 to 87.3; starting at ≥14 days)[7]	92.1% (95% CI 68.8 to 99.1; starting at >14 days) - Statistically non-significant reduction before 14 days	72.8% (starting at 22 days up to 60 days)[3]	Single dose vaccine	Unknown	35.1% (95% CI, -6.6 to -60.5) [conducted in a setting with high P.1 transmission][8] 15.5% for prevention of COVID-19 and 37.4% for the prevention of hospitalization, 44.7% for the prevention of admission to the ICU, and 45.7% for the prevention of COVID-19 related death.
Efficacy against variants	Two doses of the vaccine effectively neutralize the B.1.1.7 variant and the D614G substitution. Neutralization of the B.1.351 was diminished by a	NAbs remained high and consistent with titres of the wildtype for the B.1.1.7 variant. For the B.1.351 variant NAbs were 6-fold lower. The NAbs against the B.1.351	Two doses of the vaccine had no efficacy against the B.1.351 (VE = 21.9%; 95% CI, -49.9 to 59.8).[11]	Efficacy against moderate-severe-critical Covid-19 due to the 20H/501Y.V2 variant was 52.0% (>14 days) and 64.0% (>28 days). Efficacy against severe-critical	Sinopharm has a reduced neutralizing capacity to B.1.617.2 and B.1.351. However, there were no differences in the NAbs titres against B.1.617.2 and B.1.351. in	49.6% against P.1 (>14 days after 1st dose)[8] Demonstrated 42% effectiveness in a setting with high P.1 transmission, in

	factor of 5. Despite this, the BNT162b2 mRNA vaccine provides some protection against B.1.351.[9]	variant were still found to be protective.[10]		COVID-19 was 73.1% (>14 days) and 81.7% (>28 days).[4]	vaccinated individuals vs. those naturally infected, suggesting the vaccines have a similar level of protection against infection as natural infections.[12]	individuals aged 70 and above.[13]
SAFETY AND ADVERSE EVENTS						
Safety (adverse events)	Common side effects: pain at the injection site, fatigue, headache, myalgia, chills and fever.[14] Rare adverse events: axillary lymphadenopathy, paroxysmal ventricular arrhythmia, leg paresthesia[1]. Myocarditis[15,16], anaphylaxis and swelling of the lips, face, and tongue related to anaphylaxis[17] (11 anaphylaxis cases per million doses	Common side effects: pain at injection site, headache, fatigue, myalgia, arthralgia[2], Covid arm[22]. Rare adverse events: Myocarditis[15,16], orofacial swelling & anaphylaxis[17].	Common side effects: fatigue, myalgia, arthralgia, headache[23], lethargy, fever, & nausea[24]. Rare adverse events: transverse myelitis, high fever[23], vasculitis[25], cerebral venous sinus thrombosis[26], thromboembolism[27], vaccine induced immune thrombotic thrombocytopenia[28], small vessel vasculitis[29]. Vaccination in individuals with	Common adverse events: headache, fever, chills, fatigue, myalgia, and nausea.[31] Common adverse events: headache, fever, chills, fatigue, myalgia, and nausea.[31] Rare adverse events: thrombosis, thrombocytopenia, cerebral venous sinus thrombosis.[32] 97% of reported reactions after vaccine	Common side effects: pain at the injection site, dizziness, headache, fatigue, nausea, vomiting, & allergic dermatitis[33]. Common adverse events: pain at the injection site and fever[33]. Unsolicited adverse reactions were similar among the vaccine groups and control group within 7 days[5].	Common side effects: pain at injection site, headache, fatigue, tremors, & flushing[6]. Rare adverse events: myalgia & fever[6]. Serious adverse events were similar in number in the vaccine and placebo groups (judged unrelated to the vaccine)[6].

	administered)[18], lymphocytic vasculitis[19]. Potential association: cerebral venous sinus thrombosis and intracranial haemorrhage (causal link not yet proven).[20] Serious adverse events were observed in a similar proportion of vaccine (0.6%) and placebo (0.5%) recipients, which also occur at a similar frequency within the general population[14,21].		adrenal insufficiency can lead to adrenal crises[30].	administration were non-serious.[31]		
TRANSMISSION, PREVENTION, PROTECTION						
Severe disease/death prevention	100% (after 7 days)	100% (≥14 days)	100% (after 21 days)	76.7% (≥14 days) or 85.4% (≥28 days)	100% (>14 days)	100% (>14 days)[6]
Transmission prevention	46% (limited data)	Limited data	48% (limited data)	Limited data	Unknown	Unknown

Duration of protection	Limited data[34]	Limited data[34]	Limited data[34]	Limited data[34]	Limited data[34]	A phase I/II clinical trial found that NAbs titres dropped below the seropositive cut-off of 8, 6 months after the administration of the first dose[35].
Asymptomatic prevention in/outside clinical trials	90% (starting at 14 days) regardless of symptom status[36].	90% (starting at 14 days)	Statistically non-significant reduction of 22.2% (95% CI -9.9 to 45.0) for asymptomatic cases	At day 71, vaccine efficacy against asymptomatic infections was 65.5% (95% CI 39.9 to 81.1)[4].	Efficacy against symptomatic and asymptomatic cases was 64% (95% CI 48.8 to 74.7; in WIV04 vaccine) or 73.5% (95% CI 60.6 to 82.2; in HBO2 vaccine)[5].	Unknown
CHILDREN VACCINATION						
Efficacy	Adolescents (12-15): After one dose had efficacy of **75% (CI, 7.6-95.5)** After second dose efficacy of **100% (CI, 78.1-100)**[37] Children (6months-11): Ongoing trials[38]	Adolescents (12-17): After one dose had efficacy of **92.7% (CI, 67.8-99.2)** After second dose efficacy of **93.3% (CI, 47.9-99.9)**[39] Children (6month-11): Ongoing trials[40]	No available data Paused ongoing trials in children aged 6-17 due to concerns over rare blood clots reported in adult population[41].	No available data Announced at begging of April ongoing study in adolescents but paused to investigate blood clots in adult population[41].	Children (3-17): Ongoing clinical trial[42] Countries such as China and UAE have approved its use in children[43].	Children (3-17): Unknown. Clinical trial only looked at safety, tolerability and immunogenicity[44].

Immunogenicity	Adolescents (12-15) serum-neutralizing titer: 1 month after 2nd dose had **1283.0 GMN_{50} (CI, 1095.5-1402.5)**[37] Adolescents/young adult (16-25) serum-neutralizing titer: 1 month after 2nd dose had **705.1 GMN_{50} (CI, 621.4-800.2)**[37] Children (6months-11): Ongoing trials[38]	Adolescents (12-17): Neutralizing antibody titer after 2nd dose was **1401.7 GMN_{50} (CI, 1276.3-1539.4)** Serological response was **98.8% (CI, 97.0-99.7)** Children (6month-11): Ongoing trials[40]	No available data	No available data	Ongoing clinical trial[42]	Children (3-17): Neutralizing antibody response after 2nd dose **(100%)** with GMT ranging from **45.9-212.6**[44]
Safety and Adverse events	Adolescents (12-15): Local and systemic events were generally mild to moderate Severe injection-site pain **(1.5%)** Fever **(20%)** High Fever **(0.1%)** Adverse events **(6%)** Severe adverse events **(0.6%)**[37]	Adolescents (12-17): Solicited local reactions after 2nd dose **(93.4%)** Most common solicited adverse reactions were Injection-site pain **(92.7%)** Headache **(70.2%)** Fatigue **(67.8%)** Grade 3 adverse events **(6.8%)**	No available data	No available data	Ongoing clinical trial[42]	Children (3-17): Adverse reactions in 12–17 year group **(35%)**, 3-5 year group **(26%)**, and 6-11 year group **(18%)** Reported at least one adverse event **(27%)** Most reported events were mild and moderate and only **(<1%)** grade 3 events

	Adolescent/young adults (16-25): Local and systemic events were generally mild to moderate Severe injection-site pain **(3.4%)** Fever **(17%)** Adverse events **(6%)** Severe adverse events **(1.7%)**[37] Few reported cases of acute myocarditis and pericarditis (mainly in males)[45] Children (6months-11): Ongoing trials[38]	Few reported cases of acute myocarditis and pericarditis (mainly in males)[45] Children (6month-11): Ongoing trials[40]				Injection-site pain **(13%)** Fever **(25%)**[44]
HETEROLOGOUS VACCINATION						
Heterologous vaccines schedule	BNT162b2/ChAdOx1 Administration of ChAdOx1 as second/booster dose	ChAdOx1/mRNA-1273 Administration of mRNA-1273 as second/booster dose	ChAdOx1/BNT162b2 Administration of BNT162b2 as second/booster dose	Not Applicable (one dose schedule)	BBIBP/BNT162b2	Press releases have confirmed that Thailand will use the AstraZeneca vaccine as the second dose for individuals whose

						first dose was Sinovac[ii]
Heterologous vaccines immunogenicity	GMCs of SARS-CoV-2 anti-spike IgG at 28 days post booster: Heterologous **(7133 ELU/mL, CI 6415-7932)** vs. Homologous **(14,080 ELU/mL, CI 12491-15871)**[46] SFC frequency (T0cell ELISpot): Heterologous **(99 SFC/10^6 PBMCs)** vs. Homologous **(80 SFC/10^6 PBMCs)**[46]	*Spike-specific IgG antibodies: Heterologous **(3602 BAU/mL)** vs. Homologous **(4189 BAU/mL)**[48] *Neutralizing antibodies: Heterlogous **(100%)** vs. Homologous **(100%)**[48] *Results based on immunosuppressed population	RBD antibody titres: Heterologous **(7756.68 BAU/mL, CI 7371.53-8161.96)** vs. Homologous **(99.84 BAU/mL, CI 76.93-129.59)** at day 14[47] IgG antibody titres: Heterologous **(3684 BAU/mL)** vs. Homologous **(101.2 BAU/mL)** at day 14[47] Neutralizing antibodies: Heterologous **(100%)** at day 14 vs. Homologous **(30%)** at day 14[47]	Not Applicable (one dose schedule)	Unknown (on-going clinical trial)[49]	Unknown

[ii] Malaysia to stop using Sinovac vaccine after supply ends - minister. *Reuters* [press release]. https://www.reuters.com/world/asia-pacific/malaysia-stop-using-sinovac-vaccine-after-supply-ends-minister-2021-07-15/

Heterologous vaccines reactogenicity	Observed increase in systemic reactogenicity after boost in heterologous schedules in comparison with homologous schedules[46] Adverse events in heterologous: Adverse events **(90)** Grade 1 **(54.4%)** Grade 2 **(37.8%)** Grade 3 **(7.8%)** Grade 4 **(0%)** Arthralgia, Migraine, Back Pain[46] Adverse events in homologous: Adverse events **(81)** Grade 1 **(59.3%)** Grade 2 **(39.5%)** Grade 3 **(1.2%)** Grade 4 **(0%)**[46]	*Adverse events in heterologous and homologous vaccination groups were very similar[48] *Majority of adverse events self-reported were Pain at injection site, Swelling at injection site, Fever, Headaches, Fatigue, Chills, GI effects, Myalgia, Arthralgia[48] *Results based on immunosuppressed population	Adverse events in heterologous: Headache **(44%)**, Myalgia **(43%)**, Malaise **(42%)**, Fever **(2%)**, Injection site pain **(88%)**, Induration **(35%)**, Erythema **(31%)**[47] Severity of adverse events in heterologous: Mild **(68%)**, Moderate **(30%)**, Severe **(2%)**[47]	Not Applicable (one dose schedule)	Unknown (on-going clinical trial)[49]	Unknown
OTHER						

Third dose/prime boosters	Booster trial of third dose of current BNT162b2 vaccine are ongoing. Initial data demonstrates that given 6 months after second dose has consistent tolerability and high immunogenicity against wild type and Beta variant[50].	Phase II booster trial of three booster doses are ongoing[50] Preliminary results of booster doses of mRNA-1273 vaccine show robust antibody response against Delta variant and similar safety and tolerability compared to second dose[51].	Preliminary results on tolerability and immunogenicity of third dose of ChAdOx1 vaccines showed strong boost to the immune response[51] Preprint reported that antibody levels 28 days after third dose were significantly higher than second dose antibodies after 28 days and that third dose provided higher antibody titters against Alpha, Beta, and Delta variants[52].	No available data	No further available data Study using animal model suggests that heterologous prime-boost with two doses of inactivated vaccine followed by either recombinant RBD, adenovirus-vectored or mRNA vaccine improves humoral immune response[53].	A third (booster) dose was administered to healthy adults ≥60 years, 8 months after the primary vaccination. The third dose significantly increased NAbs, which had previously dropped below the seropositive cut-off. The most common side effect was pain at the injection site. All other adverse events were considered unrelated to the vaccination. The third shot is considered to be safe[35]. Indonesia and Thailand are considering a third booster shot to HCW that were vaccinated with CoronaVac. Turkey and the United Arab Emirates have

						already began to give booster shots to those vaccinated with Sinovac/ CoronaVac.[iii] Study using animal model suggests that heterologous prime-boost with two doses of inactivated vaccine followed by either recombinant RBD, adenovirus-vectored or mRNA vaccine improves humoral immune response[53].

[iii] Indonesia, Thailand consider booster shots amid doubts over Sinovac vaccine. *Reuters* [press release]. https://www.reuters.com/world/china/indonesia-thailand-consider-booster-shots-amid-doubts-over-sinovac-vaccine-2021-07-08/

Comments /ongoing studies	Specific populations were excluded (HIV and immunocompromised patients, pregnant women, and younger adults) were excluded from the current analysis. No data related to asymptomatic protection or transmission. Risk of myocarditis and pericarditis is added to the vaccine information sheet	Evaluation of the incidence of asymptomatic or subclinical infection and viral shedding would have been interesting. Calculation of efficacy were not based on the total number of confirmed Covid-19 cases. Risk of myocarditis and pericarditis is added to the vaccine information sheet	Blood clots, thrombotic events and thrombocytopenia were reported in real-world settings, although quite rare.	Blood clots, thrombotic events and thrombocytopenia were reported in real-world settings, although quite rare.	Only 2 severe cases occurred in the control group and none in the vaccine group (very few cases to get a reliable estimate).	Death reports on fully vaccinated doctors (10 cases during June 2021 in Indonesia). It may be related to new variants. [media report][iv]

[iv] Indonesian Covid deaths add to questions over Sinovac vaccine. *The Guardian* [press release]. https://www.theguardian.com/world/2021/jun/28/indonesian-covid-deaths-add-to-questions-over-sinovac-vaccine

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