Australian Government
Department of Health
Therapeutic Goods Administration

COVID-19 vaccines not registered in Australia but in current international use- TGA advice on ‘recognition’

Edition 3 – January 2022

TGA Health Safety Regulation

Contents

Executive summary

This document provides an updated assessment by the Therapeutic Goods Administration (TGA) of the protection offered by certain COVID-19 vaccines that are administered internationally but are not currently registered in Australia. The advice is based on an assessment of published data and, in some cases, regulatory information provided in-confidence. This advice is subject to change as new information becomes available.

The information within this document has been prepared to serve as advice only, it has no standing in law and does not represent assessment for regulatory approval in Australia. However, this information will help inform decisions made elsewhere in Government in relation to incoming travel across Australia's international borders in the coming months. It will be updated regularly as new evidence on the effectiveness of globally used vaccines emerges, and as assessments are completed by international regulatory bodies. Note that while certain vaccines may be considered by the TGA as 'recognised', decisions on inbound travel are made by the Department of Home Affairs. In addition, State and Territory governments, or organisations such as universities, may apply additional post-border considerations around vaccine requirements.

This advice has been prepared by comparing the data available for selected vaccines with data on efficacy and the protection offered by the vaccines that have been approved for use in Australia. While this assessment is based on data for two-dose schedules of the vaccines not registered in Australia, public health officials may wish to consider whether a post-arrival booster dose of another vaccine should be considered.

- *People's Republic of China:* Coronavac (Sinovac), BBIBP-CorV (Sinopharm), and Convidecia (Cansino).
- *India*: Covishield (AstraZeneca-Serum Institute of India) and Covaxin (Bharat Biotech)
- *Russian Federation*: Sputnik V (Gamaleya Research Institute)

Effective 1 October 2021, Coronavac (Sinovac) and Covishield (AstraZeneca-Serum Institute of India) were 'recognised' for the purposes of travel into Australia. In November 2021, the TGA updated this advice to include the 'recognition' of BBIBP-CorV (Sinopharm) and Covaxin (Bharat Biotech).

This January 2022 Update involves the 'recognition' of one further vaccine that has been considered by TGA:

- Sputnik V

Potential use of this information

Identifying incoming travellers as being fully vaccinated against COVID-19 (or, alternatively, not fully vaccinated) helps to achieve two main outcomes. Effective vaccination reduces the probability that an incoming traveller would:

1. **transmit COVID-19 infections to others while in Australia**
2. **become acutely unwell due to COVID-19**, potentially requiring acute healthcare services

Recommendations regarding TGA-registered vaccines

Four COVID-19 vaccines have been granted provisional approval in Australia from the following sponsors:

1. Pfizer Australia Pty Ltd (Comirnaty)
2. AstraZeneca Pty Ltd (Vaxzevria)
3. Janssen-Cilag Pty Ltd (COVID-19 Vaccine Janssen)
4. Moderna Australia Pty Ltd (Spikevax)

The TGA and the Australian Technical Advisory Group on Immunisation (ATAGI) consider people to be fully vaccinated if:

a. they have completed a two dose schedule of Comirnaty, Vaxzevria or Spikevax with the two doses at least 14 days apart, or received a single dose of COVID-19 Vaccine Janssen and

b. at least 7 days have elapsed since completing their vaccination schedule.

All TGA-approved vaccines are recognised for incoming international travellers.

How the estimates were determined

The protection offered by a vaccine against a person requiring hospital care if they develop COVID-19 is either directly measured in Vaccine Efficacy and Effectiveness (VE) data from clinical trials, or inferred from protection against 'severe' infection. VE measures the reduction in the odds of a person developing infection or hospitalisation, after vaccination, compared to unvaccinated people with the same exposure to COVID. Vaccine Efficacy trials are designed to directly measure the protection a vaccine offers against a person becoming infected with COVID-19 when exposed to the virus. This can be used as an imperfect surrogate for reducing the chance of transmitting COVID-19, because a person must first be infected with COVID-19 to transmit it. There are also challenges in making accurate comparisons between the effectiveness of vaccines, given the inconsistent effectiveness measures, study confounders and efficacy endpoints used in clinical trials.

Vaccines approved in Australia

Effectiveness information has been assessed for the four vaccines that are TGA-approved for use in Australia (registered vaccines) for the sake of completeness and to provide comparative data.

All TGA approved vaccines are recognised for incoming travellers.

Vaccine	Outcome prevented	Average Vaccine Efficacy
Vaxzevria (AstraZeneca)	Symptomatic infection	65%
	Severe infection/hospitalisation	85%
Comirnaty (Pfizer)	Symptomatic infection	81%
	Severe infection/hospitalisation	88%
Spikevax (Moderna)	Symptomatic infection	86%
	Severe infection/hospitalisation	81%
COVID-19 Vaccine Janssen (Janssen-Cilag)	Symptomatic infection	66%
	Severe infection/hospitalisation	85%

Table 1. Vaccine Efficacy of TGA-registered vaccines, adapted from National Centre Immunisation Research and Surveillance update to ATAGI on 13 September 2021

Of the four vaccines currently granted provisional regulatory approval in Australia, the minimal average vaccine effectiveness (VE) from two doses of Vaxzevria (AstraZeneca) has been used as the minimal effectiveness comparator based on published results for Vaxzevria.

The average VE against symptomatic infection is 65% and severe infection and/or hospitalisation is 85%.

TGA's updated recommendations on the recognition of vaccines not registered in Australia

Coronavac (Sinovac) showed an average VE against symptomatic infection of 64% and an average VE against hospitalisation of 90%.

- VE against symptomatic infection (surrogate for transmission) of 54%, 54%, 64%, 66% and 84% in five studies.
- VE against severe infection/hospitalisation of 100%, 100%, 88% and 73% in four trials.

The standard schedule of Coronavac is two doses administered 14-28 days apart.

Based on regulatory, published and pre-print data this suggests the efficacy of Coronavac is comparable to the Australian-approved vaccines, although marginally lower in protection against symptomatic infection.

The TGA considers Coronovac (Sinovac) vaccine to be a 'recognised' vaccine.

BBIBP-CorV (Sinopharm) showed an average VE against symptomatic infection of 65%. VE against hospitalisation has not been estimated.

- VE against symptomatic infection (surrogate for transmission) of 50% and 79% from two studies.
- VE against severe infection/hospitalisation of 79% in people under 60 years of age based on information provided in confidence to TGA.

Based on published and pre-print data this suggests that the average efficacy of BBIBP-CorV against symptomatic infection is marginally lower than Australian-approved vaccines and the VE effectiveness against severe infection/hospitalisation is 6% lower than Australian-approved vaccines.

The TGA considers BBIBP-CorV (Sinopharm) to be a 'recognised' vaccine for people 59 years of age and under (inclusive) at the time of entry into Australia. In this case, the TGA has recognised a slightly lower vaccine effectiveness against severe infection/hospitalisation than Australian-appproved vaccines due to the lower absolute risk of severe disease/hospitalisation in younger people contracting COVID-19 compared to older cohorts.

Covishield (AstraZeneca/Serum Institute of India) is manufactured using the same ChAdOx1-S recombinant virus as the AstraZeneca (Vaxzevria) vaccine to produce the same dose of virus in the final product. The two are considered interchangeable by the World Health Organisation. The TGA considers Covishield to have the same clinical efficacy as Vaxzevria for this assessment. Two major global regulators, the UK Medicines and Health products Regulatory Agency and Health Canada have provided regulatory approvals for the AstraZeneca vaccine manufactured by the Serum Institute of India. These regulators are viewed as 'Comparable Overseas Regulators' by the TGA.

Therefore, the clinical efficacy and effectiveness data for Vaxzevria (AstraZeneca) are relevant in this case. The average VE against symptomatic infection is 65% and severe infection and/or hospitalisation is 85%.

The TGA considers Covishield (AstraZeneca- Serum Institute of India) vaccine to be a 'recognised' vaccine.

Covaxin (Bharat Biotech) showed an average VE against symptomatic infection of 78% and an average VE against hospitalisation of 94%.

- VE against symptomatic infection (surrogate for transmission) of 78% in one study.
- VE against hospitalisation of 91% in two studies.

The standard schedule of Covaxin is two doses administered 28 days apart.

Based on additional information (provided in confidence) supporting the efficacy and effectiveness of Covaxin (Bharat Biotech), the TGA considers it to be a 'recognised' vaccine.

Sputnik V (Gamaleya Institute) showed an average VE against symptomatic infection of 89% and VE against hospitalisation of 100%.

- VE against symptomatic infection (surrogate for transmission) of 92% and 86% from two studies.
- VE against hospitalisation of 100% from one study.

Based on published studies the vaccine efficacy of Sputnik V meets current criteria for efficacy.

The TGA considers Sputnik V to be a 'recognised' vaccine.

For **Convidecia (Cansino)**, there is currently insufficient published data on which to base an assessment of the efficacy of Convidecia and the TGA has not yet been provided with a regulatory dossier.

As there is insufficient data to evaluate the efficacy Convidecia (Cansino) vaccine against all of the criteria, the vaccine is not 'recognised' by the TGA.

For the unregistered vaccines that are 'recognised', effective vaccination would be considered to extend from 7 days after the last dose of the schedule (which is currently two doses for all TGA-registered vaccines except for Janssen), or a booster dose after the last dose of the schedule. This is based on generalising the data from duration of immunity studies reviewed in the absence of specific studies in the unregistered vaccines.

Assessment of vaccination status in schedules containing vaccines not registered in Australia

The use of TGA-registered vaccines in Australia to complete vaccine schedules commenced with vaccines not registered in Australia should follow the advice of the Australian Technical Advisory Group on Immunisation (ATAGI).

ATAGI has considered several issues arising from the 'recognition' of vaccines not currently registered in Australia including:

- The appropriate advice for people who have received vaccines that are not 'recognised' (either because TGA has not Recognised them or they are not registered in Australia) and wish to become fully vaccinated to undertake activity in Australia.
- The status of mixed-product schedules where both products are 'recognised' vaccines (e.g. Sinovac/Comirnaty).

The determination of the vaccination status of a person who has received a 'recognised' vaccine (e.g. fully vaccinated, partially vaccinated, requiring a booster *etc*) will follow ATAGI's advice on these matters.

Omicron COVID-19 variant of concern

The TGA notes that the emergence of the Omicron Strain of COVID-19 (B.1.1.529) in November 2021 has posed challenges for the assessment of the efficacy of vaccines, as clinical trials may have been conducted on other COVID-19 variants. It is likely that extended schedules (i.e. 'boosters') will be required in some populations to provide additional protection.

The use of 2-dose primary schedules for vaccines not registered in Australia should be considered in conjunction with ATAGI recommendations for third or further doses of appropriate products (e.g. mRNA vaccines), and its advice regarding the definition of 'fully vaccinated'.

Appendix 1.1 Coronavac

Product	Coronavac
Product Developer	Sinovac
Country of origin	China
Vaccine Type	Inactivated virus/alum adjuvanted SARS-CoV-2-HBO2 strain
Schedule	2 doses, 14-28 days apart

Coronovac: countries deployed

Deployed in 40 countries and listed by the WHO for emergency use.

Albania	Argentina	Armenia	Azerbaijan	Bangladesh
Benin	Brazil	Cambodia	Chile	China
Colombia	Dominican Republic	Ecuador	Egypt	El Salvador
Georgia	Hong Kong	Indonesia	Kazakhstan	Lao Peoples Democratic Republic
Malaysia	Mexico	Nepal	Oman	Pakistan
Panama	Paraguay	Philippines	South Africa	Sri Lanka
Tajikistan	Thailand	Timor-Leste	Togo	Tunisia
Turkey	Ukraine	Tanzania	Uruguay	Zimbabwe

Coronovac: main clinical efficacy and effectiveness data using standard schedules

Study	Population	Strain	Schedule	Primary Endpoint	VE Asy	VE Sy	VE Hos	VE Death	Advantages	Disadvantages
(Tanriover et al. 2021)	COVID exposed HCW and volunteers 18-59 years old with no prior COVID infection and PCR negative screening.	Neutralising antibodies to B1.1.128 and P2 (Gamma) tested	2 dose day 0 and 14	Symptomatic PCR confirmed COVID at least 14 days after second dose.		83.5 %	100%		• Randomised • Published • Examines health care workers (HCW) at relatively high risk	• Young population <60 years of age • Gamma strain
(Palacios et al. 2020) PREPRINT	COVID exposed HCW in two aged cohorts, 18-59 and 60+ years of age with	Neutralising antibodies to B1.1.128 and P2 (Gamma) tested	2 dose day 0 and day 14-28	Symptomatic PCR confirmed COVID at least 14 days after second dose.		54.1 %	100%		• Randomised • Included cohort>60 years • Examines HCW at relatively high risk	• Low percentage of participants >60 years of age • Gamma strain • Not peer reviewed (pre-print)
CORONA06 (Dossier)	COVID exposed HCW aged	Not noted	2 doses Day 0	PCR confirmed COVID at least 14 days after second dose.		64.3 %				

	18-59 in Indonesia		Day 14							
(Alencar et al. 2021)	313228 recipients of COVID vaccines >75 years of age in Brazilian vaccination program	Gamma	2 doses. Interval not specified.	Death				99.1 %	• Large real-world study • Examines people >75 years of age	• Observational, non-randomised • Only assessed Death as an endpoint • Gamma strain
(Jara et al. 2021)	10187720 recipients of COVID vaccines >16 years of age in Chilean vaccination program.	Alpha and Gamma	2 doses. Day 0 and 28 days.	Symptomatic COVID, Hospitalisation, ICU admission and Death in people >14 days post second dose		65.9 %	87.5% (all) 90.3% (ICU)	86.3 %	• Large real-world study • Examines all age groups >16 years	• Observational, non-randomised • Reports VE against ICU as a subset (90.3%) • Alpha and Gamma strain
(Cerqueira-Silva et al. 2021) PREPRINT	21933237 recipients of Coronavac >18 years of age in Brazilian vaccination program	Alpha and Gamma	2 doses at 0 and 28 days	Symptomatic COVID, Hospitalisation, ICU admission and death		54.2 %	72.6% (all) 74.2%(ICU)	74%	• Large real-world study • Examines all age groups >18 years • Prospective cohort study	• Not peer reviewed (Pre-print) • Alpha and Gamma Strain • May have overestimated protection against hospitalisation/ICU due to capacity constraints in-country.

Coronovac: data in non-standard schedules

(Li et al. 2021) is a preprint study examining the use of a third booster dose in older people receiving Sinovac. It examined 303 patients over 60 years of age recruited from a phase I/II trial in whom neutralising antibody levels were recorded at 6 months. Neutralising antibodies had fallen to below cut-off in 70% of recipients by 6 months after the primary course of vaccination. A third booster was given at 8 months after the primary vaccination course. This led to a 7-fold increase in neutralising antibodies compared to 28 days after the second dose. The duration of this response is not noted.

(Pan et al. 2021) is a pre-print of a placebo controlled, double blinded phase II study in 18-59 year olds who were assigned to receive a third dose either 28 days or 6 months after completing a primary vaccination schedule in which doses were at 0 and 14, or 0 and 28 days. Only a portion of subjects in each schedule were randomised to receive the presentation of Sinovac marketed. Overall, 540 subjects received a third dose. Subjects who received the third dose recorded an increase of 3-5 fold in neutralising antibody titres compared to 28 days following their second dose.

Coronovac: main safety data

TGA has reviewed the first Periodic Safety Update Report (PSUR) for Coronavac, covering the reporting period between 5 Feb 2021 and 14 March 2021. The estimated exposure to vaccine covered in this report is 17.91 million people in China and an estimated 71.06 million people worldwide. No safety related action by regulatory agencies was reported in the PSUR.

The most common Adverse Events among the 1109 cases reported were fever (12.5%), asthenia (9.85%), dizziness (8.90%), allergic dermatitis (8.34%), nausea (6.50%), headache (4.12%), myalgia (7.18%). A total of 49 cases of serious adverse events were reported in which relatedness to vaccination was not ruled out, including 6 cases of anaphylactic shock. A total of 6 deaths occurred among reported Adverse Events, of which 4 were considered unrelated to vaccination and 2 in which the cause of death was unclear.

	Palacios et al AE within 28 days or 2nd dose		Palacios et al AE within 14 days of 1st dose		Tanriovier et al AE from day 0 to unblinding	
	Vac	**Plac**	**Vac**	**Plac**	**Vac**	**Plac**
Number	6202	6194	6196	6200	6646	3568
Local pain	3742	2014	2750	1387	157	40
Local swelling	359	130	162	72	4	4
Local pruritis	263	181	147	126	2	2
Local redness	241	89	95	48	12	4
Local paraesthesia	N.A.	N.A.	N.A.	N.A.	9	5
Local induration	235	67	88	34	3	2
Headache	2128	2157	1944	1996	393	212
Fatigue	989	922	860	798	546	248
Myalgia	727	648	604	545	315	106
Nausea	490	522	423	445	46	7
Diarrhoea	492	501	451	454	106	59
Arthralgia	353	321	293	276	47	18
Cough	343	322	337	318	50	24
Chills	309	313	252	266	164	63
Pruritis	263	225	213	194	3	0
Decreased appetite	217	243	188	213	1	2
Vomiting	61	61	47	49	17	8
Hypersensitivity	58	58	47	44	5	1
Rash	49	42	36	30	7	6
Fever	9	4	7	8	120	52

Table 2. Consolidated rates of elicited adverse events from Tanrovier *et al.* and Palacios *et al.*

Tanrovier *et al.*and Palacios *et al.* examined the rates of a set of elicited adverse reactions and provide placebo controlled rates of these, as shown in the table above.

Coronovac: evaluator's comments

(Tanriover et al. 2021) was an interim analysis that examined a cohort of 10 214 (ITT) participants randomised to vaccination (n=6646) or placebo (n=3568). Included subjects were initially HCW exposed to COVID patients, and then non-HCW volunteers recruited via a web system. This study was conducted in Turkey between Sep 2020 and Jan 2021. Symptoms were measured according to the WHO scale outlined in (Marshall et al. 2020) as >=3. It is noted that the relatively young subjects (mean age of 45) had a low risk of severe disease or death. The short follow-up for infection of 43 days may limit validity of more severe disease endpoints. There were no fatal cases of COVID noted, and hence no estimate of VE against death.

(Palacios et al. 2020) examined a cohort of 12396 participants randomised 1:1 to vaccine (n=6195) or placebo (n=6201). Included subjects were mostly 18-59 years of age, but 5.1% were >60 years of age. This study was conducted in Brazil between Jul and Dec 2020. Subjects were followed for the duration of the study to detect COVID cases. The authors postulate that the relatively low efficacy may indicate the detection of very mild symptoms. Vaccine efficacy was 83.7% (95%CI 58.0-93.7) against cases scoring >=3 on the WHO scale (Marshall et al. 2020) and 100% against cases scoring >4 (hospitalised). Vaccine efficacy against the primary endpoint was 62.3% (95%CI 13.9-83.5) for a small subgroup with dose intervals >21 days.

The Evaluator notes that a review of the regulatory dossier of this trial (COR04) provided a sensitivity analysis based on the case definition. The pre-specified case definition included saliva-positive PCR tests, which is a potentially less accurate methodology and PHLN currently does not generally support its use in Australia[1]. The Evaluator has therefore used the results of a sensitivity analysis which excluded saliva PCR tests in this analysis.

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Figure: **WHO clinical progression scale**
ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. NIV=non-invasive ventilation. pO_2=partial pressure of oxygen. SpO_2=oxygen saturation. *If hospitalised for isolation only, record status as for ambulatory patient.

Figure 1. WHO working group symptom scoring system used in (Tanriover et al. 2021) and (Palacios et al. 2020), from (Marshall et al. 2020)

[1] file:///U:/WORK/COVID%20papers/Downloaded/phln-guidance-on-laboratory-testing-for-sars-cov-2-the-virus-that-causes-covid-19.pdf

(Alencar et al. 2021) is an observational study in 313,328 elderly recipients of COVID vaccines in Brazil between Jan and May 2021. The study compares rates of death in vaccinated and unvaccinated individuals using state death records and immunisation registers. Two doses of Coronavac were received by 159,970 of the people examined. This indicated an attributable protection ratio (e.g. Death rate vaccinated/death rate unvaccinated) of between 86.3% in 75-79 year olds and 99.3% in over 90-year olds. This study is subject to the biases found in observational studies. It does, however, provide evidence to balance the relatively young cohort in the phase III trials.

Table 1. Protection ratios for death and percentage attributable protection ratios for deaths by COVID-19, stratified by number of doses applied, vaccine type and age group over 75 year-olds in the state of Ceará, Brazil, 2021.

Variables	N	Deaths	% Deaths	Protection Ratio (95% CI)	Attributable Protection Ratio (%) (95%CI)
Number of doses and type of vaccine:					
Oxford-AstraZeneca/Fiocruz 1st dose	139,322	716	0.51	17.91 (16.55–19.39)	94.4 (93.9–94.8)
CoronaVac-Sinovac/Butantan 1st dose	174,006	778	0.45	20.59 (19.07–22.22)	95.1 (94.7–95.5)
Vaccinated 1st dose	313,328	1494	0.48	19.31 (18.20–20.48)	94.8 (94.5–95.1)
Oxford-AstraZeneca/Fiocruz 1st and 2nd dose	27,193	3	0.01	834.45 (269.03–2588.18)	99.8 (99.6–99.9)
CoronaVac-Sinovac/Butantan 1st and 2nd dose	132,777	108	0.08	113.17 (93.50–136.99)	99.1 (98.9–99.3)
Vaccinated 1st and 2nd dose	159,970	111	0.07	132.67 (109.88–160.18	99.2 (99.1–99.4)
Not vaccinated	40,941	3769	9.21	1	-
Age Group–1st dose only:					
75 to 79 years					
Oxford-AstraZeneca/Fiocruz	32,749	141	0.43	8.39 (7.03–10.00)	88.0 (85.8–90.0)
CoronaVac-Sinovac/Butantan	97,072	481	0.50	7.29 (6.54–8.12)	86.3 (84.7–87.7)
Vaccinated	129,821	622	0.48	7.53 (6.82–8.33)	86.7 (85.3–88.0)
Not vaccinated	26,857	1010	3.76	1	-
80 to 89 years					
Oxford-AstraZeneca/Fiocruz	78,474	371	0.47	31.89 (28.59–35.58)	96.8 (96.5–97.2)
CoronaVac-Sinovac/Butantan	70,327	256	0.36	41.42 (36.42–47.12)	97.6 (97.2–97.9)
Vaccinated	148,801	627	0.42	35.78 (32.77–39.07)	97.2 (96.9–97.4)
Not vaccinated	13,336	2011	15.08	1	-
90 years or more					
Oxford-AstraZeneca/Fiocruz	28,099	204	0.73	137.74 (120.13–157.92)	99.2 (99.1–99.4)
CoronaVac-Sinovac/Butantan	6,607	41	0.62	161.14 (118.76–218.64)	99.3 (99.1–99.5)
Vaccinated	34,706	245	0.71	141.65 (125.04–160.48)	99.3 (99.2–99.4)
Not vaccinated	748	748	100.00	1	-

Table 3. Summary of efficacy results from (Alencar, Cavalcanti et al. 2021)

While this paper did not directly compare the efficacy of AstraZeneca's ChAdOx1 based vaccine with Coronavac, the Evaluator notes that the effect on rates of death were similar.

(Cerqueira-Silva et al. 2021) was a pre-print of large retrospective study of people who received either AstraZeneca or Coronavac in the Brazilian mass vaccination program between January and June 2021. It estimated the rates of infection, hospitalisation, and death from administrative records in the Brazilian public medical system. There would be overlap between the populations in this study and (Alencar et al. 2021), but since Coronavac was only used in Brazil from April 2021 this study provides a larger cohort vaccinated with this product. Biasing in the allocation of people to Coronavac or Vaxzevria was not controlled for, and the cohort receiving Coronavac was older than that receiving Vaxzevria.

(Jara et al. 2021) is a very large prospective cohort study that included all recipients of Coronavac >16 years of age in the Chilean mass vaccination program between Feb and May 2021. Cases of COVID were acquired through a national mandatory notification system, and correlated with administrative data on hospitalisations, deaths etc. Of the 10187720 people included in the cohort, 5,471,728 were unvaccinated, 542,418 had received one dose of vaccine and 4,173,574 had received two doses of vaccine at the time of reporting.

Table 2. Effectiveness of CoronaVac Vaccine in Preventing Covid-19 Outcomes in Overall Study Cohort, According to Immunization Status.*

Outcome and Immunization Status	Study Cohort	Persons with Covid-19		Vaccine Effectiveness (95% CI)		
	No. of Person-Days	No. of Persons	Incidence Rate *no. of events/ 1000 person-days*	Analysis Adjusted for Sex and Age	Analysis Adjusted for All Covariates† *percent*	Stratified Analysis‡
Covid-19						
Unvaccinated	614,868,240	185,633	0.3019	—	—	—
Partially immunized	69,788,352	20,865	0.2990	8.0 (6.5–9.4)	15.5 (14.2–16.8)	17.2 (15.8–18.6)
Fully immunized	91,671,797	12,286	0.1340	61.2 (60.3–62.0)	65.9 (65.2–66.6)	63.7 (62.8–64.6)
Hospitalization						
Unvaccinated	620,894,706	18,034	0.0290	—	—	—
Partially immunized	70,690,796	3,370	0.0477	31.4 (28.6–34.0)	37.4 (34.9–39.9)	40.3 (37.6–42.8)
Fully immunized	92,445,333	1,462	0.0158	86.0 (85.1–86.8)	87.5 (86.7–88.2)	86.5 (85.6–87.4)
Admission to ICU						
Unvaccinated	621,226,431	6,359	0.0102	—	—	—
Partially immunized	70,836,597	1,154	0.0163	37.5 (33.1–41.5)	44.7 (40.8–48.3)	45.3 (41.2–49.2)
Fully immunized	92,622,083	360	0.0039	88.8 (87.4–90.0)	90.3 (89.1–91.4)	90.2 (88.9–91.4)
Confirmed death						
Unvaccinated	621,426,477	2,786	0.0045	—	—	—
Partially immunized	70,854,187	847	0.0120	39.8 (34.4–44.7)	45.7 (40.9–50.2)	46.0 (40.7–50.8)
Fully immunized	92,514,261	409	0.0044	84.4 (82.4–86.2)	86.3 (84.5–87.8)	86.7 (84.9–88.3)

* Participants were classified into three groups: those who were unvaccinated, those who were partially immunized (≥14 days after receipt of the first vaccine dose and before receipt of the second dose), and those who were fully immunized (≥14 days after receipt of the second dose). The 13 days between vaccine administration and partial or full immunization were excluded from the at-risk person-time. ICU denotes intensive care unit.

† The analysis was adjusted for age, sex, region of residence, income, nationality, and whether the patient had underlying conditions that have been associated with severe Covid-19.

‡ A stratified version of the extended Cox proportional-hazards model was fit to test the robustness of the estimates to model assumptions, with stratification according to age, sex, region of residence, income, nationality, and whether the patient had underlying conditions that have been associated with severe Covid-19.

Table 4. Single and two dose vaccine efficacy data for Coronavac from (Jara et al. 2021)

It was noted by the Authors that ICUs were operating near capacity at the time of the study, which might have biased estimates of efficacy as people could not be admitted according to need.

Cor06 was a study reviewed in a submitted regulatory dossier. It was an interim analysis of VE in health-care workers aged 18-59 years of age in Indonesia. This provides an additional estimate of vaccine efficacy that is somewhat higher than in the Brazilian and Chilean data.

The Evaluator concludes that there is sufficient evidence of the effectiveness of Coronavac to support Recognition, although the estimates of VE against infection are wide and the average is only just 65%. The VE against hospitalisation is measured in multiple studies, with good evidence from South American studies.

Coronovac: references

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Appendix 1.2 BBIBP-CorV (Sinopharm)

Product	BBIBP-CorV (CorV)
Product Developer	Sinopharm
Country of origin	China
Vaccine Type	Inactivated virus/ alum adjuvanted
Schedule	Strain SARS-CoV-WIV04

Sinopharm: countries deployed

Sinopharm is deployed in 65 countries and listed by the WHO for emergency use.

Angola	Argentina	Bahrain	Bangladesh	Belarus
Belize	Bolivia	Brazil	Brunei Darussalam	Cambodia
Cameroon	Chad	China	Comoros	Cuba
Egypt	Equatorial Guinea	Gabon	Gambia	Georgia
Guyana	Hungary	Indonesia	Iran	Iraq
Jordan	Kenya	Kyrgyzstan	Lao People's Democratic Republic	Lebanon
Malaysia	Maldives	Mauritania	Mauritius	Mexico
Mongolia	Montenegro	Morocco	Mozambique	Namibia
Nepal	Niger	Nigeria	North Macedonia	Pakistan
Papua New Guinea	Paraguay	Peru	Philippines	Congo
Senegal	Serbia	Seychelles	Sierra Leone	Solomon Islands
Somalia	Sri Lanka	Thailand	Trinidad and Tobago	Tunisia
United Arab Emirates	Vanuatu	Venezuela	Vietnam	Zimbabwe

Sinopharm: main clinical efficacy and effectiveness data using standard schedules

Study	Population	Strain	Schedule	Primary Endpoint	VE ASy	VE Sy	VE Hos	VE Death	Advantages	Disadvantages
(Al Kaabi et al. 2021)	People >18 years of age without known history of COVID, MERS or SARS, or symptoms at screening.	Not noted	Two 5µg dose at day 0 and 21	Laboratory confirmed symptomatic COVID from 14 days after the second dose	64%	72.8%			• Randomised	• Strain prevalent in the trial not noted • Mainly enrolled healthy young men, mean age of 36.2%.
(Xia et al. 2021)	192 healthy people aged 18-80 with negative screening.	Not relevant 2 to 8 µg	Two does on day 0 and day 14,21 or 28	Phase I/II safety study with seroconversion endpoints						
Silva-Valencia, Javier *et al.*2021 PREPRINT	400 000 HCW	Lambda and Gamma	Two doses Interval unknown	Symptomatic infection and Death		50.4%		94%	• Large real-world study in 400 000 people in Peru • Provides estimate of protection against death.	• Lambda and Gamma strain • Only reported VE against symptomatic infection and death in tabulated results • Not peer-reviewed (Pre-print)

(AlQahtani et al. 2021)	569054 people residents of Bahrain	Beta and Delta	Two doses	Symptomatic infections, hospitalisations, ICU admissions, Deaths		45.5%	44.5% (72% over 50 years old)	63%	• Large study • Includes delta strain	Relatively young population
(Al-Hosani 2021) PREPRINT	176640 residents of UAE	Alpha and Beta	Two doses	Hospitalisation, ICU admissions and Death			79.8%	97.1%	Large study	• Relatively young population • Observational • Not peer reviewed

Sinopharm: main safety data

(Saeed et al. 2021) was a cross-sectional survey of recipients of BBIBP-CorV in the UAE between January and April 2021. The survey was voluntary and self-administered, and offered to potential recipients over 18 years of age who had received 1 or 2 doses of vaccine by email or social media sites. 1102 survey responses were received, of whom 1080 were included in the study as being from people 18 years and old. The number of vaccines administered to the survey population was not reported.

Adverse event reported	**After 1st dose (rate)**	**After 2nd dose (rate)**
Number of participants	**1080**	**1080**
Local pain (normal)	456	352
Local pain (severe)	28	88
Tenderness	56	108
Local pruritis	12	12
Local redness	8	16
Headache	104	108
Fatigue	132	176
Lethargy	100	148
Myalgia	68	
Nausea	16	12
Diarrhoea	8	8
Cough	12	8
Hypersensitivity	12	0
Fever	12	32
Abdominal pain	20	16
Backpain	44	32
Other	8	8
None	264	152

Table 5. Rate of adverse events reported in survey of recipients, Saeed *et al.* (PREPRINT)

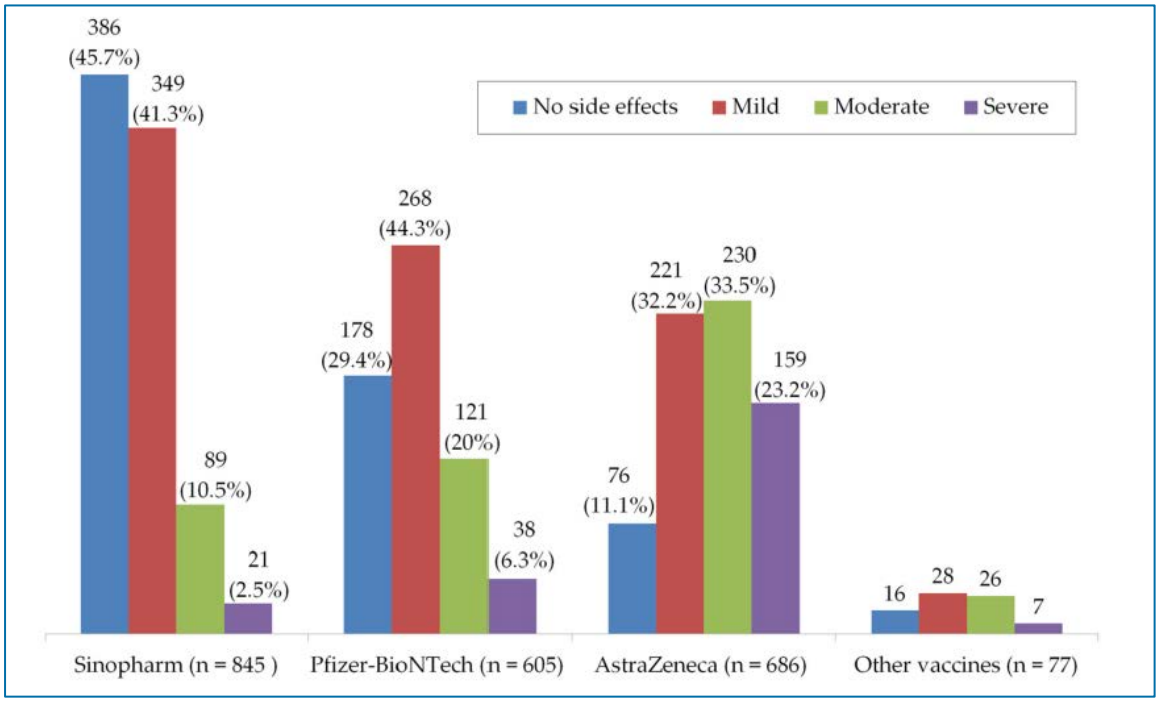
(Hatmal et al. 2021) was a study that administered a self-administered survey to a randomised cross section of the adult Jordanian population between 9 and 15 April 2021. Participants were invited through social media (Whatsapp, Facebook, Instagram) to go to the survey website, and a total of 2213 participants provided information. The vaccinated population of Jordan was 550,000, who had received Comirnaty (BNT162b2), Vaxzevria (AZ1222) or BBIBP-CorV. The response rate was not reported.

		Vaccines				χ^2	*p*-Value
		Sino.	Pfizer.	Astra.	O.		
Severity of side effects	Non Mild Moderate Severe	386 349 89 21	178 268 121 38	76 221 230 159	16 28 26 7	12.24	0.00 **
Infected after vaccination	Yes No	33 812	39 566	39 647	2 75	2.57	0.11
Tiredness	Present Absent	354 105	319 108	563 47	52 9	0.36	0.55
Fever	Present Absent	168 291	187 240	434 176	38 23	2.33	0.13
Headache	Present Absent	276 183	260 167	460 150	44 17	0.01	0.92
Haziness or lack-of-clarity in eyesight	Present Absent	84 375	57 370	147 463	11 50	1.68	0.19
Injection site pain and swelling	Present Absent	281 178	373 54	484 126	45 16	45.68	0.00 **
Joint pain	Present Absent	220 239	201 226	456 154	41 20	0.01	0.92
Swollen ankles and feet	Present Absent	26 433	19 408	53 557	4 57	0.14	0.71
Myalgia	Present Absent	221 238	219 208	455 155	42 19	0.40	0.53
Nausea	Present Absent	107 352	96 331	193 417	20 41	0.01	0.92
Abdominal pain	Present Absent	97 362	68 359	141 469	11 50	1.80	0.18
Diarrhea	Present Absent	55 404	52 375	110 500	8 53	0.00	1.00
Vomiting	Present Absent	17 442	16 411	52 558	3 58	0.03	0.86
Bruises on the body	Present Absent	20 439	12 415	34 576	3 58	0.39	0.53
Bleeding gums	Present Absent	11 448	1 426	15 595	1 60	2.22	0.14 *
Nosebleed	Present Absent	9 450	2 425	11 599	2 59	0.99	0.32 *
Chills	Present Absent	207 252	238 189	481 129	45 16	5.63	0.02 **
Itchy skin, or irritation and allergic reactions	Present Absent	47 412	31 396	62 548	9 52	0.97	0.32
Sweating for no reason	Present Absent	93 366	71 356	224 386	13 48	0.69	0.41
Cold, numbness, and tingling in limbs	Present Absent	140 319	115 312	278 332	25 36	0.55	0.46
Dizziness	Present Absent	168 291	131 296	288 322	28 33	1.61	0.20
Clogged nose	Present Absent	115 344	70 357	108 502	15 46	5.42	0.02 **
Runny nose	Present Absent	111 348	66 361	114 496	16 45	5.52	0.02 **
Dyspnea	Present Absent	71 388	54 373	127 483	12 49	0.53	0.47
Chest pain	Present Absent	60 399	63 364	139 471	14 47	0.14	0.71
Sleepiness and laziness	Present Absent	308 151	230 197	420 190	46 15	9.06	0.00 **
Irregular heartbeats	Present Absent	66 393	72 355	158 452	13 48	0.34	0.56
Abnormal blood pressure	Present Absent	46 413	50 377	95 515	7 54	0.19	0.66
Sore or dry throat	Present Absent	153 306	100 327	180 430	21 40	5.52	0.02 **
Cough	Present Absent	61 398	57 370	100 510	12 49	0.01	0.92
Number of side effects	0 1–6 7–12 >12	386 205 169 86	178 202 147 78	76 146 248 216	16 17 24 19	18.85	0.00 **

Sino., Sinopharm; Pfizer., Pfizer-BioNTech; Astra., AstraZeneca; O., other vaccines including Sputnik V, Moderna, Covaxin, and Johnson & Johnson vaccines. * One of the expected cell frequencies is smaller than 5. ** Significant difference.

Table 6. Adverse reactions by vaccine type reported in (Hatmal et al. 2021)

Figure 2. Adverse event severity by vaccine type from (Hatmal et al. 2021)



The most common adverse events with BBIPB-CorV were fever, tiredness, headache, and injection site pain. Overall, more BBIBP-CorV recipients reported no adverse events or milder adverse events than recipients of Comirnaty or Vaxzevria. Other vaccines in this analysis included small numbers of Covaxin, Sputnik V and other vaccines.

(Cai et al. 2021) is a significant meta-analysis of published studies of several vaccines, including BBIBP-CorV, which examined reported adverse events. It has referenced the main studies used in the analyses of efficacy presented in this assessment.

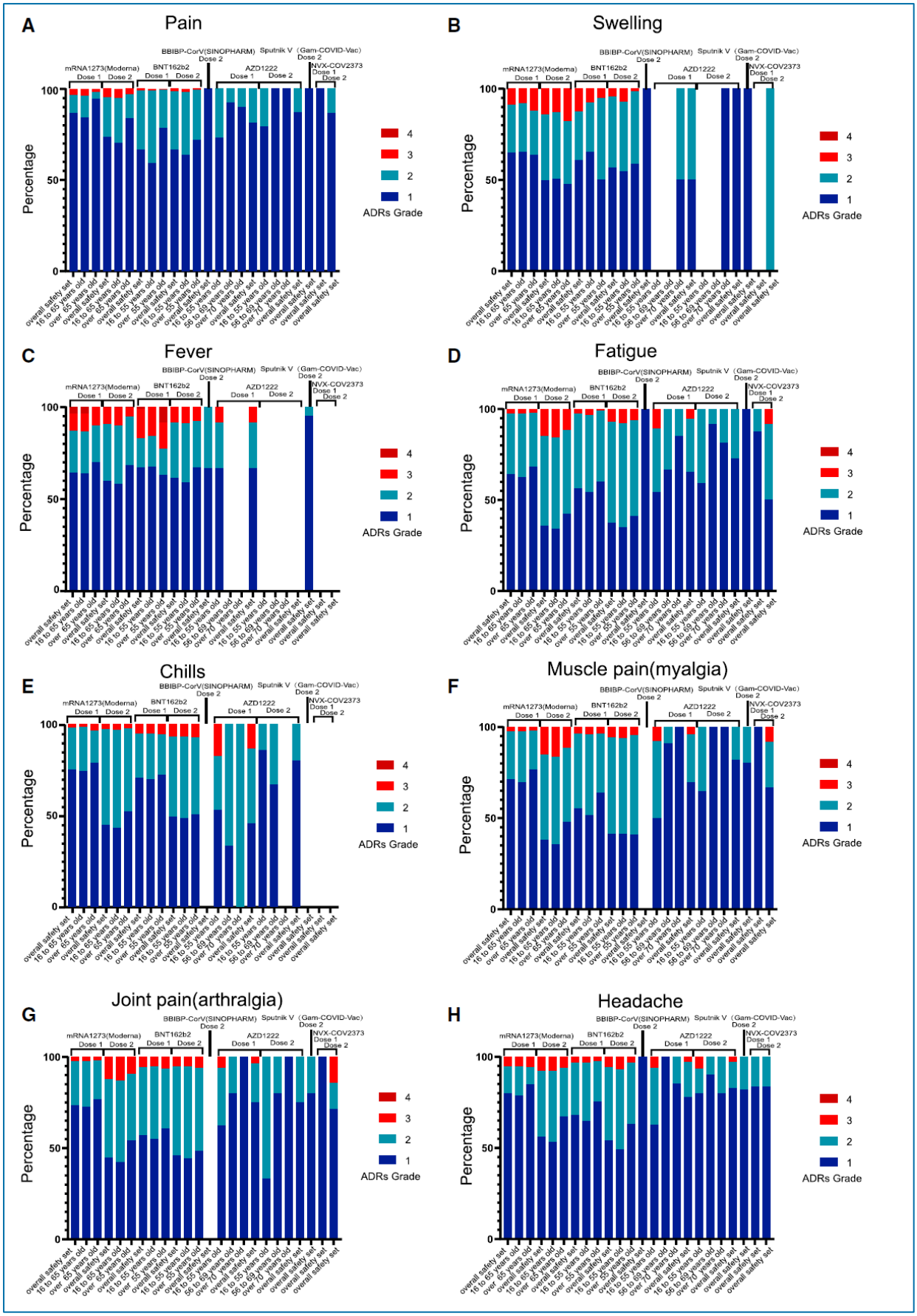


Figure 3. Reported adverse events for Comirnaty, Vaxzevria, BBIBP-CorV, Sputnik V and Spikevax from (Cai et al. 2021)

The paper only presents the vaccine sub-analysis graphically, although there is a tabulated comparison of adverse events by platform (e.g. non-replicating virus vs mRNA) but this merges several products. Overall the low rate of severe adverse events compared to Comirnaty and Vaxzevria reported by (Hatmal et al. 2021) using real world data is repeated in this analysis. The Evaluator notes that there appears to be no data for BBIPB-CorV on the incidence of myalgia, arthralgia or chills, which may reflect the limitations of published trial data, but these are reported in the survey based studies.

The WHO (SAGE 2021) has reported two serious adverse events potentially linked to vaccination with BBIBP-CorV in clinical trial data it has reviewed. These are Inflammatory Demyelination Syndrome/Disseminated Encephalomyelopathy and Severe Nausea.

Sinopharm: evaluator's comments

Al Kaabi, Zhang et al. 2021) is an interim analysis of the the main phase III data available for the Sinopharm/WIV04 vaccine. The study was conducted in 40411 healthy adults in the UAE between Jul and Dec 2020. Subjects were randomised equally to receive either BBIBP-CorV, another inactivated vaccine strain (HBO2) or alum adjuvant only, giving 13066 subjects with two doses of BBIBP-CorV and 13071 with alum only. The study enrolled mainly men (84%) of young age (mean 36.2 years). The primary endpoint was PCR confirmed symptomatic COVID, with a vaccine efficacy of 72.8% (95%CI 58.1-82.4). A post-hoc analysis identified an additional 42 asymptomatic cases, which would lower the total vaccine efficacy (symptomatic and asymptomatic) to 64% (95%CI 48.4-74.7). There were only 2 'severe' cases of COVID and the Authors note this as a limitation in the study, giving an estimate VE of 100% but with very broad confidence intervals. The grading scale for symptoms used was not described in the publication.

WHO's sage committee provided TGA with a summary of updated data at a median of 112 days followup. This indicated that there was a VE against hospitalisation of 78.7% (95%CI 26-93.9). Vaccine Efficacy in people >60 years of age was not estimated.

Vaccine efficacy in multi-country Phase 3 Trial (median follow up time 112 days)

	BBIBP-CorV Group		Placebo Group		Vaccine Efficacy
Group/Subgroup	No. at risk	No. of cases	No. at risk	No. of cases	% (95% CI)
Overall	13,765	21	13,765	95	78.1 (64.9, 86.3)
Hospitalization	13,765	3	13,765	14	78.7 (26.0, 93.9)
Severe	13,765	0	13,765	2	NE
Sex					
Male	11,598	18	11,642	83	78.4 (64.1, 87.0)
Female	2,167	2	2,123	13	75.6 (13.3, 93.1)
Age group					
18-59 years	13,556	21	13,559	95	78.1 (64.9, 86.3)
≥60 years	209	0	206	0	NE
Comorbidities					
Hypertension	374	0	367	4	NE
Diabetes	300	2	308	6	63.7 (-79.8, 92.7)
Obesity	3,040	7	3,080	36	80.7 (56.7, 91.4)
Baseline SARS-CoV-2 serostatus					
Baseline positive	NR	0	NR	1	NE
Baseline negative	NR	16	NR	83	80.8 (67.2, 88.8)

NE=Not estimated

Table 7. SAGE estimate of vaccine efficacy

The SAGE summary noted that there was a 'low level of confidence' that 2 doses of BBIBP-CorV provides efficacy against infection in older adults.

(Xia et al. 2021) was a phase I/II study that mainly examined safety in escalating doses of BBIBP-CorV, as well as seroconversion. In part 1 of the study, subjects were randomised equally to receive either placebo or vaccine at 2, 4, or 8 µg doses on day 0 and 28. In part 2 of the study, subjects were randomised equally to receive placebo of vaccine at 8 µg on days 0 and day 14, 21 or 28. The mean age of participants was 53 years of age. The study was conducted in China in 2020 (exact dates unclear).

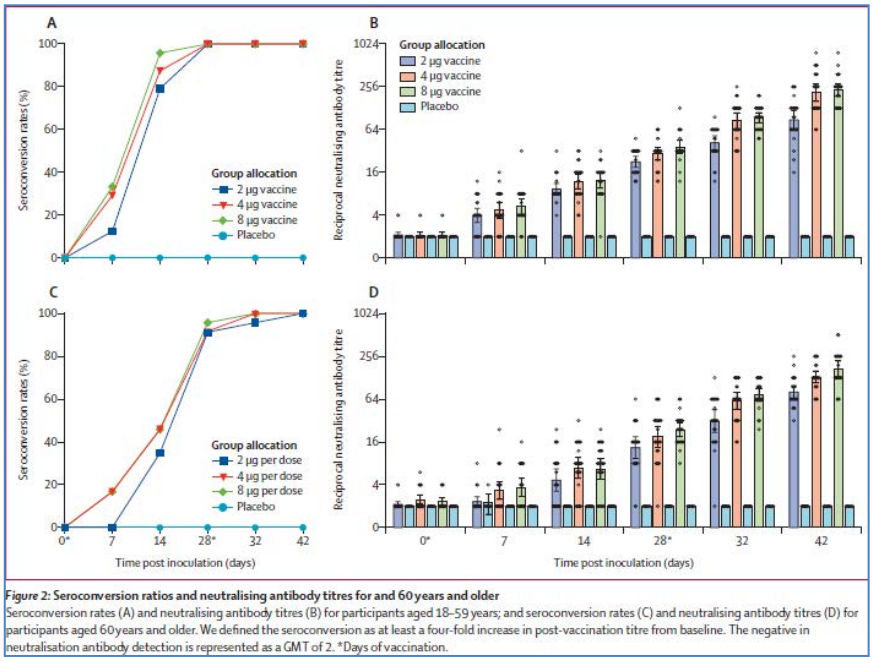


Figure 2: **Seroconversion ratios and neutralising antibody titres for and 60 years and older**
Seroconversion rates (A) and neutralising antibody titres (B) for participants aged 18–59 years; and seroconversion rates (C) and neutralising antibody titres (D) for participants aged 60 years and older. We defined the seroconversion as at least a four-fold increase in post-vaccination titre from baseline. The negative in neutralisation antibody detection is represented as a GMT of 2. *Days of vaccination.

Figure 4. Seroconversion following BBIBP-CorV vaccination in phase I/II study

The study indicates that seroconversion occurs in response to vaccination, with uncertain relevance to clinical outcomes given there is not a clear correlate of immunity for COVID.

(Silva-Valencia) was a large study examining vaccine efficacy and mortality among 400,000 Peruvian healthcare workers between February and Jun 2021. The pre-print of the study was in Spanish and so the Evaluator cannot comment on methodology, however the table presents clinical endpoints which translate readily into English. The results of this trial were reported in English in Reuters, at https://www.reuters.com/world/americas/peru-study-finds-sinopharm-covid-vaccine-504-effective-against-infections-2021-08-13/.

(AlQahtani et al. 2021) is a study from the deployment of several vaccines, including Sinopharm, in Bahrain between December 2020 and July 2021. In this, 569,054 individuals with a median age of 38 years were vaccinated. Delta and Beta strain COVID were isolated from PCR results during the period of deployment. The paper does not present vaccine effectiveness, which the Evaluator has calculated from the rates of endpoints presented below. This is notable in that there is a relatively low level of effectiveness even against Death compared to other trials.

(b)

	Unvaccinated vs Sinopharm											
	ALL				Over 50				Under 50			
	Rate (Unvax)	Rate (Sino)	p	OR	Rate (Unvax)	Rate (Sino)	p	OR	Rate (Unvax)	Rate (Sino)	p	OR
Infections	642.96	350.53	<.001	1.72	781.32	366.57	<.001	2.02	631.66	345.52	<.001	1.70
Hospitalizations	51.06	28.36	<.001	1.78	225.55	62.11	<.001	3.49	33.98	14.74	<.001	2.35
ICU admissions	6.39	2.29	<.001	2.70	41.44	6.62	<.001	5.92	2.65	0.49	**<.05**	5.09
Deaths	4.42	1.64	<.001	2.72	37.17	5.45	<.001	6.56	1.35	0.16	**NS**	7.65

Table 8. Pairwise comparisons of effectiveness of Sinopharm BBIBP-CorV in Bahrain

Table 9. Outcomes from Silva-Valencia, J et al. Note the IC 95% is not the CI for the Vaccine Efficacy

Tabla 2. Efectividad de la Vacuna BBIBP-Cor-V para infección, muerte por todas las causas y muerte por COVID-19 en trabajadores de salud del Perú, 2021

Desenlace	HR/RTI*	IC 95%	Efectividad (1-HR x 100)
Infección por SARS-CoV-2			
Inmunización parcial	0.83	0.80 - 0.85	17.2%
Inmunización completa	0.50	0.48 - 0.51	50.4%
Mortalidad por todas las causas			
Inmunización parcial	0.49	0.39 - 0.62	51.0%
Inmunización completa	0.10	0.08 - 0.13	90.1%
Mortalidad por COVID-19			
Inmunización parcial	0.54	0.41 - 0.70	46.3%
Inmunización completa	0.06	0.04 - 0.09	94.0%

* HR: Hazard Ratio calculado para Mortalidad por todas las causas y Mortalidad por COVID-19, RTI: Razones de Tasas de Incidencia calculadas para Infección por SARS-CoV-2. Todos los estimados están ajustados por edad, sexo, infección previa por COVID-19, departamento de procedencia, profesión, obesidad y las comorbilidades diabetes, hipertensión, asma, EPOC, estado de inmunosupresión, insuficiencia renal crónica y cáncer

Figura 2. Efectividad de la Vacuna BBIBP-Cor-V para infección, muerte por todas las causas y muerte por COVID-19 en trabajadores de salud del Perú, 2021.

(Al-Hosani 2021) is an observational study based on administrative records from the deployment of BBIP-CorV in the UAE between September 2020 and May 2021. A total of 214940 cases of COVID were reported to the UAE Dept of Health, of whom 176,640 could be linked to vaccine status records and were included in the study. The estimate of vaccine effectiveness is not presented stratified by age.

(Ferenci and Sarkadi 2021) published a review of neutralising antibody levels after two doses of BBIBP-CorV. This study found that age was a significant factor in the antibody response to BBIBP-CorV. 25% of recipients at 60 years of age, and 50% of recipients at 80% of age did not produce protective antibodies.

The Evaluator concludes that there is a wide range of the VE of BBIPV-CorV, but the VE against infection appears at most 73% and VE against hospitalisation is at most 80%. Partly because of the demographics of the populations in which the vaccine has been deployed there is a paucity of VE evidence in people >60 years of age. There is some evidence that immune response in older people is low. Overall, the Evaluator concludes that there is not sufficient data to conclude that BBIBP-CorV meets the criteria for Recognition in all age groups.

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Appendix 1.3 Covaxin

Product	Covaxin
Product developer	Bharat Biotech
Country of origin	India
Vaccine type	Inactivated virus with alum adjuvant
Schedule	Strain NIV-2020-770

Covaxin: countries deployed

Deployed in 9 countries and was listed by the WHO for emergency use in November 2021.

Guyana	India	Iran	Mauritius	Mexico
Nepal	Paraguay	Philippines	Zimbabwe	

Covaxin: main clinical efficacy and effectiveness data using standard schedules

Study	Population	Strain	Schedule	Primary Endpoint	VE ASy	VE Sy	VE Hos	VE Death	Advantages	Disadvantages
(Ella et al. 2021) PREPRINT	Adults 18-98 years	Many, including Delta and Kappa	Two doses at day 0 and 28	PCR confirmed symptomatic COVID >14 days after last dose	63.6	77.8% (65.2% vs Delta)	93.4[2]		• Randomised • Includes Delta strain patients	• Not peer reviewed (pre-print) • Estimate of efficacy in people >60 years of age very poor due to low numbers (median age 40.1 years) • Provides estimate of asymptomatic infection in protocol defined subgroup
Indian Department of Health	Adults >18 years of age	Not noted. Delta prevalent at the time	Two doses	Hospitalisation Death			88.2%	96.3%	• Large cohort including middle age and older • Delta strain likely to be prevalent	Short report does not include full population demographics

[2] Based on severe-symptomatic rate

Covaxin: main safety data

(Ella et al. 2021) elicited reactogenic adverse events from all 25798 participants in the trial. The study reported no deaths which were considered related to vaccination, and only 40 serious adverse events (not otherwise described in the report). The rates of adverse events were higher for the first than the second dose. The Evaluator notes that the incidence of adverse events was very low compared to that reported for other inactivated virus vaccines (e.g. Coronavac and Sinopharm). It is not clear which data set has the more accurate evaluation of the true incidence of adverse reactions, however.

Figure 5. Rates of adverse events reported in (Ella et al. 2021) for Covaxin after 1 or 2 doses

Supplementary table 5. Incidences of solicited adverse events after each dose.

Participants reporting solicited AEs within 7 days of vaccination, n(%)	**BBV152** (N = 12,879)		**Placebo** (N = 12,874)		**Total** (N = 25,798)	
	Dose 1 n (%)	Dose 2 n (%)	Dose 1 n (%)	Dose 2 n (%)	Dose 1 n (%)	Dose 2 n (%)
Any Local AE	431 (3·35)	278 (2·16)	399 (3·10)	260 (2·02)	830 (3·22)	538 (2·09
Pain	392 (3·04)	233 (1·81)	358 (2·78)	208 (1·62)	750 (2·91)	441 (1·71)
Erythema	33 (0·26)	21 (0·16)	26 (0·20)	25 (0·19)	59 (0·23)	46 (0·18)
Induration	32 (0·25)	18 (0·14)	26 (0·20)	18 (0·14)	58 (0·23)	36 (0·14)
Swelling	21 (0·16)	14 (0·11)	32 (0·25)	16 (0·12)	53 (0·21)	30 (0·12)
Any Systemic AE	331 (2·57)	231 (1·79)	247 (1·92)	205 (1·59)	578 (2·24)	436 (1·69)
Pyrexia	108 (0·84)	86 (0·67)	81 (0·63)	79 (0·61)	189 (0·73)	165 (0·64)
Fatigue	52 (0·40)	41 (0·32)	41 (0·32)	20 (0·16)	93 (0·36)	61 (0·24)
Chills	28 (0·22)	9 (0·07)	22 (0·17)	16 (0·12)	50 (0·19)	25 (0·10)
Headache	128 (0·99)	86 (0·67)	111 (0·86)	70 (0·54)	239 (0·93)	156 (0·61)
Myalgia	49 (0·38)	37 (0·29)	28 (0·22)	28 (0·22)	77 (0·30)	65 (0·25)
Arthralgia	17 (0·13)	12 (0·09)	17 (0·13)	17 (0·13)	34 (0·13)	29 (0·11)
Nausea	17 (0·13)	14 (0·11)	12 (0·09)	10 (0·08)	29 (0·11)	24 (0·09)
Vomiting	12 (0·09)	6 (0·05)	8 (0·06)	8 (0·06)	20 (0·08)	14 (0·05)

N = number of participants in the relevant population,
Events, n = number of individual events reported (one participant may have reported several AEs),
Participants, n = Number of participants reporting at least one event,
% = n participants with an event/N*100

Covaxin: evaluator's comments

(Ella et al. 2021) was reviewed as a non-peer reviewed pre-print of an interim analysis of an ongoing phase III trial. The study involved 25 798 volunteers recruited at 25 Indian hospitals between November 2020 and Jan 2021. Subjects were PCR screened to exclude COVID at enrolment and before each dose. Subjects were randomised 1:1 to receive vaccine (n=12221) or placebo (n=12198). Follow-up was stratified into three categories by study site. At Category 1 sites, post-dose phone calls were made every two weeks to detect symptoms (n=16477), at Category 2 sites swabs were taken every month to detect asymptomatic infection (n=8721) and at Category 3 sites blood samples were taken for immunological analysis (n=600). Patients were asked to contact the team on an as-needs basis. The protocol for follow-up and symptom assessment was not available in the pre-print.

The authors reported 27 variants identified during the study, but did a sub-analysis of 50 Delta-confirmed participants. This indicated a VE against symptomatic infection of 65.2% (95%CI 33.1-83). This is useful information but the small numbers make the error on this estimate too broad to be reliable.

Table 2: Efficacy against SARS-CoV-2 after at least 14 days following a second dose of BBV152 vaccine in the per protocol population.

Efficacy Endpoint	Total cases n/N (%)	BBV152 n/N (%)	Placebo n/N (%)	Vaccine efficacy (CI)*
Symptomatic COVID-19	130/16973 (0·77)	24/8471 (0·28)	106/8502 (1·25)	77·8 (65·2–86·4)
Severe Symptomatic COVID-19	16/16973 (0·09)	1/8471 (0·01)	15/8505 (0·18)	93·4 (57·1–99·8)
Symptomatic COVID-19 in participants 18–59 years	109/15115 (0·72)	19/7578 (0·25)	90/7537 (1·19)	79·4 (66·0–88·2)
Symptomatic COVID-19 in participants ≥ 60 years	21/1858 (1·13)	5/893 (0·56)	16/965 (1·66)	67·8 (8·0–90·0)
Symptomatic COVID-19 in participants with a pre-existing medical condition	49/4846 (1·01)	12/2328 (0·52)	37/2518 (1·47)	66·2 (33·8–84·0)
Asymptomatic COVID-19	47/6289 (0·73)	13/3248 (0·40)	33/3041 (1·09)	63·6 (29·0–82·4)
Symptomatic and asymptomatic COVID-19	75/6289 (1·19)	19/3248 (0·58)	56/3041 (1·84)	68·8 (46·7–82·5)

* 95.006% CI used for primary analysis of symptomatic COVID-19 to adjust for interim analyses, 95% CI otherwise. Primary efficacy was based on the per protocol population, including randomly assigned participants who were seronegative at baseline and received two doses of either vaccine or placebo, and remained on study at least 14 days after their second dose with no previous virologically-confirmed SARS-CoV-2 infection. COVID-19 cases were defined as occurring in participants who had at least two of the following symptoms: fever (temperature ≥ 38°C), chills, myalgia, headache, sore throat, or a new olfactory or taste disorder, or as occurring in those who had at least one respiratory sign or symptom (including cough, shortness of breath, or clinical or radiographic evidence of pneumonia) and at least one nasopharyngeal swab that was PCR positive for SARS-CoV-2.

Table 10. Efficacy results for (Ella, Reddy et al. 2021)

The Evaluator notes that the median age of the subjects was young (40.1 years) with a relatively few patients at high risk of illness or hospitalisation due to age. This may explain the imprecision of the estimate of efficacy in the older age group (>60 years age) which is too underpowered to be meaningful. Similarly, the imprecision of the estimate on asymptomatic COVID is too broad to allow clinically meaningful interpretation.

The TGA has reviewed a regulatory dossier that confirms the results presented in (Ella et al. 2021).

The TGA has been provided with an unpublished study of vaccine effectiveness by the Indian Council of Medial Research of the Indian Ministry of Health. This assessed the effectiveness of Covaxin against mortality and hospitalisation using linked health data in people eligible for

vaccination between April and August 2021. Over this period 1,599,723 individuals received two doses of Covaxin vaccine. This vaccination program included people >18 years of age and those over 60 years of age. This indicated a VE of 88.2% (95% 87.9-88.5) against hospitalisation and 96.3% (95%CI 95.4-96.9) for recipients of two doses of Covaxin.

The Evaluator concludes that there is sufficient evidence to conclude the efficacy of Covaxin exceeds the threshold required for Recognition, with a fair amount of leeway in these estimates and in populations exposed to Delta strain COVID.

Covaxin: references

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Appendix 1.4 Sputnik V

Product	Sputnik V/Gam-COVID-Vac
Product Developer	Gamaleya Research Institute
Country of origin	Russia
Vaccine Type	Recombinant adenoviruses (rAd26 and rAd5 in heterologous dose schedule)
Schedule	Two doses at day 0 and 21.

Sputnik V: countries deployed

Sputnik V is approved for use in 71 countries and is not WHO listed for emergency use.

Albania	Algeria	Angola	Antigua and Barbuda	Argentina
Armenia	Azerbaijan	Bahrain	Bangladesh	Belarus
Bolivia	Brazil	Cameroon	Chile	Djibouti
Ecuador	Egypt	Gabon	Guatemala	Guinea
Guyana	Honduras	India	Indonesia	Iran
Iraq	Jordan	Kazakhstan	Kenya	Kyrgyzstan
Lao People's Democratic Republic	Lebanon	Libya	Maldives	Mali
Mauritius	Mexico	Mongolia	Montenegro	Morocco
Myanmar	Namibia	Nepal	Nicaragua	Nigeria
North Macedonia	Oman	Pakistan	Panama	Paraguay
Philippines	Republic of Moldova	Congo	Russian Federation	St Vincent and the Grenadines
San Marino	Serbia	Seychelles	Sri Lanka	Syrian Arab Republic

Tunisia	Turkey	Turkmenistan	United Arab Emirates	Uzbekistan
Venezuela	Vietnam	West Bank	Zimbabwe	

Sputnik V: main clinical efficacy and effectiveness data using standard schedules

Study	Population	Strain	Schedule	Primary Endpoint	VE ASy	VE Sy	VE Hos	VE Death	Advantages	Disadvantages
(Logunov, Dolzhikova et al. 2021	People >18 years of age with negative COVID PCR, IgG and IgM on screening.	Not noted but VOC not prevalent in Russia during period of the trial	Two doses 21 days apart (rAd26 then rAd5)	PCR confirmed symptomatic COVID infection after second dose.		91.6%	100%		• Randomised • Peer reviewed	• No estimate of VE against asymptomatic transmission • No direct estimate of VE against hospitalisation • Relatively few patients >60 years (median age 45.3 years) • Relatively short period of follow-up (48 days) in interim analysis of 180-day trial
(Voko et al. 2021))	3740066 residents of Hungary 16+ years of age vaccinated between Jan and Jun 2021	Alpha	2 doses	Infection Mortality		85.7%		97.5%	• Large real world study • Peer Reviewed • Includes broad population recruitment	• Alpha strain
(González et al. 2021)	415995 residents of Argentina aged 60-79	Not noted	First dose	Infection, Hospitalisation and Mortality		78.6%	87.6%	84.4%	• Large real world study • Includes hospitalisation data	• Single dose only

	years of age between Dec 2020 and March 2021								• Examines risk groups	

Sputnik V: main safety data

(Montalti et al. 2021) was a survey of 2558 vaccine recipients in San Marino that elicited self-assessed adverse events after the first and second doses of Sputnik V between March and April 2021. All recipients of the vacine were invited to respond (San Marino has a populaton of approximately 35,000). The response rate is not reported. The Authors note that this was an interim analysis as the vaccination program was ongoing, and not sufficiently powered to detect rare adverse events.

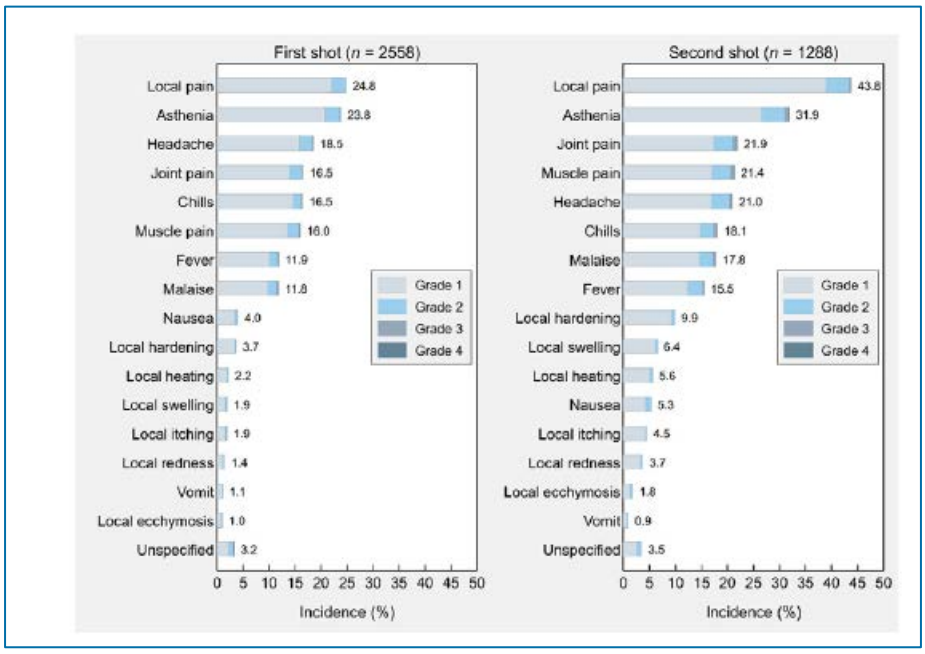

Figure 6. Percentage incidence of adverse events reported after 1st and 2nd doses of Sputnik V in (Montalti et al. 2021) *et al.*

The majority of adverse events reported were of mild severity, and included expected reactogenic effects.

(Babamahmoodi et al. 2021) is a pre-print of a study which examined 3236 reports of adverse events received from among 13435 healthcare workers who received Sputnik V in Iran between February and April 2021. Recipients of the vaccine were invited to respond to a web based survey by text message within 8 days of vaccination. It is noted that BBIPB-CorV and Covaxin were also in used in Iran but recipients of these vaccines were excluded.

	First dose (N=2194) N (%)	Second dose (N=1042) N (%)	Total (N=3236) N (%)	P value
Local side effects on the injection site				
Pain	1278 (58.2)	564 (54.1)	1842 (56.9)	**0.028**
Swelling	138 (6.3)	89 (8.5)	227 (7)	**0.022**
Redness	125 (5.7)	68 (6.5)	193 (6)	0.382
Systemic side-effects				
Fever	801 (36.5)	248 (23.8)	1049 (32.4)	**<0.0001**
Chilling	727 (33.1)	237 (22.7)	964 (29.8)	**<0.0001**
Headache	835 (38.1)	321 (30.8)	1156 (35.7)	**<0.0001**
Dizzying	318 (14.5)	129(12.4)	447 (13.8)	0.114
Body pain	1067 (48.6)	396 (38)	1463 (45.2)	**<0.0001**
Fatigue	1189 (54.2)	459 (44)	1648 (50.9)	**<0.0001**
Weakness	1023 (46.6)	397 (38.1)	1420 (43.9)	**<0.0001**
Nausea	201 (9.2)	68 (6.5)	296 (8.3)	**0.012**
Vomiting	30 (1.4)	13 (1.2)	43 (1.3)	0.870
Diarrhea	113 (5.2)	50 (4.8)	163 (5)	0.731
Constipation	1 (0.04)	2 (0.2)	3 (0.1)	0.244
Joint pain	707 (32.2)	275 (26.4)	982 (30.3)	**0.001**
Vasovagal syncope	15 (0.7)	6 (0.6)	21 (0.60)	0.818
Anaphylaxis shock	4 (0.2)	0	4 (0.1)	0.312
Rash	47 (2.1)	26 (2.5)	73 (2.3)	0.528
Depression	143 (6.5)	54 (5.2)	197 (6.1)	0.157
Drowsiness	470 (21.4)	187 (17.9)	657 (20.3)	**0.022**

Table 11. Incidence of adverse events in recipients of Sputnik V after one or two doses, reported in (Babamahmoodi *et al.* 2021)

(Cai et al. 2021) is a significant meta-analysis of published studies of several vaccines, including Sputnik V, which examined reported adverse events. It has referenced the main studies used in the analyses of efficacy presented in this Assessment.

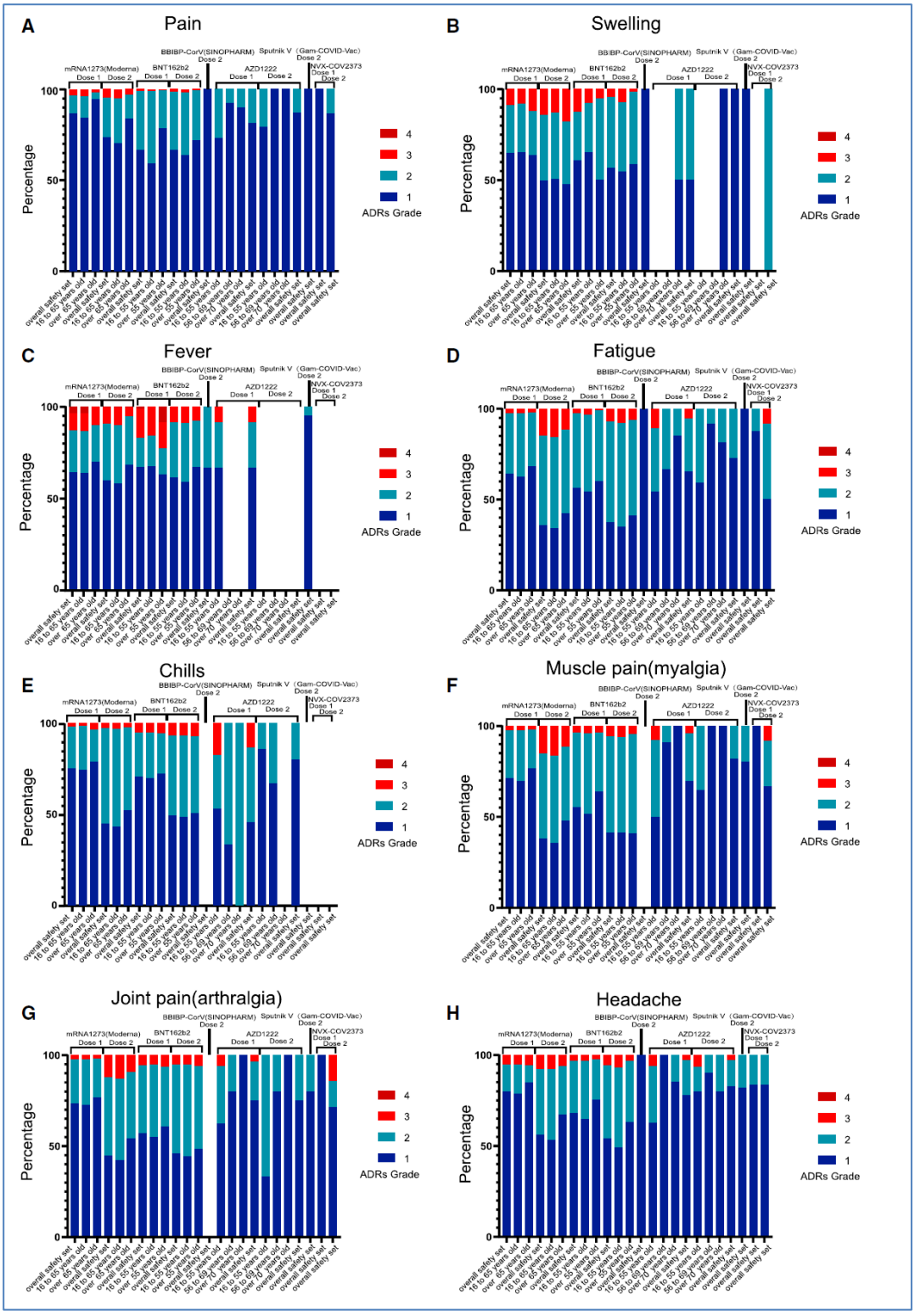

Figure 7. Reported adverse events for Comirnaty, Vaxzevria, BBIBP-CorV, Sputnik V and Spikevax from (Cai et al. 2021)

The Evaluator notes that these studies are broadly consistent with the low severity of adverse events reported, and the relative incidence of common reactogenic adverse events.

Sputnik V: additional information

The Russian Direct Investment Fund (RDIF) has announced that Sputnik V showed 97.8% vaccine effectiveness against symptomatic COVID and 100% vaccine effectiveness against severe COVID in 81000 recipients in the UAE[3]. Commentary[4] notes unpublished data on 3.8 million vaccine recipients in Russia which has a similar estimate of efficacy.

Sputnik V: evaluator's comments

Logunov et al. (2021) is an interim report from a phase III DB RCT study that was conducted on 21977 subjects recruited from 25 medical clinics in Russia between Sep and Nov 2020. Subjects were randomised 3:1 to receive vaccine (n=16501) or placebo (n=5476). Patients were monitored for self-reported COVID symptoms and cases confirmed by PCR testing. The average age of the population was relatively young (45.3 years) with a smaller number of patients (n=2144) older than 60 years of age. The study is intended to run for 180 days but the median follow-up time in this report is 48 days (IQR 39-58). The report found an overall vaccine efficacy of 91.6% (85.6-95.2) for symptomatic COVID during an outbreak in Russia (overall population rate of COVID 0.02). The study reported a 100% (95% CI 94.4-100) for severe COVID although this was a secondary stratification and it is not clear how many cases it was based on. The severity of COVID was assessed against a protocol-defined scale which the Evaluator notes would have placed these cases in hospital requiring supplemental O_2.

[3] https://rdif.ru/Eng_fullNews/6919/ accessed on 17 September 2021

[4] (Pagotto et al. 2021)

Appendix 2

COVID-19 Severity and Symptoms

COVID-19 Severity	Symptoms
Mild course	· Body temperature below 38. 5°C, cough, weakness, sore throat; · No symptoms of moderate and severe course
Moderate course	· Fever over 38. 5°C; · Respiratory rate (RR) more than 22/min; · Shortness of breath during physical exertion; · Pneumonia (confirmed by computed tomography [CT] of the lungs); · Oxygen saturation level < 95%; · C-reactive protein (CRP) of blood serum more than 10 mg/l
Severe course	· RR more than 30/min; · Oxygen saturation level ≤ 93%; · Oxygen partial pressure/inspiratory oxygen fraction ≤ 300 mmHg; · Progression of changes in the lungs according to X-ray, CT, ultrasonography (U/S) (increase in the volume of changes in the lungs by more than 50% after 24-48 hours); · Decreased level of consciousness, agitation; · Unstable hemodynamics (systolic blood pressure less than 90 mm Hg or diastolic blood pressure less than 60 mm Hg, diuresis less than 20 mL/hr); · Arterial blood lactate > 2 mmol/l; · More than 2 points on the Sequential Organ Failure Assessment Scale)SOFA) scale
Extremely severe course	· ARF with the need for respiratory support (invasive mechanical ventilation); · Septic shock; · Multiple organ failure; · Changes in the lungs on CT (X-ray) typical of a critical viral lesion (lesion volume is significant or subtotal; 4 CT) or an evidence of ARDS

Table 12. Appendix of Logunov describing COVID severity scale

The integrity of this study has been questioned (Bucci et al. 2021) due to the large number of people excluded at screening (35963 screened, of whom 21977 were randomised), poor definition of the primary endpoint and statistically improbable correlations in the data. The protocol and data has not been made public and is not intended to be until the end of the study. The Evaluator agrees that the publication (Logunov, Dolzhikova et al. 2021) does not make it clear exactly how cases were acquired, although the scale for assessing severity of symptoms is provided in the Appendix (see Table 1).

(Cabezas et al. 2021) has provided a commentary on the Sputnik efficacy data but notes some additional issues. They note a trial (Gushchin et al. 2021) showed a reduction in neutralisation of VOC in Sputnik vaccinated patients. However, a comparative trial (Ikegame et al. 2021) showed that a similar effect occurs with AstraZeneca AZ1222 vaccine.

Table 2 Summary of post-vaccine sera evaluated for neutralization potency against the indicated SARS-CoV-2 variants of concern (VOC).

			Neutralization assay (IC_{50} fold-reduction vs. WT)				
Vaccine	**Company**	**Spike construct**	**B.1.1.7 (Alpha)**	**P.1 (Gamma)**	**B.1.351 (Beta)**	**Number of samples tested (*n*)**	**Reference (PMID)**
Ad26.COV2.S	Johnson&Johnson	2P & ΔFurin	≤2× (n.s.)	NA	≤5×	8	33909009[a]
BNT162b2	Pfizer/BioNTech	2P	2×	NA	≤6.5×	10	33684923
BNT162b2	Pfizer/BioNTech	2P	2x (n.s.)	6.7×	35x	30	33743213
BNT162b2	Pfizer/BioNTech	2P	3.3x	NA	NA	25	33743891
BNT162b2	Pfizer/BioNTech	2P	NA	NA	7.9	25	33730597
mRNA-1273	Moderna	2P	1.8×	NA	≤8.6×	12	33684923
mRNA-1273	Moderna	2P	(n.s.)	4.5×	28x	35	33684923
BNT162b2 or mRNA-1273	Pfizer/BioNTech or Moderna	2P	NA	≤3×	NA	15[b]	33567448
NVX-CoV2373	Novavax	3Q - 2P	2×	NA	NA	28	33705729
AZD1222	AstraZeneca	Native	NA	NA	4×	13	33725432
AZD1222	AstraZeneca	Native	8.9x	NA	NA	49	33798499
AZD1222	AstraZeneca	Native	2.1–2.5x	NA	NA	25	33743891
AZD1222	AstraZeneca	Native	NA	NA	9x	25	33730597
CoronaVac	Sinovac	Native	NA	NA	NA	N.D.	N.D.
BBIBP-CorV	Sinopharm	Native	NA	NA E484K	1.6× (n.s.)	12	33870240
Sputnik V	Gamaleya	Native	(n.s.)	2.8x (E484K)	6.1x	12	33821288[c]

[a]Non-human Primate data.
[b]Four are post-Pfizer/BioNTech and 11 are post-Moderna vaccine samples.
[c]Current study.
Table format adapted and updated from Abdool Karim and de Oliveira[60]. *2P* 2 proline substitutions in the S2 central helix (K986P/V987P), Δ*Furin* deletion of furin cleavage site, *3Q-2P* RRAR to QQAQ to render furin cleavage site protease resistant combined with the aforementioned two proline substitutions.

Table 13: Comparative neutralisation of COVID vaccines against Variants of Concern compared to Wild Type virus, Ikegame, Siddiquey et al. 2021

(Voko et al. 2021) provides a real-world retrospective analysis of the Hungarian vaccination program over the first half of 2021, which involved 5 vaccines including Sputnik V. This found a high rate of Vaccine Effectiveness against infection, 85.7% (95%CI 84.3-86.9), and mortality, 97.5% (95%CI 95.6-98.6). The age of the vaccinated population was 16+ years with a fairly balanced representation of older age groups.

(González et al. 2021) examined the vaccine efficacy of the first dose of Sputnik V in older Argentinians in their national program. The study found a Vaccine Effectiveness of 78.6% (95%CI 74.8-81.7) against COVID infection, 87.6% (95% CI 80.3-92.2%) against hospitalisation and 84.8% (95% 75.0-90.7) against mortality compared to unvaccinated people. The study did not note the dominant strain circulating at the time, but the Evaluator notes that Gamma and Lambda were both potentially prevalent in South America at the time. First-dose studies should be interpreted with caution in the case of Sputnik V because the two components of the vaccine are different, and there is theoretical potential for induced anti-adenovirus antibodies to impact overall efficacy after booster doses. However, the Evaluator feels that this study provides additional real world support for the efficacy of Sputnik V in relevant risk populations.

(Dolzhikova et al. 2021) has published a single dose efficacy study that reported a vaccine efficacy of 69.96% (95%CI 64.0-74.7) based on registry data from Moscow. This has the advantage of being a study conducted during a Delta COVID outbreak in the city, but the methodology appears to impute an unvaccinated rate from serology data. The Evaluator feels that this study is not critical and, due to the unusual methodology, has not included it in the analysis until a peer-reviewed version is available.

The Evaluator notes that some of the information announced by the RDIF, while encouraging, appears to be unpublished and so cannot be evaluated.

The Evaluator concludes that there is sufficient data to Recognise Sputnik V.

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Appendix 1.5 Convidecia

Product	Convidecia and Pakvac (Pakistan)
Product Developer	Cansino Biologics
Country of origin	China
Vaccine Type	Recombinant Adenovirus 5 vector
Schedule	Single dose

Convidecia: countries deployed

Deployed in 9 countries and not WHO recognised for emergency use.

Argentina	Chile	China	Ecuador	Hungary
Indonesia	Malaysia	Mexico	Pakistan	

Convidecia: main clinical efficacy and effectiveness data using standard schedules

Study	Population	Strain	Schedule	Primary Endpoint	VE ASy	VE Sy	VE Hos	VE Death	Advantages	Disadvantages
(Halperin et al. 2021)	44450 residents of Pakistan, Russia, Mexico and Chile 18 years or older enrolled between Sep and Dec 2020	B.1.1.19	One dose	Symptomatic PCR confirmed COVID		57.5%			• Controlled trial	• Does not measure severe disease outcomes

Convidecia: main safety data

The main safety data is from the phase III trial and is short term follow-up of reactogenic endpoints. The Study reported headache (44.2%), muscle aches (41.2%), drowsiness (40.0%) and fever (12.5%) occurring in Convidecia recipients. There was no difference in the rate of severe adverse events between placebo and Convidecia.

Convidecia: additional information

On 22 March 2021 Cansino reported to have stated[5] interim data from (Halperin et al. 2021). In the same report, reference was made to the Pakistan authorities had announced a vaccine efficacy rate of 100% against severe COVID and 94.8% against symptomatic COVID in trials in Pakistan. The Evaluator has not been able to access the latter data.

Convidecia: evaluator's comments

(Halperin et al. 2021) provides phase III evidence supporting the primary efficacy of Convidecia in preventing infection 28 days post single dose vaccination. The Evaluator notes that a Vaccine Efficacy of 90.1% (95% CI 22.3-98.7) was reported but this is considered too broad to be useful. The Authors of the study have noted these broad confidence intervals are probably related to the smaller sample size.

There is currently insufficient evidence to conclude whether Convidecia should be a Recognised vaccine.

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Appendix 1.6 Vaxzevria/Covishield

Product	Vaxzevria
Product Developer	AstraZeneca
Country of origin	UK
Vaccine Type	Adenovirus
Schedule	2 doses, day 0 and week 4-12

Vaxzevria/Covishield: countries deployed

Vaxzevria is approved for use in 123 countries and is WHO listed for emergency use.

Covishield is approved for use in 46 countries and is WHO listed for emergency use.

Afghanistan	Antigua and Barbuda	Argentina	Bahamas	Bahrain
Bangladesh	Barbados	Bhutan	Bolivia	Botswana
Brazil	Cabo Verde	Canada	Cote d'Ivoire	Dominica
Egypt	Ethiopia	Ghana	Grenada	Honduras
Hungary	India	Jamaica	Lebanon	Madagascar
Maldives	Morocco	Myanmar	Namibia	Nepal
Nicaragua	Nigeria	Saint Kitts and Nevis	Saint Lucia	Saint Vincent and the Grenadines
Seychelles	Solomon Islands	Somalia	South Africa	Sri Lanka
Suriname	Syrian Arab Republic	Togo	Tonga	Trinidad and Tobago
Ukraine				

Vaxzevria/Covishield: main clinical efficacy and effectiveness data using standard schedules

Study	Population	Strain	Schedule	Primary Endpoint	VE ASy	VE Sy	VE Hos	VE Death
(Voysey et al. 2021)	Pooled analysis of placebo controlled studies involving 8597 adult recipients of ChAdOx1 vaccine across four studies in UK, Brazil and South Africa.	Not noted	2 doses Day 0 and Week 12	Symptomatic PCR confirmed COVID >14 days after the second dose		63.1%[6]		
(Cerqueira-Silva et al. 2021) PREPRINT	Retrospective cohort study in approximately 61 million recipients of Brazilian mass vaccination program	Gamma	2 doses Day 0 Week 12	Symptomatic infection, hospitalisation, ICU admission and death		70%	86.8% (88.1% ICU)	90.2%
(Pritchard et al. 2021)	Random survey of 383812 >16 year old participants in UK to assess COVID status post vaccination	Alpha	2 doses Day 0 Day Week 12	Symptomatic and Asymptomatic infection > 21 days after second dose	58%	64%		
(Lopez Bernal et al. 2021)	Case control study in 8300 adult subjects in UK.	Alpha and Delta	2 doses Day 0 and Week 12	Symptomatic infection >14 days after second dose		67.0% (delta)		

Vaxzevria/Covishield: data in non-standard schedules

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0·5%)	44·1 (248 299)	101/5829 (1·7%)	149·2 (247 228)	70·4% (54·8 to 80·6)†
COV002 (UK)	86	18/3744 (0·5%)	38·6 (170 369)	68/3804 (1·8%)	145·7 (170 448)	73·5% (55·5 to 84·2)
LD/SD recipients	33	3/1367 (0·2%)	14·9 (73 313)	30/1374 (2·2%)	150·2 (72 949)	90·0% (67·4 to 97·0)‡§
SD/SD recipients	53	15/2377 (0·6%)	56·4 (97 056)	38/2430 (1·6%)	142·4 (97 499)	60·3% (28·0 to 78·2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0·6%)	56·2 (77 930)	33/2025 (1·6%)	157·0 (76 780)	64·2% (30·7 to 81·5)‡
All SD/SD recipients	98	27/4440 (0·6%)	56·4 (174 986)	71/4455 (1·6%)	148·8 (174 279)	62·1% (41·0 to 75·7)
Other non-primary symptomatic COVID-19 disease¶	18	7/5807 (0·1%)	10·3 (248 299)	11/5829 (0·2%)	16·3 (247 228)	36·4% (−63·8 to 75·3)‡
Any symptomatic COVID-19 disease	149	37/5807 (0·6%)	54·4 (248 299)	112/5829 (1·9%)	165·5 (247 228)	67·1% (52·3 to 77·3)
Asymptomatic or symptoms unknown (COV002)	69	29/3288 (0·9%)	69·8 (151 673)	40/3350 (1·2%)	96·0 (152 138)	27·3% (−17·2 to 54·9)
LD/SD recipients	24	7/1120 (0·6%)	41·4 (61 782)	17/1127 (1·5%)	100·6 (61 730)	58·9% (1·0 to 82·9)‡
SD/SD recipients	45	22/2168 (1·0%)	89·4 (89 891)	23/2223 (1·0%)	92·9 (90 408)	3·8% (−72·4 to 46·3)
Any NAAT-positive swab	221	68/5807 (1·2%)	100·0 (248 299)	153/5829 (2·6%)	226·0 (247 228)	55·7% (41·1 to 66·7)

Vaccine efficacy was calculated from the robust Poisson model. The primary efficacy population (LD/SD and SD/SD) includes randomly assigned participants who were seronegative at baseline and received LD/SD or SD/SD or were in a corresponding control group, and remained on study more than 14 days after their second dose without having had a previous virologically confirmed SARS-CoV-2 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9, and 10) are included. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. NAAT=nucleic acid amplification test. *CIs are 95% unless indicated otherwise. †95·8% CI used for primary analysis. ‡Vaccine efficacy calculated from a reduced robust Poisson model that was not adjusted for age. All other models included an adjustment for age. §p value for interaction term comparing LD/SD with SD/SD is p=0·010. ¶Other non-primary symptomatic COVID-19 disease includes cases who have symptoms other than the five main symptoms that are required for inclusion in the primary analysis (eg, a participant who has diarrhoea and malaise but no fever, cough, shortness of breath, anosmia, or ageusia).

Table 2: **Efficacy against SARS-CoV-2 more than 14 days after a second dose of ChAdOx1 nCoV-19 vaccine in the primary efficacy population**

Table 14. Results (Voysey et al. 2021)

The Evaluator notes that while Voysey reported an overall VE against infection of 70.4%, this figure included two different dose schedules of the vaccine (e.g. low dose/standard dose and standard dose/standard dose). The figure given is that for the standard dose (e.g. SD/SD).

Vaxzevria/Covishield: main safety data

Table 1 Adverse Drug Reactions (ADR) interim analysis – pooled data set (safety analysis set[a])

MedDRA SOC	Adverse reaction[b]	VAXZEVRIA (N= 10, 069)	Control[c] (N= 9, 902)
Nervous system disorders	Headache	Very common (52.6%)	Very common (39.0%)
Gastrointestinal disorders	Nausea	Very common (21.9%)	Very common (13.1%)
Musculoskeletal and connective tissue disorders	Muscle pain (Myalgia)	Very common (44.0%)	Very common (21.6%)
	Joint pain (Arthralgia)	Very common (26.4%)	Very common (12.4%)
General disorders and administration site conditions	**Local**		
	Injection site tenderness	Very common (63.7%)	Very common (39.5%)
	Injection site pain	Very common (54.2%)	Very common (36.7%)
	Injection site warmth	Very common (17.7%)	Very common (14.5%)
	Injection site itch (Injection site pruritus)	Very common (12.7%)	Common (7.5%)
	Injection site swelling	Common (3.4%)	Common (1.6%)
	Injection site redness (Injection site erythema)	Common (3.1%)	Common (1.4%)
	Systemic		
	Fatigue	Very common (53.1%)	Very common (38.2%)
	Malaise	Very common (44.2%)	Very common (20.2%)
	Feverishness[d] (Pyrexia)	Very common (33.6%)	Very common (10.7%)
	Chills	Very common (31.9%)	Common (8.3%)
	Fever[d] (Pyrexia)	Common (7.9%)	Common (1.2%)

[a] Frequencies of ADRs are reported from the safety analysis set where participants received the recommended dose (5×10^{10} vp) as their first dose.

[b] Solicited event reporting terms, where applicable MedDRA preferred terms are given in parentheses

[c] Control was either meningococcal vaccine or saline solution

[d] Defined as: Feverishness, (subjective) a self-reported feeling of having a fever; Fever, (objective) ≥38°C

Table 15. Adverse events reported from pooled safety analysis in the TGA Prescribing Information for Vaxzevria

Thrombosis with thrombocytopenia syndrome (TTS) occurs in approximately 2.4 cases per 100000 vaccine recipients, most commonly after the first dose of vaccine. The onset of symptoms is usually within 4 to 42 days after vaccination and thrombosis can occur either in common sites (e.g. DVT or PE) or in unusual locations (e.g. cerebral venous sinus thrombosis). The Australian Technical Advisory Group on Immunisation (ATAGI) has provided an analysis of age specific rates of TTS[7].

Vaxzevria/Covishield: evaluator's comments

Vaxzevria is TGA-registered.

Vaxzevria/Covishield: references

[7] COVID-19 vaccination – weighing up the potential benefits against risk of harm from COVID-19 Vaccine AstraZeneca, April 2021, accessed at https://www.health.gov.au/resources/publications/covid-19-vaccination-weighing-up-the-potential-benefits-against-risk-of-harm-from-covid-19-vaccine-astrazeneca

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Appendix 1.7 Comirnaty

Product	Comirnaty/BNT162b2
Product Developer	Pfizer
Country of origin	USA
Vaccine Type	mRNA
Schedule	2 doses at day 0 and day >21

Comirnaty: countries deployed

Comirnaty is approved for use in 101 countries and is WHO listed for emergency use.

Comirnaty: main clinical efficacy and effectiveness data using standard schedules

Study	Population	Strain	Schedule	Primary Endpoint	VE ASy	VE Sy	VE Hos	VE Death	Advantages	Disadvantages
(Polack et al. 2020)	Multinational RCT trial of 43548 volunteers >16 years of age	Not noted	2 doses Day 0 Day 21	PCR confirmed symptomatic COVID >7 days after second dose		95%			• (Polack et al. 2020)	• Multinational RCT trial of 43548 volunteers >16 years of age
(Dagan et al. 2021)	596618 persons >16 years of age randomised 1:1 as vaccinated or control in observational study of mass vaccination program in Israel	Mainly Alpha	2 doses Day 0 Day 21-27	VE Asymptomatic COVID, Symptomatic COVID Severe disease, hospitalisation and death >7 days after second dose	90%	94%	% 92 (severe infection) 87% (hospital)		• (Dagan et al. 2021)	• 596618 persons >16 years of age randomised 1:1 as vaccinated or control in observational study of mass vaccination program in Israel
(Haas et al. 2021)	Study calculating rates of COVID in vaccinated and unvaccinated residents of Israel >16 years of age	Mainly alpha	2 doses Day 0 Day 21-27	VE asymptomatic COVID, Symptomatic COVID, Severe disease, Hospitalisation and Death	93.5%	97.7%	98%	98.1%	• (Haas et al. 2021)	• Study calculating rates of COVID in vaccinated and unvaccinated residents of Israel >16 years of age

(Lopez Bernal et al. 2021)	Case control study in 15800 adult subjects in England.	Alpha and Delta	2 doses	VE Asymptomatic	93.7% (alpha) 88.0% (delta)				• (Lopez Bernal et al. 2021)	• Case control study in 15800 adult subjects in England
(Chung et al. 2021)	Case control study in 324033 PCR confirmed cases of COVID in Canada	Mainly Alpha	2 doses	VE Symptomatic infection and (hospitalisation or death) composite >7 days after second dose		91%	98% (or death)	98% (or hospitalisation)	• (Chung et al. 2021)	• Case control study in 324,033 PCR confirmed cases of COVID in Canada

Study	Population	Strain	Schedule	Primary Endpoint	VE ASy	VE Sy	VE Hos	VE Death	Advantages	Disadvantages
(Frenck et al. 2021)	Placebo controlled trial in subjects 2264 12-15 years of age randomised 1:1 to receive Comirnaty (n=1134) or placebo (n=1130)	Not noted	2 doses Day 0 Day 21	Symptomatic PCR confirmed COVID >7 days post second dose		100%			• (Frenck et al. 2021)	• Placebo controlled trial in subjects 2264 12-15 years of age randomised 1:1 to receive Comirnaty (n=1134) or placebo (n=1130)

Comirnaty: data in non-standard schedules

The efficacy of a third booster shot was assessed in (Bar-On et al. 2021). This study examined the rate of infection in 1137804 Israeli residents over 60 years of age during the booster program in 2021. Endpoints were assessed retrospectively to assess the rate of confirmed infection and severe illness in fully vaccinated people who had, or had not, received a 3rd dose of Comirnaty at least five months after completing primary 2-dose vaccination. The study reported a decrease in rates of infection and severe illness among recipients of the 3rd dose, with an odds ratio of protection against severe infection of 19.5.

Table 2. Primary Outcomes of Confirmed Infection and Severe Illness.*

Outcome	Nonbooster Group	Booster Group	Adjusted Rate Ratio (95% CI)†
Confirmed infection			11.3 (10.4 to 12.3)
No. of cases	4439	934	
No. of person-days at risk	5,193,825	10,603,410	
Severe illness			19.5 (12.9 to 29.5)
No. of cases	294	29	
No. of person-days at risk	4,574,439	6,265,361	

* Listed are the results of the Poisson regression analysis in participants who received a booster vaccine and in those who did not receive a booster. The booster group includes data that were obtained at least 12 days after receipt of the booster dose.
† The rate ratio is the estimated factor reduction in the rate in the booster group as compared with the rate in the non-booster group.

Table 16. Results from Bar-On, Goldberg *et al.*

Comirnaty: main safety data

	12 – 15 years of age		16 to 25 years of age		16–55 years of age		>55 years of age	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Injection site pain	86%	79%	83%	78%	83%	78%	71%	66%
Fever	10%	20%	7%	17%	4%	16%	1%	11%
Fatigue	60%	66%	60%	66%	47%	59%	23%	51%
Headache	55%	65%	54%	61%	42%	52%	25%	39%
Chills	28%	42%	25%	40%	14%	35%	6%	23%
Muscle pain	24%	32%	27%	41%	21%	37%	14%	28%
Joint pain	10%	16%	13%	22%	11%	22%	9%	19%
Required paracetamol	37%	51%	32%	46%	28%	45%	20%	38%

Table 17. Common adverse events following Comirnaty administration, from ATAGI Clinical Guidance on use of COVID-19 Vaccine in Australia in 2021 using data from (Frenck et al. 2021) and (FDA 2020).

Myocarditis, pericarditis and myopericarditis have been reported following Comirnaty. The rate appears higher in young males (<30 years of age) at a rate of 71.5 per million vaccines in males.

Comirnaty: evaluator's comments

Comirnaty is TGA-registered.

Comirnaty: references

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Appendix 1.8 Spikevax

Product	Spikevax
Product Developer	Moderna
Country of origin	USA
Vaccine Type	mRNA
Schedule	Two doses, Day 0 and 28

Spikevax: countries deployed

Spikevax is approved for use in 76 countries and is WHO listed for emergency use.

Spikevax: main clinical efficacy and effectiveness data using standard schedules

Study	Population	Strain	Schedule	Primary Endpoint	VE ASy	VE Sy	VE Hos
(Chung et al. 2021)	Case control study in 324033 persons >16 years of age with COVID symptoms in Canada	Not noted		VE Symptomatic infection and severe outcomes (Hospitalisation or Death) >14 days post second dose		Approx. 95% (Note: Paper only presents data graphically)	Approx. 95% (Note: Paper only presents data graphically)
(Nasreen et al. 2021)	Case control study 421073 persons >16 years of age with COVID symptoms in Canada	Alpha Beta Gamma Delta		VE Symptomatic infection and severe outcomes (Hospitalisation or death) >14 days post second dose		91%	96% (>7 days after dose 2)
(Thompson et al. 2021)	Case control study	Not noted		VE Hospitalisation		`	91% (hospital)

	41552 admissions to 187 hospitals and 221 EDs in the USA.			ED visit			72% (ED)
(Ali et al. 2021)	Placebo controlled trial in 3732 12-17 year olds randomised 2:1 to Spikevax (n=2489) or placebo (n=1243)			VE Symptomatic infection >14 days after second dose		92.7%	

Spikevax: main safety data

Myocarditis, pericarditis and myopericarditis have been reported following Spikevax. The rate appears higher in young males (<30 years of age) at a rate of 37.7 per million vaccines in males 18-24 years of age (Compared to 37.1 per million for Comirnaty in this age group). Most cases developed symptoms within a week of vaccination and required hospitalisation, but have had a mild clinical course[8].

Anaphylaxis to Spikevax has been reported at a rate of 2.5 per million doses, with the majority of cases occurring within 30 minutes of vaccination[1].

Table 18. Common adverse events following Comirnaty administration, from ATAGI Clinical Guidance on use of COVID-19 Vaccine in Australia in 2021 using data from (Ali et al. 2021) and (Baden et al. 2021).

[8] **ATAGI Clinical Guidance on use of COVID-19 Vaccine in Australia in 2021**

	12 – 17 years of age		18-64 years of age		≥65 years of age	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Injection site pain	93%	92%	87%	90%	74%	83%
Lymph node swelling at the axilla	23%	21%	12%	16%	6%	9%
Fever	2.5%	12%	0.9%	17%	0.3%	10%
Fatigue	48%	68%	38%	68%	33%	58%
Headache	45%	70%	35%	63%	25%	46%
Chills	18%	43%	9%	49%	5%	31%
Myalgia	27%	47%	24%	62%	20%	47%
Arthralgia	15%	29%	17%	46%	16%	35%
Nausea/vomiting	10%	18%	9%	21%	5%	12%

Spikevax: evaluator's comments

Spikevax is TGA-registered. The Evaluator notes that the average VE against hospitalisation in the trials in this review is 94%, probably reflecting the inclusion of studies against different strains than the NCRIS review referenced in the Executive summary.

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Appendix 1.9 COVID-19 Vaccine Janssen

Product	COVID-19 Vaccine Janssen
Product Developer	Johnson and Johnson/Janssen
Country of origin	Netherlands
Vaccine Type	Non-replicating adenovirus
Schedule	One dose

Janssen: countries deployed

Deployed in 71 countries and WHO recognised for emergency use.

Janssen: main clinical efficacy and effectiveness data using standard schedules

Study	Population	Strain	Schedule	Primary Endpoint	VE ASy	VE Sy	VE Hos
(Sadoff, Gray, et al. 2021)	44,325 adults >18 years of age, mostly <60 years, recruited Latin America, USA, and South Africa	Beta Gamma	Single dose	Moderate to severe COVID >14 days after dose		66.1%	85.4

Janssen: data in non-standard schedules

(Sadoff, Le Gars, et al. 2021) is a pre-print of a study that examined immunogenicity of a second booster dose of COVID-19 Vaccine Janssen. A total of 73 participants were >18 years of age and drawn from several phase I/II studies in which they had received a primary dose of vaccine and were offered a booster dose at 6 months. Neutralising GMTs were assessed 7 and 28 days after the booster dose, in addition to after the primary dose in the respective phase I/II trials. Participants showed a 9-fold increase in GMT at day 28 post-booster dose.

Janssen: main safety data

Table 19. Adverse reactions to COVID-19 vaccine Janssen in pooled trials, from TGA Product Information

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1 000 to <1/100)	Rare (≥1/10 000 to <1/1 000)	Not known (cannot be estimated from the available data)
Immune system disorders				Hypersensitivity[a]; urticaria	Anaphylaxis[b]
Nervous system disorders	Headache		Tremor		
Respiratory, thoracic and mediastinal disorders		Cough	Sneezing; oropharyngeal pain		
Gastrointestinal disorders	Nausea				
Skin and subcutaneous tissue disorders			Rash; hyperhidrosis		
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia	Muscular weakness; pain in extremity; back pain		
General disorders and administration site conditions	Fatigue; injection site pain	Pyrexia; injection site erythema; injection site swelling; chills	Asthenia; malaise		

[a] Hypersensitivity refers to allergic reactions of the skin and subcutaneous tissue.
[b] Cases received from an ongoing open-label study in South Africa.

Janssen: additional information

In early August 2021, Johnson and Johnson reported that the results of the Sisonke phase III trial in 477,234 South African healthcare workers. The company reported that the vaccine demonstrated 67 and 71% protection against infection with the Beta and Delta variants respectively, and 91-96.2% effectiveness against mortality. This data is not available for evaluation.

Janssen: evaluator's comments

COVID-19 Vaccine Janssen is TGA-registered.

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Appendix 1.10 Sputnik Light

Product	Sputnik Light
Product Developer	Gamaleya Research Institute
Country of origin	Russia
Vaccine Type	Recombinant adenoviruses (rAd5) in single dose
Schedule	One dose

Sputnik Light: countries deployed

Sputnik Light is approved for use in 24 countries and is not WHO listed for emergency use.

Angola	Argentina	Armenia	Bahrain
Belarus	Cambodia	Egypt	Iran
Kazakhstan	Kyrgyzstan	Lao peoples Republic	Mauritius
Mongolia	Nicaragua	Philippines	Republic of the Congo
Russian Federation	San Marino	Tunisia	Turkmenistan
UAE	Tanzania	Venezuela	West Bank

Sputnik Light: main clinical efficacy and effectiveness data using standard schedules

Study	Population	Strain	Schedule	Primary Endpoint	VE ASy	VE Sy	VE Hos	VE Death	Advantages	Disadvantages
(González et al. 2021)	415995 residents of Argentina aged 60-79 years of age between Dec 2020 and March 2021	Not noted	First dose	Infection Hospitalisation and Mortality		78.6%	87.6%	84.4%	• Large real world study • Includes hospitalisation data • Examines risk groups	• No detailed safety endpoint reporting. • Strain not determined.

Sputnik Light: main safety data

Safety data is mainly available on Sputnik V vaccine, and no evaluable safety data has been provided in this study.

Sputnik Light: additional information

In May 2021 the RDIF has announced that deployment of Sputnik Light in Paraguay suggests a vaccine efficacy of 79.4% against infection.[9]

(Dolzhikova et al. 2021)has published a single dose efficacy study that reported a vaccine efficacy of 69.96% (95%CI 64.0-74.7) based on registry data from Moscow. This has the advantage of being a study conducted during a Delta COVID outbreak in the city, but the methodology appears to impute an unvaccinated rate from serology data. The Evaluator feels that this study is not critical and, due to the unusual methodology, has not included it in the analysis until a peer reviewed version is available.

Sputnik Light: evaluator's comments

There is insufficient evidence on which to base a determination whether to Recognise Sputnik Light.

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