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 1 - 27 September 2021

Executive summary

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

This information is advice only and has no standing in law and does not represent assessment for regulatory approval within Australia. This advice also does not contemplate approaches to the verification of data provided on vaccination status of individuals vaccinated overseas. It will help inform decisions made elsewhere in Government to support incoming travel across Australia's international borders in the coming months. It will be updated regularly as new evidence on the effectiveness of the currently-reported vaccines emerges, and as assessments on other vaccines is completed. 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. State and Territory governments, or organisations such as universities, may apply additional considerations around vaccine requirements post-border.

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

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, potentially requiring acute healthcare services.

How the estimates were determined

The protection offered by a vaccine against a person requiring hospital care if they develop COVID 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 directly measure the protection a vaccine offers against a person becoming infected with COVID when exposed to the virus. This can be used as an imperfect surrogate for reducing the chance of transmitting COVID because a person must first be infected with COVID in order 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 end points used in clinical trials.

In this initial report TGA has assessed six vaccines that are currently not registered in Australia;

- Peoples Republic of China - Coronavac (Sinovac), BBIBP-CoV (Sinopharm), and Convidecia (Cansino).
- India – Covishield (AstraZeneca-Serum Institute of India), Covaxin (Bharat Biotech)
- Russian Federation - Sputnik V (Gamaleya Research Institute)

These vaccines have been widely deployed in donor and other programs worldwide (including in South East Asia and the Pacific), and in national vaccination programs in countries from which Australia normally receives many international arrivals.

Recommendations regarding recognition of 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)

TGA (and ATAGI) consider people to be fully vaccinated with Comirnaty, Vaxzevria and Spikevax 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 has elapsed since completing their vaccination schedule.

The use of TGA-approved 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).

TGA's recommendations on 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 2 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.

TGA thus considers that the Coronavac (Sinovac) vaccine is a **"**recognised vaccine**"**

BBIBP-CorV (Sinopharm China) 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.
- No studies are available to determine VE against severe infection/hospitalisation

Based on published and pre-print data this suggests that the efficacy of BBIBP-CoV against symptomatic infection is slightly lower than Australian-approved vaccines, and there is currently no assessment of protection it offers against severe-infection/hospitalisation.

TGA thus considers that BBIBP-CorV (Sinopharm) not be a **"**recognised vaccine**"** at this stage, because of the absence of information on severe infection/hospitalisation.

CovishieId (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. 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 recognised in regulation 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%.

TGA thus considers that the CovishieId **(AstraZeneca/Serum Institute of India) vaccine is a "recognised"** vaccine.

Covaxin (Bharat Biotech, India) 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 93% in one study.

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

Because this is an un-refereed pre-print, and we have not yet been provided with a regulatory dossier, TGA has not reached a conclusion on whether Covaxin be a **"**recognised vaccine**".**

Sputnik V (Gamaleya Institute, Russian Federation) showed an average VE against symptomatic infection of 92% and VE against hospitalisation of 100%

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

Because this is only a single study, and we have not yet been provided with a regulatory dossier, TGA has not reached a conclusion on whether Sputnik V be a **"**recognised vaccine**".**

For the unregistered vaccines that are granted recognition, effective vaccination would be considered to extend from 14 days after the last dose of the schedule (which is currently two doses (except for Janssen)), but may be a booster doses six to twelve months 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.

For Convidecia (Cansino), there are currently no published or pre-print studies on which to base an assessment of the efficacy of Convidecia and the TGA has not yet been provided with a regulatory dossier.

Because there is insufficient data to evaluate the efficacy of the vaccine, TGA has not yet reached a conclusion on whether Convidecia (Cansino) should be a **"**recognised vaccine**".**

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
AstraZeneca (Vaxzevria)	Symptomatic Infection	65%
AstraZeneca (Vaxzevria)	Severe infection/hospitalisation	85%
Pfizer (Comirnaty)	Symptomatic Infection	81%
Pfizer (Comirnaty)	Severe Infection/hospitalisation	88%
Moderna (Spikevax)	Symptomatic Infection	86%
Moderna (Spikevax)	Severe infection/hospitalisation	81%
Janssen (COVID-19 Vaccine Janssen)	Symptomatic Infection	66%
Janssen (COVID-19 Vaccine Janssen)	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 Vaxzevria's published results. The average VE against symptomatic infection is 65% and severe infection and/or hospitalisation is 85%.

Introduction

Vaccine Efficacy and Effectiveness

The efficacy (clinical trials) or effectiveness (real world) of a vaccine is usually measured as the relative odds of a particular endpoint occurring in vaccinated people compared to unvaccinated people. If the Vaccine Efficacy (VE) of a product is 80% in reducing COVID infections, for example, it means that vaccinated people had 80% less chance (or one-fifth) the probability of acquiring an infection than nonvaccinated people. It does not mean that a vaccinated person has a 20% chance of getting COVID; it could be lower if there is little COVID in their environment, or higher in an environment more risky than the one in which the trial was performed (e.g. a healthcare worker compared to the general public).

Vaccination reduces the chance that an incoming traveller will transmit COVID in Australia mainly by lowering their odds of them contracting COVID, and therefore the opportunity to pass it on. This is measured by the VE of a vaccine against infection. Most trials measure the VE for prevention of symptomatic COVID infection as the primary endpoint, with protection against asymptomatic infection being a secondary analysis based on cases in which people did not report many symptoms. True asymptomatic infection rates require logistically more complex trials that routinely screen asymptomatic participants for COVID infection.

The protective effect of a vaccine against infection does not measure the chance that someone *who does get COVID* will transmit the infection to other people. There is far less data on this risk because it requires detailed contact traced studies that differ from standard vaccine trials. However, available evidence suggests that COVID vaccination substantially reduces the risk of a person *with COVID* passing on the infection in household settings, but the extent of this protection is difficult to generalise to other settings. This information is discussed in more detail in Appendix 2.3.

Vaccination reduces the chance of an incoming traveller requiring acute medical care both by lowering their odds of contracting COVID, and by reducing the chance of them developing severe disease of they do become infected. This effect is quantified by a combination of the VE against infection and VE against severe infection and/or hospitalisation of a product. However, no standard criteria for assessing the severity of COVID symptoms has been applied across the studies of COVID vaccines. In some studies, we have determined that VE in protecting against severe COVID can be taken as Vaccine Efficacy against hospitalisation because the criteria used in the trial meant that severe cases would be hospitalised. In many studies, however, Vaccine Efficacy in protecting against hospitalisation has been directly measured (see Appendix 2.4).

In assessing whether a vaccine that has not been registered in Australia can be recommended for recognition, TGA has considered two main elements of the available data:

1. The first element is the quality and amount of information available for a particular COVID vaccine. There has been widespread deployment of COVID vaccines in many parts of the world under various emergency-use, donor or trial arrangements and the publishing information on the effectiveness of these vaccines has lagged these programs. Real-world studies are important for vaccines because the VE is sometimes lower than in clinical trials, reflecting more diverse populations and the difficulties of ideal vaccine delivery. The much larger numbers in these trials also allow the effectiveness of a vaccine in preventing rarer events such as hospitalisation or death to be assessed. Effectiveness may also be assessed over a longer period than the duration of a clinical trial for registration.
2. The second element is whether the degree of effectiveness shown for a vaccine not registered in Australia is approximately the same as minimum level of effectiveness for the four vaccines approved for use in Australia. There is no internationally recognised threshold for acceptable vaccine

efficacy against COVID. While the WHO considers a threshold of >50% effectiveness when including vaccines on their Emergency Use Listing, the range of studies on four vaccines registered in Australia indicates that a vaccine effectiveness against symptomatic infection of approximately 65% has been found in those deployed in Australia. This has been inferred as the acceptable efficacy for the other vaccines studied herein.

Because part of the purpose of recognising vaccines is to reduce the chance that an incoming traveller will require hospital care, only vaccines which have proven an acceptable degree of vaccine efficacy for reducing severe infection and/or hospitalisation are considered suitable to be recognised. There is no internationally recognised threshold for acceptable vaccine efficacy against hospitalisation and this has also been compared to vaccines available in Australia. A comparison with Spikevax (single trial) and Vaxzevria (many trials with variable results) indicates that a vaccine effectiveness against severe infection and/or hospitalisation of approximately 85% is considered acceptable for deployment in Australia. This has been inferred as the acceptable efficacy for the other vaccines studied herein.

There is little published evidence for the duration of protection offered by several of the vaccines reported upon, but evidence of waning immunity is emerging for some of the TGA registered vaccines (see Appendix 2.2). In summary, antibodies induced by vaccination by several vaccines reduce over six to eight months to a level where protection against COVID infection may be compromised, although the duration of the cellular immune response has been less well studied. Protection against severe clinical outcomes appears to last longer.

The TGA has not yet received a registration application for the administration of booster doses of any COVID-19 vaccines, although such applications are anticipated in the coming weeks. On 22 September 2021, the US FDA amended the emergency use authorization (EUA) for the Pfizer-BioNTech COVID-19 Vaccine to allow for use of a single booster dose, to be administered at least six months after completion of the primary series in:

- individuals 65 years of age and older;
- individuals 18 through 64 years of age at high risk of severe COVID-19; and
- individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

The Australian Technical Advisory Group (ATAGI) is closely monitoring local and international data about the frequency and severity of COVID-19 in fully vaccinated individuals. ATAGI is also reviewing the international data on the efficacy, effectiveness and safety of additional doses for specific high-risk patient populations, including immunocompromised individuals, and the population more generally. ATAGI anticipates that additional booster doses for other populations may be required in the future. ATAGI is expecting to provide preliminary advice on the need and timing of additional doses in the broader population by the end of October.

For the purposes of inbound travel, it is likely that recency of vaccination will become a factor in the recognition of vaccine status in the future, but this will be the subject of subsequent report.

There is no published direct evidence on the clinical efficacy against infection or hospitalisation for mixed dosing schedules using combinations of COVID-19 vaccines. There is, however, a rapidly developing body of studies examining antibody and neutralising antibody markers of immunity in a variety of combinations for Comirnaty, Spikevax and Vaxzevria. In general, mixed vaccine schedules with these vaccines produce equivalent or better levels antibody responses than same-vaccine schedules, but the duration and clinical significance of these responses has not been determined (Appendix 2.1).

The difficulty correlating immunological studies, which examine neutralising or anti-spike antibody levels, and clinical studies, which examine clinical outcomes arises from the lack of a generally recognised correlate of immunity for COVID vaccines (e.g. a biomarker which predicts protection in vaccine recipients). Neutralising

antibody levels are probably related to protection against COVID infection, but they may not predict immune memory or effectiveness against emerging strains of the virus. At this stage, it is necessary to primarily rely on clinical data when assessing vaccine effectiveness.

Assessment of individual vaccines

Comparative efficacy and effectiveness of products assessed

A graphical summary of the evidence in support of different vaccines is provided in the figures below - bars represent the 95% confidence intervals of the point estimates shown. All estimates are against strains of COVID that were prevalent at the time and place the trials were conducted and include Alpha, Gamma and Delta results. There is, however, insufficient clinical evidence on efficacy against delta strain as many studies were conducted before delta became predominant.

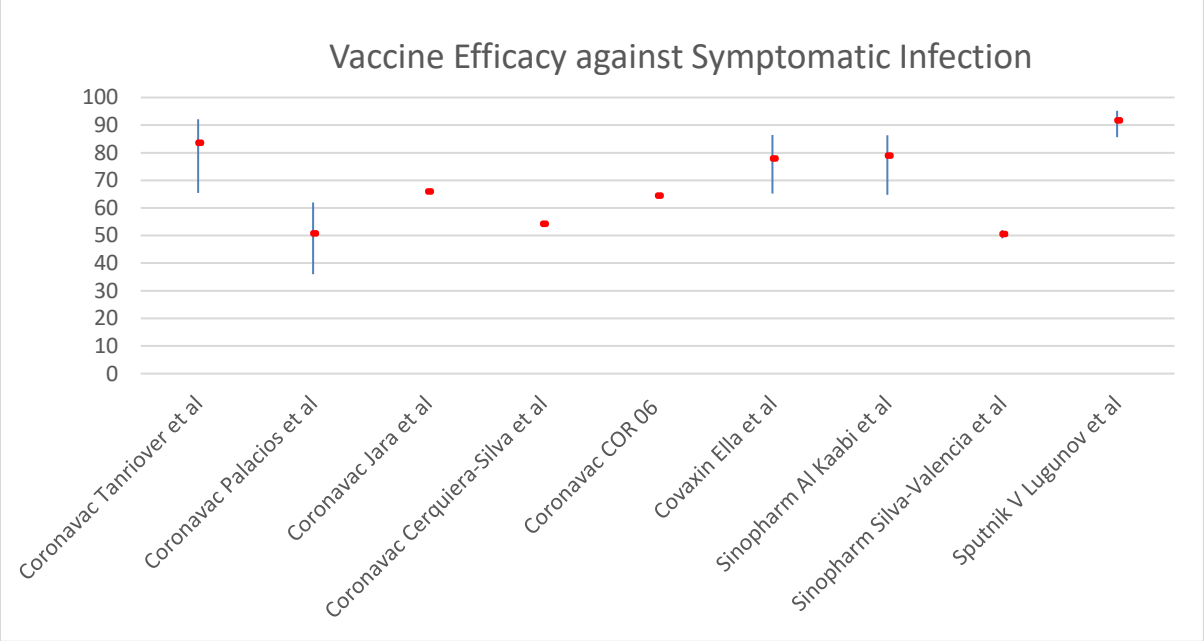

Figure 1. Estimated vaccine efficacy in preventing symptomatic COVID infection

Figure 1 indicates Coronavac has estimates from 50-83.7% and Sinopharm from 50-72% protection. This range overlaps the TGA-registered vaccines.

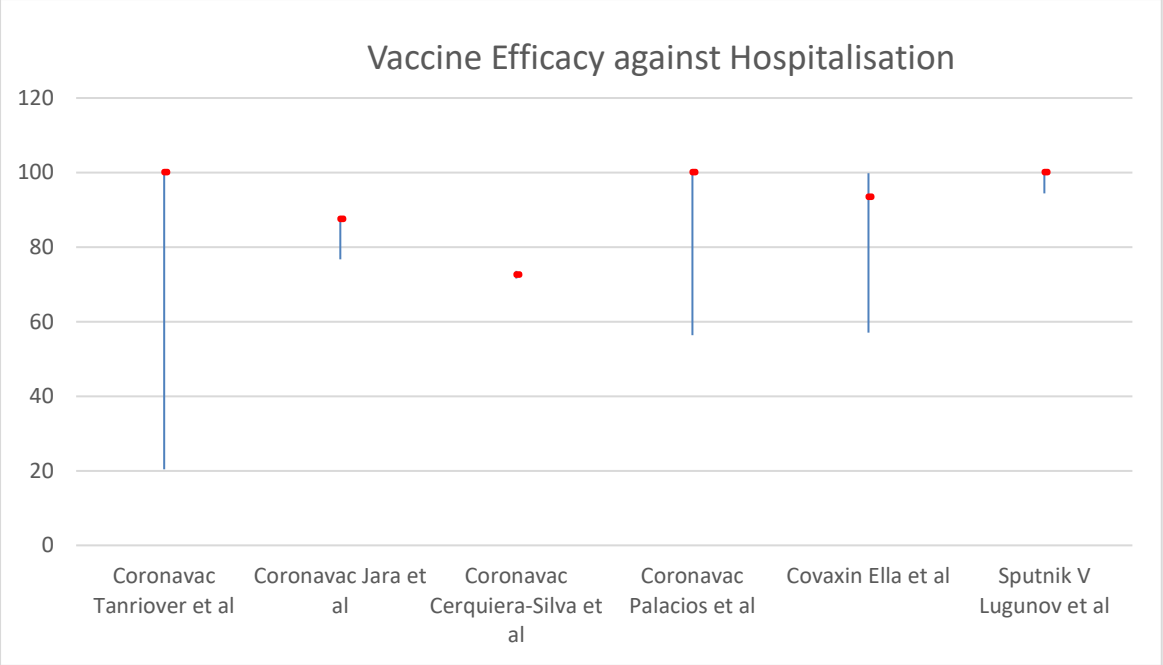

Figure 2. Estimated efficacy of vaccines in preventing hospitalisation of vaccinated people who acquire COVID.

Figure 2 indicates that where estimates are based on smaller phase III clinical trial data, as for Covaxin and Spikevax, the 95% confidence intervals are broader and this reflects the comparative uncommonness of hospitalisation compared to COVID infection overall. Evidence from real-world deployments of Coronavac provide more reliable estimates of high-level protection. Sputnik V has reported a vaccine efficacy of 100% based on a single-phase III trial, consistent with reported results (data not available for evaluation) from a large-scale deployment in the UAE.

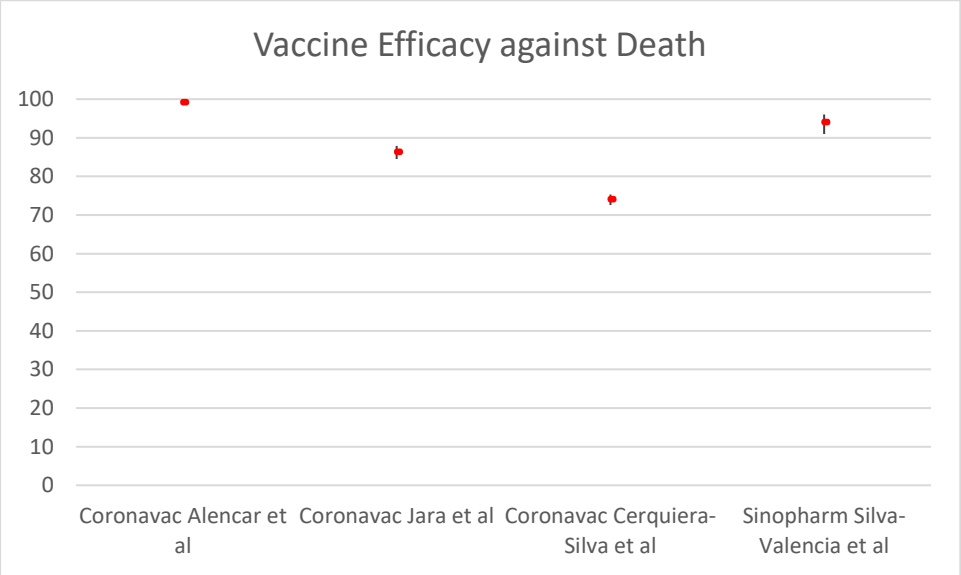

Figure 3. Estimates of vaccine efficacy in preventing death in vaccinated people who acquire COVID

Figure 3. The results from use of several vaccines indicates a high level of protection against death. This endpoint is only reliably estimated from large studies where the 95% confidence intervals are sufficiently narrow to represent 'point' estimates. Coronavac has an estimated protective effectiveness of between74-100% in three studies, and Sinopharm also provides 94% protection against death in one study.

Summary of review of some individual vaccines that are not registered in Australia

In general, the quality of information for a vaccine has been graded as:

- Registered: The vaccine is TGA approved for marketing in Australia.
- Verified: There is a phase III clinical trial and/ or a detailed real-world effectiveness study published in a peer-reviewed journal and evidence from 'real world' populations in which the vaccine has been deployed. Where the phase III data has not been published, but a real-world deployment study has been then the product would be considered to have Verified evidence.
- Baseline: There is a phase III clinical trial on which to base an assessment of vaccine efficacy and it has been published in a peer-reviewed journal.
- Limited: There is a phase III clinical trial on which to base an assessment of vaccine efficacy, but this has not been published in a peer-reviewed journal. The study is available in pre-print.
- Insufficient: There is no phase III clinical trial available on which to base an evaluation of vaccine efficacy.

In the unusual situation that the phase III data has not been published, but a real-world deployment study has been then the product would be considered to have Verified evidence.

Real-world studies are important for vaccines because the VE tends to be somewhat lower than in clinical trials, reflecting more diverse populations and the difficulties of ideal vaccine delivery. The much larger numbers in these trials also allow the effectiveness of a vaccine in preventing rarer events such as hospitalisation or death to be assessed.

Coronavac

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

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

Based on published and pre-print data this suggests the efficacy of Coronavac against symptomatic infection is marginally lower, although its efficacy against severe infection is comparable, to Vaxzevria.

A summary of the assessment of the studies is as follows:

Trial	Advantages	Disadvantages
(Tanriover, Doganay et al. 2021)	• Randomised • Published • Examines health care workers (HCW) at relatively high risk	• Young population <60 years of age • Gamma strain
(Palacios, Patino et al. 2020) PREPRINT	• 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)
(Alencar, Cavalcanti et al. 2021)	• Large real-world study • Examines people >75 years of age	• Observational, non-randomised • Only assessed Death as an endpoint • Gamma strain
(Jara, Undurraga et al. 2021)	• 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, Oliveira et al. 2021) PREPRINT	• 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.

Additional information is provided in Appendix 1.1.

Covaxin

Covaxin (from India) showed an average VE against symptomatic infection of 77.8% and an average VE against hospitalisation of 94.1%.

- VE against symptomatic infection (surrogate for transmission) of 77.8% in one study.
- VE against hospitalisation of 93.4% in one study.

Based on pre-print data this suggests that the efficacy of Covaxin is comparable to Vaxzevria. TGA thus proposes that Covaxin be a 'recognised vaccine'

A summary of the assessment of the studies is as follows:

Trial	Advantages	Disadvantages
(Ella, Reddy et al. 2021) PREPRINT	• 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

Additional information is available in Appendix 1.2

BBIBP-CorV (CorV)

CorV (from China) showed an average VE against symptomatic infection of 62%. VE against hospitalisation has not been estimated.

- VE against symptomatic infection (surrogate for transmission) of 50% and 73% from two studies.

Based on published and pre-print data this suggests that the efficacy of CorV is lower than any of the registered vaccines in Australia. In addition there are no studies available for protection against hospitalisation. TGA thus proposes that at this stage CorV not be a 'recognised vaccine'

A summary of the assessment of the studies is as follows:

Trial	Advantages	Disadvantages
(Al Kaabi, Zhang et al. 2021	• Randomised	• Strain prevalent in the trial not noted • Mainly enrolled healthy young men, mean age of 36.2%.
Silva-Valencia, Javier et al 2021 PREPRINT	• 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)

Additional information is available in Appendix 1.3

Sputnik V

Sputnik V (from Russia) showed an average VE in one published study against symptomatic infection of 92% and VE against hospitalisation of 100%

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

Because this is a single study with some limitations and more detailed data is not available, TGA has deferred a decision on whether Sputnik V be a 'recognised vaccine' at this stage.

A summary of the assessment of the studies is as follows:

Trial	Advantages	Disadvantages
Logunov, Dolzhikova et al. 2021	• Randomised • Peer reviewed	• Data integrity has been challenged • 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 followup (48 days) in interim analysis of 180-day trial

Additional information is provided in Appendix 1.4

Convidecia

Convidecia (from China) has no published or pre-print accessible estimates of VE against symptomatic infection or hospitalisation. The TGA therefore proposes that Convidecia not be a 'recognised vaccine' at this stage.

Additional information is provided in Appendix 1.9

Conclusions regarding recognition of vaccines that have not been registered in Australia

The criteria for Recognition of a vaccine that has been applied are that:

1. It has at least phase III evidence of efficacy.
2. There is an estimate of both VE against symptomatic infection and VE against hospitalisation
3. Average VE against symptomatic infection is >65% and the VE against hospitalisation is >85%.

Product	VE against asymptomatic infection	VE against symptomatic infection	VE against hospitalisation	Current TGA recognition
Coronavac	N/A	64%	90%	Yes
BBIBP-CorV	64%	62%	N/A	No
COVISHIELD	58%	65%	85%	Yes
Covaxin (Bharat)	64%	78%	94%	No
Sputnik V	N/A	92%	100%	No
Convidecia	N/A	N/A	N/A	No

Table4. Average efficacy across studies examined for vaccines that have not been registered in Australia

For the vaccines that are not registered in Australia that are granted recognition, effective vaccination would be considered to extend from 14 days after the last dose of the schedule (currently two doses) to possibly six to twelve months after the last dose of the schedule. This is based on generalising the data from duration of immunity studies.

Appendix 1.1

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

Summary of main clinical trial efficacy data

Study	Population	Strain	Schedule	Primary Endpoint	VE Asymptomatic	VE Symptoms	VE Hospital	VE Death
(Tanriover, Doganay 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%	
(Palacios, Patino 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%	
CORONA06 (Dossier)	COVID exposed HCW aged 18-59 in Indonesia	Not noted	2 doses Day 0 Day 14	PCR confirmed COVID at least 14 days after second dose.		64.3%		

Summary of main effectiveness data

Study	Population	Strain	Schedule	Primary Endpoint	VE Asymptomatic	VE Symptoms	VE Hospital	VE Death
(Alencar, Cavalcanti et al. 2021)	313228 recipients of COVID vaccines >75 years of age in Brazilian vaccination program	Gamma	2 dose. Interval not specified.	Death				99.1%
(Jara, Undurraga et al. 2021)	10187720 recipients of COVID vaccines >16 years of age in Chilean vaccination program.	Alpha and Gamma	2 dose. 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%
(Cerqueira-Silva, Oliveira 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%

Data on non-standard schedules

(Li, Yang 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, Wu 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.

Evaluators Assessment

(Tanriover, Doganay 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, Murthy 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, Patino 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, Murthy 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.

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

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, Doganay et al. 2021) and (Palacios, Patino et al. 2020), from (Marshall, Murthy et al. 2020)

(Alencar, Cavalcanti et al. 2021) is an observational study in 313328 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 159970 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 1. 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, Oliveira 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, Cavalcanti 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, Undurraga 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, 5471728 were unvaccinated, 542418 had received one dose of vaccine and 4173574 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 2. Single and two dose vaccine efficacy for Coronavac from (Jara, Undurraga 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.

Conclusion

There is Baseline phase III evidence and Verified evidence from a very large deployments of Sinovac in Chile and Brazil. Because the Chilean program was far larger, and appeared methodologically sound for the collection of a range of endpoints, this study (Jara et al) has been taken as the definitive estimate of Vaccine Effectiveness. Overall there is a VE can be considered Verified.

There is contemporary interest in deploying a third booster dose of Sinovac.

References

Alencar, C. H., et al. (2021). "High Effectiveness of SARS-CoV-2 Vaccines in Reducing COVID-19-Related Deaths in over 75-Year-Olds, Ceara State, Brazil." Trop Med Infect Dis 6(3).

> In Brazil, the SARS-CoV-2 vaccination program has so far prioritized people over 75 years of age. By the end of March 2021, in Ceara State, a total of 313,328 elderly people had received at least one dose of vaccine (45% Oxford-AstraZeneca/Fiocruz and 55% CoronaVac-Sinovac/Butantan), and 159,970 had received two doses (83% CoronaVac-Sinovac/Butantan and 17% Oxford-AstraZeneca/Fiocruz). After a single dose, there was already a significant reduction in COVID 19-related deaths (protection ratio: 19.31 (95% CI: 18.20-20.48), attributable protection ratio: 94.8%); higher protection ratios were observed after the application of two doses of the vaccine (132.67; 95% CI: 109.88-160.18), with an attributable protection ratio of 99.2%. SARS-CoV-2 vaccines are highly effective in reducing the number of COVID-19-related deaths in over 75-year-olds in Brazil, one of the hardest hit countries by the current pandemic.

Bucci, E. M., et al. (2021). "Data discrepancies and substandard reporting of interim data of Sputnik V phase 3 trial." The Lancet 397(10288): 1881-1883.

Cabezas, C., et al. (2021). "Associations of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study." BMJ 374: n1868.

> OBJECTIVE: To determine associations of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 among nursing home residents, nursing home staff, and healthcare workers. DESIGN: Prospective cohort study. SETTING: Nursing homes and linked electronic medical record, test, and mortality data in Catalonia on 27 December 2020. PARTICIPANTS: 28 456 nursing home residents, 26 170 nursing home staff, and 61 791 healthcare workers. MAIN OUTCOME MEASURES: Participants were followed until the earliest outcome (confirmed SARS-CoV-2 infection, hospital admission or death with covid-19) or 26 May 2021. Vaccination status was introduced as a time varying exposure, with a 14 day run-in after the first dose. Mixed effects Cox models were fitted to estimate hazard ratios with index month as a fixed effect and adjusted for confounders including sociodemographics, comorbidity, and previous medicine use. RESULTS: Among the nursing home residents, SARS-CoV-2 infection was found in 2482, 411 were admitted to hospital with covid-19, and 450 died with covid-19 during the study period. In parallel, 1828 nursing home staff and 2968 healthcare workers were found to have SARS-CoV-2 infection, but fewer than five were admitted or died with covid-19. The adjusted hazard ratio for SARS-CoV-2 infection after two doses of vaccine was 0.09 (95%

confidence interval 0.08 to 0.11) for nursing home residents, 0.20 (0.17 to 0.24) for nursing home staff, and 0.13 (0.11 to 0.16) for healthcare workers. Adjusted hazard ratios for hospital admission and mortality after two doses of vaccine were 0.05 (0.04 to 0.07) and 0.03 (0.02 to 0.04), respectively, for nursing home residents. Nursing home staff and healthcare workers recorded insufficient events for mortality analysis. CONCLUSIONS: Vaccination was associated with 80-91% reduction in SARS-CoV-2 infection in all three cohorts and greater reductions in hospital admissions and mortality among nursing home residents for up to five months. More data are needed on longer term effects of covid-19 vaccines.

Cerqueira-Silva, T., et al. (2021). "The effectiveness of Vaxzevria and CoronaVac vaccines: A nationwide longitudinal retrospective study of 61 million Brazilians (VigiVac-COVID19)." PRE.

Ella, R., et al. (2021).

Gushchin, V. A., et al. (2021). "Neutralizing Activity of Sera from Sputnik V-Vaccinated People against Variants of Concern (VOC: B.1.1.7, B.1.351, P.1, B.1.617.2, B.1.617.3) and Moscow Endemic SARS-CoV-2 Variants." Vaccines (Basel) 9(7).

Since the beginning of the 2021 year, all the main six vaccines against COVID-19 have been used in mass vaccination companies around the world. Virus neutralization and epidemiological efficacy drop obtained for several vaccines against the B.1.1.7, B.1.351 P.1, and B.1.617 genotypes are of concern. There is a growing number of reports on mutations in receptor-binding domain (RBD) increasing the transmissibility of the virus and escaping the neutralizing effect of antibodies. The Sputnik V vaccine is currently approved for use in more than 66 countries but its activity against variants of concern (VOC) is not extensively studied yet. Virus-neutralizing activity (VNA) of sera obtained from people vaccinated with Sputnik V in relation to internationally relevant genetic lineages B.1.1.7, B.1.351, P.1, B.1.617.2, B.1.617.3 and Moscow endemic variants B.1.1.141 (T385I) and B.1.1.317 (S477N, A522S) with mutations in the RBD domain has been assessed. The data obtained indicate no significant differences in VNA against B.1.1.7, B.1.617.3 and local genetic lineages B.1.1.141 (T385I), B.1.1.317 (S477N, A522S) with RBD mutations. For the B.1.351, P.1, and B.1.617.2 statistically significant 3.1-, 2.8-, and 2.5-fold, respectively, VNA reduction was observed. Notably, this decrease is lower than that reported in publications for other vaccines. However, a direct comparative study is necessary for a conclusion. Thus, sera from "Sputnik V"-vaccinated retain neutralizing activity against VOC B.1.1.7, B.1.351, P.1, B.1.617.2, B.1.617.3 as well as local genetic lineages B.1.1.141 and B.1.1.317 circulating in Moscow.

Ikegame, S., et al. (2021). "Neutralizing activity of Sputnik V vaccine sera against SARS-CoV-2 variants." Nat Commun 12(1): 4598.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected at least 180 million people since its identification as the cause of the current COVID-19 pandemic. The rapid pace of vaccine development has resulted in multiple vaccines already in use worldwide. The contemporaneous emergence of SARS-CoV-2 'variants of concern' (VOC) across diverse geographic locales underscores the need to monitor the efficacy of vaccines being administered globally. All WHO designated VOC carry spike (S) polymorphisms thought to enable escape from neutralizing antibodies. Here, we characterize the neutralizing activity of post-Sputnik V vaccination sera against the ensemble of S mutations present in alpha (B.1.1.7) and beta (B.1.351) VOC. Using de novo generated replication-competent vesicular stomatitis virus expressing various SARS-CoV-2-S in place of VSV-G (rcVSV-CoV2-S), coupled with a clonal 293T-ACE2 + TMPRSS2 + cell line optimized for highly efficient S-mediated infection, we determine that only 1 out of 12 post-vaccination serum samples shows effective neutralization (IC90) of rcVSV-CoV2-S: B.1.351 at full serum strength. The same set of sera efficiently neutralize S from B.1.1.7 and exhibit only moderately reduced activity against S carrying the E484K

substitution alone. Taken together, our data suggest that control of some emergent SARS-CoV-2 variants may benefit from updated vaccines.

Jara, A., et al. (2021). "Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile." N Engl J Med 385(10): 875-884.

BACKGROUND: Mass vaccination campaigns to prevent coronavirus disease 2019 (Covid-19) are occurring in many countries; estimates of vaccine effectiveness are urgently needed to support decision making. A countrywide mass vaccination campaign with the use of an inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine (CoronaVac) was conducted in Chile starting on February 2, 2021. METHODS: We used a prospective national cohort, including participants 16 years of age or older who were affiliated with the public national health care system, to assess the effectiveness of the inactivated SARS-CoV-2 vaccine with regard to preventing Covid-19 and related hospitalization, admission to the intensive care unit (ICU), and death. We estimated hazard ratios using the extension of the Cox proportional-hazards model, accounting for time-varying vaccination status. We estimated the change in the hazard ratio associated with partial immunization (>/=14 days after receipt of the first dose and before receipt of the second dose) and full immunization (>/=14 days after receipt of the second dose). Vaccine effectiveness was estimated with adjustment for individual demographic and clinical characteristics. RESULTS: The study was conducted from February 2 through May 1, 2021, and the cohort included approximately 10.2 million persons. Among persons who were fully immunized, the adjusted vaccine effectiveness was 65.9% (95% confidence interval [CI], 65.2 to 66.6) for the prevention of Covid-19 and 87.5% (95% CI, 86.7 to 88.2) for the prevention of hospitalization, 90.3% (95% CI, 89.1 to 91.4) for the prevention of ICU admission, and 86.3% (95% CI, 84.5 to 87.9) for the prevention of Covid-19-related death. CONCLUSIONS: Our results suggest that the inactivated SARS-CoV-2 vaccine effectively prevented Covid-19, including severe disease and death, a finding that is consistent with results of phase 2 trials of the vaccine. (Funded by Agencia Nacional de Investigacion y Desarrollo and others.).

Li, M., et al. (2021). "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 " PRE.

Logunov, D. Y., et al. (2021). "Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia." Lancet 397(10275): 671-681.

BACKGROUND: A heterologous recombinant adenovirus (rAd)-based vaccine, Gam-COVID-Vac (Sputnik V), showed a good safety profile and induced strong humoral and cellular immune responses in participants in phase 1/2 clinical trials. Here, we report preliminary results on the efficacy and safety of Gam-COVID-Vac from the interim analysis of this phase 3 trial. METHODS: We did a randomised, double-blind, placebo-controlled, phase 3 trial at 25 hospitals and polyclinics in Moscow, Russia. We included participants aged at least 18 years, with negative SARS-CoV-2 PCR and IgG and IgM tests, no infectious diseases in the 14 days before enrolment, and no other vaccinations in the 30 days before enrolment. Participants were randomly assigned (3:1) to receive vaccine or placebo, with stratification by age group. Investigators, participants, and all study staff were masked to group assignment. The vaccine was administered (0.5 mL/dose) intramuscularly in a prime-boost regimen: a 21-day interval between the first dose (rAd26) and the second dose (rAd5), both vectors carrying the gene for the full-length SARS-CoV-2 glycoprotein S. The primary outcome was the proportion of participants with PCR-confirmed COVID-19 from day 21 after receiving the first dose. All analyses excluded participants with protocol violations: the primary outcome was assessed in participants who had received two doses of vaccine or placebo, serious adverse events were assessed in all participants who had received at least one dose at the time of database lock, and rare adverse events were assessed in all participants who had received two doses and for whom all available data were verified in the case report form at the time

of database lock. The trial is registered at ClinicalTrials.gov (NCT04530396). FINDINGS: Between Sept 7 and Nov 24, 2020, 21 977 adults were randomly assigned to the vaccine group (n=16 501) or the placebo group (n=5476). 19 866 received two doses of vaccine or placebo and were included in the primary outcome analysis. From 21 days after the first dose of vaccine (the day of dose 2), 16 (0.1%) of 14 964 participants in the vaccine group and 62 (1.3%) of 4902 in the placebo group were confirmed to have COVID-19; vaccine efficacy was 91.6% (95% CI 85.6-95.2). Most reported adverse events were grade 1 (7485 [94.0%] of 7966 total events). 45 (0.3%) of 16 427 participants in the vaccine group and 23 (0.4%) of 5435 participants in the placebo group had serious adverse events; none were considered associated with vaccination, with confirmation from the independent data monitoring committee. Four deaths were reported during the study (three [<0.1%] of 16 427 participants in the vaccine group and one [<0.1%] of 5435 participants in the placebo group), none of which were considered related to the vaccine. INTERPRETATION: This interim analysis of the phase 3 trial of Gam-COVID-Vac showed 91.6% efficacy against COVID-19 and was well tolerated in a large cohort. FUNDING: Moscow City Health Department, Russian Direct Investment Fund, and Sberbank.

Marshall, J. C., et al. (2020). "A minimal common outcome measure set for COVID-19 clinical research." The Lancet Infectious Diseases 20(8): e192-e197.

Pagotto, V., et al. (2021). Nature.

Palacios, R., et al. (2020). "Double-Blind, Randomized, Placebo-Controlled Phase III Clinical Trial to Evaluate the Efficacy and Safety of treating Healthcare Professionals with the Adsorbed COVID-19 (Inactivated) Vaccine Manufactured by Sinovac - PROFISCOV: A structured summary of a study protocol for a randomised controlled trial." Trials 21(1): 853.

Pan, H., et al. (2021). PRE.

Tanriover, M. D., et al. (2021). "Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey." Lancet 398(10296): 213-222.

Voysey, M., et al. (2021). "Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK." The Lancet 397(10269): 99-111.

Appendix 1.2

Produce Name	Covaxin
Product Developer	Bharat Biotech
Country of Origin	India
Vaccine Type	Inactivated virus with alum adjuvant Strain NIV-2020-770
Schedule	2 doses, 0 and 28 days.

Summary of main vaccine effectiveness data

Study	Population	Strain	Schedule	Primary Endpoint	VE Asymptomatic	VE Symptoms	VE Hospital	VE Death
(Ella, Reddy 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]	

Data on non-standard schedules

Bharat is reported to have commenced a study into a third dose for Covaxin, to be administered 6-12 months after the second dose. Data regarding the efficacy of this schedule is not available.

Evaluators commentary

(Ella, Reddy 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 Nov 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.

[2] Based on severe-symptomatic rate

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 2. 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 Evaluator notes that there has been significant concern expressed in the scientific/medical community regarding the decision to approve emergency use of Covaxin before the completion of the phase III trial see (Thiagarajan 2021). The Evaluator notes the vaccine technology is similar to Sinovac except for the strain used.

Conclusion

There is Limited evidence for the effectiveness of Covaxin based on an unpublished interim analysis of a single phase III trial.

This cohort provides a poor estimate of efficacy in people over 60 years of age due to low numbers of subjects in this strata. The 95 % confidence interval for the estimate vaccine efficacy against symptomatic disease in people over 60 years of age is between 8% and 90%, which is to say virtually the entire spectrum of possible outcomes.

Because of the strong correlation between a patients age and their likelihood of developing severe illness, the Evaluator has concluded that the estimates of vaccine efficacy against severe disease should not be relied upon until final results of the phase III study are available. This limitation is equally true of the estimate of vaccine efficacy against any symptomatic disease, but patients under 60 have a sufficiently high probability of developing mild symptoms of COVID infection to allow an estimate of this endpoint (Poletti, Tirani et al. 2021).

The deployment of Covaxin prior to final results of the phase III trial being available has been criticised but it may mean that Verified data from studies of its use in mass vaccination will become available.

References

Ella, R., et al. (2021), PREPRINT

Poletti, P., et al. (2021). "Association of Age With Likelihood of Developing Symptoms and Critical Disease Among Close Contacts Exposed to Patients With Confirmed SARS-CoV-2 Infection in Italy." JAMA Netw Open 4(3): e211085.

Thiagarajan, K. (2021). "What do we know about India's Covaxin vaccine?" BMJ 373: n997.

Appendix 1.3

Produce Name	BBIBP-CorV
Product Developer	Sinopharm
Country of Origin	China
Vaccine Type	Inactivated virus/ alum adjuvanted Strain SARS-CoV-WIV04
Schedule	2 doses on day 0 and day 21

Summary of main clinical trial data

Study	Population	Strain	Schedule	Primary Endpoint	VE Asym	VE Symptoms	VE Hospital	VE Death
(Al Kaabi, Zhang 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%		

Summary of main vaccine effectiveness data

Study	Population	Strain	Schedule	Primary Endpoint	VE Symptoms	VE Hospital	VE Death
(Xia, Zhang et al. 2021)	192 healthy people aged 18-80 with negative COVID IgM or IgG on screening. Enrolled in two cohorts of 18-59 and 60+ years of age	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	Lamba and Gamma	Two doses Interval unknown	Symptomatic infection and Death	50.4%		94%

Data in non-standard schedules

None

Assessment

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.

(Xia, Zhang 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).

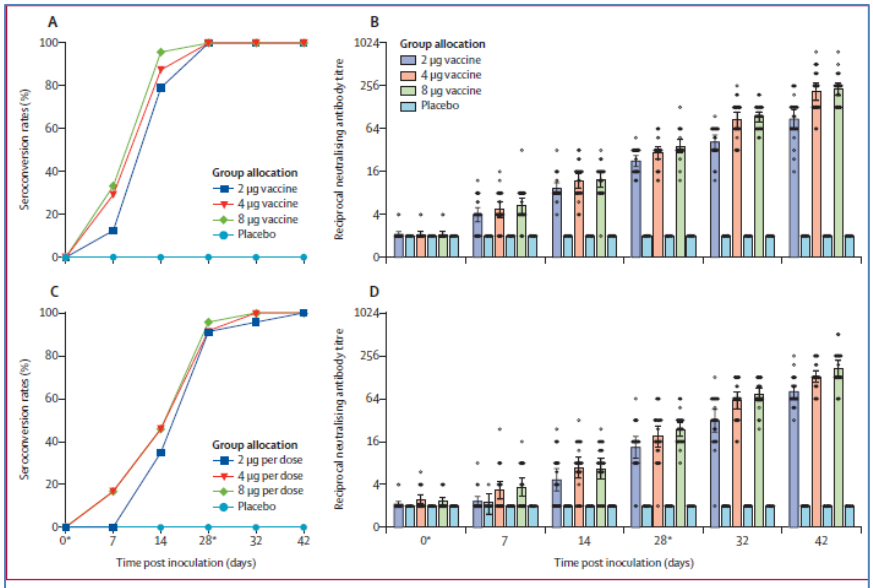

Figure 2: **Seroconversion ratios and neutralising antibody titres for and 60 years and older**
Seroconversion rates (A) and neutralising antibody titres (B) for participants aged 18–59 years; and seroconversion rates (C) and neutralising antibody titres (D) for participants aged 60 years and older. 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 1. 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 et al, 2021) was a large study examining vaccine efficacy and mortality among 400 000 Peruvian healthcare workers between Feb 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/.

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.

Table 1. Outcomes from Silva-Valencia, J et al. Note the IC 95% is not the CI for the Vaccine Efficacy

Conclusion

There is Baseline evidence for the efficacy of BBIBP-CoV based on the interim analysis of the phase III study. This is a relatively small cohort in which more severe endpoints of COVID disease have not been assessed. There is a single large study in the real world that provides some confirmatory efficacy evidence, albeit in an untranslated pre-print.

References

Al Kaabi, N., et al. (2021). "Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial." JAMA 326(1): 35-45.

Silva-Valencia, J. et al "Efectividad de la Vacuna BBIBP-Cor-V para infeccion nuerte por COVID-19 en trabajadores de salud del Peru 2021", PREPRINT

Xia, S., et al. (2021). "Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial." Lancet Infect Dis 21(1): 39-51.

Appendix 1.4

Produce Name	Sputnik V
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.

Summary of main clinical trial efficacy data

Study	Population	Strain	Schedule	Primary Endpoint	VE Symptoms	VE Hospital	VE Death
(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%	

Summary of main vaccine effectiveness data

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.

Evaluators commentary

(Logunov, Dolzhikova 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 O2.

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

[4] Pagotto, V., et al. (2021). Nature.

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 1. Appendix of Logunov describing COVID severity scale

The integrity of this study has been questioned (Bucci, Berkhof 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, Coma et al. 2021) has provided a commentary on the Sputnik efficacy data but notes some additional issues. They note a trial (Gushchin, Dolzhikova et al. 2021) showed a reduction in neutralisation of VOC in Sputnik vaccinated patients. However, a comparative trial (Ikegame, Siddiquey 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 2: Comparative neutralisation of COVID vaccines against Variants of Concern compared to Wild Type virus, Ikegame, Siddiquey et al. 2021

The Evaluator notes, however, that there are no available 'real world' studies available for evaluation that demonstrate the effectiveness of Sputnik V despite results from deployments been announced.

Conclusion

There is Baseline evidence for the vaccine efficacy of Sputnik V from an interim analysis of a phase III trial. This is not a large cohort and the Evaluator is of the view that estimates of severe COVID disease endpoints may be unreliable. It is notable that the patient population contained relatively few older people at high risk of complications of COVID infection.

The Evaluator notes that the estimate of Vaccine Efficacy against symptomatic infection is much higher than for comparable inactivated virus vaccines. This may reflect methodological issues with the acquisition of cases, which is one issue raised by critics of these results (Bucci, Berkhof et al. 2021). While this may not be relevant to an assessment of the acceptability of the vaccine for incoming travellers per se, the Evaluator feels that this estimate should be used with caution (e.g. in modelling or other uses of the data)

The Evaluator notes the academic concern raised about lack of transparency in the Sputnik V trial results and notes that the integrity of this data cannot be verified by TGA without Regulatory quality data. It is clear, however, that this vaccine is being deployed and so Vaccine Effectiveness data could be expected in the future.

References

Bucci, E. M., et al. (2021). "Data discrepancies and substandard reporting of interim data of Sputnik V phase 3 trial." The Lancet 397(10288): 1881-1883.

Cabezas, C., et al. (2021). "Associations of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study." BMJ 374: n1868.

Gushchin, V. A., et al. (2021). "Neutralizing Activity of Sera from Sputnik V-Vaccinated People against Variants of Concern (VOC: B.1.1.7, B.1.351, P.1, B.1.617.2, B.1.617.3) and Moscow Endemic SARS-CoV-2 Variants." Vaccines (Basel) 9(7).

Ikegame, S., et al. (2021). "Neutralizing activity of Sputnik V vaccine sera against SARS-CoV-2 variants." Nat Commun 12(1): 4598.

Logunov, D. Y., et al. (2021). "Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia." Lancet 397(10275): 671-681.

Pagotto, V., et al. (2021). Nature.

Appendix 1.5

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

Summary of main clinical trial efficacy data

Study	Population	Strain	Schedule	Primary Endpoint	VE Asym	VE Sym	VE Hospital	VE Death
(Polack, Thomas et al. 2020)	Multinational RCT trial of 43548 volunteers >16 years of age	Not noted	2 dose Day 0 Day 21	PCR confirmed symptomatic COVID >7 days after second dose		95%		

Summary of main effectiveness data

Study	Population	Strain	Schedule	Primary Endpoint	VE Asym	VE Sym	VE Hospital	VE Death
(Dagan, Barda 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)	
(Haas, Angulo 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%
(Lopez Bernal, Andrews 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)			
(Chung, He 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)
(Frenck, Klein 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%		

Data on non-standard schedules

The efficacy of a third booster shot was assessed in (Bar-On, Goldberg 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 Cominarty 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 1. Results from Bar-On, Golberg et al

Assessment of data

There is Verified data to support Cominarty vaccine effectiveness in a number of large studies. The use of a 3rd dose may provide additional effectiveness in people >60 years of age. The duration of protection has not been established.

References

Bar-On, Y. M., et al. (2021). "Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel." N Engl J Med.

BACKGROUND: On July 30, 2021, the administration of a third (booster) dose of the BNT162b2 messenger RNA vaccine (Pfizer-BioNTech) was approved in Israel for persons who were 60 years of age or older and who had received a second dose of vaccine at least 5 months earlier. Data are needed regarding the effect of the booster dose on the rate of confirmed coronavirus 2019 disease (Covid-19) and the rate of severe illness. METHODS: We extracted data for the period from July 30 through August 31, 2021, from the Israeli Ministry of Health database regarding 1,137,804 persons who were 60 years of age or older and had been fully vaccinated (i.e., had received two doses of BNT162b2) at least 5 months earlier. In the primary analysis, we compared the rate of confirmed Covid-19 and the rate of severe illness between those who had received a booster injection at least 12 days earlier (booster group) and those who had not received a booster injection (nonbooster group). In a secondary analysis, we evaluated the rate of infection 4 to 6 days after the booster dose as compared with the rate at least 12 days after the booster. In all the analyses, we used Poisson regression after adjusting for possible confounding factors. RESULTS: At least 12 days after the booster dose, the rate of confirmed infection was lower in the booster group than in the nonbooster group by a factor of 11.3 (95% confidence interval [CI], 10.4 to 12.3); the rate of severe illness was lower by a factor of 19.5 (95% CI, 12.9 to 29.5). In a secondary analysis, the rate of confirmed infection at least 12 days after vaccination was lower than the rate after 4 to 6 days by a factor of 5.4 (95% CI, 4.8 to 6.1). CONCLUSIONS: In this study involving

participants who were 60 years of age or older and had received two doses of the BNT162b2 vaccine at least 5 months earlier, we found that the rates of confirmed Covid-19 and severe illness were substantially lower among those who received a booster (third) dose of the BNT162b2 vaccine.

Chung, H., et al. (2021). "Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study." BMJ 374: n1943.

OBJECTIVE: To estimate the effectiveness of mRNA covid-19 vaccines against symptomatic infection and severe outcomes (hospital admission or death). DESIGN: Test negative design study. SETTING: Ontario, Canada between 14 December 2020 and 19 April 2021. PARTICIPANTS: 324 033 community dwelling people aged >/=16 years who had symptoms of covid-19 and were tested for SARS-CoV-2. INTERVENTIONS: BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccine. MAIN OUTCOME MEASURES: Laboratory confirmed SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) and hospital admissions and deaths associated with SARS-CoV-2 infection. Multivariable logistic regression was adjusted for personal and clinical characteristics associated with SARS-CoV-2 and vaccine receipt to estimate vaccine effectiveness against symptomatic infection and severe outcomes. RESULTS: Of 324 033 people with symptoms, 53 270 (16.4%) were positive for SARS-CoV-2 and 21 272 (6.6%) received at least one dose of vaccine. Among participants who tested positive, 2479 (4.7%) were admitted to hospital or died. Vaccine effectiveness against symptomatic infection observed >/=14 days after one dose was 60% (95% confidence interval 57% to 64%), increasing from 48% (41% to 54%) at 14-20 days after one dose to 71% (63% to 78%) at 35-41 days. Vaccine effectiveness observed >/=7 days after two doses was 91% (89% to 93%). Vaccine effectiveness against hospital admission or death observed >/=14 days after one dose was 70% (60% to 77%), increasing from 62% (44% to 75%) at 14-20 days to 91% (73% to 97%) at >/=35 days, whereas vaccine effectiveness observed >/=7 days after two doses was 98% (88% to 100%). For adults aged >/=70 years, vaccine effectiveness estimates were observed to be lower for intervals shortly after one dose but were comparable to those for younger people for all intervals after 28 days. After two doses, high vaccine effectiveness was observed against variants with the E484K mutation. CONCLUSIONS: Two doses of mRNA covid-19 vaccines were observed to be highly effective against symptomatic infection and severe outcomes. Vaccine effectiveness of one dose was observed to be lower, particularly for older adults shortly after the first dose.

Dagan, N., et al. (2021). "BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting." N Engl J Med 384(15): 1412-1423.

BACKGROUND: As mass vaccination campaigns against coronavirus disease 2019 (Covid-19) commence worldwide, vaccine effectiveness needs to be assessed for a range of outcomes across diverse populations in a noncontrolled setting. In this study, data from Israel's largest health care organization were used to evaluate the effectiveness of the BNT162b2 mRNA vaccine. METHODS: All persons who were newly vaccinated during the period from December 20, 2020, to February 1, 2021, were matched to unvaccinated controls in a 1:1 ratio according to demographic and clinical characteristics. Study outcomes included documented infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), symptomatic Covid-19, Covid-19-related hospitalization, severe illness, and death. We estimated vaccine effectiveness for each outcome as one minus the risk ratio, using the Kaplan-Meier estimator. RESULTS: Each study group included 596,618 persons. Estimated vaccine effectiveness for the study outcomes at days 14 through 20 after the first dose and at 7 or more days after the second dose was as follows: for documented infection, 46% (95% confidence interval [CI], 40 to 51) and 92% (95% CI, 88 to 95); for symptomatic Covid-19, 57% (95% CI, 50 to 63) and 94% (95% CI, 87 to 98); for hospitalization, 74% (95% CI, 56 to 86) and 87% (95% CI, 55 to 100); and for severe disease, 62% (95% CI, 39 to 80) and 92% (95% CI, 75 to 100), respectively. Estimated effectiveness in preventing death from Covid-19 was 72% (95% CI, 19 to 100) for days 14 through 20 after the first dose. Estimated effectiveness in specific subpopulations assessed for documented infection and symptomatic Covid-19 was consistent across age groups, with potentially slightly lower

effectiveness in persons with multiple coexisting conditions. CONCLUSIONS: This study in a nationwide mass vaccination setting suggests that the BNT162b2 mRNA vaccine is effective for a wide range of Covid-19-related outcomes, a finding consistent with that of the randomized trial.

Frenck, R. W., Jr., et al. (2021). "Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents." N Engl J Med 385(3): 239-250.

BACKGROUND: Until very recently, vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had not been authorized for emergency use in persons younger than 16 years of age. Safe, effective vaccines are needed to protect this population, facilitate in-person learning and socialization, and contribute to herd immunity. METHODS: In this ongoing multinational, placebo-controlled, observer-blinded trial, we randomly assigned participants in a 1:1 ratio to receive two injections, 21 days apart, of 30 mug of BNT162b2 or placebo. Noninferiority of the immune response to BNT162b2 in 12-to-15-year-old participants as compared with that in 16-to-25-year-old participants was an immunogenicity objective. Safety (reactogenicity and adverse events) and efficacy against confirmed coronavirus disease 2019 (Covid-19; onset, >/=7 days after dose 2) in the 12-to-15-year-old cohort were assessed. RESULTS: Overall, 2260 adolescents 12 to 15 years of age received injections; 1131 received BNT162b2, and 1129 received placebo. As has been found in other age groups, BNT162b2 had a favorable safety and side-effect profile, with mainly transient mild-to-moderate reactogenicity (predominantly injection-site pain [in 79 to 86% of participants], fatigue [in 60 to 66%], and headache [in 55 to 65%]); there were no vaccine-related serious adverse events and few overall severe adverse events. The geometric mean ratio of SARS-CoV-2 50% neutralizing titers after dose 2 in 12-to-15-year-old participants relative to 16-to-25-year-old participants was 1.76 (95% confidence interval [CI], 1.47 to 2.10), which met the noninferiority criterion of a lower boundary of the two-sided 95% confidence interval greater than 0.67 and indicated a greater response in the 12-to-15-year-old cohort. Among participants without evidence of previous SARS-CoV-2 infection, no Covid-19 cases with an onset of 7 or more days after dose 2 were noted among BNT162b2 recipients, and 16 cases occurred among placebo recipients. The observed vaccine efficacy was 100% (95% CI, 75.3 to 100). CONCLUSIONS: The BNT162b2 vaccine in 12-to-15-year-old recipients had a favorable safety profile, produced a greater immune response than in young adults, and was highly effective against Covid-19. (Funded by BioNTech and Pfizer; C4591001 ClinicalTrials.gov number, NCT04368728.).

Haas, E. J., et al. (2021). "Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data." Lancet 397(10287): 1819-1829.

BACKGROUND: Following the emergency use authorisation of the Pfizer-BioNTech mRNA COVID-19 vaccine BNT162b2 (international non-proprietary name tozinameran) in Israel, the Ministry of Health (MoH) launched a campaign to immunise the 6.5 million residents of Israel aged 16 years and older. We estimated the real-world effectiveness of two doses of BNT162b2 against a range of SARS-CoV-2 outcomes and to evaluate the nationwide public-health impact following the widespread introduction of the vaccine. METHODS: We used national surveillance data from the first 4 months of the nationwide vaccination campaign to ascertain incident cases of laboratory-confirmed SARS-CoV-2 infections and outcomes, as well as vaccine uptake in residents of Israel aged 16 years and older. Vaccine effectiveness against SARS-CoV-2 outcomes (asymptomatic infection, symptomatic infection, and COVID-19-related hospitalisation, severe or critical hospitalisation, and death) was calculated on the basis of incidence rates in fully vaccinated individuals (defined as those for whom 7 days had passed since receiving the second dose of vaccine) compared with rates in unvaccinated individuals (who had not received any doses of the vaccine), with use of a negative binomial regression model adjusted for age group (16-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, and >/=85 years), sex, and calendar week. The proportion of spike gene target failures on PCR test among a nationwide convenience-sample of SARS-CoV-2-positive specimens was used to estimate the prevelance of the B.1.1.7 variant. FINDINGS: During the analysis period (Jan 24 to April 3, 2021), there were 232 268 SARS-CoV-2 infections, 7694 COVID-19 hospitalisations, 4481 severe or critical COVID-19 hospitalisations, and

1113 COVID-19 deaths in people aged 16 years or older. By April 3, 2021, 4 714 932 (72.1%) of 6 538 911 people aged 16 years and older were fully vaccinated with two doses of BNT162b2. Adjusted estimates of vaccine effectiveness at 7 days or longer after the second dose were 95.3% (95% CI 94.9-95.7; incidence rate 91.5 per 100 000 person-days in unvaccinated vs 3.1 per 100 000 person-days in fully vaccinated individuals) against SARS-CoV-2 infection, 91.5% (90.7-92.2; 40.9 vs 1.8 per 100 000 person-days) against asymptomatic SARS-CoV-2 infection, 97.0% (96.7-97.2; 32.5 vs 0.8 per 100 000 person-days) against symptomatic COVID-19, 97.2% (96.8-97.5; 4.6 vs 0.3 per 100 000 person-days) against COVID-19-related hospitalisation, 97.5% (97.1-97.8; 2.7 vs 0.2 per 100 000 person-days) against severe or critical COVID-19-related hospitalisation, and 96.7% (96.0-97.3; 0.6 vs 0.1 per 100 000 person-days) against COVID-19-related death. In all age groups, as vaccine coverage increased, the incidence of SARS-CoV-2 outcomes declined. 8006 of 8472 samples tested showed a spike gene target failure, giving an estimated prevalence of the B.1.1.7 variant of 94.5% among SARS-CoV-2 infections. INTERPRETATION: Two doses of BNT162b2 are highly effective across all age groups (>/=16 years, including older adults aged >/=85 years) in preventing symptomatic and asymptomatic SARS-CoV-2 infections and COVID-19-related hospitalisations, severe disease, and death, including those caused by the B.1.1.7 SARS-CoV-2 variant. There were marked and sustained declines in SARS-CoV-2 incidence corresponding to increasing vaccine coverage. These findings suggest that COVID-19 vaccination can help to control the pandemic. FUNDING: None.

Lopez Bernal, J., et al. (2021). "Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant." N Engl J Med 385(7): 585-594.

BACKGROUND: The B.1.617.2 (delta) variant of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19), has contributed to a surge in cases in India and has now been detected across the globe, including a notable increase in cases in the United Kingdom. The effectiveness of the BNT162b2 and ChAdOx1 nCoV-19 vaccines against this variant has been unclear. METHODS: We used a test-negative case-control design to estimate the effectiveness of vaccination against symptomatic disease caused by the delta variant or the predominant strain (B.1.1.7, or alpha variant) over the period that the delta variant began circulating. Variants were identified with the use of sequencing and on the basis of the spike (S) gene status. Data on all symptomatic sequenced cases of Covid-19 in England were used to estimate the proportion of cases with either variant according to the patients' vaccination status. RESULTS: Effectiveness after one dose of vaccine (BNT162b2 or ChAdOx1 nCoV-19) was notably lower among persons with the delta variant (30.7%; 95% confidence interval [CI], 25.2 to 35.7) than among those with the alpha variant (48.7%; 95% CI, 45.5 to 51.7); the results were similar for both vaccines. With the BNT162b2 vaccine, the effectiveness of two doses was 93.7% (95% CI, 91.6 to 95.3) among persons with the alpha variant and 88.0% (95% CI, 85.3 to 90.1) among those with the delta variant. With the ChAdOx1 nCoV-19 vaccine, the effectiveness of two doses was 74.5% (95% CI, 68.4 to 79.4) among persons with the alpha variant and 67.0% (95% CI, 61.3 to 71.8) among those with the delta variant. CONCLUSIONS: Only modest differences in vaccine effectiveness were noted with the delta variant as compared with the alpha variant after the receipt of two vaccine doses. Absolute differences in vaccine effectiveness were more marked after the receipt of the first dose. This finding would support efforts to maximize vaccine uptake with two doses among vulnerable populations. (Funded by Public Health England.).

Polack, F. P., et al. (2020). "Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine." N Engl J Med 383(27): 2603-2615.

BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of people in a worldwide pandemic. Safe and effective vaccines are needed urgently. METHODS: In an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, we randomly assigned persons 16 years of age or older in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 mug per dose). BNT162b2 is a lipid nanoparticle-formulated, nucleoside-modified

RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. The primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety. RESULTS: A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups. CONCLUSIONS: A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.).

Appendix 1.6

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

Summary of main clinical trial efficacy data

Study	Population	Strain	Schedule	Primary Endpoint	VE Asym	VE Sym	VE Hospital	VE Death
(Voysey, Clemens 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%[5]		

Summary of main effectiveness data

Study	Population	Strain	Schedule	Primary Endpoint	VE Asym	VE Sym	VE Hospital	VE Death
(Cerqueira-Silva, Oliveira et al. 2021) PREPRINT	Retrospective cohort study in approximately 61 million recipients of Brazillian 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, Matthews 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, Andrews 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)		

Data on non-standard schedules

(Voysey, Costa Clemens et al. 2021) examined dosing intervals between < 6 weeks and 12 weeks for Vaxzevria. Vaccine efficacy increased with the time between doses, being 55.1%, 59.9%, 63.7% and 81.3% at intervals of <6 weeks, 6-8 weeks, 9-11 weeks, and >12 weeks respectively.

(Flaxman, Marchevsky et al. 2021) is a subanalysis in 90 participants recruited from ongoing phase I/II studies to receive a third dose of vaccine 28-38 weeks after their second dose. Among 73 participants in whom antibody levels were available, neutralising antibody levels were significantly higher 28 days after the third dose than 28 days after the second dose, approximately doubling.

Comment

	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 1. Results from (Voysey, Clemens 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)

References

Cerqueira-Silva, T., et al. (2021). "The effectiveness of Vaxzevria and CoronaVac vaccines: A nationwide longitudinal retrospective study of 61 million Brazilians (VigiVac-COVID19)." PRE.

Flaxman, A., et al. (2021). "Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a substudy of two randomised controlled trials (COV001 and COV002)." Lancet 398(10304): 981-990.

BACKGROUND: COVID-19 vaccine supply shortages are causing concerns about compromised immunity in some countries as the interval between the first and second dose becomes longer. Conversely, countries with no supply constraints are considering administering a third dose. We assessed the persistence of immunogenicity after a single dose of ChAdOx1 nCoV-19 (AZD1222), immunity after an extended interval (44-45 weeks) between the first and second dose, and response to a third dose as a booster given 28-38 weeks after the second dose. METHODS: In this substudy, volunteers aged 18-55 years who were enrolled in the phase 1/2 (COV001) controlled trial in the UK and had received either a single dose or two doses of 5 x 10(10) viral particles were invited back for vaccination. Here we report the reactogenicity and immunogenicity of a delayed second dose (44-45 weeks after first dose) or a third dose of the vaccine (28-38 weeks after second dose). Data from volunteers aged 18-55 years who were enrolled in either the phase 1/2 (COV001) or phase 2/3 (COV002), single-blinded, randomised controlled trials of ChAdOx1 nCoV-19 and who had previously received a single dose or two doses of 5 x 10(10) viral particles are used for comparison purposes. COV001 is registered with ClinicalTrials.gov, NCT04324606, and ISRCTN, 15281137, and COV002 is registered with ClinicalTrials.gov, NCT04400838, and ISRCTN, 15281137, and both are continuing but not recruiting. FINDINGS: Between March 11 and 21, 2021, 90 participants were enrolled in the third-dose boost substudy, of whom 80 (89%) were assessable for reactogenicity, 75 (83%) were assessable for evaluation of antibodies, and 15 (17%) were assessable for T-cells responses. The two-dose cohort comprised 321 participants who had reactogenicity data (with prime-boost interval of 8-12 weeks: 267 [83%] of 321; 15-25 weeks: 24 [7%]; or 44-45 weeks: 30 [9%]) and 261 who had immunogenicity data (interval of 8-12 weeks: 115 [44%] of 261; 15-25 weeks: 116 [44%]; and 44-45 weeks: 30 [11%]). 480 participants from the single-dose cohort were assessable for immunogenicity up to 44-45 weeks after vaccination. Antibody titres after a single dose measured approximately 320 days after vaccination remained higher than the titres measured at baseline (geometric mean titre of 66.00 ELISA units [EUs; 95% CI 47.83-91.08] vs 1.75 EUs [1.60-1.93]). 32 participants received a late second dose of vaccine 44-45 weeks after the first dose, of whom 30 were included in immunogenicity and reactogenicity analyses. Antibody titres were higher 28 days after vaccination in those with a longer interval between first and second dose than for those with a short interval (median total IgG titre: 923 EUs [IQR 525-1764] with an 8-12 week interval; 1860 EUs [917-4934] with a 15-25 week interval; and 3738 EUs [1824-6625] with a 44-45 week interval). Among participants who received a third dose of vaccine, antibody titres (measured in 73 [81%] participants for whom samples were available) were significantly higher 28 days after a third dose (median total IgG titre: 3746 EUs [IQR 2047-6420]) than 28 days after a second dose (median 1792 EUs [IQR 899-4634]; Wilcoxon signed rank test p=0.0043). T-cell responses were also boosted after a third dose (median response increased from 200 spot forming units [SFUs] per million peripheral blood mononuclear cells [PBMCs; IQR 127-389] immediately before the third dose to 399 SFUs per milion PBMCs [314-662] by day 28 after the third dose; Wilcoxon signed rank test p=0.012). Reactogenicity after a late second dose or a third dose was lower than reactogenicity after a first dose. INTERPRETATION: An extended interval before the second dose of ChAdOx1 nCoV-19 leads to increased antibody titres. A third dose of ChAdOx1 nCoV-19 induces antibodies to a level that correlates with high efficacy after second dose and boosts T-cell responses. FUNDING: UK Research and Innovation, Engineering and Physical Sciences Research Council, National Institute for Health Research, Coalition for Epidemic Preparedness Innovations, National Institute for Health Research Oxford Biomedical Research Centre, Chinese Academy of Medical Sciences Innovation Fund for Medical Science, Thames Valley and South Midlands NIHR Clinical Research Network, AstraZeneca, and Wellcome.

Lopez Bernal, J., et al. (2021). "Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant." N Engl J Med 385(7): 585-594.

BACKGROUND: The B.1.617.2 (delta) variant of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19), has contributed to a surge in cases in India and has now been detected across the globe, including a notable increase in cases in the United Kingdom. The effectiveness of the BNT162b2 and ChAdOx1 nCoV-19 vaccines against this variant has been unclear. METHODS: We used a test-negative case-control design to estimate the

effectiveness of vaccination against symptomatic disease caused by the delta variant or the predominant strain (B.1.1.7, or alpha variant) over the period that the delta variant began circulating. Variants were identified with the use of sequencing and on the basis of the spike (S) gene status. Data on all symptomatic sequenced cases of Covid-19 in England were used to estimate the proportion of cases with either variant according to the patients' vaccination status. RESULTS: Effectiveness after one dose of vaccine (BNT162b2 or ChAdOx1 nCoV-19) was notably lower among persons with the delta variant (30.7%; 95% confidence interval [CI], 25.2 to 35.7) than among those with the alpha variant (48.7%; 95% CI, 45.5 to 51.7); the results were similar for both vaccines. With the BNT162b2 vaccine, the effectiveness of two doses was 93.7% (95% CI, 91.6 to 95.3) among persons with the alpha variant and 88.0% (95% CI, 85.3 to 90.1) among those with the delta variant. With the ChAdOx1 nCoV-19 vaccine, the effectiveness of two doses was 74.5% (95% CI, 68.4 to 79.4) among persons with the alpha variant and 67.0% (95% CI, 61.3 to 71.8) among those with the delta variant. CONCLUSIONS: Only modest differences in vaccine effectiveness were noted with the delta variant as compared with the alpha variant after the receipt of two vaccine doses. Absolute differences in vaccine effectiveness were more marked after the receipt of the first dose. This finding would support efforts to maximize vaccine uptake with two doses among vulnerable populations. (Funded by Public Health England.).

Pritchard, E., et al. (2021). "Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom." Nat Med 27(8): 1370-1378.

The effectiveness of COVID-19 vaccination in preventing new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in the general community is still unclear. Here, we used the Office for National Statistics COVID-19 Infection Survey-a large community-based survey of individuals living in randomly selected private households across the United Kingdom-to assess the effectiveness of the BNT162b2 (Pfizer-BioNTech) and ChAdOx1 nCoV-19 (Oxford-AstraZeneca; ChAdOx1) vaccines against any new SARS-CoV-2 PCR-positive tests, split according to self-reported symptoms, cycle threshold value (<30 versus >/=30; as a surrogate for viral load) and gene positivity pattern (compatible with B.1.1.7 or not). Using 1,945,071 real-time PCR results from nose and throat swabs taken from 383,812 participants between 1 December 2020 and 8 May 2021, we found that vaccination with the ChAdOx1 or BNT162b2 vaccines already reduced SARS-CoV-2 infections >/=21 d after the first dose (61% (95% confidence interval (CI) = 54-68%) versus 66% (95% CI = 60-71%), respectively), with greater reductions observed after a second dose (79% (95% CI = 65-88%) versus 80% (95% CI = 73-85%), respectively). The largest reductions were observed for symptomatic infections and/or infections with a higher viral burden. Overall, COVID-19 vaccination reduced the number of new SARS-CoV-2 infections, with the largest benefit received after two vaccinations and against symptomatic and high viral burden infections, and with no evidence of a difference between the BNT162b2 and ChAdOx1 vaccines.

Voysey, M., et al. (2021). "Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK." The Lancet 397(10269): 99-111.

Appendix 1.7

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

Summary of main clinical trial efficacy data

Study	Population	Strain	Schedule	Primary Endpoint	VE Asym	VE Sym	VE Hospital	VE Death
(Baden, El Sahly et al. 2021)	Randomised placebo controlled trial in 30420 volunteers aged >18 years of age in USA.	Not noted	2 doses Day 0 Day 28	Symptomatic PCR confirmed COVID >14 days after second dose		94.1		

Summary of main effectiveness data

Study	Population	Strain	Schedule	Primary Endpoint	VE Asym	VE Sym	VE Hospital	VE Death
(Chung, He 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, Chung 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, Stenehjem et al. 2021)	Case control study 41552 admissions to 187 hospitals and 221 EDs in the USA.	Not noted		VE Hospitalisation ED visit		`	91% (hospital) 72% (ED)	
(Ali, Berman 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%		

Data on non-standard schedules

Moderna announced on 1 September it has applied to FDA for a 50 microgram booster dose at six months after the primary vaccination schedule. This is based on an analysis of a phase II study in which neutralising antibody levels had waned at six months, and were increased by 32 to 43 fold for different COVID variants following a third dose.

References

Ali, K., et al. (2021). "Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents." N Engl J Med.

BACKGROUND: The incidence of coronavirus disease 2019 (Covid-19) among adolescents between 12 and 17 years of age was approximately 900 per 100,000 population from April 1 through June 11, 2021. The safety, immunogenicity, and efficacy of the mRNA-1273 vaccine in adolescents are unknown. METHODS: In this ongoing phase 2-3, placebo-controlled trial, we randomly assigned healthy adolescents (12 to 17 years of age) in a 2:1 ratio to receive two injections of the mRNA-1273 vaccine (100 mug in each) or placebo, administered 28 days apart. The primary objectives were evaluation of the safety of mRNA-1273 in adolescents and the noninferiority of the immune response in adolescents as compared with that in young adults (18 to 25 years of age) in a phase 3 trial. Secondary objectives included the efficacy of mRNA-1273 in preventing Covid-19 or asymptomatic severe acute respiratory syndrome coronavirus 2 infection. RESULTS: A total of 3732 participants were randomly assigned to receive mRNA-1273 (2489 participants) or placebo (1243 participants). In the mRNA-1273 group, the most common solicited adverse reactions after the first or second injections were injection-site pain (in 93.1% and 92.4%, respectively), headache (in 44.6% and 70.2%, respectively), and fatigue (in 47.9% and 67.8%, respectively); in the placebo group, the most common solicited adverse reactions after the first or second injections were injection-site pain (in 34.8% or 30.3%, respectively), headache (in 38.5% and 30.2%, respectively), and fatigue (in 36.6% and 28.9%, respectively). No serious adverse events related to mRNA-1273 or placebo were noted. The geometric mean titer ratio of pseudovirus neutralizing antibody titers in adolescents relative to young adults was 1.08 (95% confidence interval [CI], 0.94 to 1.24), and the absolute difference in serologic response was 0.2 percentage points (95% CI, -1.8 to 2.4), which met the noninferiority criterion. No cases of Covid-19 with an onset of 14 days after the second injection were reported in the mRNA-1273 group, and four cases occurred in the placebo group. CONCLUSIONS: The mRNA-1273 vaccine had an acceptable safety profile in adolescents. The immune response was similar to that in young adults, and the vaccine was efficacious in preventing Covid-19. (Funded by Moderna and the Biomedical Advanced Research and Development Authority; Teen COVE ClinicalTrials.gov number, NCT04649151.).

Baden, L. R., et al. (2021). "Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine." N Engl J Med 384(5): 403-416.

BACKGROUND: Vaccines are needed to prevent coronavirus disease 2019 (Covid-19) and to protect persons who are at high risk for complications. The mRNA-1273 vaccine is a lipid nanoparticle-encapsulated mRNA-based vaccine that encodes the prefusion stabilized full-length spike protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes Covid-19. METHODS: This phase 3 randomized, observer-blinded, placebo-controlled trial was conducted at 99 centers across the United States. Persons at high risk for SARS-CoV-2 infection or its complications were randomly assigned in a 1:1 ratio to receive two intramuscular injections of mRNA-1273 (100 mug) or placebo 28 days apart. The primary end point was prevention of Covid-19 illness with onset at least 14 days after the second injection in participants who had not previously been infected with SARS-CoV-2. RESULTS: The trial enrolled 30,420 volunteers who were randomly assigned in a 1:1 ratio to receive either vaccine or placebo (15,210 participants in each group). More than 96% of participants received both injections, and 2.2% had evidence (serologic, virologic, or both) of SARS-CoV-2 infection at

baseline. Symptomatic Covid-19 illness was confirmed in 185 participants in the placebo group (56.5 per 1000 person-years; 95% confidence interval [CI], 48.7 to 65.3) and in 11 participants in the mRNA-1273 group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; P<0.001). Efficacy was similar across key secondary analyses, including assessment 14 days after the first dose, analyses that included participants who had evidence of SARS-CoV-2 infection at baseline, and analyses in participants 65 years of age or older. Severe Covid-19 occurred in 30 participants, with one fatality; all 30 were in the placebo group. Moderate, transient reactogenicity after vaccination occurred more frequently in the mRNA-1273 group. Serious adverse events were rare, and the incidence was similar in the two groups. CONCLUSIONS: The mRNA-1273 vaccine showed 94.1% efficacy at preventing Covid-19 illness, including severe disease. Aside from transient local and systemic reactions, no safety concerns were identified. (Funded by the Biomedical Advanced Research and Development Authority and the National Institute of Allergy and Infectious Diseases; COVE ClinicalTrials.gov number, NCT04470427.).

Chung, H., et al. (2021). "Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study." BMJ 374: n1943.

OBJECTIVE: To estimate the effectiveness of mRNA covid-19 vaccines against symptomatic infection and severe outcomes (hospital admission or death). DESIGN: Test negative design study. SETTING: Ontario, Canada between 14 December 2020 and 19 April 2021. PARTICIPANTS: 324 033 community dwelling people aged >/=16 years who had symptoms of covid-19 and were tested for SARS-CoV-2. INTERVENTIONS: BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccine. MAIN OUTCOME MEASURES: Laboratory confirmed SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) and hospital admissions and deaths associated with SARS-CoV-2 infection. Multivariable logistic regression was adjusted for personal and clinical characteristics associated with SARS-CoV-2 and vaccine receipt to estimate vaccine effectiveness against symptomatic infection and severe outcomes. RESULTS: Of 324 033 people with symptoms, 53 270 (16.4%) were positive for SARS-CoV-2 and 21 272 (6.6%) received at least one dose of vaccine. Among participants who tested positive, 2479 (4.7%) were admitted to hospital or died. Vaccine effectiveness against symptomatic infection observed >/=14 days after one dose was 60% (95% confidence interval 57% to 64%), increasing from 48% (41% to 54%) at 14-20 days after one dose to 71% (63% to 78%) at 35-41 days. Vaccine effectiveness observed >/=7 days after two doses was 91% (89% to 93%). Vaccine effectiveness against hospital admission or death observed >/=14 days after one dose was 70% (60% to 77%), increasing from 62% (44% to 75%) at 14-20 days to 91% (73% to 97%) at >/=35 days, whereas vaccine effectiveness observed >/=7 days after two doses was 98% (88% to 100%). For adults aged >/=70 years, vaccine effectiveness estimates were observed to be lower for intervals shortly after one dose but were comparable to those for younger people for all intervals after 28 days. After two doses, high vaccine effectiveness was observed against variants with the E484K mutation. CONCLUSIONS: Two doses of mRNA covid-19 vaccines were observed to be highly effective against symptomatic infection and severe outcomes. Vaccine effectiveness of one dose was observed to be lower, particularly for older adults shortly after the first dose.

Nasreen, S., et al. (2021).

Thompson, M. G., et al. (2021). "Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings." N Engl J Med.

BACKGROUND: There are limited data on the effectiveness of the vaccines against symptomatic coronavirus disease 2019 (Covid-19) currently authorized in the United States with respect to hospitalization, admission to an intensive care unit (ICU), or ambulatory care in an emergency department or urgent care clinic. METHODS: We conducted a study involving adults (>/=50 years of age) with Covid-19-like illness who underwent molecular testing for severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2). We assessed 41,552 admissions to 187 hospitals and 21,522 visits to 221 emergency departments or urgent care clinics during the period from January 1 through June 22, 2021, in multiple states. The patients' vaccination status was documented in electronic health records and immunization registries. We used a test-negative design to estimate vaccine effectiveness by comparing the odds of a positive test for SARS-CoV-2 infection among vaccinated patients with those among unvaccinated patients. Vaccine effectiveness was adjusted with weights based on propensity-for-vaccination scores and according to age, geographic region, calendar time (days from January 1, 2021, to the index date for each medical visit), and local virus circulation. RESULTS: The effectiveness of full messenger RNA (mRNA) vaccination (>/=14 days after the second dose) was 89% (95% confidence interval [CI], 87 to 91) against laboratory-confirmed SARS-CoV-2 infection leading to hospitalization, 90% (95% CI, 85 to 93) against infection leading to an ICU admission, and 91% (95% CI, 89 to 93) against infection leading to an emergency department or urgent care clinic visit. The effectiveness of full vaccination with respect to a Covid-19-associated hospitalization or emergency department or urgent care clinic visit was similar with the BNT162b2 and mRNA-1273 vaccines and ranged from 81% to 95% among adults 85 years of age or older, persons with chronic medical conditions, and Black or Hispanic adults. The effectiveness of the Ad26.COV2.S vaccine was 68% (95% CI, 50 to 79) against laboratory-confirmed SARS-CoV-2 infection leading to hospitalization and 73% (95% CI, 59 to 82) against infection leading to an emergency department or urgent care clinic visit. CONCLUSIONS: Covid-19 vaccines in the United States were highly effective against SARS-CoV-2 infection requiring hospitalization, ICU admission, or an emergency department or urgent care clinic visit. This vaccine effectiveness extended to populations that are disproportionately affected by SARS-CoV-2 infection. (Funded by the Centers for Disease Control and Prevention.).

Appendix 1.8

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

Summary of main clinical trial efficacy data

Study	Population	Strain	Schedule	Primary Endpoint	VE Asym	VE Sym	VE Hospital	VE Death
(Sadoff, Gray et al. 2021)	44325 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	

Summary of main effectiveness data

Study	Population	Strain	Schedule	Primary Endpoint	VE Asym	VE Sym	VE Hospital	VE Death

In early August Johnson and Johnson reported that the results of the Sisonke phase III trial in 477234 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.

Data on 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.

References

Sadoff, J., et al. (2021). "Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19." N Engl J Med 384(23): 2187-2201.

> BACKGROUND: The Ad26.COV2.S vaccine is a recombinant, replication-incompetent human adenovirus type 26 vector encoding full-length severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein in a prefusion-stabilized conformation. METHODS: In an international, randomized, double-blind, placebo-controlled, phase 3 trial, we randomly assigned adult participants in a 1:1 ratio to receive a single dose of Ad26.COV2.S (5x10(10) viral particles) or placebo. The primary end points were vaccine efficacy against moderate to severe-critical coronavirus disease 2019 (Covid-19) with an onset at least 14 days and at least 28 days after administration among participants in the per-protocol population who had tested negative for SARS-CoV-2. Safety was also assessed. RESULTS: The per-protocol population included 19,630 SARS-CoV-2-negative participants who received Ad26.COV2.S and 19,691 who received placebo. Ad26.COV2.S protected against moderate to severe-critical Covid-19 with onset at least 14 days after administration (116 cases in the vaccine group vs. 348 in the placebo group; efficacy, 66.9%; adjusted 95% confidence interval [CI], 59.0 to 73.4) and at least 28 days after administration (66 vs. 193 cases; efficacy, 66.1%; adjusted 95% CI, 55.0 to 74.8). Vaccine efficacy was higher against severe-critical Covid-19 (76.7% [adjusted 95% CI, 54.6 to 89.1] for onset at >/=14 days and 85.4% [adjusted 95% CI, 54.2 to 96.9] for onset at >/=28 days). Despite 86 of 91 cases (94.5%) in South Africa with sequenced virus having the 20H/501Y.V2 variant, vaccine efficacy was 52.0% and 64.0% against moderate to severe-critical Covid-19 with onset at least 14 days and at least 28 days after administration, respectively, and efficacy against severe-critical Covid-19 was 73.1% and 81.7%, respectively. Reactogenicity was higher with Ad26.COV2.S than with placebo but was generally mild to moderate and transient. The incidence of serious adverse events was balanced between the two groups. Three deaths occurred in the vaccine group (none were Covid-19-related), and 16 in the placebo group (5 were Covid-19-related). CONCLUSIONS: A single dose of Ad26.COV2.S protected against symptomatic Covid-19 and asymptomatic SARS-CoV-2 infection and was effective against severe-critical disease, including hospitalization and death. Safety appeared to be similar to that in other phase 3 trials of Covid-19 vaccines. (Funded by Janssen Research and Development and others; ENSEMBLE ClinicalTrials.gov number, NCT04505722.).

Sadoff, J., et al. (2021).

Appendix 1.9

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

Summary of main clinical trial efficacy data

Study	Population	Strain	Schedule	Primary Endpoint	VE Asym	VE Sym	VE Hospital	VE Death

Summary of main effectiveness data

Study	Population	Strain	Schedule	Primary Endpoint	VE Asym	VE Sym	VE Hospital	VE Death

Data on non-standard schedules

Cansino has investigated the potential for intranasal administration of Convidecia. (Wu, Huang et al. 2021) has reported that intranasal administration is well tolerated an immunogenic in preliminary results from a phase I study.

Assessment

There are several phase III trials ongoing in Convidecia but these have not reached the stage of reporting.

On 22 March 2022 Cansino was reported to have stated[6] that interim data from Phase III trials indicate Convidecia has a 68.83% vaccine efficacy in preventing symptomatic COVID 14 days post vaccination and a 65.28% vaccine efficacy in preventing symptomatic COVID 28 days post vaccination. It was reported that Convidecia had a 90.07% and 95.47% vaccine efficacy in preventing severe COVID at 28 and 14 days post vaccination respectively. In the same report, reference was made to the Pakastan authorities had announced a vaccine efficacy rate of 100% against symptomtic COVID and 94.8% against symptomatic COVID in trials in Pakistan.

[6] https://www.prnewswire.com/news-releases/cansinobio-announces-approval-for-its-single-dose-covid-19-vaccine-convidecia-in-hungary-301252978.html

This data is not available for evaluation.

There is currently insufficient information on which to evaluate the efficacy of Convidecia.

References

Wu, S., et al. (2021). "Safety, tolerability, and immunogenicity of an aerosolised adenovirus type-5 vector-based COVID-19 vaccine (Ad5-nCoV) in adults: preliminary report of an open-label and randomised phase 1 clinical trial." The Lancet Infectious Diseases.

Appendix 2.1 Heterologous dose schedules

Summary of main clinical trial efficacy data

Study	Population	Product	Schedule	Primary Endpoint	Results
(Borobia, Carcas et al. 2021)	676 COVID naïve people 18-60 years of age randomised to two vaccine doses or a single vaccine dose from 5 hospitals in Spain	ChAdOx1 BNT162b2	ChAdOx1 (day 0) BNT162b2 (8-12 weeks)	Antibody levels at 14 days post second dose	37-fold increase in Binding Antibody Units per mL after second dose compared to single dose.
(Dimeglio, Herin et al. 2021) PREPRINT	66 HCW in France given the choice of homologous or heterologous vaccination with ChAdOx1 or BNT162b2	ChAdOx1 BNT162b2	Not recorded but either ChAdOx1/ChAdOx1 BNT162b2/BNT162b2 ChAdOx1/BNT162b2	Neutralising antibody titres on live virus assay 1 month after vaccination	ChAdOx1/BNT162b2 produced a higher proportion of subjects with >2 fold increase in antibody titres 1 month after vaccination (95.4%) compared to either homologous dose, ChAdOx1 63.6% and BNT162b2 68.2% respectively
(Hammerschmidt, Bosnjak et al. 2021)	Plasma from 85 individuals who had either received ChAdOx1/ChAdOx1 or ChAdOx1/BNT162b2	ChAdOx1 BNT162b2	Not recorded	Neutralising antibody titre against Delta strain at a mean of 17 days after second vaccine dose	Heterologous dosing resulted in a significantly higher neutralising titre than homologous ChAdOx1 dosing, but similar to homologous BNT162b2 dosing
(Hillus, Schwarz et al. 2021)	340 HCW vaccinated at a university hospital in Germany	ChAdOx1 BNT162b2	BNT162b2/BNT162b2 day 0 and 21 ChAdOx1/BNT162b2 day 0 and Week 8-12	IgG seroconversion and neutralising antibodies is COVID S1 protein three weeks after second dose	Neutralising antibodies were present in 100% of homologous and 99% of heterologous dose recipients
(Liu, Shaw et al. 2021)	Randomised phase 2 trial in 830 COVID naïve patients >50 years of age in UK	ChAdOx1 BNT162b2	ChAdOx1/ChAdOx1 ChAdOx1/BNT162b2 BNT162b2/ChAdOx1 BNT162b2/BTN162b2 All Day 0 and Day 28	Serum anti-spike IgG concentration 28 days after second dose	ChAdOx1/BNT162b2 was statistically superior to ChAdOx1/ChAdOx1. The two BNT162b2/ChAdOx1 was inferior to BNT162b2/BNT162b2.
(Tenbusch, Schumacher et al. 2021)	Plasma from 480 individuals who had received either homologous or heterologous vaccination	ChAdOx1 BNT162b2	ChAdOx1/ChAdOx1 ChAdOx1/BNT162b2 BNT162b2/BTN162b2 Interval not recorded	Neutralising antibodies	Heterologous ChAdOx1/BNT162b2 produced higher antibody levels than either homologous schedule, and similar to homologous BNT162b2 (at a shorter interval of 21 days)
(Normark, Vikstrom et al. 2021)	Correspondence regarding analysis of plasma from 88 HCW who had received either homologous or heterologous vaccination recruited from ongoing trial.	ChAdOx1 mRNA-1273	ChAdOx1/ChAdOx1 ChAdOx1/mRNA-1273 Day 0 and week 9-12.	Neutralising antibodies on live virus assay 1 month after second dose	Data not numerically presented. Both homologous and heterologous schedules induced neutralising antibodies but the heterologous dose had higher levels. ChAdOx1/ChAdOx1 did not produce neutralising antibodies against Beta strain, while the heterologous schedule did
(Yorsaeng, Vichaiwattana et al. 2021) PREPRINT	234 HCW who opportunistically received homologous or heterologous doses depending on vaccine availability in Thailand	ChAdOx1 Coronavac	ChAdOx1/ChAdOx1 (n=80) Day 0 and Week 10 Coronavac/Coronavac (n=80) Day 0 and Week 3 Coronavac/ChAdOx1 (n=54) Day 0 and 4 weeks	Serum anti-spike antibodies compared to COVID convalescent serum	The GMT of antibodies after Coronavac/Coronavac was 96.4U/mL and not not significantly different from convalescent serum. The GMT of antibodies after heterologous dosing was 797U/mL and similar to 2 doses of ChAdOx1 (818U/mL)
(Li, Hou et al. 2021) PREPRINT	Randomised study of 300 subjects 18-59 years of age who received one of four	Convidecia Coronavac	Coronavac 2 doses + Convidecia booster 3-6 months (n=96)	GMT (PRNT50) of neutralising antibodies in live virus assay 14	GMT following Coronavac and Convidecia 3 dose schedule was 33.6 and 197.4 respectively. With the two

	dose regimens in China		Coronavac 2 doses+ Coronavac booster 3-6 months (n=102) Coronavac + Coronavac (n=50) Coronavac + Convidecia (n=51)	days after booster dose	dose Coronavac and Convidecia regiment GMT was 12.8 and 54.4 respectively. This was a 78-fold increase in GMT for the Convidecia heterologous boots, and 15.2-fold increase for the 3 dose homologous Coronavac boost.

Assessment

There are a large number of studies involving heterologous dosing schedules, although these are mostly concentrated around ChAdOx1 and mRNA vaccines at present. Immunological endpoints suggest that these are as, or potentially more, effective than homologous dosing. However the clinical significance of the immunological endpoints remains uncertain as there is no established correlate of immunity for COVID vaccines.

References

Borobia, A. M., et al. (2021). "Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial." Lancet 398(10295): 121-130.

BACKGROUND: To date, no immunological data on COVID-19 heterologous vaccination schedules in humans have been reported. We assessed the immunogenicity and reactogenicity of BNT162b2 (Comirnaty, BioNTech, Mainz, Germany) administered as second dose in participants primed with ChAdOx1-S (Vaxzevria, AstraZeneca, Oxford, UK). METHODS: We did a phase 2, open-label, randomised, controlled trial on adults aged 18-60 years, vaccinated with a single dose of ChAdOx1-S 8-12 weeks before screening, and no history of SARS-CoV-2 infection. Participants were randomly assigned (2:1) to receive either BNT162b2 (0.3 mL) via a single intramuscular injection (intervention group) or continue observation (control group). The primary outcome was 14-day immunogenicity, measured by immunoassays for SARS-CoV-2 trimeric spike protein and receptor binding domain (RBD). Antibody functionality was assessed using a pseudovirus neutralisation assay, and cellular immune response using an interferon-gamma immunoassay. The safety outcome was 7-day reactogenicity, measured as solicited local and systemic adverse events. The primary analysis included all participants who received at least one dose of BNT162b2 and who had at least one efficacy evaluation after baseline. The safety analysis included all participants who received BNT162b2. This study is registered with EudraCT (2021-001978-37) and ClinicalTrials.gov (NCT04860739), and is ongoing. FINDINGS: Between April 24 and 30, 2021, 676 individuals were enrolled and randomly assigned to either the intervention group (n=450) or control group (n=226) at five university hospitals in Spain (mean age 44 years [SD 9]; 382 [57%] women and 294 [43%] men). 663 (98%) participants (n=441 intervention, n=222 control) completed the study up to day 14. In the intervention group, geometric mean titres of RBD antibodies increased from 71.46 BAU/mL (95% CI 59.84-85.33) at baseline to 7756.68 BAU/mL (7371.53-8161.96) at day 14 (p<0.0001). IgG against trimeric spike protein increased from 98.40 BAU/mL (95% CI 85.69-112.99) to 3684.87 BAU/mL (3429.87-3958.83). The interventional:control ratio was 77.69 (95% CI 59.57-101.32) for RBD protein and 36.41 (29.31-45.23) for trimeric spike protein IgG. Reactions were mild (n=1210 [68%]) or moderate (n=530 [30%]), with injection site pain (n=395 [88%]), induration (n=159 [35%]), headache (n=199 [44%]), and myalgia (n=194 [43%]) the most commonly reported adverse events. No serious adverse events were reported. INTERPRETATION: BNT162b2 given as a second dose in individuals prime vaccinated with ChAdOx1-S induced a robust immune response, with an acceptable and manageable reactogenicity profile. FUNDING: Instituto de Salud Carlos III. TRANSLATIONS: For the French and Spanish translations of the abstract see Supplementary Materials section.

Dimeglio, C., et al. (2021). "Heterologous ChAdOx1-S/BNT162b2 vaccination: neutralizing antibody response to SARS-CoV-2." Clin Infect Dis.

Hammerschmidt, S. I., et al. (2021). "Neutralization of the SARS-CoV-2 Delta variant after heterologous and homologous BNT162b2 or ChAdOx1 nCoV-19 vaccination." Cell Mol Immunol.

Hillus, D., et al. (2021).

Li, J., et al. (2021).

Liu, X., et al. (2021). "Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial." Lancet 398(10303): 856-869.

BACKGROUND: Use of heterologous prime-boost COVID-19 vaccine schedules could facilitate mass COVID-19 immunisation. However, we have previously reported that heterologous schedules incorporating an adenoviral vectored vaccine (ChAdOx1 nCoV-19, AstraZeneca; hereafter referred to as ChAd) and an mRNA vaccine (BNT162b2, Pfizer-BioNTech; hereafter referred to as BNT) at a 4-week interval are more reactogenic than homologous schedules. Here, we report the safety and immunogenicity of heterologous schedules with the ChAd and BNT vaccines. METHODS: Com-COV is a participant-blinded, randomised, non-inferiority trial evaluating vaccine safety, reactogenicity, and immunogenicity. Adults aged 50 years and older with no or well controlled comorbidities and no previous SARS-CoV-2 infection by laboratory confirmation were eligible and were recruited at eight sites across the UK. The majority of eligible participants were enrolled into the general cohort (28-day or 84-day prime-boost intervals), who were randomly assigned (1:1:1:1:1:1:1:1) to receive ChAd/ChAd, ChAd/BNT, BNT/BNT, or BNT/ChAd, administered at either 28-day or 84-day prime-boost intervals. A small subset of eligible participants (n=100) were enrolled into an immunology cohort, who had additional blood tests to evaluate immune responses; these participants were randomly assigned (1:1:1:1) to the four schedules (28-day interval only). Participants were masked to the vaccine received but not to the prime-boost interval. The primary endpoint was the geometric mean ratio (GMR) of serum SARS-CoV-2 anti-spike IgG concentration (measured by ELISA) at 28 days after boost, when comparing ChAd/BNT with ChAd/ChAd, and BNT/ChAd with BNT/BNT. The heterologous schedules were considered non-inferior to the approved homologous schedules if the lower limit of the one-sided 97.5% CI of the GMR of these comparisons was greater than 0.63. The primary analysis was done in the per-protocol population, who were seronegative at baseline. Safety analyses were done among participants receiving at least one dose of a study vaccine. The trial is registered with ISRCTN, 69254139. FINDINGS: Between Feb 11 and Feb 26, 2021, 830 participants were enrolled and randomised, including 463 participants with a 28-day prime-boost interval, for whom results are reported here. The mean age of participants was 57.8 years (SD 4.7), with 212 (46%) female participants and 117 (25%) from ethnic minorities. At day 28 post boost, the geometric mean concentration of SARS-CoV-2 anti-spike IgG in ChAd/BNT recipients (12 906 ELU/mL) was non-inferior to that in ChAd/ChAd recipients (1392 ELU/mL), with a GMR of 9.2 (one-sided 97.5% CI 7.5 to infinity). In participants primed with BNT, we did not show non-inferiority of the heterologous schedule (BNT/ChAd, 7133 ELU/mL) against the homologous schedule (BNT/BNT, 14 080 ELU/mL), with a GMR of 0.51 (one-sided 97.5% CI 0.43 to infinity). Four serious adverse events occurred across all groups, none of which were considered to be related to immunisation. INTERPRETATION: Despite the BNT/ChAd regimen not meeting non-inferiority criteria, the SARS-CoV-2 anti-spike IgG concentrations of both heterologous schedules were higher than that of a licensed vaccine schedule (ChAd/ChAd) with proven efficacy against COVID-19 disease and hospitalisation. Along with the higher immunogenicity of ChAd/BNT compared with ChAD/ChAd, these data support flexibility in the use of heterologous prime-boost vaccination using ChAd and BNT COVID-19 vaccines. FUNDING: UK Vaccine Task Force and National Institute for Health Research.

Normark, J., et al. (2021). "Heterologous ChAdOx1 nCoV-19 and mRNA-1273 Vaccination." N Engl J Med.

Tenbusch, M., et al. (2021). "Heterologous prime-boost vaccination with ChAdOx1 nCoV-19 and BNT162b2." Lancet Infect Dis 21(9): 1212-1213.

Yorsaeng, R., et al. (2021).

Appendix 2.2 Duration of immunity

The duration of protection offered by COVID vaccine is not known because there is ongoing uncertainty about the correlate of immunity, and the relevance of different aspects of the immune response to vaccination in offering protection against transmission, disease progression or death. However, there is emerging evidence that the level of protection measured for vaccines soon after the schedule is completed does decline over several months.

(Khoury, Cromer et al. 2021) published a predictive model of the decay in protection based on a high degree of correlation between neutralising antibody levels and the protective effect of vaccines against infection reported in trials. The authors predicted that the duration of immunity offered by a vaccine would depend on the amount it boosted neutralising antibodies above an estimated protective threshold (against infection) of 28.6% of mean levels in convalescent serum. The model estimated that the level of neutralising antibodies required to protect against severe infection was approximately 6 times lower than that required to protect against infection. On this basis they predicted that protection against infection may wane within 6-8 months of vaccination, but protection against severe disease may last for years.

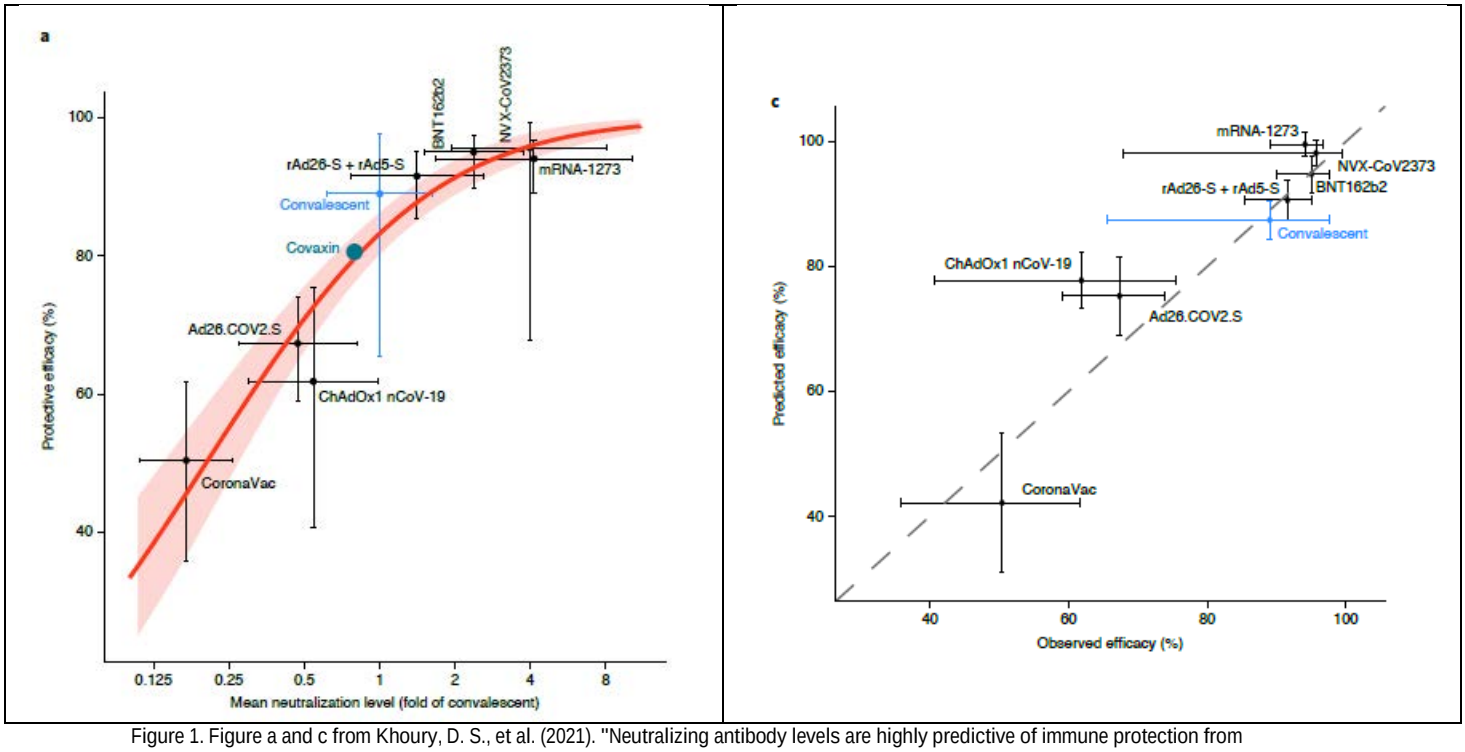

Figure 1. Figure a and c from Khoury, D. S., et al. (2021). "Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection." Nat Med 27(7): 1205-1211 indicating relationship between neutralising antibody levels and reported efficacy against infection in different vaccines.

There are several studies which demonstrate a decay in neutralising antibodies after vaccination. (Doria-Rose, Suthar et al. 2021) reported that the half-life of decay for neutralising antibodies in a live-virus assay was 202 days (95%CI 159-272 days) when measures six months after vaccination with nMRA-1273. Antibody levels remained high at this point.

(Naaber, Tserel et al. 2021) reported anti-spike antibody levels over six months post vaccination with BNT162b2. They reported that at six months antibody levels were similar to those after a single dose of BNT162b2, or in covalescent individuals. The waning of antibody levels was more pronounced in older individuals.

Similar waning in anti-spike antibody levels has been reported in (Shrotri, Navaratnam et al. 2021) for BNT162b2 and ChAdOx1 vaccines over 3-10 weeks post completion of a vaccination schedule in COVID naïve individuals.

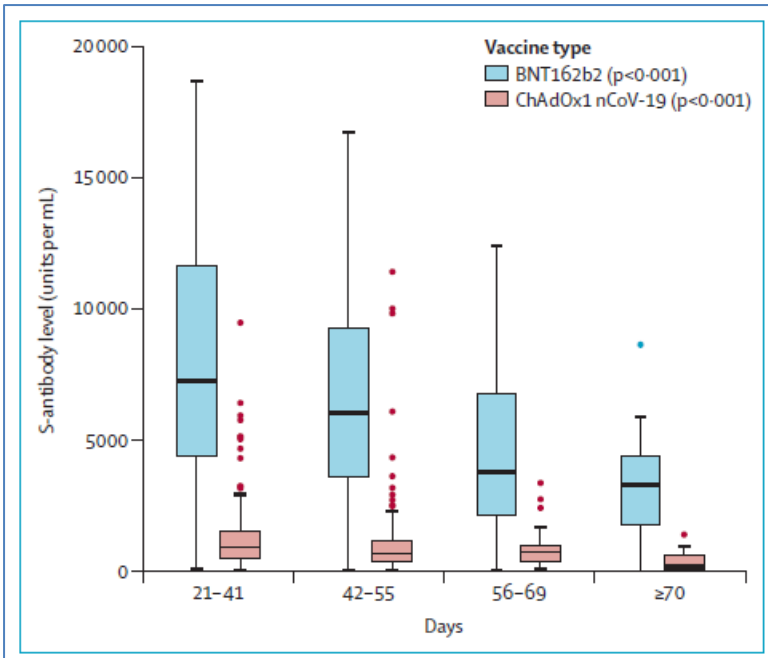

***Figure*: Levels of antibody against the spike glycoprotein of SARS-CoV-2 (S-antibody) at defined timepoints after second dose of vaccination (with extended dose intervals) in individuals with no previous infection, stratified by vaccine type**
p values derived from non-parametric tests for trend for each vaccine subgroup are given in parentheses in the key.

Figure 2: Anti-spike antibody levels after BNT162b2 and ChAdOx1 vaccination, from (Shrotri, Navaratnam et al. 2021)

(Li, Yang et al. 2021) was a pre-print that examined the immunogenicity of a third booster dose for Sinovac in healthy adults >60 years of age. It found that antibody levels had fallen below cutoff levels in the majority of participants by eight months (day 228).

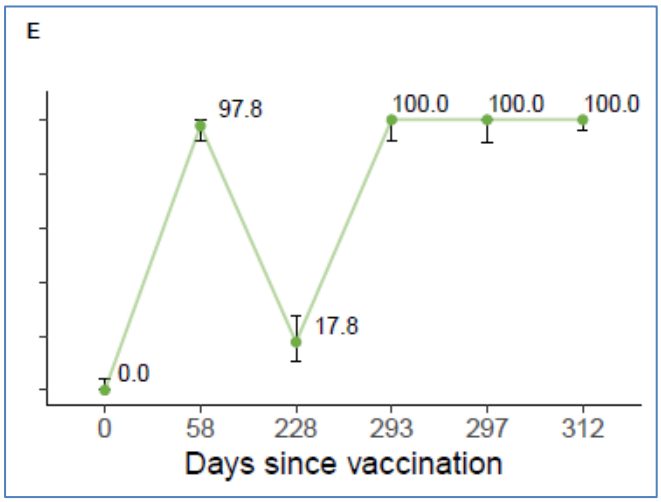

Figure 3. Percentage of participants seropositive at day 228 after two dose schedule and before a third dose of vaccine, from (Li, Yang et al. 2021)

Clinical evidence of waning immunity has been reported from large-scale vaccine deployments. (Chemaitelly, Tang et al. 2021) is a pre-print of a case-control study examining the long term vaccine efficacy of BTN162b2 in a large scale deployment in Qatar.

Supplementary Table 2. Effectiveness of the BNT162b2 vaccine against any SARS-CoV-2 infection and against any severe, critical, or fatal COVID-19 disease, stratified by age (<60 years or ≥60 years).

	Effectiveness against infection					Effectiveness against severity				
	Cases* (PCR-positive)		Controls* (PCR-negative)		Effectiveness in % (95% CI)†	Cases* (Severe, critical, or fatal disease)‡		Controls* (PCR-negative)		Effectiveness in % (95% CI)†
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
Age <60 years										
0-13 days after first dose	3,997	137,429	3,819	137,607	0.0 (0.0-0.0)	200	3,630	212	3,618	6.0 (0.0-23.3)
≥14 days after first dose and no second dose	2,182	137,862	3,474	136,570	37.8 (34.3-41.1)	65	3,651	235	3,481	73.6 (65.0-80.4)
0-4 weeks after the second dose	2,925	139,313	10,139	132,099	72.6 (71.5-73.8)	18	3,681	481	3,218	96.7 (94.8-98.1)
5-9 weeks after the second dose	1,377	138,053	4,077	135,353	66.9 (64.8-68.9)	9	3,650	212	3,447	96.0 (92.2-98.2)
10-14 weeks after the second dose	833	137,664	1,909	136,588	56.7 (53.0-60.1)	3	3,624	89	3,538	96.7 (90.1-99.3)
15-19 weeks after the second dose	531	137,338	734	137,135	27.8 (19.1-35.5)	4	3,626	30	3,600	86.8 (62.4-96.6)
20-24 weeks after the second dose	575	137,219	478	137,316	0.0 (0.0-0.0)	1	3,623	14	3,610	92.9 (53.2-99.8)
≥25 weeks after the second dose	416	137,245	369	137,292	0.0 (0.0-2.2)	1	3,631	7	3,625	85.7 (0.0-99.7)
Age ≥60 years										
0-13 days after first dose	197	1,471	157	1,511	0.0 (0.0-0.0)	49	352	39	362	0.0 (0.0-19.1)
≥14 days after first dose and no second dose	163	1,487	185	1,465	13.9 (0.0-31.0)	33	366	54	345	42.4 (7.0-64.7)
0-4 weeks after the second dose	216	1,621	520	1,317	66.3 (59.7-71.8)	14	397	117	294	91.1 (84.1-95.4)
5-9 weeks after the second dose	235	1,641	533	1,343	63.9 (57.1-69.7)	12	400	122	290	92.9 (86.7-96.5)
10-14 weeks after the second dose	173	1,566	333	1,406	53.4 (42.9-61.9)	12	376	86	302	88.8 (78.9-94.5)
15-19 weeks after the second dose	50	1,490	91	1,449	46.6 (23.1-63.2)	3	358	21	340	86.4 (53.8-97.4)
20-24 weeks after the second dose	33	1,457	45	1,445	27.3 (0.0-55.3)	0	348	7	341	100.0 (46.0-100.0)
≥25 weeks after the second dose	67	1,457	56	1,468	0.0 (0.0-17.4)	3	348	7	344	57.6 (0.0-93.0)

Abbreviations: CI, confidence interval; PCR, polymerase chain reaction.
*Cases and controls were matched one-to-one by sex, 10-year age group, nationality, reason for PCR testing, and calendar week of PCR test.
†Vaccine effectiveness was estimated using the test-negative, case-control study design.[12,13]
‡Severity,[1] criticality,[1] and fatality[2] were defined as per World Health Organization guidelines.

Table 1: Efficacy of BNT162b2 in Qatar over six months after two dose schedule, from (Chemaitelly, Tang et al. 2021)

As shown in Table 1, this study found a rapid waning in protection against infection from COVID although significant protection against severe disease remained. The waning in protection was greater in people >60 years of age compared to those <60 years of age.

(Goldberg, Mandel et al. 2021) was a pre-print of a study which correlated the rate of infection in recipients of BNT162b2 in the Israeli mass vaccination program between 16 Jan and 31 May.

Figure 4: Rate of severe COVID-19 (per 1,000 persons) from July 11, 2021 to July 31, 2021, stratified by period of second dose of COVID-19 vaccine and age group. White bars represent periods at which only persons at higher risk were allowed to receive vaccination.

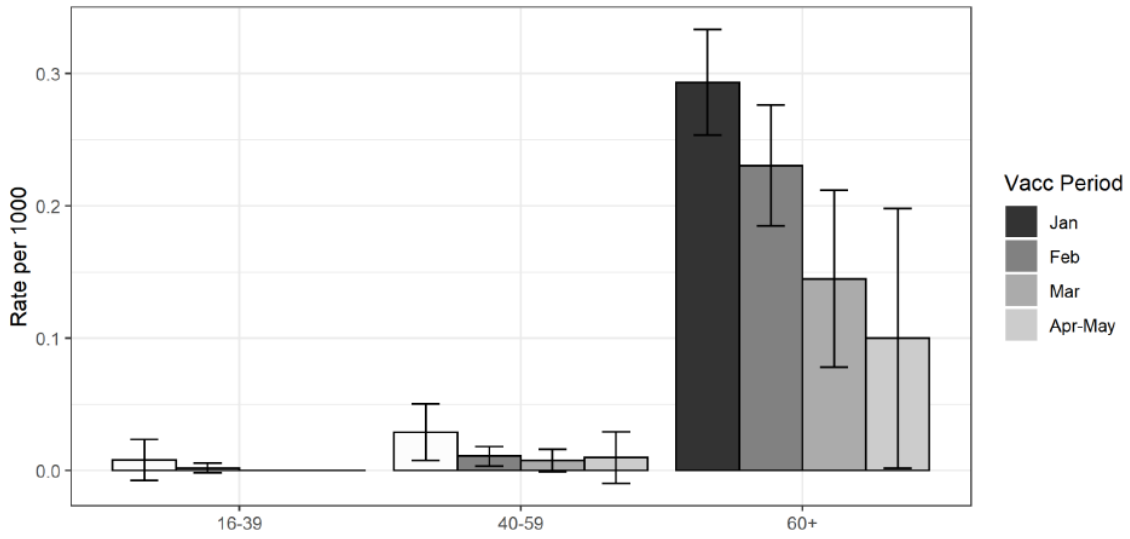

Figure 3. Age stratified rate of infection (per 1000 persons) in Israel by time of vaccination, from (Goldberg, Mandel et al. 2021)

This study demonstrated a correlation between the time since vaccination with BNT162b2 and the rate of infection with COVID.

Assessment

Neutralising antibodies to COVID fall from convalescent levels after natural infection. The same pattern appears to be displayed with most vaccines and there is a clinical trend towards reduced protection against infection after approximately 6 months with several vaccines, which is consistent with immunological analyses and a predictive model of antibody kinetics. Protection against severe disease appears longer lasting, but protection against infection and severe outcomes is less well preserved in the elderly.

Several vaccine manufacturers have proposed a booster dose in all, or elderly, recipients of vaccine. This has not currently been adopted as standard practice in Australia and it would therefore be difficult to recommend it for returning travellers. If this advice were to change, then it would be likely that recency of vaccination status would become an element of the recommendation for Unregistered Vaccines. This would raise the issue of whether heterologous dosing would be considered appropriate on the basis of scant clinical safety data.

In the interim, the Evaluator considers that immunisation within six months is likely to confer protection against severe outcomes of COVID infection. The level of immunity against infection is likely to wane over this time, but this is also true of vaccines deployed within Australia.

References

Chemaitelly, H., et al. (2021).

Doria-Rose, N., et al. (2021). "Antibody Persistence through 6 Months after the Second Dose of mRNA-1273 Vaccine for Covid-19." N Engl J Med 384(23): 2259-2261.

Goldberg, Y., et al. (2021).

Khoury, D. S., et al. (2021). "Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection." Nat Med 27(7): 1205-1211.

Predictive models of immune protection from COVID-19 are urgently needed to identify correlates of protection to assist in the future deployment of vaccines. To address this, we analyzed the relationship between in vitro neutralization levels and the observed protection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection using data from seven current vaccines and from convalescent cohorts. We estimated the neutralization level for 50% protection against detectable SARS-CoV-2 infection to be 20.2% of the mean convalescent level (95% confidence interval (CI) = 14.4-28.4%). The estimated neutralization level required for 50% protection from severe infection was significantly lower (3% of the mean convalescent level; 95% CI = 0.7-13%, P = 0.0004). Modeling of the decay of the neutralization titer over the first 250 d after immunization predicts that a significant loss in protection from SARS-CoV-2 infection will occur, although protection from severe disease should be largely retained. Neutralization titers against some SARS-CoV-2 variants of concern are reduced compared with the vaccine strain, and our model predicts the relationship between neutralization and efficacy against viral variants. Here, we show that neutralization level is highly predictive of immune protection, and provide an evidence-based model of SARS-CoV-2 immune protection that will assist in developing vaccine strategies to control the future trajectory of the pandemic.

Li, M., et al. (2021). "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 " PRE.

Naaber, P., et al. (2021). "Dynamics of antibody response to BNT162b2 vaccine after six months: a longitudinal prospective study." Lancet Reg Health Eur: 100208.

Background: SARS-CoV-2 mRNA vaccines have proven high efficacy, however, limited data exists on the duration of immune responses and their relation to age and side effects. Methods: We studied the antibody and memory T cell responses after the two-dose BNT162b2 vaccine in 122 volunteers up to 6 months and correlated the findings with age and side effects. Findings: We found a robust antibody response to Spike protein after the second dose. However, the antibody levels declined at 12 weeks and 6 months post-vaccination, indicating a waning of the immune response over time. At 6 months after the second dose, the Spike antibody levels were similar to the levels in persons vaccinated with one dose or in COVID-19 convalescent individuals. The antibodies efficiently blocked ACE2 receptor binding to SARS-CoV-2 Spike protein of five variants of concern at one week but this was decreased at three months. 87% of individuals developed Spike-specific memory T cell responses, which were lower in individuals with increased proportions of immunosenescent CD8(+) TEMRA cells. We found antibody response to correlate negatively with age and positively with the total score of vaccination side effects. Interpretation: The mRNA vaccine induces a strong antibody response to SARS-CoV-2 and five VOCs at 1 week post-vaccination that decreases thereafter. T cell responses, although detectable in the majority, were lower in individuals with higher T cell immunosenescence. The deterioration of vaccine response suggests the need to monitor for the potential booster vaccination.

Shrotri, M., et al. (2021). "Spike-antibody waning after second dose of BNT162b2 or ChAdOx1." Lancet 398(10298): 385-387.

Appendix 2.3

Transmission studies

Few studies have directly examined the probability that a vaccinated person can transmit COVID to other people if the do contract COVID. This is somewhat of a 'reverse protection' measurement, since vaccines are meant to protect against acquiring COVID not spreading it. The reduced transmission which is observed with high COVID vaccination coverage is a population immunity effect, rather than simply a reduction in the infectivity of vaccinated individuals.

(Harris, R and Hall et al, 2021) is a study conducted by Public Health England that examined the effect of vaccination with either ChAdOx1 or BNT162b2 on the incidence of COVID in unvaccinated household contacts. It compared people in priority vaccinated groups who acquired COVID in the UK with unvaccinated people who acquired COVID, and linked household contacts through an address database. People who lived at the same address as a vaccinated person with COVID and developed COVID themselves within 14 days of that first case were considered to be cases of household transmission. In households where the index case was not vaccinated, 10.1% potential household contacts developed COVID, and where the index case was vaccinated 5.72% of potential household contacts developed COVID. This gave an Odds Ratio of 0.51 (95% CI 0.42-0.62) for the probability of household transmission where the index case was vaccinated with BNT162b2 versus when the index case was not vaccinated. There was an Odd Ratio of 0.62 (95%CI 0.48-0.79) for the probability of household transmission where the index case was vaccinated with ChAdOx1 versus when the index case was not vaccinated.

(V Shah, Gribben et al. 2021) was a pre-print of a similar study that linked documented COVID cases and hospitalisations in unvaccinated household members of vaccinated and unvaccinated household members in the UK between Dec 2020 and Mar 2021. The cohort comprised 194362 household members of 144525 healthcare workers. The study examined secondary cases 14 days after the healthcare worker receiving a second dose of vaccine. The study found an Odds Ratio of 0.48 (95%CI 0.32-0.73) of COVID infection among household contacts of vaccinated healthcare workers versus unvaccinated healthcare workers, and an Odds Ratio of 0.71 (95% 0.17-2.92(for the probability of hospitalisation among household contacts of vaccinated healthcare workers compared to versus unvaccinated healthcare workers.

These trials indicate there is a reduction in transmission from cases who have received ChAdOx1 or BNT162b2 vaccines in households, which is a close contact setting in which secondary attack rates of COVID are high. It is not clear how applicable this reduction is to transmission of COVID in this general community or with patients who have used other vaccines.

References

Harris, R and Hall et al, Impact of vaccination on household transmission of SARS-COV-2 in England, Public Health England (2021)

"<Impact of vaccination on household transmission of SARS-COV-2 in England.pdf>."

V Shah, A. S., et al. (2021). PRE.

Appendix 2.4

COVID vaccines in use worldwide

In addition to the four vaccines registered by TGA there are approximately 18 other COVID vaccines that have been deployed worldwide[7]. Some of these have low levels of distribution or are used only in countries with limited international travel to Australia, but the vaccines used in India, China and Russia are of particular relevance. The importance of these three originating countries arises from them being active donors to worldwide vaccination programs and, in the case of India and China, being a source of many arrivals in Australia. This Assessment has, therefore, initially prioritised these vaccines.

Vaccine	Developer	Country of origin	Australian registration status	Number of countries registered	Australian arrivals in 2019 from registered countries (excluding Australians)
Comirnaty	Pfizer	USA	Provisional	98	8612050
Vaxzevria	AstraZeneca	UK	Provisional	122	7466290
Spikevax	Moderna	USA	Provisional	71	8444580
Janssen COVID-19 Vaccine	Johnson and Johnson	Netherlands	Provisional	58	7250940
Coronavac	Sinovac	China	Unregistered	36	3756180
BBIBP-CorV	Sinopharm	China	Unregistered	61	3506400
COVIDSHEILD[8]	AstraZeneca/Serum Institute of India	India	Unregistered	39	1404680
Sputnik V	Gamaleya Research Institute	Russia	Unregistered	70	1728790
Covaxin	Bahrat Biotech	India	Unregistered	9	1086770
ZyCoV	Zydus Cadila	India	Unregistered	2	736910

Table 2. Arrivals in Australia during 2019 (pre-pandemic) from countries in which un-registered and provisionally registered COVID vaccines are used.[9]

India and China have 7 and 6 COVID vaccines in use respectively, providing a wide range of potential products being used by travellers arriving in Australia from these countries or those using their products.

[7] Data from Regulatory Affairs Professional Society Vaccine-tracker, available online at https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker

[8] COVIDSHEILD is a formulation of AstraZeneca's AZ1222 (Vaxzevria) vaccine but has separate registration status in some countries.

[9] Arrivals data from Australian Bureau of Statistics arrivals by country of citizenship. Registration status obtained from McGill University COVID-19 Vaccine Tracker, https://covid19.trackvaccines.org/