Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Cuban Abdala vaccine: Effectiveness in preventing severe disease and death from COVID-19 in Havana, Cuba; A cohort study

Pedro I. Más-Bermejo,[a] Félix O. Dickinson-Meneses,[a] Kenia Almenares-Rodríguez,[b] Lizet Sánchez-Valdés,[c] Raúl Guinovart-Díaz,[d] María Vidal-Ledo,[b] Enrique Galbán-García,[e] Yadira Olivera-Nodarse,[f] Isabel Morgado-Vega,[f] Santiago Dueñas-Carrera,[g] Merardo Pujol,[g] Francisco Hernández-Bernal,[g] Miladys Limonta-Fernández,[g] Gerardo Guillén-Nieto,[g] Verena L. Muzio-González,[g] and Marta Ayala-Ávila[g]*

[a]Pedro Kourí Tropical Medicine Institute, Havana, Cuba
[b]National School of Public Health, Havana, Cuba
[c]Molecular Immunology Centre, Havana, Cuba
[d]Mathematics and Computing Department, University of Havana, Havana, Cuba
[e]National Institute of Gastroenterology, Havana, Cuba
[f]Provincial Hygiene, Epidemiology and Microbiology Centre, Havana, Cuba
[g]Genetic Engineering and Biotechnology Centre, Havana, Cuba

The Lancet Regional Health - Americas 2022;16: 100366
Published online xxx
https://doi.org/10.1016/j.lana.2022.100366

Summary

Background COVID-19 vaccines have proven safe and efficacious in reducing severe illness and death. Cuban protein subunit vaccine Abdala has shown safety, tolerability and efficacy (92·3% [95% CI: 85·7–95·8]) against SARS-CoV-2 in clinical trials. This study aimed to estimate Abdala's real-world vaccine effectiveness (VE).

Methods This retrospective cohort study in Havana analyzed Cuban Ministry of Public Health databases (May 12-August 31, 2021) to assess VE in preventing severe illness and death from COVID-19 (primary outcomes). Cox models accounting for time-varying vaccination status and adjusting by demographics were used to estimate hazard ratios. A subgroup analysis by age group and a sensitivity analysis including a subgroup of tested persons (qRT-PCR) were conducted. Daily cases and deaths were modelled accounting for different VE.

Findings The study included 1 355 638 persons (Mean age: 49·5 years [SD: 18·2]; 704 932 female [52·0%]; ethnicity data unavailable): 1 324 vaccinated (partially/fully) and 31 433 unvaccinated. Estimated VE against severe illness was 93·3% (95% CI: 92·1-94·3) in partially- vaccinated and 98·2% (95% CI: 97·9-98·5) in fully-vaccinated and against death was 94·1% (95% CI: 92·5-95·4) in partially-vaccinated and 98·7% (95% CI: 98·3-99·0) in fully-vaccinated. VE exceeded 92·0% in all age groups. Daily cases and deaths during the study period corresponded to a VE above 90%, as predicted by models.

Interpretation The Cuban Abdala protein subunit vaccine was highly effective in preventing severe illness and death from COVID-19 under real-life conditions.

Funding Cuban Ministry of Public Health. Genetic Engineering and Biotechnology Centre.

Keywords: COVID-19; SARS-CoV-2; Vaccines; Effectiveness; Vaccination; Cohort studies; Cuba

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a massive global disease burden.[1] Non-pharmacological interventions have been the main public health strategies and policies implemented.[2] Likewise, several COVID-19 vaccines have been rapidly developed and approved for emergency use to tackle the prolonged pandemic, and mass

*Corresponding author at: Epidemiology Department, Pedro Kourí Tropical Medicine Institute, Address: Autopista Novia del Mediodía, Km 6 1/2, Municipio La Lisa, La Habana 17100, Cuba.
E-mail addresses: felixodickinson@gmail.com, dickinson@ipk.sld.cu (F.O. Dickinson-Meneses).

Research in context

Evidence before this study

We searched PubMed and preprint archives (MedRxiv) for articles published in English and Spanish between December 1st, 2021 and February 28 2022, using the keywords "COVID-19", "SARS-CoV-2", "vaccine", "vaccination", "effectiveness", "real world" and "cohort study". We selected articles containing information about COVID-19 vaccine effectiveness in the real world. Our search returned 268 studies, 31 of which were relevant to this topic. Previous studies have mainly focused on the effectiveness conferred by messenger RNA, viral-vector and inactivated virus vaccines in high and middle-income countries, but data about the effectiveness conferred by protein subunit vaccines in low-income countries are limited. To our knowledge, there is no previous real-world effectiveness assessment of the Cuban Abdala vaccine.

Added value of this study

The analysis of the effectiveness of the Abdala protein subunit vaccine in real-world conditions is the first carried out in Cuba and is similar to others carried out in the world. Demonstrates its high protective effect against severe forms and death from SARS-Cov-2 infection, with a complete schedule of three doses (0-14-28 days), in a scenario with a clear predominance of the variant of concern Delta. Likewise, it shows that implemented vaccination strategy, with a reduced scheme, accelerated and massive application in the population, provided satisfactory results against severe disease and fatal outcomes in adults and may be viable in a low-income country.

Implications of all the available evidence

Data from this study, compared with others in different countries, support the benefit of vaccines against COVID-19 as public health measures and suggest that their rapid, organized and massive use is a correct strategy to control pandemic, always considering the health system's characteristics. The inability of the available COVID-19 vaccines to effectively prevent infection, their potential effectiveness against the different variants of concern, the duration of their long-term protection and the need for booster doses are issues that require further attention.

vaccination campaigns have been implemented in many countries.[3,4] However, these achievements have not been made available equitably, and huge access asymmetries remain between rich and poor countries.[5]

In Cuba, the first COVID-19 cases were detected on March 11, 2020. Since then, the infection has reached epidemic levels, with thousands of cases and deaths, constituting the country's main health problem.[6] From the start of the epidemic, Havana accounted for the majority of cases and the highest incidence, despite the population being subject to non-pharmacological interventions established by the Ministry of Public Health (MINSAP).[6–8]

By July 9, 2021, there were 608 confirmed cases (284·4 per 1 000 000 population) and 3 deaths (1·4 per 1 000 000 population) in Havana, which increased notably, reaching a peak of 1994 cases (932·7 per 1 000 000 population) on July 30 and 10 deaths (4·7 per 1 000 000 population) on August 1st (*Appendix Figure* S-I). There was higher transmission in municipalities with higher population densities and more appreciable transmission in paediatric age groups.[7] Of the circulating SARS-CoV-2 variants, Delta was detected in Cuba at the end of April, spread rapidly countrywide and replaced other variants by July, resulting in high disease transmission and dispersion.[9]

Cuba's strategy to address the pandemic's challenges was to develop its own vaccine, taking advantage of biotechnological institutions with over three decades' experience.[10] By March 2021, Cuba had developed five vaccine candidates, all based on the protein subunit technological platform: Abdala, Mambisa, and Soberana 01, 02, and Plus.[11]

Abdala is a recombinant protein subunit vaccine developed by the Genetic Engineering and Biotechnology Centre (CIGB) that uses the yeast *Pichia pastoris* as the microorganism for expression.[12,13] Its formulation includes SARS-CoV-2's recombinant protein receptor binding domain (RBD), with aluminium hydroxide gel as an adjuvant. Abdala's complete vaccination schedule (per manufacturer guidelines, CIGB, Havana, Cuba), consists of three doses of 0·5 mL, administered intramuscularly (IM) in the deltoid region on days 0-14-28. It may be used as a booster or combined with other vaccines.[12] Abdala's clinical trials (RPCECo0000346, RPCECo0000359, RPCECo0000363), assessing safety, immunogenicity and efficacy, showed that it was well-tolerated, and no severe adverse events were reported.[12] In a phase 1/2, randomized, double-blind, placebo-controlled trial carried out in "Saturnino Lora" Hospital, Santiago de Cuba, Abdala vaccine was safe, well tolerated, and induced humoral immune responses against SARS-CoV-2 with a 50 mg dose, applied in a 0-14-28 days schedule.[14] In a multi-centre, randomized, double-blind placebo-controlled phase 3 study in 48 290 adult volunteers, Abdala demonstrated an efficacy of 92·3% (95% CI: 85·7–95·8), but, so far, peer-reviewed manuscript of phase 3 randomized clinical trials from Abdala are still unpublished.[12]

Considering these results, the Cuban regulatory agency (Centre for State Control of Medicines, Equipment and Medical Devices, CECMED, Spanish) issued an emergency use authorization (EUA) for Abdala on July 9, 2021.[15]

The complex epidemiological situation previously described increased the burden on healthcare services

in Havana, prompting the accelerated application of the Abdala vaccine,[7,15] reaching a vaccination coverage of 88·4% in the adult population by August 31, 2021.

This study's objective was to estimate Abdala's real-world effectiveness in preventing severe illness and death from COVID-19 in fully and partially vaccinated adult persons in Havana, Cuba, compared to those who were unvaccinated. Estimates obtained for Abdala's effectiveness were contrasted with vaccine effectiveness forecasts made, considering a 70% vaccine effectiveness; 90% vaccine effectiveness; and no vaccination to produce a sensitivity analysis for these estimates.

Methods

Study context

The study was carried out in Havana, Cuba, which is comprised of 15 municipalities with an estimated population of 2 137 936 inhabitants as of June 30, 2021, according to the National Statistics and Information Office (ONEI; www.onei.gob.cu).

From the start of the epidemic, Havana's population was subject to the general measures established by the Ministry of Public Health (MINSAP) including mandatory masking, social distancing, restrictions on movement, and isolation of positive cases. These conditions and guidelines were maintained throughout the study period.[6]

Design

To estimate the real-world effectiveness of the Abdala vaccine, we conducted an observational retrospective cohort study including persons aged ≥19, residing in Havana, and unvaccinated at the start of the study, which received subsequently the vaccine during a massive vaccination campaign. From this population, and after considering eligibility criteria, study cohorts were formed according to vaccination status: unvaccinated and vaccinated (partially and fully), and followed for 111 days. Inclusion in the three groups was dynamic throughout the study period; participants who did not receive vaccination were initially counted in the unvaccinated group until they had received their first dose, after which they were transitioned into the partially vaccinated group, where they stayed until received the third dose and 14 days elapsed, then they were moved to the fully vaccinated cohort. Havana's primary health-care system covers the resident population regardless of socioeconomic, political or cultural status, gender, race or ethnicity. Primary care data from family doctors' office records were linked to laboratory test results, vaccination registries, patients' clinical histories and epidemiological survey forms.

Exposure

Abdala vaccine sufficient doses were available for the entire Havana adult population. The vaccine was administered free of charge in stages in each of the city's municipalities, using both personnel and vaccination sites that were duly accredited by CECMED and MINSAP.[15]

For the purpose of this study, persons were considered fully vaccinated if they had received the complete vaccination schedule and were ≥14 days past their third dose and partially vaccinated if they had received 1-2 doses or 3 doses and less than 14 days past their third dose. Those who did not meet this criterion were included in the unvaccinated group.

A short follow-up study of the cohort was carried out for 111 days (from May 12 through August 31, 2021) via surveillance mechanisms implemented by MINSAP. For fully-vaccinated individuals, follow-up was carried out 14 days after the third vaccine dose was administered, until event occurrence or study's end. For partially-vaccinated individuals, follow-up was carried out after the first dose was administered until they become fully-vaccinated, event occurrence or study's end. Unvaccinated persons were observed from the start of the study until either the event occurrence, study's end or vaccination. The median contribution of fully-vaccinated was 43 person-days at risk, partially-vaccinated 42 person-days at risk and unvaccinated 34 person-days at risk.

The Cuban health system is based on primary health care strategy and a single integrated public model. It guarantees free, equitable and universal healthcare coverage, supported by neighbourhood family practice offices. This facilitated consistent active surveillance at the community level, led by family doctors and health workers. During the SARS-CoV-2 pandemic, this allowed active daily screening for symptomatic cases and notification, as well as admission and care of all newly diagnosed cases.[16]

Data collection and sourcing

Data on the cohort's participants were obtained from the national online registry ANDARIEGO.HIGIA (GEOCUBA, Cuba, http://higia.andariego.cu)—a database whose access is limited to authorized users—which includes, among other data, an identifier unique to each individual, demographic information, the vaccine used, and the dates doses were applied, according to the vaccine's schedule.[12,13] Information on vaccine coverage was obtained from the daily report issued by MINSAP's National Statistics and Medical Records Division.

The national online registry ANDARIEGO.HIGIA was used to acquire information on their ages, sex and residential area. Clinical evolution summaries for those admitted to wards designated for severe COVID-19 patients provided information on disease severity and death. MINSAP's COVID-19 case registries and epidemiological survey forms include diagnostic confirmation by the microbiology laboratories at Havana's

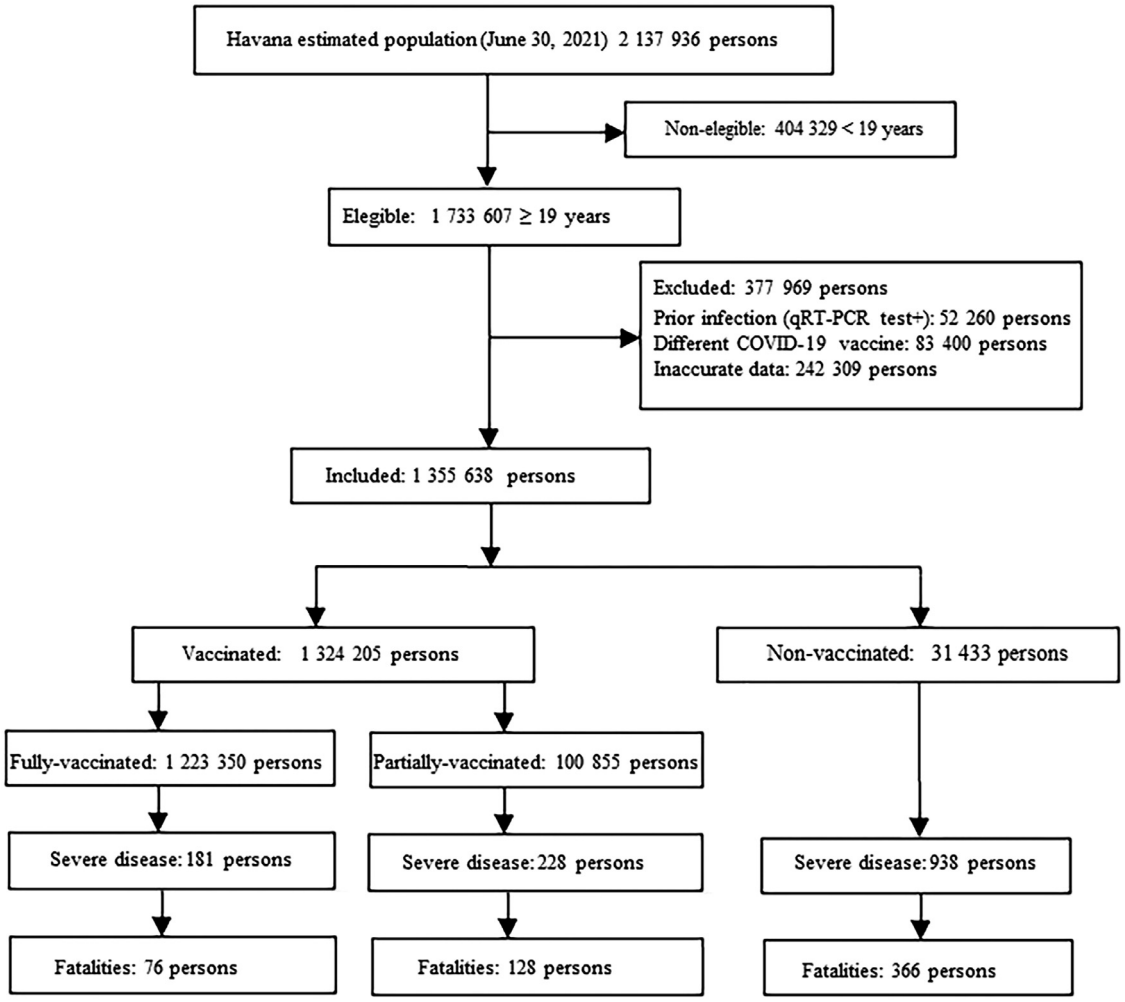

Figure 1. Abdala vaccine effectiveness study participants: eligibility, exposure and outcomes. Havana, Cuba, May 12–August 31, 2021.

Provincial Hygiene, Epidemiology and Microbiology Centre via real-time reverse transcriptase polymerase chain reaction (qRT-PCR, STAT-NAT COVID-19 MULTI, Italy) using nasopharyngeal swab samples, according to World Health Organization (WHO) guidelines for qRT-PCR,[17] applied free of charge for the general population, including all participants in this study.

Participants

For the purpose of this study, we considered inclusion criteria to be 19 years of age or older, not having been diagnosed with SARS-Cov-2 infection (qRT-PCR test+) prior to the start of the study, being residents of Havana, and having complete and accurate data.

Eligible for the study were 1 733 607 persons aged ≥19 years whose data were available and correctly registered. Of these, 377 969 were excluded: 52 260 whose qRT-PCR tests confirmed SARS-CoV-2 infection prior to study start; 83 400 who received a COVID-19 vaccine other than Abdala; and 242 309 who had inaccurate data.

Study inclusion criteria were met by 1 355 638 persons who were divided into two cohorts: 1 324 205 individuals in the vaccinated cohort (1 223 350 fully vaccinated and 100 855 partially vaccinated), and 31 433 in the unvaccinated cohort (Figure 1).

Variables

In both cohorts, the COVID-19 outcomes measured included severe disease, defined by MINSAP's COVID-19 National Action Protocol,[18] and death according to WHO.[19] All cases included in the study were confirmed positive for COVID-19 by qRT-PCR.

The following criteria were considered for variables:

- Age: four groups were established (19–40, 41–60, 61–80, >80 years).

- SARS-CoV-2 infection: an individual with or without characteristic COVID-19 symptoms,[18] with a positive qRT-PCR test from a nasopharyngeal swab sample taken at a healthcare institution.
- Severe clinical illness due to COVID-19: patients with fever, cough, polypnea, infiltrate/condensation in radiological examination or lung ultrasound, oxygen saturation <90%, or who required mechanical ventilation.[18]
- Death from COVID-19: a person who died as a result of confirmed COVID-19, with symptoms clinically compatible with the disease.[19]

Statistical methods

We estimated the vaccine effectiveness with Cox proportional hazards models, using vaccine status as a time-varying covariate for all individuals included. Primary outcomes of interest were severe disease and death. We right-censored individuals at the time of an event (Intensive Care Units [ICU] admission or death associated with COVID-19) and at the end of the follow-up period (31th of August). Exposure was specified according to vaccination status (fully-vaccinated, partially-vaccinated or unvaccinated). The same cohort contributed person-time at risk to unvaccinated and vaccinated exposure categories, with all individuals starting in the unvaccinated state and sequentially transitioning through vaccinated exposure states until the outcome of interest or being censored at the point of the follow-up period. Hazard ratio (HR) estimates were obtained with 95% confidence intervals (95% CI).

For crude vaccine effectiveness estimates, we only used vaccine status as a time-varying covariate with no adjustments for covariates. The adjustment was made using stratification by age, sex and municipality in the survival R package. To estimate specific vaccine effectiveness for age groups we implemented independent Cox models still adjusting for the remaining covariates. Vaccine effectiveness (%) was estimated as (1–HR) × 100.[2] The same procedure was used to calculate the effectiveness in each age group. All models were implemented in the statistical software R, using the survival package.

To assess whether the effectiveness results were affected by potential differences in access to health care services between vaccinated and unvaccinated, we performed sensitivity subgroup analysis only on individuals who had been qRT-PCR tested for SARS-CoV-2 during the study period as was proposed in Jara.[20]

Additionally, a compartmental dynamic mathematical model of the differential equations type Susceptible-Infected-Quarantine-Recovered-Protected-Deceased-Vaccinated was used to predict daily confirmed COVID-19 cases and deaths in Havana,[21] that could be expected during the study period. This type of model is standard and has been commonly used in modelling vaccination of other virus-induced diseases.[22,23] This model allowed us to simulate the effect of daily vaccine effectiveness on COVID-19 cases and deaths considering 70% vaccine effectiveness; 90% vaccine effectiveness; and no vaccination. Given direct contact with an infected person, those vaccinated had a probability of becoming ill of (1-η), representing an estimate of vaccine ineffectiveness. Data was analysed with R (4.1.1), Foundation for Statistical Computing, Vienna, Austria. Forecasting cases were estimated with MATLAB and Statistics Toolbox Release 2018b software, The MathWorks, Inc., Natick, Massachusetts, United States.

Ethics

The study protocol was approved by the Research Ethics Committee of the Pedro Kourí Tropical Medicine Institute (IPK)—CEI-IPK protocol 31-21, November 2021. The study complies with the bioethical framework for this type of medical research. Data for the study come from records of the MINSAP entity responsible for collecting infectious disease notifications, as well as for epidemiological population health surveillance and management, and thus their use does not require informed consent. This information is protected, and the confidentiality of all participants is preserved. Demonstrating the effectiveness of the Abdala vaccine against COVID-19 provides essential information and is the benefit of this study.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Throughout the study period of May 12 through August 31, 2021, 1 355 638 persons met the inclusion criteria. Of these, 1 223 350 were fully-vaccinated, 100 855 were partially-vaccinated, and 31 433 were unvaccinated. The mean age was 49·5 years (SD: 18.2), thus most individuals were aged 19-40 years (469 383/1 355 638 [34·6%]) and 41-60 years (507 362/1 355 638 [37·4%]). Overall, there were more females (52·0%) than males and most participants inhabited Boyeros (10·8%) and Arroyo Naranjo (10·0%) municipalities. More than 70·0% of severe disease cases (946/1347 [70·3%]) and deaths (441/579 [70·4%]) were observed in individuals >60 years and males predominated in both outcomes (738/1347 [54·8%] and 312/570 [54·7 %]), respectively. The highest numbers of severe disease cases and deaths were observed in municipalities Diez de Octubre and Plaza (Table 1).

	Vaccination status				COVID-19 outcome	
	Unvaccinated (*n*=31 433)	Partially Vaccinated (*n*=100 855)	Fully Vaccinated (*n*=1 223 350)	Total (*N*=1 355 638)	Severe disease (*n*=1347)	Deaths (*n*= 570)
Age, years						
19 – 40	11208 (35·7%)	49001 (48·6%)	409174 (33·4%)	469383 (34·6%)	79 (5·8%)	21 (3·7%)
41 – 60	12189 (38·8%)	31715 (31·4%)	463458 (37·9%)	507362 (37·4%)	322 (23·9%)	108 (18·9%)
61 – 80	6923 (22·0%)	16142 (16·0%)	290628 (23·8%)	313693 (23·2%)	638 (47·4%)	277 (48·6%)
>80	1113 (3·5%)	3997 (4·0%)	60090 (4·9%)	65200 (4·8%)	308 (22·9%)	164 (28·8%)
Sex						
Male	11910 (37·9%)	42261 (41·9%)	596417 (48·8%)	650588 (48·0%)	738 (54·8%)	312 (54·7%)
Female	19523 (62·1%)	58594 (58·1%)	626933 (51·2%)	705050 (52·0%)	609 (45·2%)	258 (45·3%)
Municipalities						
Arroyo Naranjo	2602 (8·3%)	5916 (5·9%)	126723 (10·4%)	135241 (10·0%)	124 (9·2%)	47 (8·2%)
Boyeros	1484 (4·7%)	6101 (6·0%)	138251 (11·3%)	145836 (10·8%)	102 (7·6%)	41 (7·2%)
Centro Habana	2796 (8·9%)	6337 (6·3%)	67613 (5·5%)	76746 (5·7%)	112 (8·3%)	51 (8·9%)
Cerro	1961 (6·2%)	3654 (3·5%)	64958 (5·3%)	70573 (5·2%)	70 (5·2%)	23 (4·0%)
Cotorro	1164 (3·7%)	3404 (3·4%)	52184 (4·3%)	56752 (4·2%)	40 (3·0%)	15 (2·7%)
Diez de Octubre	4379 (13·9%)	12563 (12·5%)	93346 (7·6%)	110288 (8·1%)	156 (11·6%)	69 (12·1%)
Guanabacoa	1388 (4·4%)	6532 (6·5%)	78447 (6·4%)	86367 (6·4%)	49 (3·6%)	19 (3·3%)
Habana del Este	1293 (4·1%)	7578 (7·5%)	109989 (9·0%)	118860 (8·8%)	87 (6·5%)	28 (4·9%)
Habana Vieja	1493 (4·7%)	4245 (4·2%)	44124 (3·6%)	49862 (3·7%)	54 (4·0%)	24 (4·2%)
La Lisa	1350 (4·3%)	6210 (6·2%)	75713 (6·2%)	83273 (6·1%)	108 (8·0%)	40 (7·0%)
Marianao	2795 (8·9%)	8871 (8·8%)	71964 (5·9%)	83630 (6·2%)	102 (7·6%)	48 (8·5%)
Playa	2756 (8·9%)	12892 (12·8%)	90576 (7·4%)	106224 (7·8%)	98 (7·3%)	45 (7·9%)
Plaza de la Revolución	2752 (8·8%)	10074 (10·0%)	72847 (6·0%)	85673 (6·3%)	136 (10·1%)	72 (12·7%)
Regla	918 (2·9%)	1993 (2·0%)	27580 (2·3%)	30491 (2·2%)	15 (1·0%)	4 (0·7%)
San Miguel del Padrón	2302 (7·3%)	4485 (4·4%)	109035 (8·8%)	115822 (8·5%)	94 (7·0%)	44 (7·7%)

***Table 1*: Cohort socio-demographics characteristics. Havana, May 12-August 31 2021.**

During follow-up, COVID-19 severe disease occurred among 181 fully-vaccinated individuals, 228 partially-vaccinated individuals and 938 unvaccinated individuals, with incidence rates per 10 000 person-years of 0·03, 0·04 and 0·23, respectively (Table 2). All participants received specialized medical care in Havana hospitals' ICU. Death from COVID-19 was reported in 76 patients who had been fully-accinated, 128 patients partially-vaccinated and 366 who were unvaccinated. Among COVID-19 fatalities, lower incidence densities were observed in fully-vaccinated (0·01 per 10 000 person-years) and partially-vaccinated (0·02 per 10 000 person-years), compared to unvaccinated individuals (0·09 per 10 000 person-years) (Table 2).

The overall estimated effectiveness against severe disease reached 93·3% (95% CI: 92·1-94·3) in partially-vaccinated and 98·2 % (95% CI: 97·9-98·5) in fully-vaccinated (Table 2), with the highest numbers in

Outcome	Total person-time, days	Number of event	Incidence density per 10 000 person-days	Unadjusted hazard ratio (95% CI)	Adjusted[a] hazard ratio (95% CI)	Vaccine effectiveness (95% CI)
Severe disease						
Unvaccinated	40 550 127	938	0·23	-	-	-
Partially vaccinated	58 783 518	228	0·04	0·07 (0·06-0·08)	0·06 (0·05-0·07)	93·3 (92·1-94·3)
Fully vaccinated	51 071 360	181	0·03	0·02 (0·01-0·02)	0·01 (0·01-0·02)	98·2 (97·9-98·5)
Deaths						
Unvaccinated	40 550 363	366	0·09	-	-	-
Partially vaccinated	58 783 994	128	0·02	0·08 (0·06-0·10)	0·06 (0·05-0·08)	94·1 (92·5-95·4)
Fully vaccinated	51 071 345	76	0·01	0·02 (0·01-0·03)	0·01 (0·01-0·02)	98·7 (98·3-99·0)

***Table 2*: Abdala vaccine effectiveness in preventing severe disease and death from COVID-19. Havana, Cuba, May 12-August 31 2021.**
[a] Adjusted by Age, Sex and Resident Area (Municipality).

	Age, years	Severe Disease		Death	
		Effectiveness (%)	95% CI	Effectiveness (%)	95% CI
Partially vaccinated	19-40	95,2	(90,3−97,7)	93,3	(77,4−98,0)
	41-60	94,3	(91,8−96,0)	96,3	(93,1−98,1)
	61-80	93,2	(91,3−94,6)	92,4	(89,3−94,6)
	>80	96,1	(94,5−97,2)	95,5	(93,0−97,0)
Fully vaccinated	19-40	99,4	(98,2−99,8)	99,5	(95,2−100,0)
	41-60	98,0	(97,0−98,6)	97,9	(96,3−98,8)
	61-80	98,7	(98,2−98,9)	98,8	(98,3−99,2)
	>80	99,1	(98,6−99,4)	98,7	(97,8−99,2)

***Table 3*: Abdala vaccine effectiveness in preventing severe disease and death from COVID-19 according to age. Havana, Cuba, May 12-August 31 2021.**
*Adjusted by Sex and Resident Area (Municipality).

individuals 19-40 years (99·4 [95% CI: 98·2-99·8] and >80 years (99·1 [95% CI: 98·6-99·4]) fully-vaccinated (Table 3). Likewise, effectiveness in preventing death from COVID-19 was greater in fully-vaccinated 98·7% (95% CI: 98·3-99·0) than those partially-vaccinated 94·1% (95% CI: 92·5-95·4) (Table 2). Similarly, the highest figures were observed in persons fully-vaccinated 19-40 years (99·5 [95% CI: 95·2-100·0] and 61-80 years (98·8 [95% CI: 98·3-99·2]) (Table 3).

Sensitivity analyses of potential differences in access to health care services between vaccinated and unvaccinated by immunization status, adjusted by age group, sex and resident area including only individuals who took an qRT-PCR during the study period, showed vaccine effectiveness estimates against severe disease COVID-19 and death above 90.0% (***Appendix, Tables* S-I *and* S-II**), similar to those of the main analysis; confirming that effectiveness in the vaccinated cohort was consistent. These results address the concern that the observed vaccine effectiveness might be affected by healthcare access because all individuals included in the analysis had demonstrated access to the Cuban healthcare system.

At the beginning of the study, daily cases and deaths reported by MINSAP agreed with forecasts that aligned with vaccine effectiveness of 90%, but by the study's midpoint, when vaccination coverage was 75%−80%, cases and deaths began to steadily decrease. This was much more apparent in the last weeks of the study period, indicative of effectiveness above 90% and thus consistent with the estimated effectiveness (Figure 2).

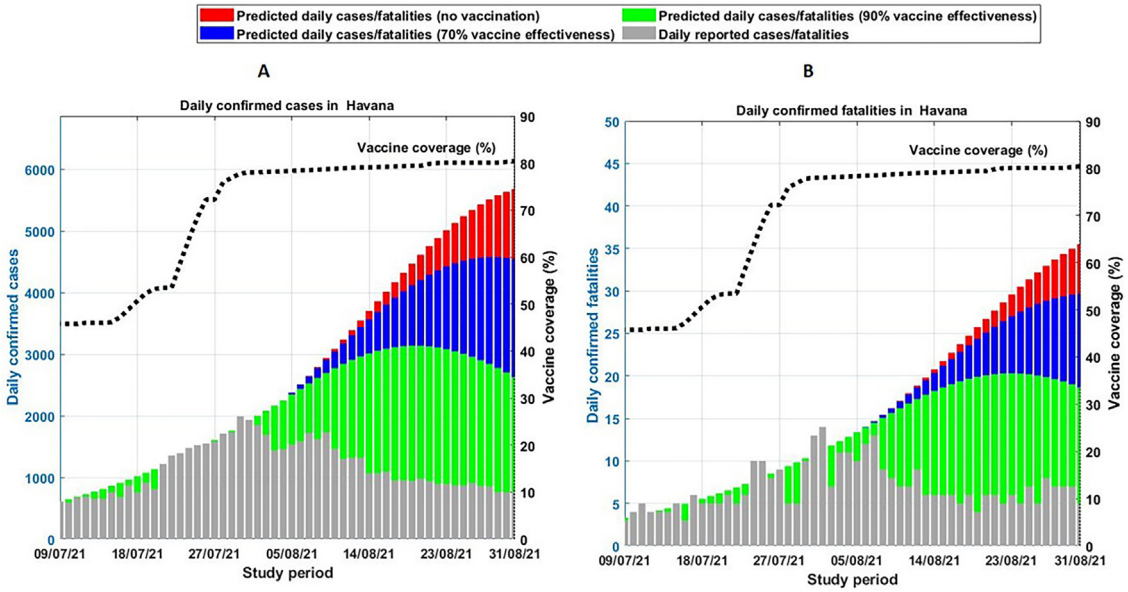

Figure 2. Daily confirmed, actual, and predicted confirmed cases (A) and deaths (B), with and without the Abdala vaccine. Havana, Cuba, July 9–August 31, 2021.

Discussion

This study was conducted under real-world conditions amidst COVID-19 Delta variant transmission, in a middle-income country, and included a large segment of Cuba's most populous city. The results validate the high effectiveness of the protein subunit Abdala vaccine in preventing severe COVID-19 disease and death, when measured from 14 days after administration of the full three-dose schedule (following the manufacturer's recommended application at 0-14-28 days),[12,13] achieving the desired effect in a relatively short time. In partially vaccinated individuals (1-2 doses or 3 doses and less than 14 days past their third dose), similar results were obtained for both outcomes (vaccine effectiveness 93·3% and 94·1% respectively).

Severe disease has important implications for public health and policy making, since it may not only lead to death but also long-lasting sequels, with substantial repercussions for populations and healthcare systems. Our results demonstrate that the Abdala vaccine provides substantial protection for older adult populations and adds to the knowledge base of real-world COVID-19 vaccine effectiveness. In both outcomes (preventing severe disease and death), the Abdala vaccine's effectiveness was satisfactory (>90%) for all age groups, and the vaccine has received EUA in several other countries.[13]

Similar results in preventing severe disease and death have been reported in other countries.[20,24,25] Systematic reviews including a wide variety of study types and settings, including 107 real-world vaccine effectiveness studies in adults which covered eight vaccines across all vaccine platforms, demonstrated protection against COVID-19 severe infection or death in the general population of, at least, 60% and most often close to 100%.[26–28] However, it should be noted that variations in estimated effectiveness reported in other studies could result from differing study designs, settings, testing protocols, study populations, types of vaccine, schedules and time intervals considered appropriate to best measure each vaccine's immunological effects. More real-world effectiveness studies of longer durations are required in low-and middle-income countries since the majority of such research has been carried out in high-income nations.[29]

A major unresolved issue regarding COVID-19 vaccines is their inability to effectively prevent infection. Additionally, authorizations for their use have been given via accelerated regulatory pathways, with limited supporting clinical data, making it imperative to continue research to provide additional, more robust information on their safety, efficacy, effectiveness, and long-term protection; all of which are important to consider risk, minimize damage and maintain public confidence over time.

An observational study under real-world conditions is difficult to conduct without introducing bias, given the lack of vaccine randomization and of balance between vaccinated and unvaccinated persons with respect to the risk of contracting the disease. The main biases of concern for this study (the search for and access to healthcare, diagnosis confirmation, exclusion of persons with prior COVID-19 infection, and previous vaccine administration, among others) coincide with the bias described by WHO.[30] Overall, our adjusted sensitivity analyses of qRT-PCR tested individuals by immunization status were qualitatively similar to those obtained by considering the complete cohort, and provides empirical evidence that they are unaffected by a potential differential health care access. Potential under-testing, under-diagnosis and under-notification bias cannot be ruled out and should be considered as a limitation. All three were minimized by performing confirmatory qRT-PCR tests on everyone with COVID-19 symptoms, as well as on their contacts, a practice established in the Cuban National COVID-19 Action Protocol (Version 1.6)[18] and backed by the characteristics of the Cuban health system described previously.[16]

To control for prior infection bias those who were confirmed positive for SARS-CoV-2 (PCR+) before the start of the study were excluded. During the study period, the number of tests was considerably expanded nationwide, increasing the number of qRT-PCR and antigen tests performed.

Selection biases and confounding effects due to possible imbalances caused by comorbidities associated with the disease were unavoidable potential limitations and should be considered when assessing our study. It was not possible either to fix propensity bias to get vaccinated, or propensity to get vaccinated early in the study period. Data on ethnicity were not collected either, considering that Cuba is a country with an important mix of race among the population and no particular ethnic groups share economic, cultural and social characteristics.

Outcome misclassification due to false negatives cannot be completely ruled out, even if a test with high SARS-CoV-2 specificity was used. Finally, although vaccination registries may have missed some vaccinated individuals within the Cuban healthcare system, automated data collection via the ANDARIEGO.HIGIA registry minimized this effect. Although genomic sequencing in Havana detected a switch from beta to delta as the main variant of concern with the highest circulation during the study period,[9] we lack representative contextual data from that period.

The study period encompasses the most complex epidemiological situation of the COVID-19 epidemic in Havana. From our point of view, the accelerated and high coverage vaccination campaign carried out and including all population (regardless of age, sex, skin colour, economic status, religion or political trends), based on community participation and supported by governmental institutions, contributed decisively to a fast decline of cases, severe disease and deaths, allowing for the recovering of social and productive activities -

including the opening of airports - a few weeks later, which continued until today.

Our results contribute to a better understanding of Abdala's effects on SARS-CoV-2 infection and highlight the importance of these studies in demonstrating vaccine protection against severe illness and death from COVID-19, and ratify the usefulness of vaccines as essential tools to control the disease and improve its outcomes. These data may also be useful to health policymakers for use in controlling COVID-19 in their respective settings.

Follow-up on these effectiveness values over time and the need to apply booster doses to maintain effective protection are pending tasks requiring further research. However, it merits repeating that vaccines alone will not solve the problems associated with the pandemic; success in meeting these challenges requires a health system capable of rapid and organized action. This was a great strength that contributed to our ability to achieve results in a comparatively short time.

The Abdala vaccine showed high effectiveness in preventing severe illness and death under real-world conditions. Future studies will make it possible to assess the duration of the vaccine's protection over the long term, as well as the advisability of booster doses.

Contributors

PIM-B participated in the conceptualization and study design, data analysis and interpretation, conduct and supervision of research process, literature search, writing initial draft, critical review & editing of pre- or post-publication stages. FOD-M contributed in the conceptualization and study design. Data analysis and interpretation, supervision of research, literature search, figures, writing initial draft, critical review & editing of pre- or post-publication stages. KA-R participated in conceptualization and study design. Data/evidence management, collection, analysis, and interpretation. Statistical analysis. Visualization and data presentation. Writing the initial draft. Review of pre- or post-publication stages. Literature search. LS-V contributed in conceptualization and study design. Data management, collection, analysis, and interpretation. Statistical analysis and modelling. Literature search, writing initial draft, critical review & editing of pre- or post-publication stages. RG-D performed data analysis and interpretation. Mathematical analysis and modelling. Writing the initial draft, critical review & editing or revision of pre- or post-publication stages and Figures. MV-L took part in the data/evidence collection interpretation. Writing the initial draft. Critical review and commentary. Critical review of pre or post-publication stages. Literature search. Figures. EG-G participated in conceptualization and study design. Data interpretation. Writing the initial draft. Critical review and commentary of pre- or post-publication stages. Literature search. YO-N and IM-V took part in the data/evidence collection and management. Critical review & revision of pre- or post-publication stages. SD-C, MP, FH-B, ML-F, G G-N, VLM-G AND MA-A contributed to study design. Data analysis and interpretation. Critical review & revision of pre- or post-publication stages.

Data sharing statement

Data on participant vaccination were obtained from the national online registry database which is limited to authorized users. Data on other related documents are also not available. Aggregate data on vaccination, incidence and mortality are publicly available at https://covid19cubadata.github.io/#cuba

Declaration of interests

The Public Health Ministry of Cuba guaranteed the payment of the salaries to the authors through their respective institutions. Genetic Engineering and Biotechnology Centre paid for the article processing charges.

Acknowledgements

We would like to express our deep gratitude to Professor Luis E Cuevas, DSC, MTrop Med, MD at Liverpool School of Tropical Medicine, United Kingdom and Professor Francisco Javier Ballesteros Rodriguez, University of the Basque Country, Spain UPV/EHU Department of Neuroscience – Psychiatry Senior Researcher CIBERSAM & Co-director Cochrane Associated Centre at UPV/EHU for their valuable and constructive suggestions during the planning and development of this research work. Their willingness to give their precious time so generously has been very much appreciated.

We are also grateful for the insightful comments offered by the anonymous peer reviewers. The kindness and expertise of all have improved this study in innumerable ways and prevented many errors; those that inevitably remain are entirely our responsibility. Finally, we would also like to extend our thanks to the family doctors and nurses, epidemiologists, technicians and other health workers in Havana for their unconditional dedication to this noble labour.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2022.100366.

References

1 Ritchie H, Mathieu E, Rodés-Guirao L, et al. Coronavirus pandemic (COVID-19). *Our World in Data*2020. https://ourworldindata.org/coronavirus. Accessed 13 February 2022.
2 Li Y, Campbell H, Kulkarni D, et al. The temporal association of introducing and lifting non-pharmaceutical interventions with the

time-varying reproduction number (R) of SARS-CoV-2: a modelling study across 131 countries. *Lancet Infect Dis*. 2021;21:193–202. https://doi.org/10.1016/S1473-3099(20)30785-4.

3 Anand U, Jakhmola S, Indari O, et al. Potential therapeutic targets and vaccine development for SARS-CoV-2/COVID-19 pandemic management: a review on the recent update. *Front Immunol*. 2021;12:658519. https://doi.org/10.3389/fimmu.2021.658519.

4 Picazo JJ. *Vacuna frente al COVID-19*. Madrid: Sociedad Española de quimioterapia; 2021. https://seq.es/wp-content/uploads/2021/12/vacunas-covid-6.3.pdf. Spanish Accessed 13 January 2022.

5 Batista C, Hotez P, Amor YB, et al. The silent and dangerous inequity around access to COVID-19 testing: a call to action. *EClin Med*. 2022;43:101230. https://doi.org/10.1016/j.eclinm.2021.101230.

6 Galbán-García E, Más-Bermejo P. COVID-19 in Cuba: assessing the national response. *MEDICC Rev*. 2020;22(4):29–34. https://doi.org/10.37757/MR2020.V22.N4.5.

7 Portal-Miranda J. Intervención sanitaria con candidatos vacunales, como estrategia temporal de enfrentamiento a la COVID-19, Cuba, 2021. *Rev Cubana Salud Pública*. 2021;48(1):e3512. http://www.revsaludpublica.sld.cu/index.php/spu/article/view/3513. Spanish Accessed 14 February 2022.

8 Más-Bermejo P, Vidal-Ledo M, Baldoquín-Rodríguez W, et al. Organización de la investigación epidemiológica para la lucha antiepidémica contra la COVID-19 en Cuba. Rev Inf Científ Dir Salud *(INFODIR)*. 2020;32. http://www.revinfodir.sld.cu/index.php/infodir/article/view/831. Spanish Accessed 03 February 2022.

9 Noda Alonso S, Fernández Perdomo Y. *Variantes Genéticas Aumentan la Severidad de la COVID-19. Mesa Redonda con la Dra. Guadalupe Guzmán*. Havana: MINSAP; 2021. https://salud.msp.gob.cu/variantes-geneticas-aumentan-la-severidad-de-lacovid-19/. Spanish Accessed 20 September 2021.

10 World Health Organization. *Cuban Experience with Local Production of Medicines, Technology Transfer and Improving Access to Health*. Geneva: World Health Organization; 2015. https://www.who.int/phi/publications/Cuba_case_study121115.pdf. Accessed 26 December 2021.

11 Taylor L. Why Cuba developed its own covid vaccine—and what happened next. *Brit Med J*. 2021;374:n1912. https://doi.org/10.1136/bmj.n1912.

12 Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (CECMED) (CU). ABDALA 50 µg (Vacuna anti COVID-19 de subunidad proteica). *Resumen de las Características del Producto*. 2021. Havana: CECMED; 2021. https://www.cecmed.cu/registro/rcp/biologicos/abdala-50-mg-vacuna-anti-covid-19-subunidad-proteica. Spanish Accessed 13 January 2022.

13 Gorry C. Vaccines and public trust: containing COVID-19 in Cuba. Verena Muzio-González PhD DSc. Director of clinical research, genetic engineering and biotechnology center. *MEDICC Rev*. 2022;24(1):9–13. https://doi.org/10.37757/MR2022.V24.N1.11.

14 Hernández-Bernal F, Ricardo-Cobas MC, Martin-Bauta Y, et al. Safety, tolerability, and immunogenicity of a SARS-CoV-2 recombinant spike RBD protein vaccine: a randomised, double-blind, placebo-controlled, phase 1-2 clinical trial (ABDALA Study). *EClinicalMedicine*. 2022. https://doi.org/10.1016/j.eclinm.2022.101383. Accessed 2 January 2022.

15 Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (CECMED) (CU). *Aprobación uso de emergencia Abdala. Resolución 113 AUE, Abdala, Jul 2021*. Havana: CECMED; 2021. 20212021; https://www.cecmed.cu/covid-19/aprobaciones/abdala. Spanish Accessed 13 January 2022.

16 Mas Bermejo P, Sánchez Valdés L, Somarriba López L, et al. Equity and the Cuban National Health System's response to COVID-19. *Rev Panam Salud Pública*. 2021. https://doi.org/10.26633/RPSP.2021.80. Accessed 1 January 2022.

17 World Health Organization (WHO). *Laboratory Testing Strategy Recommendations for COVID-19: Interim Guidance, 21 March 2020*, Geneva: WHO; 2020. https://apps.who.int/iris/handle/10665/331509. Accessed 14 January 2022.

18 Ministry of Public Health (MINSAP) (CU). *Protocolo de Actuación Nacional para la COVID-19 (Versión 1.6) 28 marzo 2021*. Havana: MINSAP; 2021. https://temas.sld.cu/coronavirus/covid-19/minsap-estrategia-e-indicaciones/. Spanish Accessed 13 January 2022.

19 World Health Organization (WHO). International guidelines for certification and classification (coding) of COVID-19 as cause of death. *Based on ICD International Statistical Classification of Diseases (16 April 2020)*. Geneva: WHO; 2020. https://www.who.int/classifications/icd/Guidelines_Cause_of_Death_COVID-19.pdf . Accessed 14 January 2021.

20 Jara A, Undurraga EA, González C, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. *New Eng J Med*. 2021;385(10):875–884. https://doi.org/10.1056/NEJMoa2107715. https://www.nejm.org/doi/10.1056/NEJMoa2107715?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed. Accessed 30 January 2022.

21 Guinovart-Sanjuan D, Guinovart-Díaz R, Vajravelu K, Morales-Lezca W, Abello-Ugalde I. Multi-population analysis of the Cuban SARS-CoV-2 epidemic transmission before and during the vaccination process. *Phys Fluids*. 2021;33:107107. https://doi.org/10.1063/5.0066912. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8561656/. Accessed 30 January 2022.

22 Nuraini N, Khairudin K, Hadisoemarto P, Susanto H, Hasan A, Sumarti N. Mathematical models for assessing vaccination scenarios in several provinces in Indonesia. medRxiv *BMJ*. 2020. https://doi.org/10.1101/2020.12.21.20248241. Accessed 1 January 2022.

23 Li Qian, Tang Biao, Bragazzi Nicola Luigi, Xiao Yanni, Wu Jianhong. Modeling the impact of mass influenza vaccination and public health interventions on COVID-19 epidemics with limited detection capability. *Math Biosci. NIH*. 2020;325:08378. https://doi.org/10.1016/j.mbs.2020.108378. Accessed 1 January 2022.

24 Rosenberg ES, Dorabawila V, Easton D, Bauer UE, Kumar J, Hoen R. Covid-19 vaccine effectiveness in New York state. *N Engl J Med*. 2022;386:116–127.

25 Caifang Z, Weihao S, Xiaorui C, Bowen Z, Gaili W, Weidong Z. Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis. *Int J Infect Dis*. 2021(21). https://doi.org/10.1016/j.ijid.2021.11.009. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8561656/. Accessed 30 January 2022.

26 Higdon MM, Wahl B, Jones CB, et al. A systematic review of coronavirus disease 2019 vaccine efficacy and effectiveness against severe acute respiratory syndrome coronavirus 2 infection and disease. *Open Forum Infect Dis*. 2022. https://doi.org/10.1093/ofid/ofac138.eCollection. https://academic.oup.com/ofid/article/9/6/ofac138/6570021?login=false. Accessed 1 January 2022.

27 Mohammed I, Nauman A, Paul P, et al. The efficacy and effectiveness of the COVID-19 vaccines in reducing infection, severity, hospitalization, and mortality: a systematic review. *Hum Vaccin Immunother*. 2022. https://doi.org/10.1080/21645515.2022.2027160. https://www.tandfonline.com/doi/pdf/10.1080/21645515.2022.2027160?needAccess&. Accessed 1 January 2022.

28 Feikin DR, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *Lancet*. 2022;5(399(10328)):924–944. https://doi.org/10.1016/S0140-6736(22)00152-0.

29 Teerawattananon Y, Anothaisintawee T, Pheerapanyawaranun C, et al. A systematic review of methodological approaches for evaluating real-world effectiveness of COVID-19 vaccines: advising resource-constrained settings. *PLoS One*. 2022;17(1):e0261930. https://doi.org/10.1371/journal.pone.0261930. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0261930.

30 Patel MK, Bergeri I, Bresee JS, et al. Evaluation of post-introduction COVID-19 vaccine effectiveness: summary of interim guidance of the world health organization. *Vaccine*. 2021;39(30). https://doi.org/10.1016/j.vaccine.2021.05.099. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8166525/pdf/main.pdf. Accessed 30 January 2022.