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.

Effectiveness of rAd26-rAd5, ChAdOx1 nCoV-19, and BBIBP-CorV vaccines for risk of infection with SARS-CoV-2 and death due to COVID-19 in people older than 60 years in Argentina: a test-negative, case-control, and retrospective longitudinal study

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Summary

Background In January, 2021, a vaccination campaign against COVID-19 was initiated with the rAd26-rAd5, ChAdOx1 nCoV-19, and BBIBP-CorV vaccines in Argentina. The objective of this study was to estimate vaccine effectiveness at reducing risk of SARS-CoV-2 infection and COVID-19 deaths in people older than 60 years.

Methods In this test-negative, case-control, and retrospective longitudinal study done in Argentina, we evaluated the effectiveness of three vaccines (rAd26-rAd5, ChAdOx1 nCoV-19, and BBIBP-CorV) on SARS-CoV-2 infection and risk of death in people with RT-PCR confirmed COVID-19, using data from the National Surveillance System (SNVS 2.0). All individuals aged 60 years or older reported to SNVS 2.0 as being suspected to have COVID-19 who had disease status confirmed with RT-PCR were included in the study. Unvaccinated individuals could participate in any of the analyses. People with suspected COVID-19 who developed symptoms before the start of the implementation of the vaccination programme for their age group or district were excluded from the study. The odds ratio of SARS-CoV-2 infection was evaluated by logistic regression and the risk of death in individuals with RT-PCR confirmed COVID-19 was evaluated by proportional hazard regression models, adjusted for possible confounders: age at the time of the symptom onset date, sex, district of residence, epidemiological week corresponding to the symptom onset date, and history of COVID-19. The estimation of vaccine effectiveness to prevent death due to COVID-19 was done indirectly by combining infection and death estimates. In addition, we evaluated the effect of the first dose of viral vector vaccines across time.

Findings From Jan 31, to Sept 14, 2021, 1 282 928 individuals were included, of whom 687 167 (53·6%) were in the rAd26-rAd5 analysis, 358 431 (27·9%) in the ChAdOx1 nCoV-19 analysis, and 237 330 (18·5%) in the BBIBP-CorV analysis. Vaccine effectiveness after two doses was high for all three vaccines, adjusted odds ratio 0·36 (95% CI 0·35–0·37) for rAd26-rAd5, 0·32 (0·31–0·33) for ChAdOx1 nCoV-19, and 0·56 (0·55–0·58) for BBIBP-CorV. After two doses, the effect on deaths was higher than that on risk of infection: adjusted hazard ratio 0·19 (95% CI 0·18–0·21) for rAd26-rAd5, 0·20 (0·18–0·22) for ChAdOx1 nCoV-19, and 0·27 (0·25–0·29) for BBIBP-CorV. The indirectly estimated effectiveness on deaths was 93·1% (95% CI 92·6–93·5) for rAd26-rAd5, 93·7% (93·2–94·3) for ChAdOx1 nCoV-19, and 85·0% (84·0–86·0) for BBIBP-CorV following two doses. First dose effect of viral vector vaccines remained stable over time.

Interpretation The vaccines used in Argentina showed effectiveness in reducing infection and death by SARS-CoV-2 and COVID-19.

Funding None.

Introduction

In the context of the pandemic, clinical trials of several COVID-19 vaccines have shown their efficacy.[1–3] At least 19 vaccines have been approved for emergency use in different countries, and others are under investigation.[4] Reports on the efficacy of different vaccines are varied.[5] Evaluating vaccine effectiveness for emerging pathogens during a public health emergency presents challenges, including spatiotemporal variability in the incidence and circulation of different variants of the virus. In addition, the accuracy of the estimates might be limited by the availability of high-quality surveillance data.[6] Estimates of the effectiveness of the implementation of COVID-19 vaccination programmes are essential

Research in context

Evidence before this study

As of Feb 25, 2022, According to the International Vaccine Access Center of the Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA, 216 studies of the effectiveness of COVID-19 vaccines have been published in 31 countries: Pfizer–BioNTech Oxford-AstraZeneca, and Moderna, were the vaccines with more studies. We searched in PubMed for studies of the effectiveness of COVID-19 vaccines, with no language restrictions, from June 1, 2020, to Feb 25, 2022, using the terms "COVID-19 vaccine effectiveness", "effectiveness of ChAdOx1 nCoV-19", "effectiveness of rAd26-rAd5 Sputnik V", and "effectiveness of BBIBP-CorV Sinopharm". Two vaccine studies from Argentina have been published; both report results consistent with ours, although each study evaluated the vaccination campaign in a single district. One study was an age-matched cohort study of people older than 60 years; however, is this study only the effect of first dose could be evaluated. The other study took an ecological approach and evaluated whether the application of the three COVID-19 vaccines available in Argentina was associated with a reduction in morbidity and deaths due to COVID-19. Before initiation of our study, there were no publications to date on the effectiveness of the BBIBP-CorV vaccines. However, since trial initiation a cohort study done in Hungary evaluated effectiveness of complete schedules of rAd26-rAd5 and BBIBP-CorV vaccines, and a cohort study of people confirmed to have COVID-19 from Abu Dhabi evaluated effectiveness of partial and complete schedules of BBIBP-CorV. Both studies reported high effectiveness for complete schedules of both vaccines to prevent death. Additionally, for people who had received one vaccine dose of BBIBP-CorV, some protection against death and infection was apparent, although statistically insignificant. Of the studies of ChAdOx1 effectiveness, one reported results similar to ours: 75% effectiveness with one dose in people older than 70 years in the UK. However, the study did not have a sufficient number of observations to estimate the effectiveness of the full vaccination schedule or sufficient follow-up time to estimate the effectiveness of the vaccine 35 days after the first application. A test-negative, case-control study has been done in the UK, which reported 80·4% effectiveness to prevent hospitalisation in people at least 80 years old. Other effectiveness studies with different designs—mainly cohort studies—with 2–4 months follow-ups, and mainly in specific groups (eg, people older than 80 years or health-care workers, etc) were analysed. The effectiveness estimates were higher in these studies, mainly due to the design and follow-up times.

Added value of this study

Although the effect of COVID-19 on low-income and middle-income countries (LMICs) is widely recognised, little is known about the effectiveness of national vaccine campaigns in these regions. In the context of emergency approval of vaccines for COVID-19, the generation of evidence in a real-world context is crucial. Reports of the effectiveness of the rAd26-rAd5 and the BBIBP-CorV vaccines are scarce; for this reason our findings are important for countries that have used these vaccines in their national vaccination campaigns. In comparison with other reports on the effectiveness of ChAdOx1, the circulating COVID-19 variants in Argentina were mainly gamma (p.1), lambda (C.37), and alpha (B.1.1.7), compared with mainly the alpha strain assessed in previous studies. Furthermore, because of the global shortage of vaccines and difficulty in their supply—especially in LMICs—our study provides evidence of the effectiveness of one-dose prioritisation strategies to reach as many people as possible in the shortest possible time.

Implications of all the available evidence

These findings are of international importance as vaccination programmes increase in the rest of the world, suggesting that other countries can similarly achieve marked and sustained decreases in SARS-CoV-2 infections and deaths if they can achieve high vaccine coverage; even with single dose regimens and with gamma, lambda, and alpha variants. This evidence can support decision making regarding the implementation of national or district vaccination campaigns.

because they reflect real-world challenges, such as logistics, cold chains, vaccination schedules, and follow-up, and because they involve more diverse populations than those selected in randomised trials.[7]

Until September, 2021, in Argentina, COVID-19 vaccines developed in non-replicative virus platforms were authorised and widely used in people older than 60 years: rAd26-rAd5 (Sputnik V), ChAdOx1 nCoV-19 (Oxford–AstraZeneca), and the inactivated vaccine BBIBP-CorV (Sinopharm). The administration of vaccines to people older than 60 years began in January, 2021, with rAd26-rAd5 V and ChAdOx1 nCoV-19 used from February, 2021; BBIBP-CorV was used from March, 2021.

The goal of the National Vaccination Campaign against COVID-19 in Argentina is to vaccinate 100% of the prioritised population. Prioritisation was established according to the risk of disease severity, risk of exposure, and social vulnerability. The deployment of the programme was gradual and progressive. Due to the international availability of vaccines, in March, 2021, the first dose of viral vector vaccines (rAd26-rAd5 and ChAdOx1 nCoV-19) was prioritised, with the goal of vaccinating a higher proportion of the population with their first dose—delaying the second dose for at least 90 days. The intervals between doses with the BBIBP-CorV vaccine were maintained at 28 days. Starting in July, 2021, taking into account the high

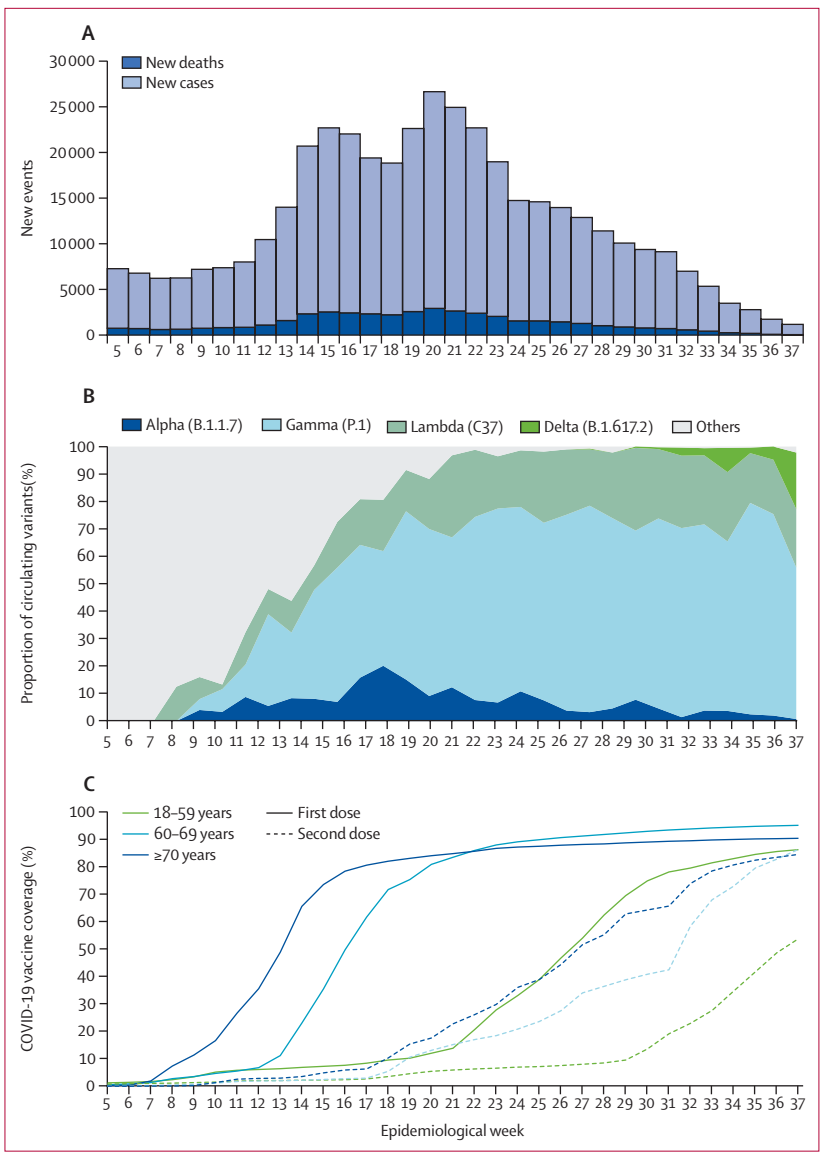

Figure 1: **Characteristics of the COVID-19 pandemic and vaccine response in Argentina**
(A) Incident cases and number of deaths from COVID-19. (B) Circulating SARS-CoV-2 variants. (C) Vaccination coverage by age group .

See Online for appendix

coverage with one dose, schedule completion with second vaccine doses was prioritised, primarily in individuals older than 50 years, with the goal of vaccinating the highest possible number of people with complete schedules (appendix pp 2–7).

Effectiveness studies have been published in the UK, Israel, and Chile; they have shown encouraging results in accordance with efficacy studies.[7–9] Due to the differences between the strategies implemented worldwide, evaluation of the effectiveness of each vaccination programme under different scenarios is important. Before inititiation of our study, no studies had evaluated the effectiveness of BBIBP-CorV according to the recommended dose schedule or alternative dose intervals of rAd26-rAd5. However, since November, 2021, two cohort studies have evaluated rAd26-rAd5 and BBIBP-CorV vaccines effectiveness. In a study done in Hungary,[10] the effectiveness to prevent infection and death in people older than 18 years old who completed rAd26-rAd5 vaccine schedule was estimated to be more than 95%; for people who completed the BBIBP-CorV vaccine schedule, the effectiveness estimated to prevent infection was 66·1% and death was 87·8%. Another cohort study of people confirmed to have COVID-19 in Abu Dhabi estimated that in people who had received two doses of BBIBP-CorV vaccine, the effectiveness to prevent hospitalisation was 80% and effectiveness to prevent death was 97%.[11] The effectiveness of vaccination programmes with a risk prioritisation strategy that placed a focus on individuals older than 60 years in the context of the circulation of different variants of interest of SARS-CoV-2 has not been reported.

We aimed to estimate the effectiveness of the rAd26-rAd5, ChAdOx1 nCoV-19, and BBIBP-CorV vaccines to reduce infection by SARS-CoV-2 and death due to COVID-19 in people aged 60 years and older. In addition, we evaluated the effect over time of the first dose of viral vector vaccines.

Methods

Study design and participants

We did a test-negative case-control study to evaluate the effectiveness of the different vaccines in the reduction of SARS-CoV-2 infection. Test-negative case-control designs are considered powerful enough to estimate the effectiveness of vaccines and have been widely used to estimate the effectiveness of vaccines against influenza and other respiratory viruses (appendix p 7).[6,8,12] The effect of vaccines on the risk of death in people with COVID-19 was evaluated through a retrospective longitudinal study that included only people with RT-PCR confirmed COVID-19.

All individuals aged 60 years or older reported to National Surveillance System (SNVS 2.0) as being suspected to have COVID-19 who had had their disease status confirmed with RT-PCR were included in the case-control study. The definition of suspected cases was dynamic during the study period; however, the definition of cases and controls were consistent throughout the study. Unvaccinated individuals could participate in any of the analyses. People with suspected COVID-19 who developed symptoms before the start of the implementation of the vaccination programme for their age group or district were excluded from the study (appendix pp 2–7). Individuals reported as being suspected to have COVID-19 were classified as a case if they had RT-PCR detectable COVID-19 and as controls if they had RT-PCR undetectable COVID-19.

The study used epidemiological surveillance data from SNVS 2.0, preserving the confidentiality of the individuals according to the Helsinki declaration and local

regulations.[13] We followed the STROBE checklist.[14] The trial is registered in the National Registry of Health Research, IS003333.

Procedures

Argentina began the National Vaccination Campaign against COVID-19 in January, 2021, which was implemented across the whole country with equitable distribution of doses according to population size (appendix pp 2–7). The study was done from January to September, 2021, (epidemiological week 5 to 37). Figure 1A shows the number of incident cases and the number of deaths from COVID-19 in Argentina during the study period. Figure 1B describes the distribution of circulating variants and Figure 1C shows vaccination coverage according to epidemiological week.

The notification of suspected cases of COVID-19 and their confirmation and outcomes were done by certified users (professionals, technicians, administrative, and health authorities of the 24 districts) of the public health-care, private health-care, and social security subsectors. The information was reported by all districts through the SNVS 2.0. For the death registry, each district systematically reviewed and verified data from other death records, such as bureaus of vital records (death certificate data), hospitals, and funeral companies. These data were incorporated into SNVS 2.0 (appendix p 8).

Vaccine information is reported in the Nominalized Federal Vaccination Registry (NOMIVAC). All vaccinated individuals had their the date of vaccination, the number of doses, the type of vaccine, the vaccine lot number, and the vaccination centre recorded in NOMIVAC.

The symptom onset date was recorded in the definition of the suspected case and was reported according to the epidemiological week. The same analysis was done for each vaccine independently. Because participants could have more than one RT-PCR test, each individual was only included once, with the first record as valid—in cases of conflicting results, the first positive record was used.

Vaccination status was classified into five categories according to the time elapsed between the administration of the vaccine and the symptom onset date: unvaccinated, vaccinated with a first dose before 21 days, first dose after 21 days, vaccinated with a second dose before 21 days, and vaccinated with a second after 21 days.

To evaluate the effect of the time interval between the first dose and the symptom onset date on the odds of infection by SARS-CoV-2 and on the risk of death due to RT-PCR confirmed COVID-19, time intervals of 14 days were analysed: unvaccinated, 0–14 days, 15–28 days, 29–42 days, successively up to 113–126 days.

RT-PCR has high sensitivity and specificity. To minimise the chance of false positives in the pre-analytical phase (eg, due to contamination), the Ministry of Health of Argentina developed standards that all laboratories had to comply with. Standards were also developed for the collection and transportation of test samples and district-level training to minimise the chance of false negatives.[15] In the population with RT-PCR confirmed COVID-19, the outcome of death reported in SNVS 2.0 was assessed.

Covariates

A variety of factors can be associated with the probability that an individual is offered and accepts a vaccine, the risk of exposure to SARS-CoV-2, or having an RT-PCR test, including personal factors (eg, age, sex, geography, and time period). The incidence of COVID-19 varied by region and by epidemiological week during the study period, as well as the availability of vaccines. The variables evaluated as possible confounders were age at the time of the symptom onset date, sex, district of residence, epidemiological week corresponding to the symptom onset date, and history of COVID-19.

The registry of the comorbidities reported to the SNVS 2.0 consisted of the determination of the presence or absence of eight pre-existing medical conditions, determined by self-report (appendix p 8).

Statistical analysis

Logistic regression was used to estimate the odds of SARS-CoV-2 infection as a function of vaccination status. The estimation of the crude model included the epidemiological week of symptom onset as an adjustment variable because both the incidence of the disease and the availability of vaccines in Argentina varied during the study period. Thus, an analysis without including time would not have been adequate.

Because treatment assignment was not random, adjustment for possible confounding factors was required. On the basis of the knowledge of each individual and the previous literature, we used a directed acyclic graph to identify and select variables potentially associated with both vaccination and the results of the study (appendix pp 10–12).[16,17] Possible confounding factors (age [expressed in years], sex, district, history of COVID-19, and epidemiological week of symptom onset date) were included in the fully adjusted logistic regression model. The results are presented as odds ratios (ORs) and adjusted ORs (aORs) with 95% CIs (appendix pp 12–13).

The effect of vaccines on the risk of death in people with COVID-19 was evaluated using a Cox proportional hazard regression model taking individuals who did not receive any vaccine as the reference category; the same covariates as the logistic model were included in the hazard regression model. The results are presented as hazard ratios (HRs) and adjusted HRs (aHRs) with 95% CIs.

Vaccine effectiveness was calculated as (1–relative risk measure)×100.[18–20] The overall effectiveness of vaccines to reduce death was calculated from a combination of the estimates of the effect of vaccination to prevent infection

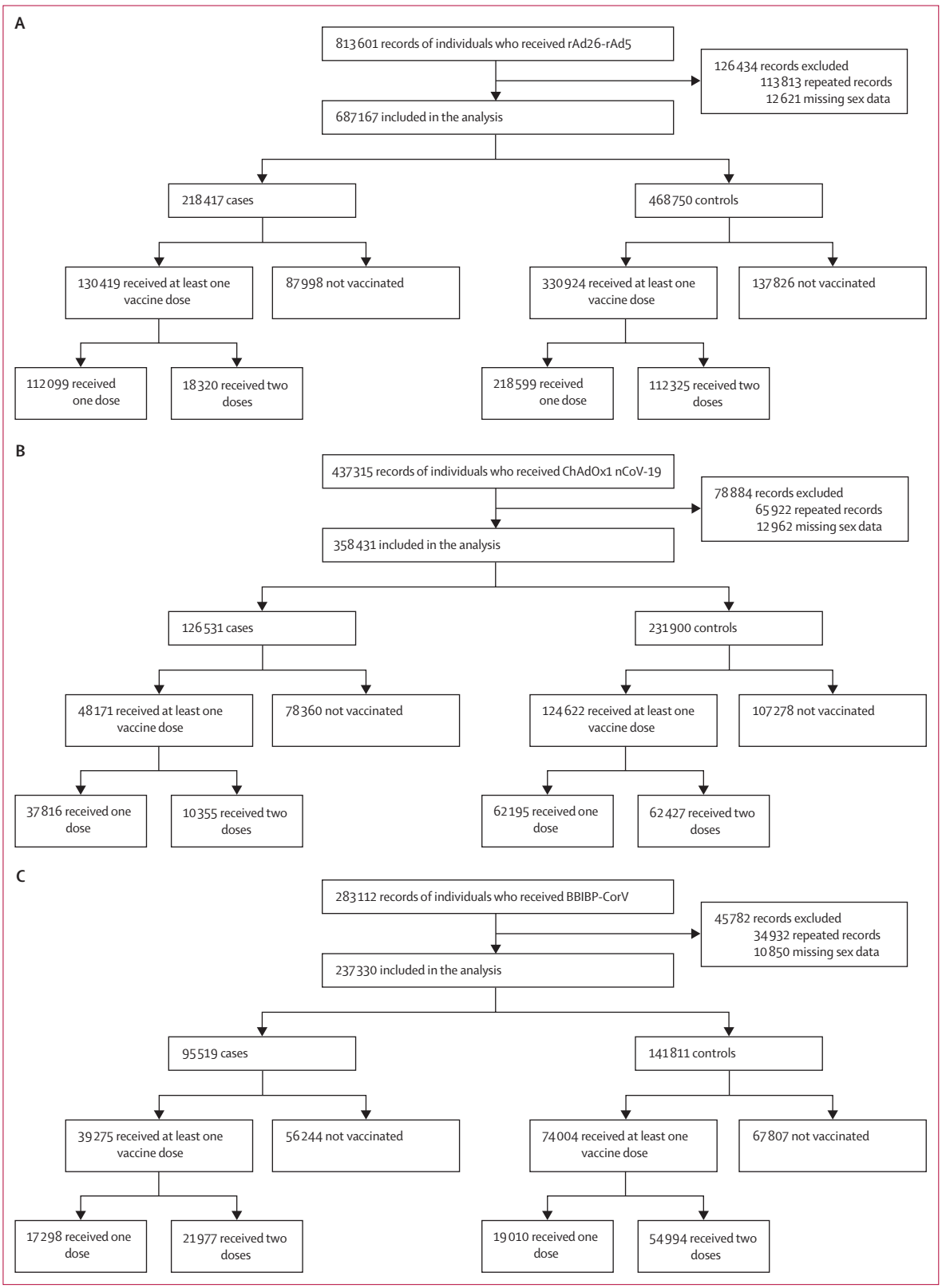

Figure 2: **Study profile**
(A) Individuals included in the analysis of rAd26-rAd5. (B) Individuals included in the analysis of ChAdOx1 nCoV-19. (C) Individuals included in the analysis of BBIBP-CorV.

by SARS-CoV-2 (aOR) and death in cases of COVID-19 (aHR).[21,22] The 95% CIs were estimated with the delta method.

To evaluate whether the vaccine effectiveness estimators were modified as a function of age, an interaction between vaccination status and age categories (60–69 years, 70–79 years, and ≥80 years) was added both to the logistic regression model that estimates the odds of infection and the Cox proportional hazard model that estimates the risk of dying in cases of COVID-19 (appendix pp 12–13).

Comorbidities were not recorded in all cases. To consider their effect, an analysis of the population registered in SNVS 2.0 was done (appendix p 18). Because the performance of the RT-PCR test can decrease over time symptom onset,[23] an analysis of the population who had a RT-PCR test within 6 days of the

	rAd26-rAd5		ChAdOx1 nCoV-19		BBIBP-CorV	
	Cases	Controls	Cases	Control	Cases	Control
Study population						
Overall	218 417	468 750	126 531	231 900	95 519	141 811
60–69 years	118 319 (54·2%)	252 824 (53·9%)	70 382 (55·6%)	126 164 (54·4%)	54 165 (56·7%)	78 607 (55·4%)
70–79 years	66 175 (30·3%)	142 804 (30·5%)	33 536 (26·5%)	59 529 (25·7%)	27 392 (28·7%)	43 481 (30·7%)
≥80 years	33 923 (15·5%)	73 122 (15·6%)	22 613 (17·9%)	46 207 (19·9%)	13 962 (14·6%)	19 723 (13·9%)
Deaths in cases						
Overall	30 000 (13·7%)	..	23 332 (18·4%)	..	18 733 (19·6%)	..
60–69 years	9756/30 000 (32·5%)	..	8702/23 332 (37·3%)	..	7434/18 733 (39·7%)	..
70–79 years	10 581/30 000 (35·3%)	..	7462/23 332 (32·0%)	..	6091/18 733 (32·5%)	..
≥80 years	9663/30 000 (32·2%)	..	7168/23 332 (30·7%)	..	5208/18 733 (27·8%)	..
Median age (IQR)	68 (63–76)	68 (63–76)	68 (64–76)	69 (64–77)	68 (63–75)	68 (63–75)
Sex						
Overall						
Female	112 830 (51·7%)	260 033 (55·5%)	65 731 (51·9%)	127 984 (55·2%)	49 164 (51·5%)	77 428 (54·6%)
Male	105 587 (48·3%)	208 717 (44·5%)	60 800 (48·1%)	103 916 (44·8%)	46 355 (48·5%)	64383 (45·4%)
60–69 years						
Female	58 762 (49·7%)	138 139 (54·6%)	34 638 (49·2%)	66 918 (53·0%)	26 484 (48·9%)	41 442 (52·7%)
Male	59 557 (50·3%)	114 685 (45·4%)	35 744 (50·8%)	592 46 (47·0%)	27 681 (51·1%)	37 165 (47·3%)
70–79 years						
Female	33 491 (50·6%)	76 425 (53·5%)	17 049 (50·8%)	31 357 (52·7%)	14 007 (51·1%)	23 440 (53·9%)
Male	32 684 (49·4%)	66 379 (46·5%)	16 487 (49·2%)	28 172 (47·3%)	13 385 (48·9%)	20 041 (46·1%)
≥80 years						
Female	20 577 (60·7%)	45 469 (62·2%)	14 044 (62·1%)	29 709 (64·3%)	8673 (62·1%)	12 546 (63·6%)
Male	13 346 (39·3%)	27 653 (37·8%)	8569 (37·9%)	16 498 (35·7%)	5289 (37·9%)	7177 (36·4%)
Individuals with RT-PCR confirmed COVID-19 before the study period						
Overall	1269 (0·6%)	16 658 (3·6%)	805 (0·6%)	9 722 (4·2%)	436 (0·5%)	4544 (3·2%)
60–69 years	704/1269 (55·5%)	10 146/16 658 (60·9%)	382/805 (47·4%)	4656/9 722 (47·9%)	241/436 (55·3%)	2670/4544 (58·8%)
70–79 years	345/1269 (27·2%)	4207/16 658 (25·3%)	228/805 (28·3%)	2543/9 722 (26·2%)	121/436 (27·8%)	1189/4544 (26·2%)
≥80 years	220/1269 (17·3%)	2305/16 658 (13·8%)	195/805 (24·2%)	2523/9 722 (26·0%)	74/436 (17·0%)	685/4544 (15·1%)
Vaccinated						
Vaccinated with one dose						
Overall	112 099 (51·3%)	218 599 (46·6%)	37 816 (29·9%)	62 195 (26·8%)	17 298 (18·1%)	19 010 (13·4%)
60–69 years	60 661/112 099 (54·1%)	127 470/218 599 (58·3%)	20 781/37 816 (55·0%)	33 860/62 195 (54·4%)	10 173/17 298 (58·8%)	11 520/19 010 (60.6%)
70–79 years	36 054/112 099 (32·2%)	65 485/218 599 (30·0%)	10 139/37 816 (26·8%)	15 559/62 195 (25·0%)	5651/17 298 (32·7%)	5821/19 010 (30.6%)
≥80 years	15 384/112 099 (13·7%)	25 644/218 599 (11·7%)	6896/37 816 (18·2%)	12 776/62 195 (20·5%)	1474/17 298 (8·5%)	1669/19 010 (8·8%)
Vaccinated with two doses						
Overall	18 320 (8·4%)	112 325 (24·0%)	10 355 (8·2%)	62 427 (26·9%)	21 977 (23·0%)	54 994 (38·8%)
60–69 years	6615/18 320 (36·1%)	48 014/112 325 (42·7%)	4435/10 355 (42·8%)	31 998/62 427 (51·3%)	12 848/21 977 (58·5%)	30 971/54 994 (56.3%)
70–79 years	6918/18 320 (37·8%)	40 153/112 325 (35·7%)	3255/10 355 (31·4%)	16 933/62 427 (27·1%)	7083/21 977 (32·2%)	19 740/54 994 (35·9%)
≥80 years	4787/18 320 (26·1%)	24 158/112 325 (21·5%)	2665/10 355 (25·7%)	13 496/62 427 (21·6%)	2046/21 977 (9·3%)	4283/54 994 (7·8%)

Data are n (%) or n/N (%), unless otherwise stated.

Table: **Population characteristics**

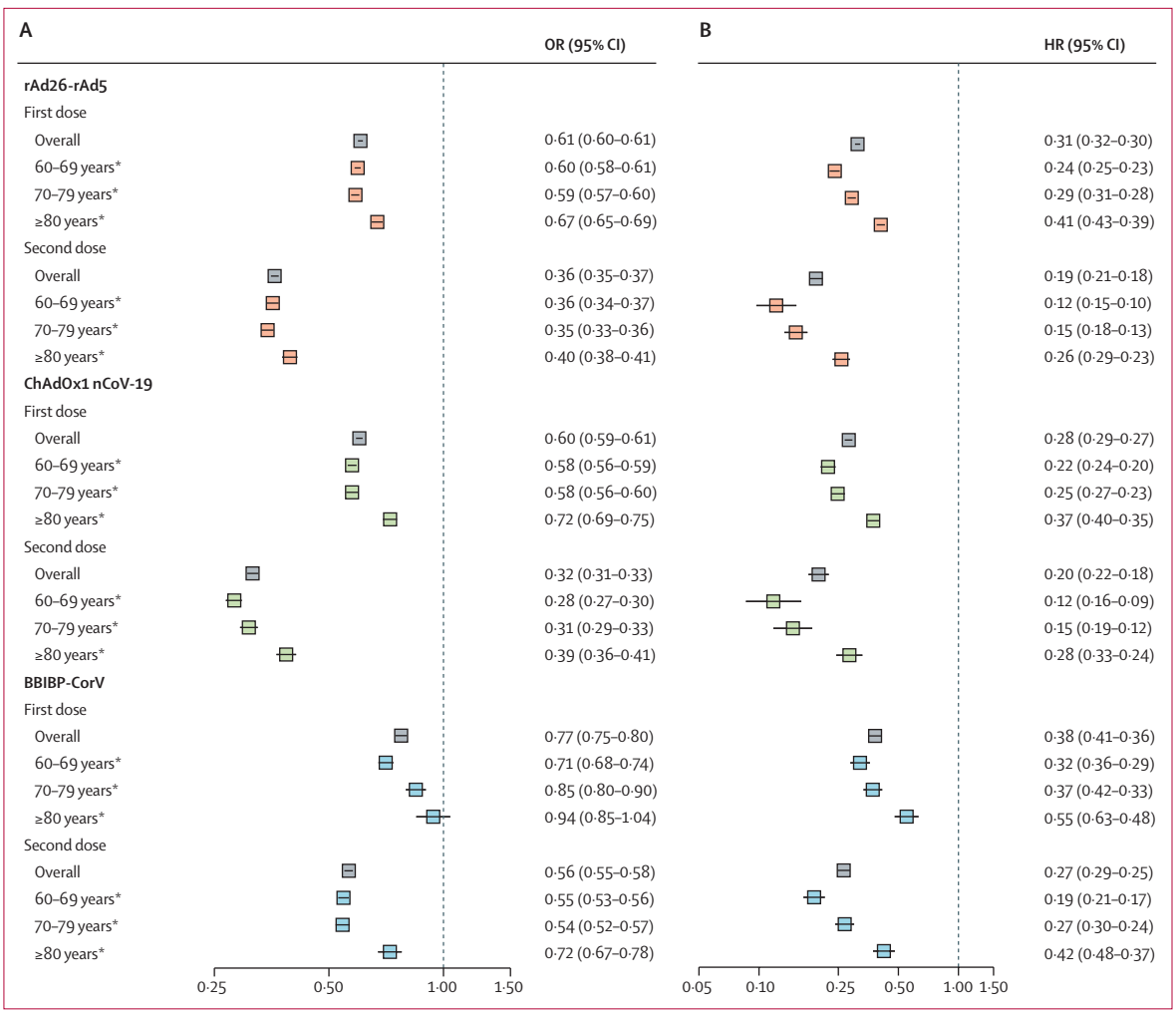

Figure 3: **Effect of the rAd26-rAd5, ChAdOx1 nCoV-19, and BBIBP-CorV vaccines on the risk of SARS-CoV-2 infection and on the risk of death**
(A) Effect of the vaccines on risk of infection. (B) Effect of the vaccines on risk of death in cases. Overall ORs were adjusted for epidemiological week, sex, history of COVID-19, and district. Overall HRs were adjusted for epidemiological week, sex, history of COVID-19 and district. Error bars are 95% CIs. HR=hazard ratio. OR=odds ratio. *Adjusted for vaccination status, age group interaction, epidemiological week, sex, history of COVID-19, and district. †Adjusted for vaccination status, age group interaction, epidemiological week, sex, history of COVID-19, and district.

symptom onset date was also done. Both analyses were done with the same models used in the analyses of the total population. Finally, for viral vector vaccines (for which the first dose prioritisation strategy was used), we evaluated the effect of the time elapsed since the application of the vaccine to the symptom onset date on the vaccine effectiveness estimators. Data processing, statistical analysis, and creation of figures were done with R statistical software (version 4.1.0).[24]

Role of the funding source

There was no funding source for this study.

Results

From Jan 31, to Sept 14, 2021, 1 282 928 individuals were included, of whom 687 167 (53·6%) were included in the rAd26-rAd5 analysis, 358 431 (27·9%) in the ChAdOx1 nCoV-19 analysis, and 237 330 (18·5%) for BBIBP-CorV (figure 2).

The table describes the characteristics of the overall population and stratified by age stratum. The number of vaccine doses administered in Argentina by epidemiological week and by district during the study period are reported in the appendix (pp 3–7).

The aORs to prevent infection by SARS-CoV-2 with one dose were 0·61 (95% CI 0·60–0·61) for rAd26-rAd5, 0·60 (0·59–0·61) for ChAdOx1 nCoV-19, and 0·77 (0·75–0·80) for BBIBP-CorV. The aORs for preventing SARS-CoV-2 infection with two doses were 0·36 (0·35–0·37) for rAd26-rAd5, 0·32 (0·31–0·33) for ChAdOx1 nCoV-19, and 0·56 (0·55-0·58) for BBIBP-CorV. This effect was higher for viral vector vaccines and decreased with age, especially in people older than 80 years who received only the first dose (figure 3A). The

crude and adjusted ORs to prevent SARS-CoV-2 infection according to vaccination status and the estimators of the same model that include the interaction term between age group and vaccination status are reported in the appendix (pp 3–7). The risk of death in people with COVID-19 treated with one dose was aHR 0·31 [95% CI 0·30–0·32] for rAd26-rAd5, 0·28 [0·27–0·29] for ChAdOx1 nCoV-19, and 0·38 [0·36–0·41] for BBIBP-CorV. The risk of death in COVID-19 patients treated with the two doses was aHR 0·19 (95% CI 0·18–0·21) for rAd26-rAd5, 0·20 (0·18-0·22) for ChAdOx1 nCoV-19, and 0·27 (0·25-0·29) for BBIBP-CorV. The increase in the magnitude of protection between the first and second doses was lower than that observed for the prevention of infection, and a pronounced decrease was observed in people older than 80 years, especially in those who received only the first dose (figure 3B). The aHR for death according to vaccination status and the aHR of the same model that includes the interaction term between age group and vaccination status are reported in the appendix (p 15).

The estimated vaccine effectiveness to prevent death due to COVID-19 in those who received one dose was 81·1% (95% CI 80·5–81·7) for ChAdOx1 nCoV-19, 83·1% (82·3–83·9) for rAd26-rAd5, and 70·4% (68·1–72·8) for BBIBP-CorV (figure 4). The effectiveness was higher with two doses for all vaccines: 93·1% (92·6–93·5) for rAd26-rAd5, 93·7% (93·2–94·3) for ChAdOx1 nCoV-19, and 85·0% (84·0–86·0) for BBIBP-CorV (figure 4).

112 839 individuals who received rAd26-rAd5, 64 444 who received ChAdOx1 nCoV-19, and 44 864 who received BBIBP-CorV were included in the sensitivity analysis to evaluate the influence of comorbidities on vaccine effectiveness. No variations were observed in the aOR for SARS-CoV-2 infection (appendix p 18). In the sensitivity analysis to evaluate the aHR of death in cases with confirmed COVID-19, a lower effectiveness was observed for the three vaccines (appendix p 18). Individuals who had a RT-PCR test within 6 days of the symptom onset date had similar risk estimates to the overall population (appendix p 19).

The aOR of SARS-CoV-2 infection, the aHR of death in cases with COVID-19, and the vaccine effectiveness to prevent death for viral vector vaccines as a function of the time between the first dose and the symptom onset date is shown in figure 5. A progressive increase in the effectiveness of both vaccines was observed from day 0 to day 42 (figure 5). These estimates were maintained until 98 days, after which the estimates lost accuracy.

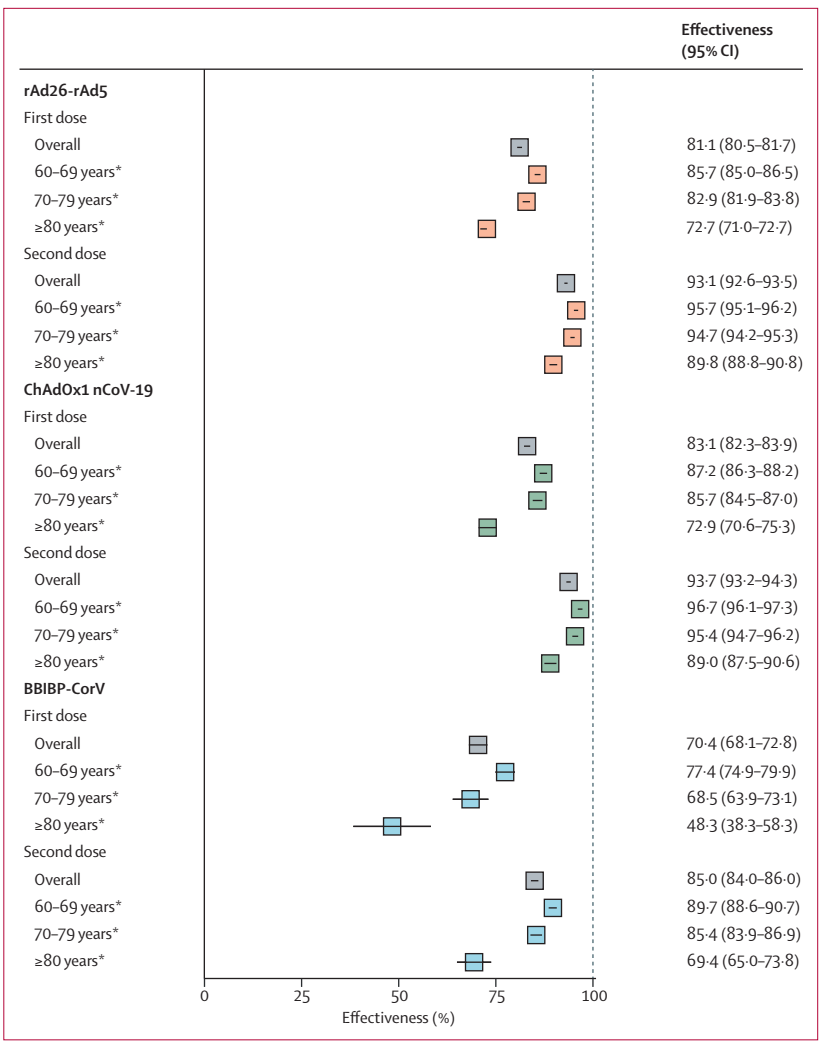

Figure 4: **Effectiveness of the rAd26-rAd5, ChAdOx1 nCoV-19, and BBIBP-CorV vaccines to prevent death due to COVID-19**

Error bars are 95% CIs. *Adjusted for the vaccination status, age group interaction, epidemiological week, sex, history of COVID-19, and district.

Discussion

Our study suggests that in people aged 60 years or older in the context of the National Vaccination Campaign of Argentina with prioritised risk groups, vaccination with rAd26-rAd5, ChAdOx1 nCoV-19, or BBIBP-CorV was effective in preventing SARS-CoV-2 infection and even more effective in preventing death in patients with COVID-19. The effectiveness in preventing death with the first dose of viral vector vaccines was more than 80%. In people with complete vaccination schedules, the effectiveness to prevent death exceeded 90% for viral vector vaccines and was more than 85% for the inactivated virus vaccine.

Randomised trials have reported a high efficacy of the ChAdOx1 nCoV-19 vaccine;[3] its effectiveness in preventing symptomatic disease has been confirmed in population studies of individuals aged 70 years or older.[8] The results of our study confirm its effectiveness in preventing SARS-CoV-2 infection, extending its effectiveness for the prevention of death. The rAd26-rAd5 vaccine showed high efficacy in preventing infection by SARS-CoV-2 and severe disease by COVID-19; however, the initial trial had no power to show an effect on death.[2] A retrospective, age-matched cohort study in individuals older than 60 years showed

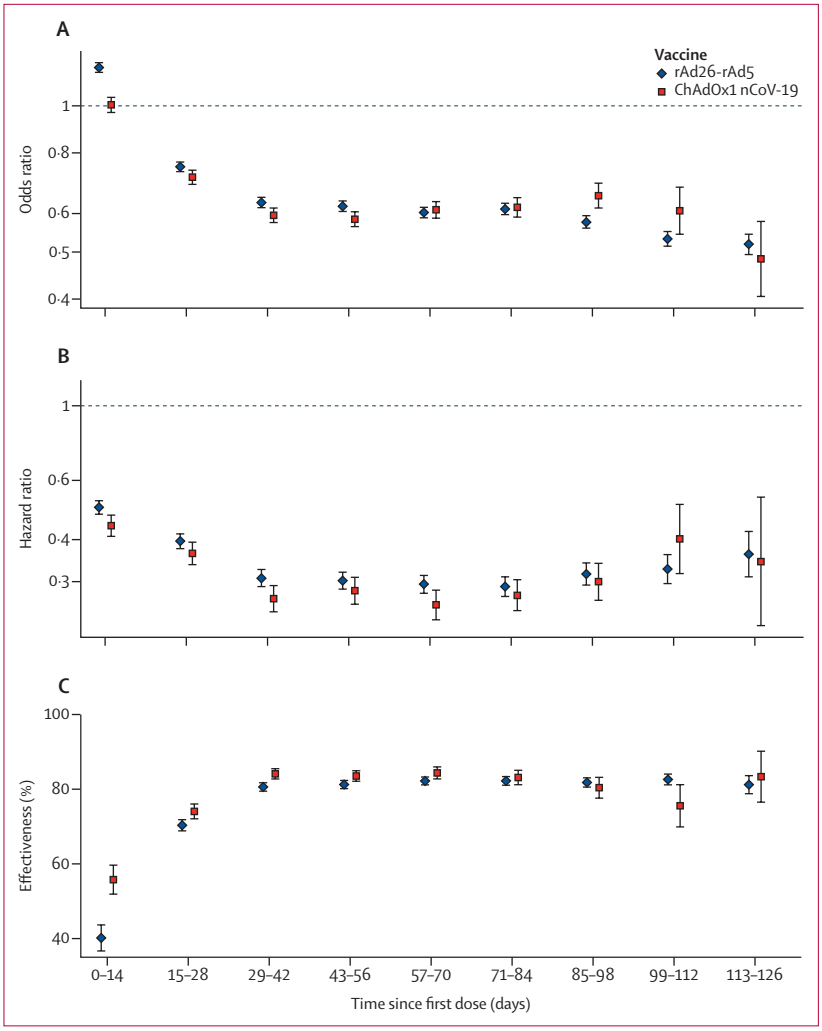

Figure 5: **Risk of SARS-CoV-2 infection, deaths due to COVID-19, and vaccine effectiveness over time for the rAd26-rAd5 and ChAdOx1 nCoV-19 vaccines**

(A) Risk of SARS-CoV-2 infection between the first dose and the symptom onset date. (B) Risk of death due to COVID-19 in cases as a function of the time elapsed between the first dose and the symptom onset date. (C) Effectiveness in preventing death by COVID-19 as a function of the time elapsed between the first dose and the symptom onset date. Error bars are 95% CIs.

high effectiveness for the prevention of SARS-CoV-2 infection (79%) and death by COVID-19 (85%);[23] however, these findings had inherent limitations to the design because only the effect of one dose could be evaluated. Before initiation of our study, no other effectiveness studies were reported for rAd26-rAd5 vaccine; however, a cohort of people older than 18 years old in Hungary reported more than 95% of effectiveness for complete schedule to prevent infection and death.[10] The results of our study suggest the effectiveness of the rAd26-rAd5 vaccine at one and two doses for the prevention of SARS-CoV-2 infection and death by COVID-19, with an effectiveness equivalent to that of ChAdOx1 nCoV-19. Before initiation of our study, no effectiveness studies had been reported in older adults for the BBIBP-CorV vaccine.

Our findings are consistent with studies from Hungary, published in 2021,[10] and Abu Dhabi, published in 2022.[11] The results of our study showed high effectiveness in the prevention of death with the complete schedule. The effects of BBIBP-CorV were less than the two viral vector vaccines, and similar to other inactivated vaccines evaluated in similar population contexts.[7] The effectiveness of one dose of viral vector vaccine to prevent SARS-CoV-2 infection increased markedly when the two-dose schedule was completed. However, if one considers the overall effectiveness of each vaccine to prevent death in people with COVID-19, more than 80% of this effect was with the first dose. The greatest effectiveness was reached at approximately 28 days, remaining constant for at least 98 days. These findings are consistent with reports from different contexts and populations for ChAdOx1 nCoV-19 and for other vaccines.[8,25–28] Our results suggest that, given the difficulty in accessing vaccines, a one-dose prioritisation schedule seems to be an appropriate strategy for prevention of death, not only for previously evaluated vaccines but also for rAd26-rAd5.

Our study also suggests that vaccine effectiveness declines with age, especially in people older than 80 years. This effect was observed in all three vaccines and most markedly with the inactivated virus vaccine. This should be taken into consideration for the implementation of vaccination campaigns and prioritisation of populations to receive other vaccines platforms or booster doses, according to vaccine accessibility.

To our knowledge, this is the first study to evaluate the effectiveness of three different vaccines in a real-life context in a middle-income country. The test-negative case-control design is appropriate for estimating the effectiveness of vaccines against SARS-CoV-2 infection: it is a cost-effective way to evaluate vaccination programmes in a real-world setting and allows estimates consistent with randomised trials.[6,18,20,29] Although there might have been persistent potential confounders, misclassification, or selection bias, it is possible to minimise them with adjustment strategies. To address the effects associated with the dynamics of the pandemic and the availability of vaccines, it was adjusted by epidemiological week and district. Additionally, we adjusted for variables such as age and sex linked to people at risk of infection and death. The quality of the epidemiological surveillance and vaccination records used confers robustness to the results. PCR is a test with a reported high sensitivity and specificity.[30] To minimise the risk of misclassification, only individuals who had a RT-PCR test were included. The recommendations from the National Reference Laboratory of the Ministry of Health to standardise the procedures of the preanalytical phase and the national standards for the laboratories ensured reliable RT-PCRs. Additionally, the national guidelines allowed for a standardisation of the definition of a suspected case of COVID-19 and the allocation of vaccines in the districts.

Our study has several limitations. Because surveillance data were used, some data, such as comorbidities and hospitalisations, were incomplete. In the subgroup of patients with comorbidities, the vaccine effectiveness to prevent death in people with COVID-19 was lower. However, given that these data were not systematically collected, the variability introduced by the method of registering and the possible reporting bias in favour of patients with the most severe disease and those who ultimately died threatens the validity of this finding. Additionally, selection bias might be inherent to the self-reporting of symptoms; many symptoms are not specific to COVID-19 and sometimes they were not evaluated by a health-care professional.

The general effects of a vaccination programme on public health depend on both the direct effects on the vaccinated and the indirect effects on the unvaccinated.[31] The effect of vaccination at a population level depends on the efficacy of the vaccines to reduce the transmission of the disease and the coverage achieved. Our study evaluates the effectiveness of vaccines to reduce death measured directly in each individual, so the real effect of vaccination on death, if the indirect effect of the decrease in transmission at the population level were added, could be even greater.

In conclusion, the three vaccines used in the National Vaccination Campaign of Argentina during the evaluated period were effective in preventing SARS-CoV-2 infection and death in people with RT-PCR confirmed COVID-19. The strategy of prioritising one dose showed sustained effectiveness during the period studied. These results support the use of the evaluated vaccines and the strategy used for their application.

Contributors

CV, ST, AR, and JMC conceived and supervised the study. CV, ST, AR, JMC, and NF were in charge of the project administration. CV, NF, MP, PBB, LEI, ML, MLB, GG, and MDVJ conceptualised the study. AR, JMC, RR, NF, VP, MP, PBB, LEI, ML, MLB, GG, ME, and MVDJ wrote the original draft. AR, JMC, RR, NF, VP, MP, PBB, LEI, ML, MLB, GG, ST, ME, and CV reviewed and edited the manuscript. AS, MP, PBB, LEI, ML, MLB, and GG cleaned and analysed the data. RR, VP, and NF did the formal analysis. AR, JMC, RR, VP, and NF did the investigation and designed the methods. VP, ME, and NF designed the figures. CMG and the Área de Vigilancia de la Salud del Ministerio de Salud de la Nación developed the supporting algorithms. All authors had full access to the deidentified data, approved the final version of the manuscript, and authorised the submission of the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Deidentified individual participant data that underlie the results reported in this Article, data dictionaries, and study protocol will be available from 9 months to 36 months after Article publication to researchers who provide a methodologically sound proposal, for any purpose of analysis. Proposals should be directed to the corresponding author; to gain access, data requestors will need to sign a data access agreement.

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References

1 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020; **383:** 2603–15.

2 Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. 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* 2021; **397:** 671–81.

3 Voysey M, Clemens SAC, Madhi SA, et al. 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. *Lancet* 2021; **397:** 99–111.

4 McGill University. COVID-19 vaccine tracker. 2021. https://covid19.trackvaccines.org/vaccines/#approved (accessed July 8, 2021).

5 Olliaro P, Torreele E, Vaillant M. COVID-19 vaccine efficacy and effectiveness—the elephant (not) in the room. *Lancet Microbe* 2021; **2:** e279–80.

6 Dean NE, Gsell P-S, Brookmeyer R, et al. Design of vaccine efficacy trials during public health emergencies. *Sci Transl Med* 2019; **11:** eaat0360.

7 Jara A, Undurraga EA, González C, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. *N Engl J Med* 2021; **358:** 875–84.

8 Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ* 2021; **373:** n1088.

9 Haas EJ, Angulo FJ, McLaughlin JM, et al. 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* 2021; **397:** 1819–29.

10 Vokó Z, Kiss Z, Surján G, et al. Nationwide effectiveness of five SARS-CoV-2 vaccines in Hungary-the HUN-VE study. *Clin Microbiol Infect* 2021; published online Nov 25. https://doi.org/10.1016/j.cmi.2021.11.011.

11 AlHosani FI, Stanciole AE, Aden B, et al. Impact of the Sinopharm's BBIBP-CorV vaccine in preventing hospital admissions and death in infected vaccinees: results from a retrospective study in the emirate of Abu Dhabi, United Arab Emirates (UAE). *Vaccine* 2022; published online Feb 19. https://doi.org/10.1016/j.vaccine.2022.02.039.

12 Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine* 2013; **31:** 2165–68.

13 Ministerio-de-Salud. Guia para investigaciones en salud humana. 2011. https://bancos.salud.gob.ar/recurso/guia-para-investigaciones-en-salud-humana (accessed April 2, 2020).

14 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370:** 1453–57.

15 Ministerio-de-Salud. Recomendaciones para equipos de salud-Laboratorio. 2020. https://www.argentina.gob.ar/salud/coronavirus/laboratorio (accessed Oct 6 of 2021).

16 VanderWeele TJ, Hernán MA, Robins JM. Causal directed acyclic graphs and the direction of unmeasured confounding bias. *Epidemiology* 2008; **19:** 720–28.

17 Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology* 2004; **15:** 615–25.

18 WHO. Evaluation of COVID-19 vaccine effectiveness: interim guidance. 2021. https://apps.who.int/iris/bitstream/handle/10665/340301/WHO-2019-nCoV-vaccine-effectiveness-measurement-2021.1-eng.pdf?sequence=1&isAllowed=y (accessed April 30, 2021).

19 Lewnard JA, Tedijanto C, Cowling BJ, Lipsitch M. Measurement of vaccine direct effects under the test-negative design. *Am J Epidemiol* 2018; **187:** 2686–97.

20 Dean NE, Hogan JW, Schnitzer ME. Covid-19 vaccine effectiveness and the test-negative design. *N Engl J Med* 2021; **385:** 1431–33.

21 Public Health England. Impact of COVID-19 vaccines on mortality in England December 2020 to February 2021. 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/977249/PHE_COVID-19_vaccine_impact_on_mortality_March.pdf (accessed July 7, 2021).

22 Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (delta) variant. *N Engl J Med* 2021; **385:** 585–94.

23 Singanayagam A, Patel M, Charlett A, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. *Euro Surveill* 2020; **25:** 2001483.

24 Bunn A, Korpela M. Crossdating in dplR. 2014. https://cran.microsoft.com/snapshot/2014-09-08/web/packages/dplR/vignettes/xdate-dplR.pdf (Aug 9, 2021).

25 González S, Olszevicki S, Salazar M, et al. Effectiveness of the first component of Gam-COVID-Vac (Sputnik V) on reduction of SARS-CoV-2 confirmed infections, hospitalisations and mortality in patients aged 60-79: a retrospective cohort study in Argentina. *EClinicalMedicine* 2021; **40:** 101126.

26 Paris C, Perrin S, Hamonic S, et al. Effectiveness of mRNA-BNT162b2, mRNA-1273, and ChAdOx1 nCoV-19 vaccines against COVID-19 in healthcare workers: an observational study using surveillance data. *Clin Microbiol Infect* 2021; **27:** 1699.e5–8.

27 Vasileiou E, Simpson CR, Shi T, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet* 2021; **397:** 1646–57.

28 Alencar CH, Cavalcanti LPG, Almeida MM, et al. High effectiveness of SARS-CoV-2 vaccines in reducing COVID-19-related deaths in over 75-year-olds, Ceará state, Brazil. *Trop Med Infect Dis* 2021; **6:** 129.

29 De Serres G, Skowronski DM, Wu XW, Ambrose CS. The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. *Euro Surveill* 2013; **18:** 20585.

30 Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. *JAMA* 2020; **323:** 2249–51.

31 Halloran ME, Struchiner CJ, Longini IM Jr. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. *Am J Epidemiol* 1997; **146:** 789–803.