Effectiveness of COVID-19 vaccines against hospitalisation in Latin America during three pandemic waves, 2021–2022: a test-negative case-control design

Francisco Nogareda,[a,*] Annette K. Regan,[a,b,c] Paula Couto,[a] Ashley L. Fowlkes,[d] Radhika Gharpure,[d] Sergio Loayza,[a] Juliana Almeida Leite,[a] Angel Rodríguez,[a] Andrea Vicari,[a] Eduardo Azziz-Baumgartner,[d] and Daniel Salas,[a] and the REVELAC-i Working Group[e]

[a]Pan American Health Organization, Washington, DC, USA
[b]School of Nursing and Health Professions, University of San Francisco, USA
[c]Fielding School of Public Health, University of California Los Angeles, USA
[d]National Center for Immunization and Respiratory Diseases, U.S. CDC, USA

The Lancet Regional Health - Americas 2023;27: 100626

Published Online xxx
https://doi.org/10.1016/j.lana.2023.100626

Summary

Background Vaccine effectiveness (VE) is essential to monitor the performance of vaccines and generate strategic information to guide decision making. We pooled data from six Latin American countries to estimate the effectiveness of COVID-19 vaccines in preventing laboratory-confirmed SARS-CoV-2 hospitalisation during three different pandemic waves from February 2021 to September 2022.

Methods We used a test-negative case-control design in hospitalised adults in Chile, Costa Rica, Ecuador, Guatemala, Paraguay, and Uruguay. We estimated adjusted VE by age group (18–64 and ≥65 years), vaccine type and product for primary series vaccination and booster vaccination and by time since last dose during the Omicron variant dominant period. We used mixed effects logistic regression models adjusting for sex, age, week of onset of symptom onset and pre-existing conditions with country fit as a random effect term.

Findings We included 15,241 severe acute respiratory infection (SARI) patients in the analysis. Among adults 18–64 years, VE estimates for primary series vaccination during pre-Delta and Delta periods ranged by product from 66.5% to 95.1% and from 33.5% to 88.2% for older adults. During the Omicron period, VE estimates for primary series were lower and decreased by time since last vaccination, but VE increased to between 26.4% and 57.4% when a booster was administered.

Interpretation mRNA and viral vector vaccines presented higher VE for both primary series and booster. While VE decreased over time, protection against severe COVID-19-associated hospitalisation increased when booster doses were administered. Vaccination with additional doses should be recommended, particularly for persons at increased risk of developing severe COVID-19.

Funding This work was supported by a grant from the U.S. Centers for Disease Control and Prevention (CDC) through cooperative agreements with the Pan American Health Organization/World Health Organization.

Keywords: Adults; Older adults; Hospitalisations; COVID-19 vaccine effectiveness; Latin America; Severe acute respiratory infections; Southern hemisphere; Test-negative case-control design

Introduction

Since late 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to substantial morbidity and mortality associated with coronavirus disease 2019 (COVID-19). Vaccination against COVID-19 is considered an important public health intervention to prevent infection and severe illness due to COVID-19, alongside other social and public health measures. COVID-19 vaccines became available in late 2020 from several manufacturers, quickly demonstrating their role in reducing mortality and severe morbidity.[1–3] Vaccine effectiveness (VE) in preventing

*Corresponding author.
E-mail address: nogaredfra@paho.org (F. Nogareda).
[e]REVELAC-i Working Group members are listed below.

Research in context

Evidence before this study

Vaccination against COVID-19 has played an important role to reducing the risk of hospitalisation and deaths caused by SARS-CoV-2 infection. Previous studies have demonstrated high protection of COVID-19 against severe disease and death, especially in pre-Omicron period and for mRNA and viral vector vaccines. Also, studies have showed that immunity protection waned over time and booster dose conferred additional protection. However, there is limited information about the effectiveness of the COVID-19 vaccines in low-middle income countries and the effect of the booster dose in the context of Omicron variant predominance. We reviewed the existing evidence of vaccine effectiveness against COVID-19 associated hospitalisations indexed in PubMed. The search strategy included key terms related to vaccine effectiveness.

Added value of this study

This evaluation pooled surveillance data from six Latin American countries to generate vaccine effectiveness estimates for multiple vaccines platforms and products. Vaccine effectiveness was obtained for three waves of the pandemic (pre-Delta, Delta and Omicron variant periods) by age group, by vaccine platform and product for primary series and booster dose. We demonstrate that vaccine effectiveness varies by age, by vaccine and by SARS-CoV-2 variant; immunity wanes over time after vaccination; and additional doses provides greater protection to reduce the risk of severe disease and hospitalisation.

Implications of all the available evidence

This evaluation provides further evidence on the vaccine effectiveness against COVID-19 associated hospitalisations. Effectiveness of COVID-19 vaccines varied by age and by vaccine type and by variant dominant period. Vaccine effectiveness was lower against Omicron variant and vaccination of primary series decreased over time. Our results underline the importance of receiving a booster dose for maintaining high level of protection and reduce the risk of hospitalisation associated with COVID-19, especially among older adults and groups at higher risk for severe disease.

hospitalisations and deaths associated with COVID-19 has been demonstrated through cohort studies in several countries[4–7]; however, vaccination programs must be continuously monitored to ensure that products and are still effective against currently circulating SARS-CoV-2 variants. Evaluation of vaccine effectiveness (VE) under real world conditions is essential for guiding vaccine policy decisions, as pre-authorization studies could not evaluate vaccines in specific populations (e.g., immunocompromised people, pregnant people), in specific settings where cold chain capacity is limited, against more severe outcomes of COVID-19, against emerging SARS-CoV-2 variants and subvariants, or for duration of protection.[8]

Vaccination against COVID-19 in Latin America and the Caribbean (LAC) countries began in December 2020. Priority groups for vaccination were defined to protect and maintain essential health services, to prevent severe disease and death in populations at increased risk of infection or severe illness, and to reduce societal and economic disruption.[9] Vaccine distribution was conducted in progressive stages as vaccine supply increased, generally starting with health care professionals and essential workers, older adults, people with chronic diseases, pregnant individuals, and later expanding to healthy adults and children.[10] As of April 2022, a total of 21 vaccine products had been authorised in LAC countries with more than two billion doses administered; based on administrative data, an estimated 72% of the total population had completed the primary series in the Region.[11]

To monitor and evaluate influenza VE in Latin America, the Pan American Health Organization (PAHO) established in 2013 the Network for the Evaluation of Vaccine Effectiveness in Latin America and the Caribbean–influenza (REVELAC-i).[12] The objective of this network is to generate annual, regional evidence about the effectiveness of Southern Hemisphere influenza vaccines in preventing influenza-associated hospitalisations to inform policy decisions about continued investments in influenza vaccines and risk communication. VE estimates generated are also reported to the Global Influenza Vaccine Effectiveness (GIVE) Report to contribute to the selection of seasonal influenza vaccine composition. REVELAC-i network builds upon data from sentinel surveillance for severe acute respiratory infections (SARI) conducted throughout the Americas, using the test-negative design to conduct vaccine effectiveness evaluations.[13] The network uses multi-country standardised data collection to facilitate data pooling and to produce estimates that countries might be unable to obtain individually (e.g., VE against hospitalisation by age group and product). Since January 2020, countries in the region progressively integrated COVID-19 into their SARI sentinel surveillance.[14] Simultaneously, REVELAC-i was adapted to generate VE estimates against laboratory-confirmed COVID-19 hospitalisations by product and target populations.

Using pooled data from Latin American countries participating in REVELAC-i, we estimated the effectiveness of COVID-19 vaccines in preventing laboratory-confirmed SARS-CoV-2-associated hospitalisation during three different pandemic waves from February 2021 to September 2022. We estimated adjusted VE (aVE) by age group (18–64 and ≥65 years

old), vaccine type (i.e., viral vector, inactivated virus, and mRNA vaccines), vaccine product, vaccination status (completed primary series and booster), and circulating SARS-CoV-2 variant predominance. We also estimated aVE by time since receipt of last vaccine dose (<90 days, 90 and 180 days, >180 days) during the Omicron variant predominant period.

Methods

Study design

We used a test-negative case-control design to estimate VE against laboratory-confirmed COVID-19 hospitalisation in six REVELAC-i network Latin American countries with available data from February 2021 to September 2022 (i.e., Chile, Costa Rica, Ecuador, Guatemala, Paraguay, and Uruguay). All countries used the REVELAC-i common protocol[15] following the PAHO guidelines for SARI sentinel surveillance.[16] Data were collected and pooled to conduct the analysis from 63 sentinel hospitals: Chile (n = 9), Costa Rica (n = 28), Ecuador (n = 12), Guatemala (n = 3), Paraguay (n = 4) and Uruguay (n = 7) (Supplementary Table S1).

Study population

The study population included patients aged 18 years and older admitted to a participating sentinel surveillance hospital meeting the WHO standard SARI case definition of acute respiratory infection with history of fever or measured fever of ≥38 °C and cough with onset within the last 10 days, requiring hospitalisation.[17] Trained staff collected a nasopharyngeal specimen for SARS-CoV-2 using reverse transcription-polymerase chain reaction (RT-PCR). Cases were defined as SARI patients who tested positive for SARS-CoV-2, and controls were defined as SARI patients who tested negative. We included only SARI patients whose respiratory specimen was collected within 10 days after symptoms onset and tested by RT-PCR for SARS-CoV-2.[18–21]

We excluded patients without laboratory testing information, those tested only by rapid antigen test, and patients who tested positive by RT-PCR for influenza as correlated COVID-19 and influenza vaccine behaviours may introduce a confounding bias where controls are included with the other vaccine-preventable acute respiratory illness.[22] Patients who were not eligible for COVID-19 vaccination at the time of the admission, based on vaccination strategy in the respective country, of unknown vaccination status, or vaccinated within 14 days before onset symptoms were also excluded.

Exposure

A total of ten different vaccines products were used in the six participating countries: Pfizer/BioNTech *Comirnaty* (Pfizer), Oxford/AstraZeneca *Vaxzevria* (AstraZeneca), Moderna *Spikevax* (Moderna), Gamaleya *Sputnik V* (Sputnik V), Sinovac *CoronaVac* (Sinovac), CanSino *Convidecia* (Cansino), Janssen-Johnson & Johnson Ad26.COV2.S (Janssen), Sinopharm Beijing *Covilo* (Sinopharm), Bharat Biotech *Covaxin* (Covaxin) and Medigen MVC-COV1901 (Medigen).

Patients who received a single dose of a vaccine that requires two doses at least 14 days before the onset of symptoms were considered partially vaccinated. Patients who completed the recommended primary series of COVID-19 immunization (i.e., received one vaccine dose for vaccines that require only one dose or two vaccine doses for vaccines that require two doses) at least 14 days before the onset of symptoms and did not receive any booster doses of vaccine were considered to have completed the primary series. For patients with immunosuppressing conditions additional doses were considered to complete the primary series. Patients who completed the primary series and had a record of one booster dose of vaccine received at least 14 days before the onset of symptoms were considered boosted. Unvaccinated patients were defined as those who had not received any dose of vaccine before or after the onset of symptoms.

Data collection

Sentinel sites reported data for all patients meeting the SARI case definition. Information collected included patients' demographic characteristics, clinical data, laboratory data and vaccination history against COVID-19. Vaccination history, including date of vaccination and vaccine product for each dose was obtained through national immunization records. Data were reported through PAHOFlu, an online data import and management package that includes an interface to enter information from paper forms[23] or imported directly through existing digital information systems.

Data analysis

We conducted descriptive and univariable analyses to measure the association between patient characteristics, laboratory test results, and COVID-19 vaccination status using Chi-square, Fisher's exact, t-, or Mann–Whitney tests, according to variable type and distribution. VE was calculated as 1-odds ratio (OR) and expressed as a percentage with the OR derived from mixed effects logistic regression models comparing the odds of vaccination accounting for potential random effects of each country. Where few countries contributed to the analysis of a particular brand, we estimated VE using a fixed effects model. Unvaccinated SARI patients were used as the reference group in all analyses, including for booster dose VE estimation. We estimated adjusted ORs (aOR) and adjusted VE (aVE) using multivariable logistic regression models adjusting for age (in years), pre-existing health conditions (presence of at least one, including: asthma, hypertension, diabetes, cardiovascular disease, immunocompromised, other respiratory diseases, and obesity), sex, and week of symptom onset

(fit as cubic spline). Models did not adjust for multiple comparisons.

The proportion of missing data ranged from <0.1% (patient sex) to 42.9% (influenza vaccination status) (Supplementary Table S2). We modelled the odds of missing information by other covariates to evaluate whether variables were missing at random. For variables missing at random (i.e., pre-existing medical conditions and patient sex), we imputed missing covariate data using multiple imputation by chained equations with 50 imputed sets with 10 iterations.

Estimates of COVID-19 VE were generated for completed primary series, by vaccine product, age group and SARS-CoV-2 variant dominant period. Age groups were based on vaccination policy targets: 18–64 years and adults ≥65 years old. To account for differences in circulating SARS-CoV-2 viruses, we restricted analyses to three time periods: Pre-Delta, Delta, and Omicron variant predominance. Time periods were assigned for each country based on predominance of a variant (>75% of the total number of sequences conducted) using the genomic surveillance data reported to GISAID Initiative.[24] For the Pre-Delta period, multiple variants were co-circulating and therefore no variant-specific estimates were obtained. We excluded from analysis patients with onset of symptoms within two weeks of variant predominant transition periods (Supplementary Table S3).

During Omicron predominance, aVE estimates were generated by time since last primary series vaccination (<90 days, 90–180 days, >180 days). In addition, we estimated the aVE for COVID-19 booster dose by target age groups and booster vaccine product (homologous and heterologous booster). We did not estimate VE where there were insufficient data (i.e., cell with n < 5), and we omitted VE estimates where the confidence intervals exceeded 140% (Supplementary Tables S4 and S5).

Pooling data and heterogeneity

Individual data were pooled across countries into one analytic dataset. To evaluate possible heterogeneity of results across countries, we used a random effects meta-analysis. We examined Cochrane's Q and the I^2 index to evaluate the magnitude of heterogeneity (Supplementary Figure S1a and S1b).

Ethical considerations

The Pan American Health Organization Ethical Review Committee reviewed the protocol and determined that this evaluation does not constitute research with human subjects research and thus does not require full PAHOERC review.[25]

Role of funding source

This work was supported by a grant from the U.S. Centers for Disease Control and Prevention (CDC) through cooperative agreements with the Pan American Health Organization/World Health Organization. The findings and conclusions in this publication are those of the authors and do not necessarily represent the views of the Pan American Health Organization (PAHO) or Centers for Disease Control and Prevention. The content of this article has not been previously presented.

Results

From 2 February 2021 to 3 September 2022, 19,374 SARI hospitalisations were reported by participating hospitals, among which 15,241 (78.7%) patients met inclusion criteria; 8201 test-positive cases and 7040 test-negative controls (Fig. 1). Most patients were admitted during Omicron variant period (46.7%) from December 2021 to March 2022 and during Pre-Delta variant predominance (33.0%) from January to August 2021 (Fig. 2). Patients representing the six countries included 4236 (27.8%) from Chile, 4032 (26.5%) from Paraguay, 3926 (25.8%) from Costa Rica, 1672 (11.0%) from Ecuador, 914 (6.0%) from Guatemala, and 461 (3.0%) from Uruguay (Table 1, Supplementary Figure S2); 7460 (48.9%) were adults 18–64 years old and 7781 (51.1%) older adults 65 years and older.

Of the 15,241 patients, 4989 (32.7%) were unvaccinated and 10,252 (67.3%) received at least one dose of vaccine. Among vaccinated patients, 2587 (25.2%) were partially vaccinated, 4459 (43.5%) completed the primary series, and 3206 (31.3%) received a booster dose. Vaccine uptake varied by country and variant period for receipt of both primary series and booster doses (Supplementary Table S2, Supplementary Figures S3 and S4). During the pre-Delta period, Pfizer represented the majority (59%) of administered vaccines, though Covaxin (21%) was also commonly received. During the Delta period, patients had most often received Pfizer and AstraZeneca, while during the Omicron period, patients had most often received Sinovac (37%), though Pfizer (23%) and AstraZeneca (21%) were also common (Supplementary Table S6).

Compared to controls, COVID-19 cases were more frequently aged less than 60 years (43.4% vs. 34.6%, p < 0.001), more frequently required ICU admission (23.5% vs. 14.3%, p < 0.0001), and were less likely to report the presence of at least one pre-existing condition (62.5% vs. 69.6%, p < 0.0001) or influenza vaccination (15.9% vs. 27.9%, p < 0.0001). By vaccination status, coverage with at least one dose was highest in Ecuador (80.3%) and lowest in Guatemala (31.2%). By sex, 61.6% of men and 59.6% of women were vaccinated. Among patients who tested positive for SARS-CoV-2, vaccination coverage with at least one dose was 46.6% compared to 76.8% in patients who tested negative (Table 1).

Vaccine effectiveness for completed primary series

Pre-Delta variant period

Several variants of SARS-CoV-2 were co-circulating during the pre-Delta period (February–August 2021)

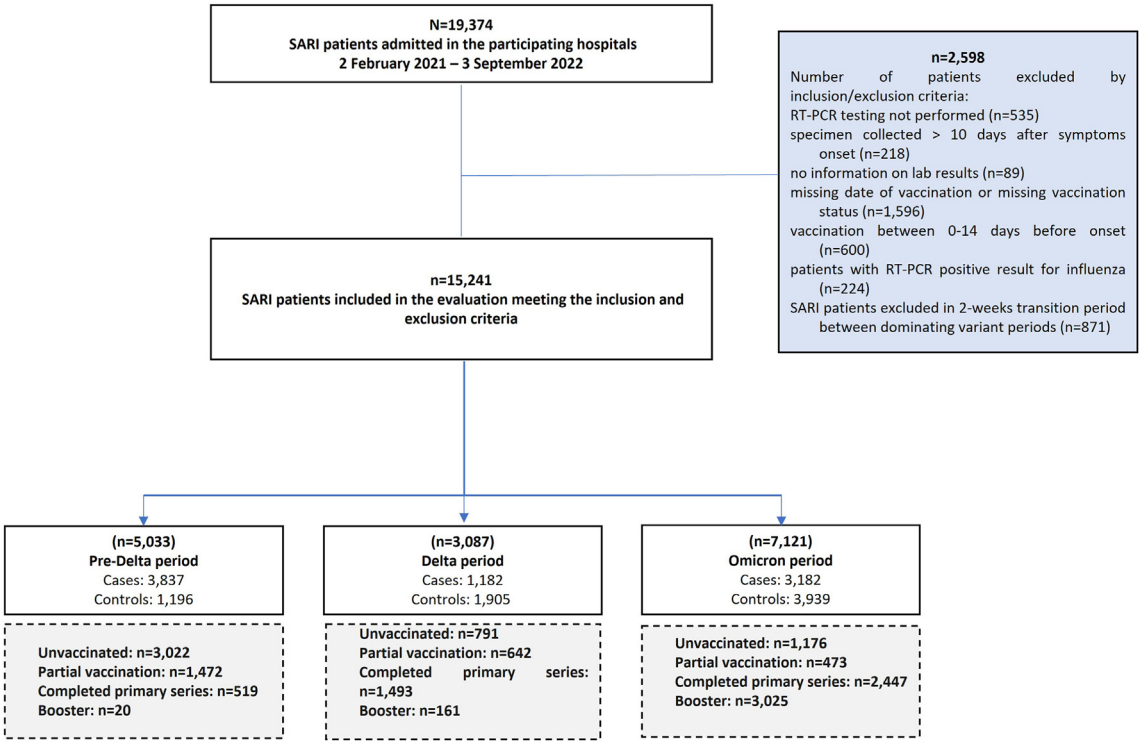

Fig. 1: Flow diagram for selection of REVELAC-i participants included in the final analysis of vaccine effectiveness.

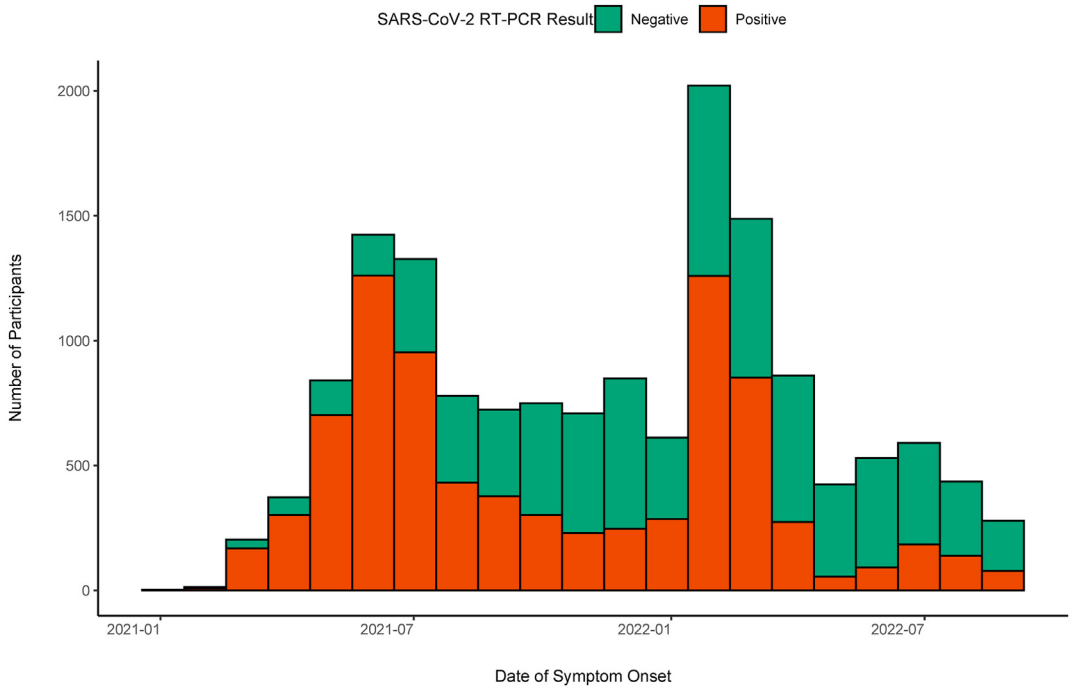

Fig. 2: Distribution of SARS-CoV-2 test positive cases and test-negative controls—REVELAC-i, January 2021–September 2022.

Patient characteristic	Total (N = 15,241)	Test-positive cases (n = 8201)	Test-negative controls (n = 7040)	Chi-squared p-value	Unvaccinated[b] (n = 4989)	Partial primary series (n = 2587)	Completed primary series (n = 4459)	Booster (n = 3206)	Chi-squared p-value
	N (%)	n (%)	n (%)		n (%)	n (%)	n (%)	n (%)	
Country				<0.0001					<0.0001
Chile	4236 (27.8)	2259 (27.5)	1977 (28.1)		1508 (30.2)	366 (14.1)	537 (12.0)	1825 (56.9)	
Costa Rica	3926 (25.8)	2079 (25.3)	1847 (26.2)		119 (2.4)	1002 (38.7)	2281 (51.2)	524 (16.3)	
Ecuador	1672 (11.0)	758 (9.2)	914 (13.0)		337 (6.8)	412 (15.9)	456 (10.2)	467 (14.6)	
Guatemala	914 (6.0)	617 (7.5)	297 (4.2)		543 (10.9)	172 (6.6)	148 (3.3)	51 (1.6)	
Paraguay	4032 (26.5)	2316 (28.2)	1716 (24.4)		2348 (47.1)	574 (22.2)	960 (21.5)	150 (4.7)	
Uruguay	461 (3.0)	172 (2.1)	289 (4.1)		134 (2.7)	61 (2.4)	77 (1.7)	189 (5.9)	
Patient age				<0.0001					<0.0001
18–44 years	3120 (20.5)	1718 (20.9)	1402 (19.9)		1194 (23.9)	787 (30.4)	813 (18.2)	326 (10.2)	
45–59 years	2874 (18.9)	1841 (22.5)	1033 (14.7)		1245 (25.0)	633 (24.5)	648 (14.5)	348 (10.9)	
60–69 years	3000 (19.7)	1676 (20.4)	1324 (18.8)		1055 (21.1)	481 (18.6)	832 (18.7)	632 (19.7)	
70–79 years	3079 (20.2)	1527 (18.6)	1552 (22.1)		812 (16.3)	412 (15.9)	977 (21.9)	878 (27.4)	
80 years+	3168 (20.8)	1439 (17.5)	1729 (24.6)		683 (13.7)	274 (10.6)	1189 (26.7)	1022 (31.9)	
Patient sex				0.0013					<0.0002
Male	7977 (52.3)	4392 (53.5)	3585 (50.9)		2655 (53.2)	1428 (55.2)	2229 (50.0)	1665 (51.9)	
Female	7264 (47.7)	3809 (46.5)	3455 (49.1)		2334 (46.8)	1159 (44.8)	2230 (50.0)	1541 (48.1)	
Pre-existing health condition[a]				<0.0001					<0.0001
≥1 pre-existing health condition	10,020 (65.7)	5122 (62.5)	4898 (69.6)		3370 (67.6)	1348 (52.1)	2746 (61.6)	2556 (79.7)	
No pre-existing health condition	5221 (34.3)	3079 (37.5)	2142 (30.4)		1619 (32.4)	1239 (47.9)	1713 (38.4)	650 (20.3)	
Influenza vaccination status				<0.0001					<0.0001
Vaccinated	3269 (21.4)	1304 (15.9)	1965 (27.9)		263 (5.3)	294 (11.4)	981 (22.0)	1731 (54.0)	
Unvaccinated	11,972 (78.6)	6897 (84.1)	5075 (72.1)		4726 (94.7)	2293 (88.6)	3478 (88.0)	1475 (46.0)	
Time period of symptom onset[b]				<0.0001					<0.0001
Pre-Delta variants	5033 (33.0)	3837 (46.8)	1196 (17.0)		3022 (60.6)	1472 (56.9)	519 (11.6)	20 (0.6)	
Delta variant	3087 (20.3)	1182 (14.4)	1905 (27.1)		791 (15.9)	642 (24.8)	1493 (33.5)	161 (5.0)	
Omicron variant	7121 (46.7)	3182 (38.8)	3939 (55.9)		1176 (23.6)	473 (18.3)	2447 (54.9)	3025 (94.4)	
ICU admission				<0.0001					<0.0001
Yes	2934 (19.3)	1930 (23.5)	1004 (14.3)		1461 (29.3)	418 (16.2)	460 (10.3)	595 (18.6)	
No	12,307 (80.7)	6271 (76.5)	6036 (85.7)		3528 (70.7)	2169 (83.8)	3999 (89.7)	2611 (81.4)	
COVID-19 vaccination status[c]				<0.0001					
Unvaccinated	4989 (32.7)	3606 (44.0)	1383 (19.6)		–	–	–	–	
Partial primary series	2587 (17.0)	1661 (20.3)	926 (13.2)		–	–	–	–	
Complete primary series	4459 (29.3)	1871 (22.8)	2588 (36.8)		–	–	–	–	
Booster	3206 (21.0)	1063 (13.0)	2143 (30.4)		–	–	–	–	
SARS-CoV-2 RT-PCR result									<0.0001
Positive	8201 (53.8)	–	–		3606 (72.3)	1661 (64.2)	1871 (42.0)	1063 (33.2)	
Negative	7040 (46.2)	–	–		1383 (27.7)	926 (35.8)	2588 (58.0)	2143 (66.8)	

[a]Asthma, hypertension, diabetes, cardiovascular disease, immunocompromised, other respiratory diseases and obesity. [b]Time periods of symptom onset were assigned based on the predominating circulating SARS-CoV-2 variant in each country. [c]SARS-CoV-2 vaccination status was defined as "partial completion of primary vaccination series" if one dose of a two-dose series was received prior to symptom onset; "completed primary vaccination series" if one dose of a one-dose series and two doses of a two-dose series were received >14 days prior to symptom onset; Patients who did not receive any vaccine dose before symptoms onset were classed as "unvaccinated". Definitions took into account additional doses required for immunosuppressed and immunocompromised individuals.

Table 1: **Characteristics of REVELAC participants, by SARS-CoV-2 test results and vaccination status (n = 15,241)—REVELAC-i, February 2021–September 2022.**

without dominance of any variant (i.e., Alpha, Beta, Gamma, Lambda, Mu, etc.), during which 5033 patients were admitted with SARI, but only 11.6% of patients received the completed primary series, mostly (77.7%) older adults ≥65 years. Among patients aged 18–64 years, the estimated aVE for completed primary series was 66.5% (95% CI: −12.8%; 90.1%) for viral vector vaccines, 73.3% (95% CI: 16.2%; 91.5%) for inactivated virus vaccines and 70.1% (95% CI: 56.2%; 91.0%) for the Pfizer mRNA vaccine (Table 2). Among patients aged ≥65 years, estimated VE for inactivated virus vaccines was 53.8% (95% CI: 24.2%; 71.9%) and Pfizer mRNA vaccine was 80.2% (95% CI: 61.3%; 89.9%). Due to small numbers, VE for viral vector vaccines could not be estimates for adults ≥65 years.

Delta variant period

During Delta variant predominance (August–December 2021), a total of 3087 SARI patients were admitted and included in the evaluation. Among patients aged 18–64 years, the aVE point estimate for completed primary series without booster for inactivated virus vaccines was 80.1% (95% CI: 79.8%; 95.1%), 93.3% (95% CI: 86.4%; 96.7%) for mRNA vaccines, and 86.4% (95% CI: 75.9%; 99.9%) for viral vector vaccines. Product-specific aVE estimates indicated that Pfizer vaccine presented the highest aVE point estimate with 95.1% (95% CI: 87.2%; 98.1%), and similar aVE for viral vector vaccines, AstraZeneca (80.1% [95% CI: 79.8%; 95.1%]) and Sputnik V (81.5% [95% CI: 44.9%; 93.9%]). Among older adults, aVE point estimates were generally similar compared to adults 18–64 years. The aVE for viral vector vaccines (75.5% [95% CI: 48.7%; 89.3%]) and mRNA vaccines (87.0% [95% CI: 74.1%; 93.5%]) were similar; however, inactivated virus vaccines had a lower aVE of 40.9% (95% CI: −32.8%; 73.8%) (Table 2).

Omicron variant period

A total of 7121 SARI patients were admitted during the Omicron variant period (from December 2021 to September 2022). Overall, VE decreased in both age groups for all vaccines during this period compared with those observed previously. Among adults aged 18–64 years, aVE for completed primary series of mRNA vaccines was 39.6% (95% CI: 10.7%; 59.2%), 24.8% (95% CI: −7.1%; 47.2%) for viral vector vaccines, and 1.1% (95% CI: −42.2%, 31.2%) for inactivated virus vaccines (Table 2). Product-specific estimates for inactivated virus vaccines varied widely from 43.8% for Sinopharm to 1.3% for Sinovac. Among older adults, we observed a similar trend. The aVE for the completed primary series with mRNA vaccines was 30.0% (95% CI: −5.5%, 53.6%), 32.5% (95% CI: 3.5%; 52.9%) for viral vector vaccines, and 26.8% (95% CI: 3.8%, 44.4%) for inactivated virus vaccines. By vaccine product, aVE ranged from 23.0% (95% CI: −50.4%; 61.5%) for Sputnik V to 40.7% (95% CI: −19.9%; 70.6%) for Sinopharm (Table 2).

Vaccine effectiveness by time since vaccination with completed primary series during the Omicron period

The aVE decreased progressively by time since last dose of vaccination for the primary series in patients admitted during the Omicron predominance period. The aVE among adults aged 18–64 years vaccinated within 90 days before symptoms onset with a viral vector vaccine was 65.1% (95% CI: 34.1%, 81.5%) and decreased to −13.8% (95% CI: −101%, 35.7%) when the last dose of the primary series was administered >180 days previously. For mRNA vaccines, aVE for recent vaccination within 90 days was 49.3% (95% CI: −8.9%, 76.4%) to 39.6% (95% CI: −3.9%, 63.7%) for vaccination >180 days. Among older adults ≥65 years vaccinated between 90 and 180 days with viral vector vaccines, the aVE was 30.2% (95% CI: −8.1%, 55.0%) with an increase to 58.4% (95% CI: 23.9%, 77.3%) for patients vaccinated >180 days. For inactivated virus vaccines, aVE was 37.7% (95% CI: −15.8%, 66.5%) for vaccination between 90 and 180 days and decreased to 24.5% (95% CI: −0.6%, 43.5%) in patients vaccinated >180 days. For mRNA vaccines, aVE was 47.4% (95% CI: −6.7%, 74.2%) for vaccination between 90 and 180 days and decreased to 3.4% (95% CI: −49.1%, 37.4%) for vaccination >180 days. In this age group, data was insufficient to estimate VE for vaccination within 90 days before symptoms onset. Product-specific estimates were like those reported for the overall vaccine types (Table 3).

Vaccine effectiveness for booster dose by vaccine product during Omicron period

The effectiveness of receiving a homologous or heterologous booster dose was assessed for the most received vaccines during Omicron variant dominant period, including AstraZeneca, Pfizer and Sinovac. Among patients aged 18–64 years with a completed primary series with AstraZeneca, the aVE associated with receipt of a heterologous booster was 55.2% (95% CI: 32.5%; 70.2%). Data were insufficient to estimate the aVE for a homologous booster with AstraZeneca. The aVE for Pfizer with a homologous booster was 57.1% (95% CI: 33.3%; 72.5%) and 32.8% (95% CI: 4.1%, 53.0%) with a heterologous booster. For Sinovac, the aVE for homologous booster was 20.9% (95% CI: −67.2%, 62.5%). Data were insufficient to estimate the aVE for a heterologous booster with Sinovac. Similar results were observed for adults ≥65 years old, with exception to receipt of a homologous booster of Sinovac, which was slightly higher compared to adults 18–64 years old (aVE 55.5%; 95% CI: 32.6%, 70.7%) (Table 4).

Heterogeneity

Where data were sufficient to estimate aVE by country, meta-analyses indicated low to moderate heterogeneity across countries during the Omicron period (Supplementary Figure S1a and S1b). Among adults

	Pre-Delta variant period					Delta variant period					Omicron variant period				
	Cases		Controls		aVE % (95% CI)[a]	Cases		Controls		aVE % (95% CI)[a]	Cases		Controls		aVE % (95% CI)[a]
	Vaccine (+)	Vaccine (−)	Vaccine (+)	Vaccine (−)		Vaccine (+)	Vaccine (−)	Vaccine (+)	Vaccine (−)		Vaccine (+)	Vaccine (−)	Vaccine (+)	Vaccine (−)	
Adults 18–64 years															
Viral vector vaccines	7	1744	5	297	66.5 (−12.8, 90.1)	39	278	120	151	86.4 (75.9, 99.9)	198	257	213	264	24.8 (−7.1, 47.2)
AstraZeneca	1	1744	4	297	ISD	30	278	100	151	80.1 (79.8, 95.1)	169	257	171	264	20.9 (−20.5, 48.2)
CanSino	4	1744	1	297	ISD	4	278	1	151	ISD	7	257	9	264	NP
Sputnik V	2	1744	0	297	ISD	5	278	19	151	81.5 (44.9, 93.9)	22	257	33	264	41.6 (−12.2, 69.7)
Inactivated virus vaccines	7	1744	7	297	73.3 (16.2, 91.5)	11	278	45	151	74.3 (40.7, 88.9)	116	257	155	264	1.1 (−42.2, 31.2)
Covaxin	4	1744	0	297	ISD	2	278	3	151	ISD	1	257	2	264	ISD
Sinovac	3	1744	2	297	ISD	5	278	25	151	NP	106	257	141	264	1.3 (−43.4, 32.0)[b]
Sinopharm (Beijing)	0	1744	5	297	ISD	4	278	17	151	ISD	9	257	12	264	43.8 (−53.5, 79.4)
mRNA vaccines	22	1744	38	297	77.4 (51.4, 89.5)	54	278	213	151	93.3 (86.4, 96.7)	338	257	269	264	23.0 (−8.9, 45.5)
Moderna	2	1744	0	297	ISD	6	278	19	151	89.2 (68.5, 96.3)	29	257	13	264	NP
Pfizer	20	1744	38	297	70.1 (56.2, 91.0)	48	278	194	151	95.1 (87.2, 98.1)	309	257	256	264	39.6 (10.7, 59.2)
Adults ≥65 years															
Viral vector vaccines	3	795	2	186	ISD	12	158	142	204	75.5 (48.7, 89.3)	112	374	115	281	32.5 (3.5, 52.9)
AstraZeneca	2	795	2	186	ISD	9	158	119	204	77.9 (49.8, 90.4)	90	374	95	281	38.9 (10.5, 58.3)
CanSino	0	795	0	186	ISD	1	158	0	204	ISD	0	374	2	281	ISD
Sputnik V	1	795	0	186	ISD	2	158	23	204	ISD	22	374	18	281	23.9 (−50.4, 61.5)[b]
Inactivated virus vaccines	53	795	33	186	53.8 (24.2, 71.9)	34	158	159	204	70.9 (55.0, 81.2)[b]	225	374	212	281	26.8 (3.8, 44.4)
Covaxin	32	795	21	186	57.5 (21.7, 76.9)	16	158	101	204	77.2 (58.9, 87.4)[b]	36	374	34	281	25.2 (−31.6, 57.5)
Sinovac	20	795	10	186	33.5 (−63.3, 73.0)	10	158	22	204	40.9 (−32.8, 73.8)[b]	172	374	152	281	25.1 (−4.7, 46.4)
Sinopharm (Beijing)	1	795	2	186	ISD	8	158	36	204	71.8 (36.2, 87.5)[b]	17	374	26	281	40.7 (−19.9, 70.6)[b]
mRNA vaccines	106	795	236	186	77.0 (57.5, 87.5)	232	158	432	204	87.0 (74.1, 93.5)	302	374	192	281	30.0 (−5.5, 53.6)
Moderna	6	795	5	186	ISD	7	158	16	204	88.2 (66.2, 95.9)	0	374	3	281	ISD
Pfizer	100	795	231	186	80.2 (61.3, 89.9)	225	158	416	204	85.4 (63.9, 94.1)	302	374	189	281	25.4 (−12.3, 50.4)

Abbreviations: CI, confidence interval; ISD, insufficient data to estimate; NP, estimate not provided when 95% CI width >140; VE, vaccine effectiveness. [a]Vaccine effectiveness was estimated as one minus the odds ratio comparing vaccination status by SARS-CoV-2 test result (case status) computed from a mixed effects logistic regression model adjusting for age (continuous), pre-existing health conditions (yes/no), sex, and week of onset (fit as cubic spline) and treating country as a random effect term. NP: estimate not provided, when 95% CI width >140. ISD: insufficient data to calculate when less than 5 patients in one category. [b]Modelled as fixed effects due to small number of contributing countries by brand.

Table 2: **Estimated effectiveness of COVID-19 vaccines for primary series vaccination by vaccine type, vaccine product, age group and SARS-CoV-2 variant dominant period—REVELAC-i, February 2021–September 2022.**

	<90 days					90–180 days					>180 days				
	Cases		Controls		aVE % (95% CI)[a]	Cases		Controls		aVE % (95% CI)[a]	Cases		Controls		aVE % (95% CI)[a]
	Vaccine (+)	Vaccine (–)	Vaccine (+)	Vaccine (–)		Vaccine (+)	Vaccine (–)	Vaccine (+)	Vaccine (–)		Vaccine (+)	Vaccine (–)	Vaccine (+)	Vaccine (–)	
18–64 years															
Viral vector vaccines	40	257	59	264	65.1 (34.1, 81.5)	99	257	101	264	21.6 (–20.6, 49.1)	59	257	53	264	–13.8 (–101, 35.7)
AstraZeneca	35	257	49	264	62.7 (22.7, 82.0)	82	257	81	264	22.3 (–29.0, 53.2)	52	257	41	264	NP
CanSino	0	257	1	264	ISD	1	257	1	264	ISD	6	257	7	264	NP
Sputnik V	5	257	9	264	72.9 (7.6, 92.1)	16	257	19	264	NP	1	257	5	264	ISD
Inactivated virus vaccines	13	257	12	264	NP	37	257	31	264	NP	66	257	112	264	12.3 (–32.5, 41.9)
Covaxin	0	257	0	264	ISD	0	257	0	264	ISD	1	257	2	264	ISD
Sinovac	13	257	11	264		37	257	31	264	NP	56	257	99	264	7.3 (–45.7, 41.0)
Sinopharm (Beijing)	0	257	1	264	ISD	0	257	0	264	ISD	9	257	11	264	41.2 (–62.0, 78.8)
mRNA vaccines	36	257	33	264	40.9 (–22.2, 71.4)	178	257	120	264	6.3 (–47.4, 40.4)	124	257	116	264	24.4 (–21.5, 52.9)
Moderna	2	257	2	264	ISD	18	257	6	264	NP	9	257	5	264	NP
Pfizer	34	257	31	264	49.3 (–8.9, 76.4)	160	257	114	264	22.5 (–28.9, 53.5)	115	257	111	264	39.6 (–3.9, 63.7)
≥65 years															
Viral vector vaccines	18	374	6	281	NP	74	374	59	281	30.2 (–8.1, 55.0)	20	374	50	281	58.4 (23.9, 77.3)
AstraZeneca	18	374	5	281	NP	57	374	44	281	32.4 (–9.6, 58.4)	15	374	46	281	69.3 (40.5, 84.2)
CanSino	0	374	0	281	ISD	0	374	2	281	ISD	0	374	0	281	ISD
Sputnik V	0	374	1	281	ISD	17	374	13	281	36.4 (–37.9, 70.7)[b]	5	374	4	281	ISD
Inactivated virus vaccines	8	374	8	281	NP	33	374	24	281	37.7 (–15.8, 66.5)[b]	184	374	180	281	24.5 (–0.6, 43.5)
Covaxin	0	374	0	281	ISD	0	374	1	281	ISD	36	374	33	281	22.4 (–37.1, 56.1)
Sinovac	8	374	8	281	NP	32	374	21	281	29.9 (–34.7, 63.5)[b]	132	374	123	281	23.8 (–9.0, 46.7)
Sinopharm (Beijing)	0	374	0	281	ISD	1	374	2	281	ISD	16	374	24	281	36.2 (–31.9, 69.2)
mRNA vaccines	7	374	9	281	NP	25	374	26	281	47.4 (–6.7, 74.2)	270	374	157	281	3.4 (–49.1, 37.4)
Moderna	0	374	0	281	ISD	0	374	3	281	ISD	0	374	0	281	ISD
Pfizer	7	374	9	281	NP	25	374	23	281	33.4 (–38.9, 67.9)	270	374	157	281	3.4 (–49.1, 37.4)

Abbreviations: CI, confidence interval; ISD, insufficient data to estimate; NP, estimate not provided when 95% CI width >140; VE, vaccine effectiveness. [a]Vaccine effectiveness was estimated as one minus the odds ratio comparing vaccination status by SARS-CoV-2 test result (case status) computed from a mixed effects logistic regression model adjusting for age (continuous), pre-existing health conditions (yes/no), sex, and week of onset (fit as cubic spline) and treating country as a random effect term. [b]Model fit as fixed effects due to small number of countries contributing brand data.

***Table 3*: Estimated effectiveness of COVID-19 vaccines, by vaccine product, age group and time since last vaccination for completed primary series in Omicron variant dominant period—REVELAC-i, February 2021–September 2022.**

	Adults 18–64 years					Adults ≥65 years				
	Cases		Controls		aVE % (95% CI)[a]	Cases		Controls		aVE % (95% CI)[a]
	Vaccine (+)	Vaccine (–)	Vaccine (+)	Vaccine (–)		Vaccine (+)	Vaccine (–)	Vaccine (+)	Vaccine (–)	
Primary series with AstraZeneca[b]										
Any booster	88	257	200	264	47.0 (22.9, 63.5)	320	374	529	281	47.8 (32.8, 59.5)
Heterologous booster	68	257	174	264	55.2 (32.5, 70.2)	306	374	522	281	51.1 (36.7, 62.2)
Homologous booster	20	257	23	264	NP	14	374	7	281	NP
Primary series with Pfizer										
Any booster	160	257	440	264	43.1 (21.9, 58.5)	452	374	950	281	57.4 (45.5, 66.7)
Heterologous booster	61	257	156	264	32.8 (4.1, 53.0)	203	374	566	281	60.4 (47.3, 70.3)
Homologous booster	99	257	284	264	57.1 (33.3, 72.5)	248	374	382	281	55.5 (37.5, 68.3)
Primary series with Sinovac										
Any booster	19	257	47	264	26.4 (–36.9, 60.4)[b]	88	374	134	281	48.2 (24.1, 64.6)
Heterologous booster	6	257	20	264	NP	15	374	20	281	NP
Homologous booster	13	257	27	264	20.9 (–67.2, 62.5)[c]	73	374	114	281	55.5 (32.6, 70.7)

Abbreviations: CI, confidence interval; ISD, insufficient data to estimate when less than 5 patients in one category; NP, estimate not provided when 95% CI width >140; VE, vaccine effectiveness. [a]Vaccine effectiveness was estimated as one minus the odds ratio comparing vaccination status by SARS-CoV-2 test result (case status) computed from a mixed effects logistic regression model, adjusting for age (continuous), pre-existing health conditions (yes/no), sex, and week of onset (fit as cubic spline) and treating country as a random effect term. [b]Brand unknown for three AstraZeneca primary series for each age group. [c]Modelled as fixed effects due to small number of contributing countries.

Table 4: **Estimated effectiveness of COVID-19 vaccines, by primary series and booster vaccine product, age group and type of booster dose in Omicron variant dominant period—REVELAC-i, February 2021–September 2022.**

aged 18–64 years, the pooled VE estimate for primary series was 43% (95% CI: –42%, 77%) for AstraZeneca (I^2 = 40.7%; p = 0.19) and 52% (95% CI: 18%, 71%) for Pfizer (I^2 < 0.1%, p = 0.98). Among adults ≥65 years old, the pooled estimate of aVE was 48% (95% CI: –26%, 89%) for AstraZeneca (I^2 = 49.1%; p = 0.15) and 74% (95% CI: 35%, 89%) for Pfizer (I^2 < 0.1%, p = 0.49).

Discussion

Leveraging the standardised methodology for COVID-19 surveillance across multiple countries in Latin America, we pooled data to demonstrate COVID-19 vaccines as a substantially effective measure to reduce the odds of COVID-19-associated hospitalisation among working-age and older adults. Our results demonstrate that moderate variability was observed for COVID-19 vaccine effectiveness by type of vaccine and product, age, and SARS-CoV-2 variant circulation. In Pre-Delta period, VE were observed lower VE probably due to co-circulation of multiple variants and small proportion of patients who had completed the primary series of vaccination. In addition, patients vaccinated during pre-Delta period were individuals at higher risk for severe disease such as older adults with comorbidities, very elderly or patients with serious health conditions. Further, while VE was shown to wane over time, some level of protection was sustained from primary series vaccination and booster doses significantly increased protection against hospitalisation.

Effectiveness varied by age and by vaccine type

Overall, vaccine effectiveness in preventing COVID-19-associated hospitalisation was lower among older adults than adults aged 18–64 years. Other studies have similarly demonstrated that older adults may present blunted responses to vaccination, including to COVID-19 and other vaccines such as inactivated influenza vaccines.[26–28] Variation in VE was also apparent across vaccine type and specific products. Viral vector and mRNA vaccines, mainly AstraZeneca and Pfizer, presented generally higher VE estimates than inactivated vaccines such as Sinovac and Sinopharm. These results were consistent with another study conducted in Brazil, in which VE in the first four weeks after vaccination in individuals aged 20–59 years with primary series vaccination with was 81.1% for AstraZeneca, 90.3% for Pfizer and 84.7% for Sinovac.[29] Similar results were recently reported by a multi-centre study in Latin America, which found aVE during Delta predominance was 76% and 82% for Pfizer and Moderna primary series vaccination, while estimates for other vaccines ranged only from approximately 53%–57%.[30]

Decreasing protection of primary series over time

We observed lower VE against COVID-19-associated hospitalisation during the Omicron variant dominant period compared to the Delta and pre-Delta periods. Omicron is antigenically the most distant variant in our evaluation from the ancestral strain and has been associated with greater immune evasion and reduced VE.[31–34] We also analysed VE during the Omicron period by time since vaccination, among those vaccinated with primary series without a booster, to assess the waning and duration of protection. We observed that patients with recent vaccination (<90 days) were between 41% and 73% (depending on the vaccine type and age group) less likely

to be hospitalised compared with unvaccinated patients, while those who completed the primary vaccination >180 days before symptom onset were between 0% and 41% less likely to be hospitalised compared with unvaccinated patients. VE in older adults vaccinated >180 days with viral vector vaccines was higher than vaccination between 90 and 180 days, probably because AstraZeneca was introduced early in the region, thus early adopters may represent more risk averse individuals.[35] These results reaffirm that vaccine protection wanes over time, with lower effectiveness against hospitalisation in those vaccinated more than six months before symptom onset. Our results were consistent with systematic review demonstrating decline in protection against infection or mild disease, and to a lesser extent, against severe disease, prior to[36] and during the Omicron period,[37] suggesting the value of booster doses.

Importance of booster vaccination in Omicron variant period

Overall, vaccination with a booster provided protection against hospitalisation compared to primary series vaccination only. The vaccine effectiveness of the booster dose after AstraZeneca or Pfizer vaccines (either homologous and heterologous booster vaccination) compared to non-vaccination reduced the odds of hospitalisation between 33% and 57% in adults aged 18–64 years and between 48% and 60% in adults aged ≥65 years. This underlines the importance of receiving a booster dose for maintaining high level of protection and reduce the risk of hospitalisation associated with COVID-19, especially among older adults and groups at higher risk for severe disease. Boosters using a different COVID-19 vaccine platform from that used for the primary series (i.e., heterologous boosting) may provide superior immunogenicity to use of a homologous booster.[38,39] In our study, we observed that individuals 18–64 years who received Pfizer as a homologous booster had similar VE compared to booster vaccination with a different vaccine. However, heterologous booster seemed more effective in older adults who received completed primary series with AstraZeneca. Vaccine effectiveness for completed primary series with inactivated vaccine Sinovac was lower compared to mRNA and viral vector vaccines for both adults and older adults, and we obtained similar effectiveness for homologous and heterologous booster.

With the now widespread relaxation of social measures to prevent infection, and the greater immune evasion of new SARS-CoV-2 variants, vaccination with additional doses may be justified, particularly for persons at increased risk of developing severe COVID-19. Older adults and people with comorbidities continue to be at greatest risk of severe disease and mortality because of Omicron and sub-lineages and make up most of the COVID-19 deaths[40]; thus, even minor decreases in vaccine effectiveness over time translate into a rise in severe disease and deaths in such vulnerable persons. Vaccination with additional doses should be continued for individuals at high risk of developing severe disease, as recommended in the recent WHO SAGE roadmap.[41]

Strengths

Test-negative design has been widely used in the past decades to measure influenza VE, and since 2021, to evaluate the effectiveness of COVID-19 vaccines. Using this approach, we were able to collect and pool data from six REVELAC-i participating countries across multiple periods with different variant predominance. All participating countries provided data using the standard PAHO regional surveillance guidelines that recommend use of a common SARI case definition, collection of a minimum set of variables, and systematic specimen collection from all SARI cases. Such an approach promoted methodological consistency and minimized heterogenicity across the countries.[42] Additionally, REVELAC-i presents an opportunity to obtain data about understudied products used in low- and low middle-income countries, such as those in the Latin American region. Another strength of this evaluation was the vaccination status ascertainment of the patients included. During COVID-19 pandemic, most countries in the region implemented universal electronic vaccination registries that considerably reduced the effort required to retrieve and document the vaccination history as well as minimise the recall bias.

Limitations

This evaluation had several limitations. First, multiple vaccines were used simultaneously, targeting different groups in different countries. Some vaccines were only used in specific groups (e.g., older adults, hard to reach populations) and for specific periods of time. Thus, for some vaccines, the sample size was too small to get meaningful estimates. Second, some countries had difficulty enrolling test-negative controls during periods of high COVID-19 incidence, and in enrolling unvaccinated patients in countries with high vaccination coverage. Unvaccinated individuals during the Omicron period, when vaccine roll out was completed, may not be representative of those from earlier in the study period, potentially affecting our results.[43] Also, we did not evaluate the distribution of vaccines in specific settings where cold chain capacity is limited which could explain some of the low VE results. Finally, in any multi-country study such as this, heterogeneity between sites could introduce bias that could lead to over- or underestimation of the true association between COVID-19 vaccination and the outcome. This is caused by differences in data collection processes, vaccination roll-out strategies, and SARS-CoV-2 variant circulation in each country over time. The results of this analysis should be interpreted with caution because we assumed that the

underlying exposure was similar in analysed countries and that the association of covariates with the outcome was similar in countries. Last, in this evaluation, we did not assess the effect of prior infection (infection-induced immunity) that could affect the interpretation of estimated VE.

Summary and recommendations

The REVELAC-i network provides a unique opportunity to systematically monitor and evaluate the performance of vaccines for several reasons. First, it is an efficient approach to evaluate VE because it leverages existing national surveillance systems when data are collected from the hospitals and laboratories as part of the SARI routine surveillance. It allows one to conduct joint evaluations of VE against hospitalisation for both influenza and COVID-19 vaccines because the same surveillance platform and study population are used tonbsp;identify illnesses with both viruses. Second, the test-negative design provides VE estimates with highly specific outcome (i.e., RT-PCR lab-confirmed) and minimizes health-care-seeking behaviours biases. These VE evaluations can be carried out systematically every season or during changes in the epidemiology of the disease, when new vaccines are introduced or new COVID-19 variants emerge and contribute to the selection of potential vaccine candidates for future COVID-19 vaccines.

This evaluation demonstrates the importance of vaccination against COVID-19 with additional doses, especially in persons at increased risk of developing severe disease. Periodic vaccination with booster doses of mRNA or viral vector vaccines should be offered for these higher risk groups to optimize impact against severe disease, hospitalisation, and death, and to protect health systems and essential services, as recommended in the recent WHO SAGE roadmap.

REVELAC-i Working Group

Chile: María Fernanda Olivares Barraza, Natalia Vergara Mallegas, Paula Rodríguez Ferrari and Viviana Sotomayor Proschle (Departamento de Epidemiología, Ministerio de Salud), Rodrigo Fasce Pineda and Patricia Bustos Alister (Instituto de Salud Pública), Marcela Avendaño and Iván Brstilo (Programa Nacional de Inmunizaciones, Ministerio de Salud). **Costa Rica:** Roberto Arroba Tijerino (Comisión Nacional de vacunas y epidemiología. Ministerio de Salud); Guiselle Guzmán Saborío (Área de Salud Colectiva, Caja Costarricense del Seguro Social); Hebleen Brenes Porras (Centro Nacional de Referencia de Virología. Instituto Costarricense de Investigación y Enseñanza en Nutrición y Salud, INCIENSA). **Guatemala:** Lorena Gobern, Antonio Paredes y Maribel Cuyan (Dirección de Epidemiología y Gestión del Riesgo, Ministerio de Salud Pública y Asistencia Social); Claudia Estrada y Christa Leal (Dirección del Laboratorio Nacional de Salud); Liz Parra, Pablo Galindo y Lucas Santos (Programa de Emergencias en Salud, Organización Panamericana de la Salud). **Ecuador:** Raúl Francisco Pérez Tasigchana (Dirección Nacional de Vigilancia Epidemiológica, Ministerio de Salud Pública); Lucía Alexandra Astudillo Vallejo (Dirección Nacional de Inmunizaciones, Ministerio de Salud Pública); Alfredo Bruno Caicedo (Instituto Nacional de Investigación en Salud Pública, INSPI); Álvaro Whittenbury (Programa Especial de Inmunización Integral, Organización Panamericana de la Salud). **Paraguay:** Marta Von Horoch y Silvia Battaglia (Programa Ampliado de Inmunizaciones, Ministerio de Salud y Bienestar Social); Chavely Domínguez y Elena Penayo (Dirección General de Vigilancia de la Salud, Ministerio de Salud y Bienestar Social); Cynthia Vázquez y Maria José Ortega (Laboratorio Nacional de Salud Pública); Fabiana Michel (Programa Especial de Inmunización Integral, Organización Panamericana de la Salud). **Uruguay:** María Emilia Nieto and Dahiana Tritten (Departamento de Vigilancia en Salud, Ministerio de Salud Pública); Viviana Ramas, Natalia Goñi and Héctor Chiparelli (Departamento de Laboratorios de Salud Pública, Ministerio de Salud Pública).

Contributors

Francisco Nogareda (FN): conceptualisation, literature search, study design, data collection, data management and analysis, data interpretation, writing, review and editing.

Annette K. Regan (AK): study design, data management and analysis, data interpretation, figures, tables and writing.

Paula Couto (PC): Data interpretation, review and editing.

Ashley L. Fowlkes (AF): Literature search, data interpretation, writing, review and editing.

Radhika Gharpure (RG): Literature search, data interpretation, writing, review and editing.

Sergio Loayza (SL): Data interpretation, review and editing.

Juliana Almeida Leite (JL): Data interpretation, review and editing.

Angel Rodriguez (AR): Data interpretation, review and editing.

Andrea Vicari (AV): Data interpretation, review and editing.

Eduardo Azziz-Baumgartner (EA): Literature search, data interpretation, writing, review and editing.

Daniel Salas (DA): Supervision, validation, data interpretation, writing, review and editing.

Data sharing statement

Surveillance data collected for the study are not publicly available and the research team does not have permission to make these data available to others. The protocol used for this project is publicly available and can be downloaded from the PAHO website.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the national epidemiological and virological influenza surveillance and immunization teams in participating countries, Antonio Mendez (PAHO consultant), Rafael Chacón, Robin Spratling, Eva Leidman, Ruth Link-Gelles (CDC), and the PAHO immunization focal points Mario Cruz Penate (PAHO Chile), Ana María Jiménez and Jorge Victoria (PAHO Costa Rica) and Grisel Rodríguez (PAHO Uruguay) for their support in the implementation of the REVELAC-i

network. We also acknowledge Minal Patel, Esther Kissling and Angie Rose for their technical feedback and valuable exchanges. Finally, we thank the US CDC for their technical and financial support.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100626.

References

1 Strategic Advisory Group of Experts on Immunization (SAGE). Available at: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.
2 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. https://doi.org/10.1136/bmj.n1088.
3 Skowronski DM, Setayeshgar S, Zou M, et al. Comparative single-dose mRNA and ChAdOx1 vaccine effectiveness against severe acute respiratory syndrome coronavirus 2, including variants of concern: test-negative design, British Columbia, Canada. *J Infect Dis*. 2022;226(3):485–496. https://doi.org/10.1093/infdis/jiac023.
4 Chodick G, Tene L, Patalon T, et al. Assessment of effectiveness of 1 dose of BNT162b2 vaccine for SARS-CoV-2 infection 13 to 24 days after immunization. *JAMA Netw Open*. 2021;4(6):e2115985. https://doi.org/10.1001/jamanetworkopen.2021.15985.
5 Bahl A, Johnson S, Maine G, et al. Vaccination reduces need for emergency care in breakthrough COVID-19 infections: a multicenter cohort study. *Lancet Reg Health Am*. 2021;4:100065. https://doi.org/10.1016/j.lana.2021.100065.
6 Corchado-Garcia J, Zemmour D, Hughes T, et al. Analysis of the effectiveness of the Ad26.COV2.S adenoviral vector vaccine for preventing COVID-19. *JAMA Netw Open*. 2021;4(11):e2132540. https://doi.org/10.1001/jamanetworkopen.2021.32540.
7 Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A. 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(10285):1646–1657. https://doi.org/10.1016/S0140-6736(21)00677-2.
8 Interim Guidance. *Evaluation of COVID-19 vaccine effectiveness*. WHO; 2021. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1.
9 WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination. Available at: https://apps.who.int/iris/bitstream/handle/10665/334299/WHO-2019-nCoV-SAGE_Framework-Allocation_and_prioritization-2020.1-eng.pdf?ua=1.
10 WHO SAGE roadmap for prioritizing use of COVID-19 vaccines. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Vaccines-SAGE-Prioritization-2022.1.
11 COVID-19 vaccination coverage in the Americas. Dashboard PAHO/WHO. Available at: https://ais.paho.org/imm/IM_DosisAdmin-Vacunacion.asp.
12 Network for the evaluation of vaccine effectiveness in Latin America and the Caribbean – influenza (REVELAC-i). Available at: https://www.paho.org/en/network-evaluation-vaccine-effectiveness-latin-america-and-caribbean-influenza-revelac-i.
13 Sullivan SG, Feng S, Cowling BJ. Potential of the test-negative design for measuring influenza vaccine effectiveness: a systematic review. *Expert Rev Vaccines*. 2014;13(12):1571–1591. https://doi.org/10.1586/14760584.2014.966695.
14 *Influenza and other respiratory viruses: surveillance in the Americas surveillance in the Americas 2021*. Washington, D.C.: Pan American Health Organization; 2022. https://doi.org/10.37774/9789275124994. License: CC BY-NC-SA 3.0 IGO https://iris.paho.org/handle/10665.2/56544.
15 REVELAC-i generic protocol for evaluation of vaccine effectiveness of COVID-19 vaccines. Available at: https://www.paho.org/en/documents/revelac-covid-19-generic-protocol.
16 Guía operativa para la vigilancia centinela de la Infección Respiratoria Aguda Grave (IRAG). OPS/OMS. Available at: https://www.paho.org/hq/dmdocuments/2015/2015-cha-guia-operativa-vigilancia-centinela-irag.pdf; 2014.
17 *Case definitions for COVID-19 surveillance*. World Health Organization; 2022. Available at: https://www.paho.org/en/case-definitions-covid-19-surveillance.
18 Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill*. 2020;25(3):2000045. https://doi.org/10.2807/1560-7917.ES.2020.25.3.2000045.
19 Leite JA, Gresh L, Vicari A, et al. COVID-19 laboratory preparedness and response in the Americas Region: lessons learned. *PLoS One*. 2021;16(6):e0253334. https://doi.org/10.1371/journal.pone.0253334.
20 Centers for Disease Control and Prevention. CDC's influenza SARS-CoV-2 multiplex assay. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/multiplex.html.
21 Leite JA, Vicari A, Perez E, et al. Implementation of a COVID-19 Genomic Surveillance Regional Network for Latin America and Caribbean region. *PLoS One*. 2022;17(3):e0252526. https://doi.org/10.1371/journal.pone.0252526.
22 Doll MK, Pettigrew SM, Ma J, Verma A. Effects of confounding bias in coronavirus disease 2019 (COVID-19) and influenza vaccine effectiveness test-negative designs due to correlated influenza and COVID-19 vaccination behaviors. *Clin Infect Dis*. 2022;75(1):e564–e571. https://doi.org/10.1093/cid/ciac234.
23 Organización Panamericana de la Salud/Organización Mundial de la Salud. Sistema electrónico para la vigilancia integrada de influenza, SARS-CoV-2 y otros virus respiratorios. [Washington, D.C.: OPS/OMS]. https://surveillanceflu.paho.org/Account/Login?ReturnUrl=%2F. Accessed October 2023.
24 COVID-19 Genomic Surveillance Regional Network. SARS-CoV-2 variants tracking in the region of the Americas. Dashboard PAHO/WHO. Available at: https://ais.paho.org/phip/viz/SARS_CoV2_variants_regional.asp.
25 Pan American Health Organization Ethics Review Committee (PAHOERC). Research proposal evaluation form. Available at: https://www.paho.org/sites/default/files/revelac-pahoercexempt_e_0.pdf.
26 *Interim analysis of COVID-19 vaccine effectiveness against severe acute respiratory infection due to SARS-CoV-2 in individuals aged 20 years and older – third update. Technical report ECDC*; 2022. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/Interim-analysis-COVID-19-vaccine-over-20.pdf.
27 Cerqueira-Silva T, de Araújo Oliveira V, Boaventura VS, et al. Influence of age on the effectiveness and duration of protection of Vaxzevria and CoronaVac vaccines: a population-based study. *Lancet Reg Health Am*. 2022;6:100154. Available at: https://www.thelancet.com/action/showPdf?pii=S2667-193X%2821%2900150-2.
28 Wilkinson K, Wei Y, Szwajcer A, et al. Efficacy and safety of high-dose influenza vaccine in elderly adults: a systematic review and meta-analysis. *Vaccine*. 2017;35(21):2775–2780. https://doi.org/10.1016/j.vaccine.2017.03.092.
29 dos Santos B, Valiati NCM, Noronha TG, et al. The effectiveness of COVID-19 vaccines against severe cases and deaths in Brazil from 2021 to 2022: a registry-based study. *Lancet Reg Health Am*. 2023;20:100465. Available at: https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(23)00039-X/fulltext#secsectitle0010.
30 Kahn R, Janusz CB, Castro MC, et al. The effectiveness of COVID-19 vaccines in Latin America, 2021: a multicenter regional case–control study. *Lancet Reg Health Am*. 2023;20:100474. Available at: https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(23)00048-0/fulltext#secsectitle0065.
31 Stowe J, Andrews N, Kirsebom F, et al. Effectiveness of COVID-19 vaccines against Omicron and Delta hospitalisation, a test negative case-control study. *Nat Commun*. 2022;13:5736. https://doi.org/10.1038/s41467-022-33378-7.
32 Feikin DR, Abu-Raddad LJ, Andrews N, et al. Assessing vaccine effectiveness against severe COVID-19 disease caused by omicron variant. Report from a meeting of the World Health Organization. *Vaccine*. 2022;40(26):3516–3527. https://doi.org/10.1016/j.vaccine.2022.04.069.
33 Kirsebom FCM, Andrews N, Stowe J, et al. COVID-19 vaccine effectiveness against the omicron (BA.2) variant in England. *Lancet Infect Dis*. 2022;22(7):931–933. https://doi.org/10.1016/S1473-3099(22)00309-7.
34 Andrews N, Stowe J, Kirsebom F, et al. COVID-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *N Engl J Med*. 2022;386:1532–1546. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2119451.
35 Keser C, Rau HA. Determinants of people's motivations to approach COVID-19 vaccination centers. *Sci Rep*. 2023;13:5282. https://doi.org/10.1038/s41598-023-30244-4.
36 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;399(10328):924–944. Available at: https://pubmed.ncbi.nlm.nih.gov/35202601/.

37 Higdon MM, Baidya A, Walter KK, et al. Duration of effectiveness of vaccination against COVID-19 caused by the omicron variant. *Lancet Infect Dis*. 2022;22(8):1114–1116. https://doi.org/10.1016/S1473-3099(22)00409-1.

38 Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27:1205–1211.

39 Khoury DS, Docken SS, Subbarao K, Kent SJ, Davenport MP, Cromer D. Predicting the efficacy of variant modified COVID-19 vaccine boosters. *medRxiv*. 2022. https://doi.org/10.1101/2022.08.25.22279237, 2022.08.25.22279237.

40 WHO health emergency dashboard. Available at: https://covid19.who.int/more-resources.

41 WHO SAGE roadmap on uses of COVID-19 vaccines in the context of Omicron and substantial population immunity. Available at: https://apps.who.int/iris/handle/10665/366671; 2023.

42 *Operational guidelines for sentinel severe acute respiratory infection (SARI) surveillance*; 2014. Available at: https://www.paho.org/en/node/52153.

43 Feikin DR, Higdon MM, Andrews N, et al. Assessing COVID-19 vaccine effectiveness against omicron subvariants: report from a meeting of the World Health Organization. *Vaccine*. 2023;41(14):2329–2338. https://doi.org/10.1016/j.vaccine.2023.02.020.