Real-world effectiveness of the heterologous SOBERANA-02 and SOBERANA-Plus vaccine scheme in 2–11 years-old children during the SARS-CoV-2 Omicron wave in Cuba: a longitudinal case-population study

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Summary

Background Increased pediatric COVID-19 occurrence due to the SARS-CoV-2 Omicron variant has raised concerns about the effectiveness of existing vaccines. The protection provided by the SOBERANA-02-Plus vaccination scheme against this variant has not yet been studied. We aimed to evaluate the scheme's effectiveness against symptomatic Omicron infection and severe disease in children.

Methods In September 2021, Cuba implemented a mass pediatric immunization with the heterologous SOBERANA-02-Plus scheme: 2 doses of conjugated SOBERANA-02 followed by a heterologous SOBERANA-Plus dose. By December, before the Omicron outbreak, 95.4% of 2–18 years-old had been fully immunized. During the entire Omicron wave, we conducted a nationwide longitudinal post-vaccination case-population study to evaluate the real-world effectiveness of the SOBERANA-02-Plus scheme against symptomatic infection and severe disease in children without previous SARS-CoV-2 infection. The identification of COVID-19 cases relied on surveillance through first line services, which refer clinical suspects to pediatric hospitals where they are diagnosed based on a positive RT-PCR test. We defined the Incidence Rate ratio (IRR) as IRvaccinated age group/IRunvaccinated 1-year-old and calculated vaccine effectiveness as VE = (1—IRR)*100%. 24 months of age being the 'eligible for vaccination' cut-off, we used a regression discontinuity approach to estimate effectiveness by contrasting incidence in all unvaccinated 1-year-old versus vaccinated 2-years-old. Estimates in the vaccinated 3–11 years-old are reported from a descriptive perspective.

Findings We included 1,098,817 fully vaccinated 2–11 years-old and 98,342 not vaccinated 1-year-old children. During the 24-week Omicron wave, there were 7003/26,241,176 person-weeks symptomatic COVID-19 infections in the vaccinated group (38.2 per 10^5 person-weeks in 2-years-old and 25.5 per 10^5 person-weeks in 3–11 years-old) against 3577/2,312,273 (154.7 per 10^5 person-weeks) in the unvaccinated group. The observed overall vaccine effectiveness against symptomatic infection was 75.3% (95% CI, 73.5–77.0%) in 2-years-old children, and 83.5% (95% CI, 82.8–84.2%) in 3–11 years-old. It was somewhat lower during Omicron BA.1 then during Omicron BA.2 variant circulation, which took place 1–3 and 4–6 months after the end of the vaccination campaign. The effectiveness against severe symptomatic disease was 100.0% (95% CI not estimated) and 94.6% (95% CI, 82.0–98.6%) in the respective age groups. No child death from COVID-19 was observed.

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Translation: For the Spanish translation of the abstract see Supplementary Materials section.

Interpretation Immunization of 2–11 years-old with the SOBERANA-02-Plus scheme provided strong protection against symptomatic and severe disease caused by the Omicron variant, which was sustained during the six months post-vaccination follow-up. Our results contrast with the observations in previous real-world vaccine effectiveness studies in children, which might be explained by the type of immunity a conjugated protein-based vaccine induces and the vaccination strategy used.

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Keywords: SARS-COV-2; COVID-19; Omicron variant; Vaccine; Effectiveness; Pediatric; Children; SOBERANA; Conjugated vaccine; RBD-Subunit vaccine; Heterologous scheme; Cuba

Research in context

Evidence before this study

We searched PubMed on December 1st, 2023 for available evidence on real-world effectiveness of COVID-19 vaccines in children. We used the search term "(COVID-19 OR SARS-CoV-2) AND vaccine* AND (effective* OR efficacy*) AND (infant* OR child*)" with no restrictions on date or language. A few randomized clinical trials, early in the COVID-19 pandemic, documented high immunogenicity, safety, and vaccine efficacy in children.

However, observational studies during the Omicron wave have been revealing substantially reduced, rapidly waning effectiveness against SARS-CoV-2 infection and disease. A systematic review and meta-analysis of such studies yielded a pooled vaccine effectiveness in children of 45.2% for symptomatic COVID-19, and of 71.0% for COVID-19-related hospitalization. Published studies deal mainly with mRNA and inactivated vaccines in older children, and information on vaccination effectiveness following nationwide child vaccination strategies is scarce.

Added value of this study

Data on the effectiveness against pediatric COVID-19 of subunit conjugated vaccines targeting the Receptor Binding Domain (RBD) is completely lacking. The SOBERANA-02-Plus immunization scheme consists of 2 doses SOBERANA-02 (FINLAY-FR-2), a subunit protein-based conjugated RBD vaccine, followed by a heterologous dose of SOBERANA Plus (FINLAY-FR-1A, a dimeric RBD vaccine, 28 days apart. During a nationwide child mass vaccination campaign with that scheme in Cuba, 1,098,817 children aged 2-11 years-old, without previous SARS-CoV-2 infection, were fully vaccinated. We document a total of 190 vaccine-associated adverse events (5.58 per 10^5 applied doses). The observed vaccine effectiveness against symptomatic SARS-CoV-2 infection during the Omicron variant wave -which occurred from 1 to 6 months after the end of the vaccination campaign-was 75.3% (95% CI, 73.5–77.0%) in 2-years-old children and 83.5% (95% CI, 82.8–84.2%) in 3–11 years-old and did not decrease during the six months post-vaccination follow-up. The effectiveness against severe symptomatic disease was 100.0% and 94.6% in the respective age groups. No child death from COVID-19 was observed.

Implications of all the available evidence

Our results confirm that subunit SARS-CoV-2 vaccines are safe. They contrast favorably with the findings in previous studies on the real-world effectiveness in children of vaccines built on other platforms. This may be explained by the type of immunity a conjugated protein-based vaccine induces and by the vaccination strategy used. For bacterial polysaccharide antigens it has been shown that conjugation stimulates B-cell response and T-cell specific immunity. Our result can further stimulate the development of other protein–protein conjugate vaccines. Whether high vaccination coverage in children has an impact on SARS-CoV-2 transmission at the population level is an area for in-depth cross-context research. COVID-19 is no longer a global health emergency, but SARS-CoV-2 will continue to circulate, be it at lower intensity, and unvaccinated or previously not infected children and all infants to be born are susceptible to infection and disease. The virus generally causes less morbidity and mortality in healthy children than in adults, but they may need hospitalization when infected and can develop severe complications. This study indicates that the SOBERANA-02-Plus scheme provides a safe and effective preventive option to protect a country's child population. Notwithstanding, future SARS-CoV-2 mutations will give rise to new virus variants and continued assessment of the scheme's effectiveness in the pediatric population is needed.

Introduction

SARS -CoV-2 infection causes less morbidity and mortality in healthy children and adolescents than in adults.[1] However, the number of COVID-19 cases in children peaked dramatically during the 2021–2022 Omicron variant surge.[2] In many countries this resulted in a sharp rise in pediatric hospitalizations.[3] The increase in symptomatic cases has been attributed to Omicron's

higher transmissibility and ability to circumvent antibodies from past infection or vaccination, together with easing of public health measures and low COVID-19 vaccination rates.[4]

The emergency use authorization of mRNA and inactivated virus vaccines was extended in some countries to children from the age of 6 months onwards[5] and several COVID-19 vaccines not yet listed by WHO obtained specific local approval for pediatric use.[6] Nevertheless, recommendations to routinely vaccinate children are frequently not followed by parents due to safety concerns, under five years-old are often not eligible for immunization, and for many countries access to vaccines remains a major obstacle. Hence, full coverage in pediatric populations is poor globally and varies widely.[7]

In September 2021, relying on safety, immunogenicity and efficacy results provided for adults[8–10] and for children,[11] emergency use authorization for the pediatric population from 2 to 18 years-old was granted in Cuba[12] to the recombinant SOBERANA-02 (FINLAY-FR-2) and SOBERANA-Plus (FINLAY-FR-1A) COVID-19 vaccines developed by the Finlay Vaccine Institute, Havana, hereafter the SOBERANA-02-Plus scheme. The Cuban Ministry of Public Health subsequently launched a nationwide mass vaccination campaign with that scheme in the corresponding age group that, serendipitously, was completed before the start of Omicron wave.

A few randomized clinical trials have demonstrated high vaccine immunogenicity and efficacy in children prior to the predominance of the Omicron variant.[13–15] However, during the Omicron wave of the pandemic, various observational studies have documented substantially reduced and rapid waning effectiveness against SARS-CoV-2 infection and symptomatic disease, while protection against serious illness and death was largely maintained.[16–18] The published studies dealt mainly with mRNA and inactivated vaccines in older children. Data on the effectiveness of other vaccine types against pediatric COVID-19, and on subunit conjugate vaccines in particular, is completely lacking.

The objective of this study is to evaluate the real-world effectiveness of the heterologous SOBERANA-02-Plus immunization scheme to protect 2–11 years-old children from symptomatic COVID-19 infection, severe disease and death during the 2022 SARS-CoV-2 Omicron wave in Cuba.

Methods

Context

SOBERANA-02 (FINLAY-FR-2) is a subunit protein, the antigen is the recombinant SARS-CoV-2 RBD (25 μg), chemically conjugated to tetanus toxoid and adsorbed on 500 μg alumina.[19] The SOBERANA-Plus (FINLAY-FR-1A) antigen is a dimeric RBD (50 μg) adsorbed on 1250 μg alumina.[20] Both vaccines are manufactured by Finlay Vaccine Institute, Havana, Cuba. As of September 5th, 2021, a nationwide child mass vaccination campaign was launched with 2 doses of SOBERANA-02 followed by a heterologous SOBERANA-Plus dose with intervals of 28 days, the SOBERANA-02-Plus scheme. Children without documented previous SARS-CoV-2 infection were immunized, while previously infected ones received a single dose of SOBERANA-Plus only. A history of a severe allergic reaction to a component of the vaccines or presence of a not controlled non-communicable disease were further exclusion criteria.

The start of the vaccination campaign in children coincided with the peak of the SARS-CoV-2 Delta variant wave, which hit Cuba end May 2021. Three dose coverage began to build up near the end of that wave, and upon completion of the campaign on December 11th, almost 3 weeks before the detection of the Omicron variant, 95.4% of the 2–18 years-old population was fully vaccinated. Catch up vaccination for the non-eligible below 2-years-old was organized in the policlinic network and occurred around their second anniversary. Booster vaccination was only offered from August 2022 onwards.

Symptoms based passive cases detection and active surveillance for the identification of COVID-19 cases relied on the primary health care services, which consist of family doctor/nurse practices and policlinics. Clinical suspects under 18 years-old were referred to pediatric hospitals, where they were admitted upon a positive RT-PCR test, regardless of the severity of their symptoms.

Mid-November 2021, near the end of the campaign, the Ministries of Education and Public Health instructed resuming classroom teaching and reopening all primary and secondary schools in the country. As was already being done in daycare centres, daily active screening for respiratory and febrile syndromes by primary health care staff was introduced in all schools, symptomatic children were referred for further medical evaluation and testing, and absentees were traced and examined by their general practitioner. At the very end of the year the Omicron variant wave started building up. It lasted until June 2022, but schools remained open, while all other COVID-19 transmission prevention measures, including closure of non-essential stores, bars and restaurants, and prohibition of gatherings, were maintained.

Study design, data sources, study subjects and statistical analysis

We conducted a longitudinal post-vaccination case-population study. We used in our analysis official data collected and reported by the Cuban Ministry of Public Health. The centralized national SARS-CoV-2 database contains all confirmed cases occurring in the territory, with municipality of residence and demographic details, clinical information including symptoms, test results

and severity classification based on WHO guidelines,[21] epidemiological variables, and vaccination status data. In all health care facilities that attend SARS-CoV-2 cases this information is entered on standardized forms by the physician in charge of the patient and, following verification of completeness and consistency by the health area's epidemiologist responsible for case reporting, digitized by trained data operators. Vaccination coverage was derived from the national COVID-19 vaccination registry. In all COVID-19 immunization centers set up in Cuba the nurse administering a vaccine records each dose dispensed, and the recipient's identity and demographic characteristics. Completed forms are checked daily by the person responsible for the immunization program implementation in the health area and then entered in the national register by the area's data operators.

The longstanding countrywide routine surveillance system of vaccine-associated adverse events established and maintained by the National Immunization Program and fed by all primary health care and hospital facilities in the country, yielded the data on SARS-CoV-2 vaccine-associated adverse events. Based on passive surveillance, whatever symptom a patient attends after vaccination is reported, and the case is further sorted out by the Provincial Centre of Epidemiology and Hygiene before being introduced in the national vaccine-associated adverse events database. The "Pedro Kourí" Tropical Medicine Institute ensures genomic surveillance of SARS-CoV-2 and reports the distribution of circulating variants.[22,23] The number of Cuban citizens by municipality and age group was provided by the National Office of Statistics and Information.

We extracted from the above databases anonymized whole country data on the 1-11 years-old for the period from May 23rd, 2021 (epi-week 21/2021) to June 4th, 2022 (epi-week 22/2022), corresponding to the extent of the Delta and Omicron waves. We cross validated the information on key variables to be used in the subsequent analyses and, where necessary, verified and/or supplemented the data through the relevant responsible person at the Ministry of Health. We performed a complete case analysis. We plotted the global weekly incidence rate of symptomatic SARS-CoV-2 infection by age, and mapped the attack rate (cumulative incidence proportion) during the 2 waves by age and municipality.

All 1-11 years-old Cuban residents present during the Omicron wave were potential study participants for estimating the SOBERANA-02-Plus scheme's real-world effectiveness. We did not include in this analysis 8.7% of the 1-year-old, 7.8% of the 2-year-old and 6.6% of the 3–11 years-old that had a documented SARS-CoV-2 infection before the start of the Omicron wave. We also excluded children that were infected outside the country, and the 2–11 years-old children who did not receive the full 3 doses of the scheme. The pediatric mass vaccination campaign resulted in a quasi-experiment with a population eligible for vaccination and an ineligible population, infants and 1-year-old children. Since 24 months of age was the cut-off, we estimated the vaccine effectiveness by using a regression discontinuity approach[24,25] and contrasting COVID-19 incidence in the unvaccinated 1-year-old versus vaccinated 2-years-old child population. Effectiveness results in the vaccinated 3–11 years-old are reported from a purely descriptive perspective. Participants in the 168 municipalities in the country were stratified according to residence and age group (unvaccinated 1-year-old, and fully vaccinated 2 and 3–11 years-old). We estimated stratified symptomatic COVID-19 incidence rates (IR) assuming dynamic steady state population subgroups.[26] The subgroup membership of a given individual is not fixed, as is the case with a cohort, but changes dynamically over time along with the individual's vaccination status and age. In a steady state, the number of persons present in a subgroup is approximately constant, with 'outgoing members' being replaced by 'incoming members'. The numerators of the person-weeks IRs in our vaccine effectiveness study are the number of children of a subgroup who develop symptomatic COVID-19 during a particular period. The denominators are the 'on average' present number of children at risk multiplied by the number of weeks in the period. We defined the Incidence Rate ratio (IRR) as IRvaccinated age group/IRunvaccinated 1-year-old and calculated vaccine effectiveness as VE = (1—IRR)*100%, with 95% Wald confidence intervals.

We examined differences over time in the cumulative incidence rate evolution in the unvaccinated and vaccinated child population during the 24 weeks of the Omicron wave. We fitted a multilevel model for repeated measurements[27] with as response variable the cumulative incidence rate observed on 24 occasions (weekly) in each of the 504 strata formed by the 168 Cuban municipalities and the 3 age groups mentioned above. We normalized the distribution by log transformation. The data were analyzed as a 3-level hierarchical system with the cumulative incidence rate in each of the weeks (level-1) nested within the municipality/age group subgroups (level-2) and these within the municipalities (level-3). Since a curvature was observed in the cumulative incidence rate profiles, the expected weekly values were estimated as a polynomial function with the degree determined by the best fit. During model development, additional level-2 variables (age groups by vaccination status) and level-3 variables (being a provincial capital or not) were included to explain the observed variability between the strata. Improvement of model fit was assessed with the log likelihood ratio statistic. We checked for violations of model assumptions with histograms of residuals, normal plots of residual components, and scatter plots between the residuals of different levels. The p values and 95%

confidence intervals for the parameter estimates were calculated with the Wald test.

We mapped the COVID-19 incidence data stratified by SARS-CoV-2 variant, municipality and age group using Jenks natural breaks classification method[28] and we performed statistical analyses using R version 4.2.0 and MLwinN version 2.19.

We followed the STROBE guidelines[29] in reporting our research.

Ethics

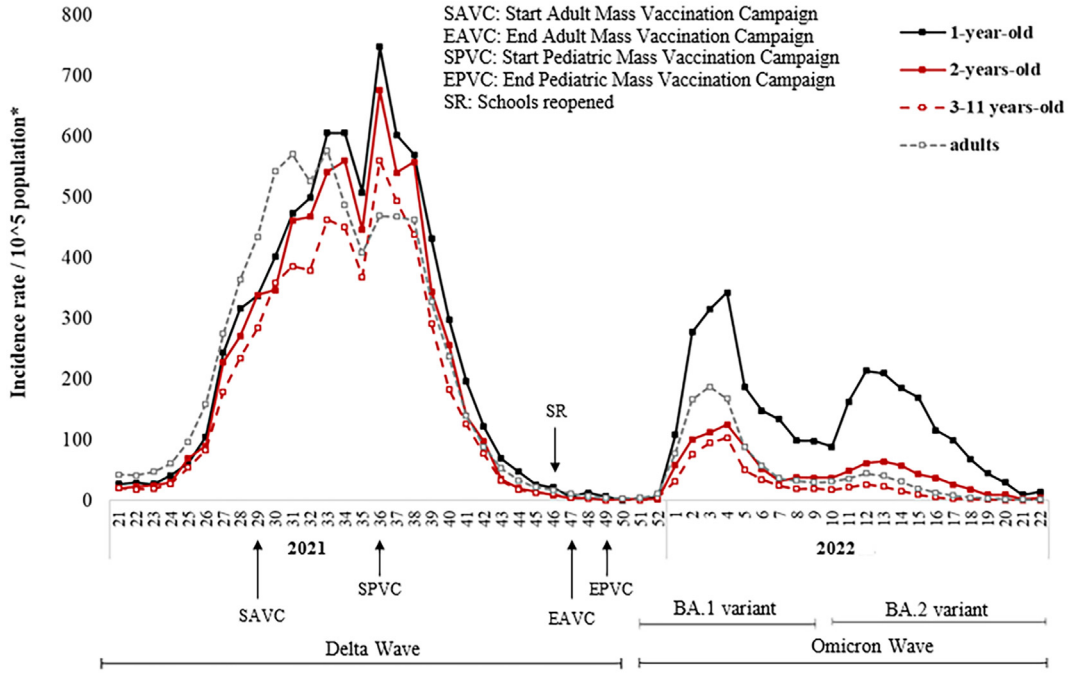
The study was approved by the Central Ethics Committee for medical research of the Ministry of Public Health and by the National Expert Group for Pandemic Control. Since we retrospectively analyzed routine public health program data the study was exempted from informed consent.

Results

Fig. 1 displays the incidence rate of COVID-19 disease in the 1–11 years-old Cuban population during the Delta and subsequent Omicron wave, stratified by age, and indicates the timing of the vaccination campaign with the SOBERANA-02-Plus scheme in the 2–11 years-old. The Omicron wave was bimodal. Sub-variant Omicron BA.1 dominated from week 51/2001 to 9/2022, to be replaced by Omicron BA.2 between week 10/2022 and 22/2022.[24] Compared to the Delta wave, COVID-19 incidence rates were substantially lower in all age groups during the Omicron wave, and the difference-in-difference between the 1-year-old and the other age groups increased considerably. The test positivity rate was below the WHO recommended threshold during both waves: between 1% and 3% during the Delta wave and between 1% and 4% during the Omicron wave.

Mapping puts the striking contrast between the incidence figures during the two waves into perspective (Fig. 2). During the Delta wave, transmission was not homogeneous across the country, but specific regions were more severely affected. However, geographic heterogeneity was similar between age groups. During the circulation of the Omicron variant noticeable differences appear in the symptomatic COVID-19 attack rates. Cumulative incidence has decreased in the 1-year-old children, but pre-existing geographic heterogeneity persists. In the vaccinated 2 and 3–11 years, on the other hand, the incidence has fallen strikingly, and the disease burden becomes distributed geographically almost completely homogeneously.

In our longitudinal post-vaccination case-population study we included 1,098,817 children 2–11 years-old that were fully vaccinated and 98,342 not vaccinated 1-year-old children without PCR confirmed SARS-CoV-2



* Incidence rate of symptomatic COVID-19 disease in the Cuban population of the corresponding age groups

Fig. 1: **Delta and Omicron COVID-19 waves and timing of the SARS-CoV-2 national mass vaccination campaigns with Abdala vaccine (mainly) in adults and with the SOBERANA-02-Plus scheme in children 2–11 years-old. Cuba, 2021–2022.**

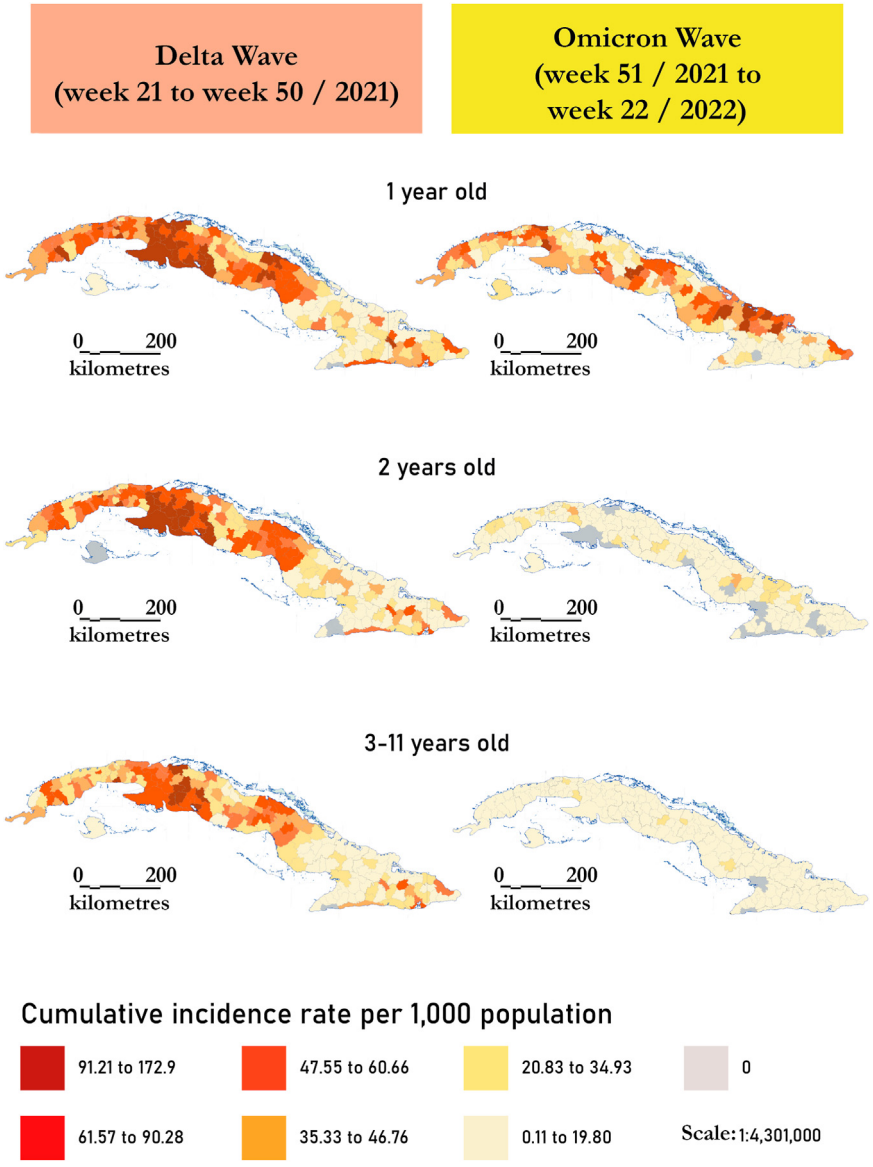


Fig. 2: **Cumulative incidence rate of symptomatic COVID-19 infection in children by age group and municipality during the Delta and Omicron waves. Cuba, 2021–2022.**

infection before the onset of the Omicron wave (Fig. 3). The countrywide routine vaccine-associated adverse events surveillance system recorded 113 children with any adverse event up to 4 weeks after the end of the campaign, 8 in the 2- and 105 in the 3–11 years-old group. The total number of reported adverse events was 190/3,407,538 applied doses, corresponding to 5.58 (95% CI, 4.78–6.37) events per 10^5 doses, which classifies as very rare. 17/319,514 of them (5.32 per 10^5 doses; 95% CI, 2.79–7.85) and 173/3,088,024 (5.60 per 10^5 doses; 95% CI, 4.77–6.43) happened in the respective age groups, and 165, 12 and 13 after the 1st, 2nd, and 3rd dose, respectively. Only 3 serious vaccine-associated adverse events occurred, all in the 3–11 years-old, equivalent to a rate of 0.09 (95% CI, 0.02–0.28) per 10^5 applied doses (one hypersensitivity reaction, and two severe local reactions). No cases of myocarditis, pericarditis or deaths were observed.

During the 24 weeks duration of the Omicron wave, there were 7003 and 3577 symptomatic COVID-19 infections in the vaccinated and unvaccinated study population, respectively (Fig. 3). The observed overall vaccine effectiveness against symptomatic COVID-19 disease during the Omicron wave was 75.3% in

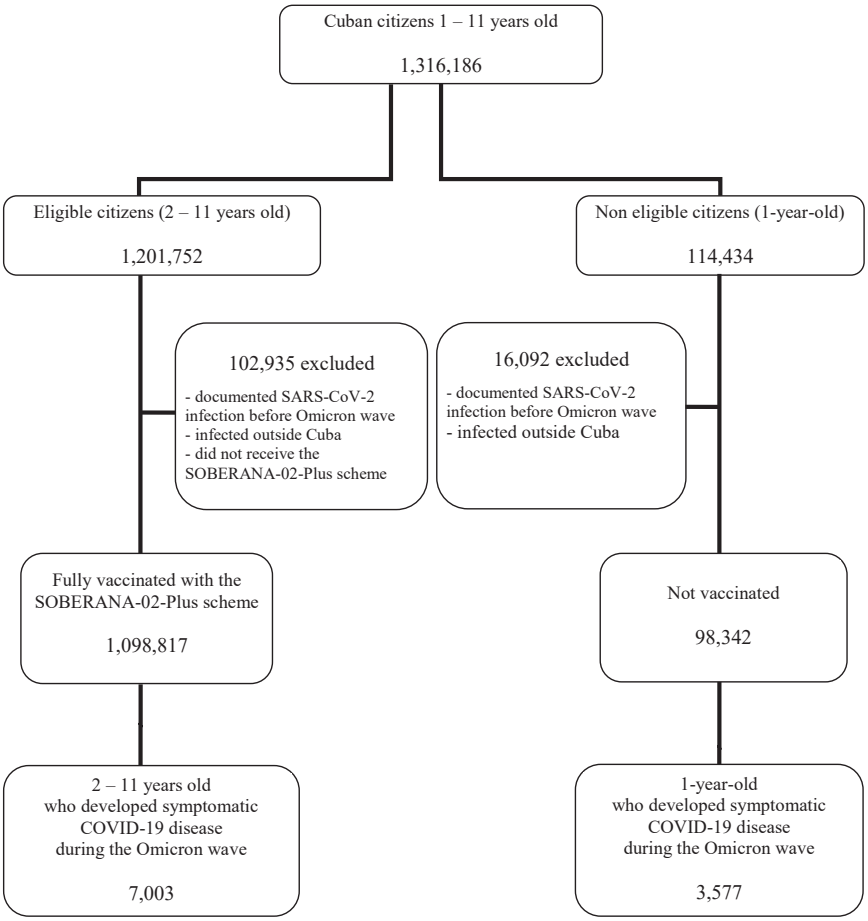


Fig. 3: **Study population by eligibility for SARS-CoV-2 immunization during the national SOBERANA-02-Plus vaccination campaign. Cuba, 2021–2022.**

2-years-old children, and 83.5% in children 3–11 years-old (Table 1). It these age groups, respectively, it was 72.4% and 76.3% during the Omicron BA.1 first half of the Omicron wave –on average 52 days after the last dose of the vaccine- and 78.8% and 92.2% during the Omicron BA.2 s half of the wave—on average 143 days after the last dose. The overall effectiveness against severe symptomatic infection in the corresponding age groups was 100.0% and 94.6%. No child death from COVID-19 was reported.

Table 2 shows the multilevel model of the weekly cumulative incidence rate of symptomatic COVID-19 infection with the best fit. We found no evidence for violations of the model assumptions. The cumulative incidence rate during the Omicron wave and its growth rate varied between age groups and municipalities. With the unvaccinated 1-year-old age group as reference category, the estimates of the age group*Week interaction effects were negative ($p < 0.001$) for the vaccinated 2 and 3–11 age groups, and they provided clear evidence that the average weekly cumulative incidence rate growth in these two groups was substantially lower than in the 1-year-old. On the other hand, the effect of being a provincial capital, although significant ($p < 0.05$) was small. Finally, while the variances continued to be significantly different from zero, after including age group as a covariate in the model, their estimates were very close to zero and given the precision of their confidence intervals it can be safely assumed that the difference between the subgroups is small after controlling for age, a proxy of vaccination status, and confounding.

Discussion

The real-world effectiveness of the heterologous SOBERANA-02-Plus vaccine scheme during the Omicron wave in Cuba was 75.3% and 83.5% among children 2 and 3–11 years-old, respectively. Effectiveness did not decrease during the six months post-vaccination follow-up but, on the contrary, somewhat increased during the second half of the wave, when sub-variant Omicron BA.1 had been replaced by Omicron BA.2.

Age	Person weeks at risk	Number of cases	Incidence/10^5 person-weeks	Vaccine effectiveness (VE) (95% CI for VE)
COVID-19 symptomatic disease				
Omicron BA.1 (week 51/2021-week 9/2022)				
1 y/o	1,070,955	1965	183.5	
2 y/o	1,136,161	576	50.7	72.4 (69.7; 74.8)
3–11 y/o	10,916,960	4750	43.5	76.3 (75.0; 77.5)
Omicron BA.2 (week 10/2022-week 22/2022)				
1 y/o	1,241,318	1612	129.9	
2 y/o	1,333,799	367	27.5	78.8 (76.3; 81.1)
3–11 y/o	12,854,256	1310	10.2	92.2 (91.6; 92.7)
Total omicron wave (week 51/2021- week 22/2022)				
1 y/o	2,312,273	3577	154.7	
2 y/o	2,469,960	943	38.2	75.3 (73.5; 77.0)
3–11 y/o	23,771,216	6060	25.5	83.5 (82.8; 84.2)
COVID-19 severe symptomatic disease				
Total omicron wave (week 51/2021- week 22/2022)				
1 y/o	2,312,273	9	0.40	
2 y/o	2,469,960	0	–	100.0 (–; –)
3–11 y/o	23,771,216	5	0.02	94.6 (82.0; 98.6)

IR, Incidence rate; new cases/person-week at risk; IRR, Incidence Rate Ratio; IR vaccinated age group/IR unvaccinated 1 y/o; VE = (1- IRR)×100. CI, Confidence Interval.

Table 1: **Effectiveness of the SOBERANA-02-Plus vaccines scheme to prevent COVID-19 symptomatic and severe disease during the Omicron variant epidemic wave. Cuba, 2021–2022.**

Parameter	Estimate	95% CI	
		LL	UL
Fixed part			
Constant	0.365**	0.335	0.395
$(week)$	0.756**	0.728	0.784
$(week)^2$	−0.061**	−0.064	−0.058
$(week)^3$	0.0024**	0.0022	0.0026
$(week)^4$	−0.000036**	−0.000041	−0.000031
$(age_group_{2\ y/o})*(week)$	−0.041**	−0.046	−0.035
$(age_group_{3\text{–}11\ y/o})*(week)$	−0.064**	−0.069	−0.058
$(provincial\ capital) * (week)$	−0.012*	−0.021	−0.002
Random Part (Variance/Covariance) *municipality level*			
σ^2_{r1}	0.012**	0.008	0.016
σ^2_{r2}	0.00001**	0.000008	0.00002
$\sigma^2_{r_1 r_2}$	−0.0004**	−0.0005	−0.0003
Subgroup level (municipalities/age_groups)			
$\sigma^2_{u_1}$	0.017**	0.014	0.019
$\sigma^2_{u_2}$	0.000029**	0.000024	0.000034
$\sigma^2_{u_1 u_2}$	−0.0007**	−0.0008	−0.0006
Residuals			
σ^2_e	0.182**	0.178	0.187

Cuba, 2021–2022. **p < 0.001; *p < 0.05; CI, Confidence Interval; LL, Lower Limit; UL, Upper Limit. (week) $(week)^2$, $(week)^3$, $(week)^4$: estimated coefficients for the adjusted polynomial function of time. (age_groups) *(week): estimated coefficients for the interaction between each age groups and time. (provincial capital) *(week): estimated coefficients for the interaction between being a provincial capital and time. Random part (variance and covariance) at each level indicates how the cumulative incidence rates vary with respect to the mean growth rate at the municipality level and at the subgroup level. σ^2_e: captures the variation not explained by the terms in the model.

Table 2: **Multilevel repeated measurements model of the weekly cumulative incidence rate evolution of COVID-19 symptomatic disease during the Omicron variant epidemic wave.**

Vaccination reduced the risk of severe disease in younger and older children with 100.0% and 94.6%, respectively. The scheme had a favorable safety profile.

We conducted our analysis with routine health information data, which may be a limitation of our study. However, the Cuban health system has attained universal health coverage and implements Primary Health Care based surveillance. Well established, supervised and adhered to SARS-CoV-2/COVID-19 protocols for case ascertainment amongst symptomatic patients attending health services, in combination with active case finding in daycare centers and schools, feed a centralized national registry. Testing of suspects is standardized, based on signs and symptoms, and must be performed similarly in vaccinated and unvaccinated subjects. Under-notification of symptomatic SARS-CoV-2 cases should hence not be sizable, or considerably non-random. This enabled linking nationwide individual data on symptomatic SARS-CoV-2 cases with coverage data from the online vaccination registry to estimate vaccine effectiveness. We did not perform an analysis stratified by ethnicity, which is not recorded in the databases, nor by sex, which was assumed not to act as a confounding variable in the age groups considered.

The completion of the Cuban child vaccination campaign in a short period, before the start of the Omicron wave, and with very high coverage, precluded a test-negative case–control study or a classical cohort analysis. Even more since the vast majority of the 2–11 years-old who did not receive the SOBERANA-02-Plus

scheme presented an exclusion criterium for immunization and do not constitute a valid comparison group. However, the regression discontinuity design we adopted produces robust estimates of vaccine effectiveness. This design can be used when a pre-specified threshold value for a variable measured on a continuous scale, such as age, determines the allocation to an intervention, for instance immunization. If the continuity -or "exchangeability"- assumption is met, individuals who are below the threshold can serve as a valid comparison group for those above the threshold, since the distribution of measured and unmeasured confounding factors is expected to be the same. Close to the cut-off such assignment is considered as good as random, and it would permit causal inference.[25]

We excluded infants from the unvaccinated comparator group given their immature immune system[30] and the potential transmission of antibodies after maternal COVID-19 vaccination or infection.[31] In addition, a comparison of 1-year and, say, 5- or 10 years-old children would be rather artificial. Therefore, we report results on the vaccinated 3–11 years-old from a merely descriptive perspective. However, one can safely assume that the continuity (or exchangeability) assumption is met in the comparison between unvaccinated 1-year and vaccinated 2-years-old, which are around the 24-month eligibility for vaccination cut-off. To start with, they have immune systems with comparable maturity in terms of T cell development[32] and antibody response.[30] Moreover, virtually all vaccinations for young children included in the Cuban immunization calendar are scheduled in the first year of life, which puts them also on an equal footing. Furthermore, the vast majority of them enters daycare at 12 months after birth, when mothers' statutory maternity leave ends, and they have limited other social contacts and restricted mobility patterns until more advanced ages. This makes the compared groups also exchangeable regarding exposure to SARS-CoV-2. Besides, the COVID-19 incidence was quite close in both age groups before the start of the vaccination campaign, which corroborates that 1- and 2-years-old pre-school children are also similar in terms of other risk factors that could cause a leap in the potential of infection. Finally, the surveillance procedure in place in the daycare centers guarantees uniform COVID-19 case ascertainment in these age groups, and since it includes tracing of absentees it is also unlikely that cases will go undetected when parents would be hesitant to seek medical care for children who are kept at home with mild symptoms.

The frequency of occurrence of adverse events during the pediatric mass vaccination campaign reflects the results of the safety evaluation in previous phase I/II clinical trials, where the SOBERANA-02-Plus scheme showed lower rates of adverse events in children than mRNA vaccines, particularly for systemic adverse events.[11] This is also in line with a recent systematic review confirming that subunit vaccines are safer than mRNA, viral vector and inactivated vaccines.[33]

Our estimates of the effectiveness of the SOBERANA-02-Plus scheme against confirmed symptomatic SARS-CoV-2 infections and severe disease during the Omicron variant wave are high and they do not reveal rapidly waning protection, contrary to what was observed in previous studies on other vaccine platforms. Real-world VE studies conducted in adult populations generally showed limited, below 50% effectiveness against Omicron symptomatic disease.[34] The same holds for the VE in pediatric populations, as evidenced in studies in Chile (3–5 y/o, 38.2%),[35] Brazil (6–11 y/o, 39.8%),[36] Singapore (5–11 y/o, 36.8%),[37] Qatar (5–7 y/o, 46.3%)[38] and USA (5–11 y/o, 60.1%).[39] A recent systematic review and meta-analysis yielded a pooled estimate of real-world VE against symptomatic Omicron variant COVID-19 of 45.2% (95% CI, 30.0–60.4%) in children, while the VE was 71.0% (95% CI, 63.3–78.6%) for hospitalization.[16] Of note, the findings of this review indicate that the VE for symptomatic COVID-19 -but not for hospitalization-was somewhat higher in adolescents than in children, which is consistent with the age gradient seen in our results.

The better and preserved SOBERANA-02-Plus protection cannot be primarily attributed to previous infections conferring partial immunity. Children with documented SARS-CoV-2 infection before the Omicron wave were excluded from the analysis. Additionally, circulation of pre-Omicron variants in Cuba was below global average, infection with these variants confers rather modest relatively short-term protection against Omicron,[40] and undocumented previous asymptomatic infections will have occurred at quite comparable rates in the different age groups. Furthermore, a somewhat larger natural immunity proportion in the 1-year-old than in other age groups, which cannot be excluded, would imply that our analysis underestimates the true VE.

The VE of the Pfizer BioNTech vaccine against symptomatic Omicron infection in children has been reported to rapidly decrease to 28.9% during the second month after primary vaccination.[39] While the Omicron wave in our study took off some 4 weeks after the end of the immunization campaign, when conferred immunity and protection against COVID-19 disease might be expected to be at their highest, we find, overall, a VE of more than 75% during a period of over 6 months after completion of the SOBERANA-02-Plus scheme. Additionally, more than 3 months after the end of the vaccination campaign, when the Omicron BA.2 variant replaced Omicron BA.1, the scheme's VE remained stable. This contrasts with the findings of a systematic review on the waning of vaccine-induced immunity that found for 5 studies, all reporting on mRNA vaccines, a pooled VE estimate against symptomatic Omicron disease in children and adolescents of 38.7%, 13.1%, and

6.4% at 1, 6 and 9 months, respectively, after completing the primary vaccination cycle.[41] We are not aware of studies on waning in children after completing the primary immunization schedule with vaccines built on other platforms. However, there evidence in adults that effectiveness against the Omicron variant markedly decreases over time for mRNA,[41] vector[42] as well as inactivated[43] SARS-CoV-2 vaccines.

The level and duration of protection against symptomatic infection that we document here is in line with immunological findings in a previous pediatric phase I/II trial with the SOBERANA-02-Plus. It evidenced strong neutralization of the SARS-CoV-2 Omicron BA.1 variant, robust specific T-cell immunity, and B and T (CD4+ and CD8+) memory cells response.[11,44] The induction of effector and memory T cells is particularly relevant in a context of Omicron circulation because this variant conserves most of the T cell epitopes of the ancestral strain and cannot escape the patrol role of specific T cells, even when neutralizing antibodies fail.[45,46]

Together with the slow waning of the humoral immunity after the last dose of the scheme previously evidenced in adults,[9] the above findings may explain the lasting immune protection elicited by the SOBERANA-02-Plus scheme in children and the high effectiveness against Omicron, and perhaps also against other new SARS-CoV-2 variants. The somewhat lower VE for Omicron BA.1, then, might be related to the presence of two critical RBD mutations at amino acid G446S and G496S in Omicron BA.1, which are absent in Omicron BA.2, that participate in contact with the ACE2 receptor.[47]

Immune escape of the Omicron variant is well documented for natural as well as vaccine associated immunity.[48] Since COVID-19 vaccines employ various platforms, can be based on full length or partial S glycoprotein, and target differing antigens, the immunological response after vaccination, and the magnitude of escape and real-world effectiveness against new SARS-CoV-2 variants differs.[49] SOBERANA-02 is a recombinant viral RBD conjugated to tetanus toxoid, a well-known carrier that contributes with T epitopes to orchestrate an effective immune response to the linked antigen. From experience with the weak bacterial polysaccharide antigens of *Haemophilus influenza* type b, *Streptococcus pneumoniae* and *Neisseria meningitidis,* conjugate vaccines stimulate a strong B-cell immune response characterized by maturation, as well as vigorous T-cell specific immunity.[50] Consistent with that, other authors demonstrated in mice that protein–protein conjugation enhances the immunogenicity of SARS-CoV-2 receptor-binding domain.[51] As far as we could ascertain, for no other existing subunit SARS-CoV-2 vaccine the real-world effectiveness outcome in children has been reported. In particular, we cannot contrast with findings on the Novavax vaccine, that is non-conjugated and uses a saponin-based adjuvant, but is not approved for use in children below 12 years of age.

Our favorable results compared to observations previously made in effectiveness studies in children with other SARS-CoV-2 vaccines can probably be explained by the mass vaccination strategy used and by the type of immunity the SOBERANA-02-Plus scheme induces, that is characterized by a combination of high neutralizing antibodies response and effector and memory T cell response.[11,43] Whether high vaccination coverage in children in itself may have an impact on transmission is another, debated,[52] matter and benefits at population level will in any case be context specific. The preceding adult immunization campaign, which mainly relied on the Abdala vaccine, is also of note. Still, all schools in Cuba reopened after the mass vaccination campaign in the 2-18 years-old children and adolescents, that attained more than 95% full coverage, and the COVID-19 incidence in the Cuban population remained substantially lower during the Omicron wave than during the Delta wave -unlike in other countries with similarly high rates of adult vaccination.[2]

Finally, while a SARS-CoV-2 infection generally causes less morbidity and mortality in healthy children than in adults,[1] they may also need hospitalization when infected and can, although rarely, develop multi-system inflammatory syndrome and long-COVID.[53] Moreover, absences from school or nursery due to illness or quarantine can lead to undesirable follow-on effects. WHO declared an end to COVID-19 as a global health emergency, but the disease is still a threat. SARS-CoV-2 will continue to circulate, be it at lower intensity, and unvaccinated or previously not infected children and all infants to be born are susceptible to infection and disease. This study indicates that the SOBERANA-02-Plus scheme provides a safe and effective preventive option to protect a country's child population. Continued assessment of the scheme's effectiveness is obviously needed when future SARS-CoV-2 mutations give rise to new virus variants.

Contributors

METR, CVS, MMD, YVB, DGR, PVdS and VVB conceptualized the study. METR, MCRG, RPG, MMC were clinical investigator during the vaccination campaign. CVS, MMD and PVdS performed the statistical analysis. LIR, AGA, LLG and IMS extracted the epidemiological data. SFC, YCR, DD and DSM were responsible for vaccine development and manufacturing. METR, CVS, DGR, PVdS and VVB drafted the manuscript. All authors critically reviewed the manuscript for important intellectual content and approved the final version. METR, LIR and CVS have directly accessed and verified the underlying data reported in the manuscript. VVB and METR were responsible for the decision to submit the paper.

Data sharing statement

Proposals for full data sharing should be sent to: mariaeugenia@ ipk.sld.cu or vicente.verez@finlay.edu.cu. These proposals will be reviewed and must be approved by the Ministry of Health and the senior investigators. Eventually, a data access agreement must be signed.

Declaration of interests

MCRG, MMC, SFC, YCR, DSM, YVB, DGR and VVB are employees of the Finlay Vaccine Institute that developed and manufactures the SOBERANA vaccines.

VVB, YVB, DGR, YCR, SFC and DSM are authors of two patent applications related with the vaccines.

The other authors have no potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100750.

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