Real-world effectiveness of the SOBERANA02 and SOBERANA-Plus vaccine combination in children 2 to 11 years of age during the SARS CoV-2 Omicron wave in Cuba: a regression discontinuity study

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ABSTRACT

Background

Increased paediatric Covid-19 occurrence due to the SARS-CoV-2 0micron variant has raised concerns about the effectiveness of existing vaccines.

Methods

In September 2021, the Cuban Ministry of Health launched a nationwide mass paediatric immunisation campaign with the recombinant SOBERANA COVID-19 vaccines. At the end of the campaign in early December, shortly before the Omicron outbreak, 95.4% of the 2 to 18-year-old population was fully vaccinated (2 doses of conjugated SOBERANA-02 followed by a heterologous SOBERANA-Plus dose). We assessed the real-world effectiveness of the SOBERANA-02+SOBERANA-Plus scheme against symptomatic and severe SARS-CoV-2 infection during the complete course of the Omicron wave. We conducted a post vaccination case-population study using a regression discontinuity design with 24 months of age as cut-off. Vaccine effectiveness was calculated for children without previously documented SARS-CoV-2 infection.

Results

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 and 3577 symptomatic COVID 19 infections in the vaccinated and unvaccinated group, respectively. The vaccine effectiveness against symptomatic COVID 19 infection was similar in children 2 to 4 years-old, 83.8% (95% confidence interval [95%CI], 82.9-84.7%), and in children 5 to 11 years-old, 82.3% (95%CI, 81.5-83.1%). The effectiveness against severe symptomatic infection was 97.0% (95%CI, 78.8-99.9%) and 95.0% (95%CI, 82.7-98.9%), respectively. Effectiveness did not wane over time. No child death from COVID-19 was observed.

Interpretation

Immunization of 2 to 11 years-old with the SOBERANA-02+SOBERANA-Plus scheme provided strong durable protection against symptomatic and severe disease caused by

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the Omicron variant. These favourable results contrast with observations in previous real-world SARS-CoV-2 vaccine effectiveness studies in children. They may be explained by the type of immunity SOBERANA's conjugated protein-based platform induces.

Funding

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Keywords:

SARS-COV-2; COVID-19 vaccine; SOBERANA; Vaccine effectiveness; Pediatric; Children; Omicron variant; Conjugate-vaccine; RBD-subunit vaccine; Heterologous scheme

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Research in context

Evidence before this study

We searched PubMed on March 1, 2023 for available evidence on real world effectiveness of COVID-19 vaccines in children. We used the search terms “(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 from early in the COVID-19 pandemic have documented high immunogenicity, safety and vaccine efficacy in children. However, during the omicron outbreak observational studies revealed substantially reduced and rapid waning effectiveness against SARS-CoV-2 infection and disease. A systematic review and meta-analysis showed a pooled vaccine effectiveness for symptomatic COVID-19 in children of 45.2% (95%CI, 30.0–60.4%) and of 71.0 % (95%CI, 63.3–78.6%) for COVID-19-related hospitalization. Furthermore, published studies conducted in real-world setting dealt mainly with mRNA and inactivated vaccines in older children, and data regarding vaccination effectiveness of national child vaccination strategies is scarce. Data on the effectiveness against pediatric COVID-19 of subunit vaccines targeting the Receptor Binding Domain is completely lacking.

Added value of this study

We evaluate the real-world effectiveness of 2 doses SOBERANA-02, a subunit protein-based conjugated vaccine, followed by a heterologous dose of SOBERANA Plus, a dimeric RBD vaccine, to protect 2-11 year-old children from symptomatic COVID-19 infection, severe disease and death during the 2022 SARS-CoV-2 omicron wave. A nationwide child mass vaccination campaign was launched in Cuba in September 2021. At the end of the campaign in early December, shortly before the Omicron outbreak, 1,098,817 children 2-11 years-old (95.4%) were fully vaccinated. The total number of reported vaccine-associated adverse events (AE) was 179, attained for 5.43 AE per 10^5 applied doses. Only 5 serious vaccine-associated AE occurred. The vaccine effectiveness against symptomatic COVID 19 infection by the Omicron variant was similar in young children 2 to 4 years-old, 83.8% (95% confidence interval [95%CI], 82.9-84.7%), and in children 5 to 11 years-old, 82.3% (95%CI, 81.5-83.1%). The

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effectiveness against severe symptomatic infection was 97.0% (95%CI, 78.8-99.9%) and 95.0% (95%CI, 82.7-98.9%), respectively. Effectiveness did not wane over time. No child death from COVID-19 was observed

Implications of all the available evidence

Our results contrast with observations in previous real-world SARS-CoV-2 vaccine effectiveness studies in children. They can be explained by the type of immunity SOBERANA's conjugated protein-based platform induces. While SARS-CoV-2 infection generally causes less morbidity and mortality in healthy children than in adults, they may need hospitalization when infected and can develop complications. This study indicates that SOBERANA-02-Plus provides a safe and effective preventive option to protect a country's child population. Notwithstanding, COVID-19 mutations will give rise to new variants and continuous assessment of vaccine effectiveness in the pediatric population is needed.

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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 2021-22 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[6]. However, 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, 9, 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 and SOBERANA-Plus COVID-19 vaccines developed by the Finlay Vaccine Institute, Havana. The Cuban Ministry of Public Health launched a nationwide mass vaccination campaign in the corresponding age group that, serendipitously, was completed just before the omicron outbreak.

A few randomized clinical trials have demonstrated high vaccine immunogenicity and efficacy in children prior to the predominance of the omicron variant.[13, 14, 15] However, during the omicron outbreak various observational studies have exposed their 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] Each type of COVID-19 vaccine targets a different antigen set to induce immunity, and therefore their effectiveness can be expected to be influenced to a different extent by SARS CoV-2 variants. Published studies conducted in a real-world

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setting dealt mainly with mRNA and inactivated vaccines in older children[17]. Data on the effectiveness of subunit vaccines against pediatric COVID-19, and vaccines targeting Receptor Binding Domain in particular, is completely lacking.

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

METHODS

Study design and context

The Cuban national child vaccination campaign resulted in a quasi-experiment with a population eligible for vaccination, the 2 to 18 years-old, and an ineligible population, infants and 1-year-old children. This permitted to conduct a post vaccination case-population study to estimate vaccine effectiveness, using a regression discontinuity design[18] with 24 months of age as cut-off.

Comprehensive primary health care services with a defined population of responsibility are a key element of the Cuban health care system. They consist of family doctor/nurse practices and policlinics, which guarantees universal access to care. The family practices are the systems' entry point, while policlinics provide diagnostic and support services and more specialized care. The identification of COVID-19 cases is based on these first line services, which refer clinical suspects to hospitals. Upon a positive RT-PCR test they are admitted until symptom resolution. Contacts of cases are isolated for 5 days and routinely tested for SARS CoV-2 infection.

The Finlay Vaccine Institute, Havana, Cuba has developed and manufactures the SOBERANA COVID-19 vaccines. SOBERANA -02 is a subunit protein-based product base on pediatric conjugate vaccine platform. 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 antigen is a dimeric RBD (50 µg) adsorbed on 1250 µg alumina.[20] Both can be stored at 2–8 ^{o}C. Immunization against SARS-CoV-2 is done

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with 2 doses of SOBERANA -02 followed by a heterologous SOBERANA -Plus dose with intervals of 28 days, hereafter the SOBERANA-02-Plus scheme.

After phase 1 and 2/3 studies in adults as well as pediatric populations[8-11] which demonstrated the safety and efficacy of the vaccines, the Centre for State Control of Medicines and Medical Devices extended authorization for their emergency use to 2-18 years-old children at the same dose as in adults[12]. A nationwide child mass vaccination campaign was launched as of September 5, 2021. Primary health care workers administered the vaccines in immunization centers and schools. Children without documented previous SARS-CoV-2 infection were immunized with the full SOBERANA-02-Plus scheme. A history of a severe allergic reaction to a component of the vaccines or presence of a not controlled non-communicable disease were exclusion criteria.

The start of the vaccination campaign in children coincided with the peak of the SARS CoV-2 delta variant wave that hit Cuba between the end of May and the beginning of December 2021. At the end of the campaign on December 11, 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. Mid-November 2021, near the end of the campaign, the Ministries of Education and Health instructed resuming classroom teaching and reopening all primary and secondary schools in the country. At the very end of 2021 an omicron variant wave started building up. It lasted until the end of May 2022, but schools remained open while other COVID-19 transmission prevention and control measures were tightened.

Data sources, study subjects and statistical analysis

We used in our analysis official data collected and reported by the Cuban Ministry of Health. Its centralized national SARS-CoV-2 database contains all confirmed symptomatic cases occurring in the territory, with related 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. The established countrywide routine surveillance system of vaccine-

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associated adverse events (VAAE), set up at all health care levels by the National Immunization Program, yielded the data on SARS CoV-2 VAAEs. Information on the number of Cuban citizens by municipality and age group was provided by the National Office of Statistics and Information and vaccination coverage was derived from the national online COVID-19 vaccination registry.

We extracted from the above database anonymized whole country data on the 1-11 years-old for the period from 23/05/2021 (epi-week 21/2021) to 04/06/2022 (epi-week 22/2022), corresponding to the extent of the delta and omicron waves. We first performed a descriptive analysis by plotting the weekly incidence rate of symptomatic SARS-CoV-2 infection by age, and by mapping 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 real-world SOBERANA-02-Plus vaccine effectiveness. We excluded from the analysis all children with any documented SARS-CoV-2 infection before epi week 51, 2021 -the start of the wave- or that were infected or vaccinated outside the country, and in the 2-11 age group the children who did not receive the full 3 doses SOBERANA-02-Plus schedule. Participants in the 168 municipalities in the country were stratified according to three age groups (unvaccinated 1-year-old, and fully vaccinated 2-4 and 5-11 years-old), giving rise to 504 population subgroups.

We estimated the person time at risk for becoming a symptomatic COVID-19 case in the vaccinated and non-vaccinated age groups assuming a steady state dynamic population and case occurrence spread evenly over the observation period, and computed the incidence rate (IR) of disease in each age group as the number of new cases divided by the number of person-weeks at risk[22]. 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.

To examine differences between the unvaccinated and vaccinated groups with respect to changes of the cumulative incidence rate (CIR) over time during the omicron wave, we fitted a multilevel model for repeated measurements to the 24 weekly CIR in the 504

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population subgroups defined above, whose distributions were normalized by log transformation.[23] The data were analyzed as a 3-level hierarchical system with the observed CIR in each week (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 CIR profiles, the expected weekly values were estimated as polynomial functions. During model development, level-2 (age groups by vaccination status) and level-3 (being a provincial capital or not) variables were added to explain the observed variability between the subgroups. Improvement of model fit was assessed with the log likelihood ratio statistic. The p values and 95% confidence intervals for the parameter estimates were calculated with the Wald test.

We mapped the COVID-19 incidence data using Jenks natural breaks classification method[24] and we performed statistical analyses using R version 4.2.0 and MLwinN version 2.19.

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.

Role of the funding source

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

RESULTS

Figure 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 the timing of the vaccination campaign with SOBERANA-02-Plus in the 2-11 years-old. The

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omicron wave was bimodal. Sub-variant BA1 dominated from week 51/2001 to 9/2022, to be replaced by BA2 between week 10/2022 to 22/2022.[25] Compared to the delta wave, COVID-19 incidence rates were substantially lower in all age groups during the omicron wave but the difference between the 1-year-old and the other age groups increased substantially.

Mapping confirms the striking contrast between the two waves (Figure 2). The delta wave caused more morbidity overall and during the circulation of the omicron variant, noticeable differences appear in the symptomatic COVID-19 attack rates for the 1 year-old and 2-11 years-old children. Furthermore, the disease burden distribution becomes geographically far more homogeneous in the latter age group.

The countrywide routine surveillance system of vaccine-associated adverse events (AE) recorded 123 children with any AE up to 4 weeks after the end of the campaign. The total number of reported AE was 179, corresponding to 5.43 AE per 10^5 applied doses, which classifies as very rare. Only 5 serious vaccine-associated AE occurred, equivalent to a rate of 0,76 x 10^5 applied doses (one acute crisis of bronchial asthma, febrile seizure, idiopathic thrombocytopenic purpura, and two severe local reaction). No cases of myocarditis, pericarditis or deaths were observed.

In our 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, all with no documented previous SARS-CoV-2 infection. During the full 24 weeks of the omicron wave, there were 7003 and 3577 symptomatic COVID 19 infection in the vaccinated and unvaccinated study population, respectively (Figure 3).

The overall vaccine effectiveness against symptomatic COVID 19 infection was similar in children 2 to 4 years-old, 83.8%, and in children 5 to 11 years-old, 82.3%. Compared to the first half of the omicron wave –on average 52 days after the last dose of the vaccine- the effectiveness increased during the second half of the wave – on average

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143 days after the last dose- from 79.5 to 88.9% and from 74.4 to 91.7% in children 2 to 4 and 5 to 11 years-old, respectively (Table 1). The overall effectiveness against severe symptomatic infection in the corresponding age groups (table 2) was 97.0% (95% CI, 78.8 to 99.9%) and 95.0% (95% CI, 82.7 to 98.9%). No child death from COVID-19 was reported.

Table 3 shows the multilevel model of the weekly cumulative incidence rate (CI) of symptomatic COVID-19 infection with the best fit. The CI during the omicron wave and its growth rate vary between age groups and municipalities. With the unvaccinated age group 1-year-old as reference category, the estimates of the Age Group*Week interaction effect were negative ($p<0.001$) for the vaccinated 2-4 and 5-11 age groups, providing clear evidence that the average weekly CI growth in these two groups is lower and similar to each other. On the other hand, the effect of being a provincial capital, although significant ($p<0.01$) can be considered small. Finally, while the variances continue to be significantly different from zero after including Age Group as a covariate in the model, considering that the estimates are very close to zero and given the precision of their confidence intervals, it can be assumed that the differences between the subgroups is small after controlling for age.

DISCUSION

The effectiveness of the heterologous SOBERANA-02-Plus vaccine scheme during the omicron outbreak in Cuba was 82.5% and 81.2% among children 2-4 and 5-11 years-old, respectively. Effectiveness did not wane but on the contrary marginally increased during the second half of the wave, when sub-variant BA.1 had been replaced by BA.2. Vaccination reduced the risk of severe disease in younger and older children with 96.7% and 94.6%, respectively. The scheme had a favourable safety profile.

We conducted our analysis with routine health information data. The Cuban health system has attained universal health coverage and implements Primary Health Care based surveillance. Well established and adhered to routine SARSCoV-2/COVID-19 activities for case finding and ascertainment feed a centralized national database. This

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enabled linking nationwide individual data on symptomatic SARS-CoV-2 cases with coverage data from the online vaccination registry to base our effectiveness estimates on. It also permitted to exclude from our analysis children who went through a COVID-19 episode before the omicron wave. The long post vaccination follow-up during circulation of two sub-variants constitutes a further strength of our study.

The completion of the Cuban child vaccination campaign in a short period and the very high coverage precluded a test-negative case-control study or a classical cohort analysis. However, the regression discontinuity design we adopted produces robust estimates of effects when individuals are assigned to an intervention that depends on whether they fall below or above a pre-specified cut-off on a variable like age [15]. Assignment to such intervention is even considered as good as random close to the cut-off and would permit causal inference[26].We excluded infants from the unvaccinated comparator age group given their immature immune system[27] and the potential presence of antibodies after maternal COVID-19 vaccination or infection[28]. Furthermore, during the delta wave the disease incidence in the 1-year-old had been quite close to that in the 2-4 and 5-11 years-old, and the younger pre-school children in particular are also comparable in terms of behaviour and exposure to infection.

Our estimates of the effectiveness of the SOBERANA-02-Plus scheme against confirmed symptomatic SARS-CoV-2 infections during omicron variant predominance are high and do not reveal rapid waning of 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.[29] The same holds for the VE in paediatric populations, as evidenced in studies in Chile (3-5 y/o, 38.2%),[30] Brazil (6-11 y/o, 39.8%) [31] and Singapore (5-11 y/o, 36.8%)[32]. A recent systematic review and meta-analysis showed a pooled protection against symptomatic COVID-19 in children of 45.2% (95%CI, 30.0–60.4%), while, the VE was around 70 % for hospitalization and severe disease [14].

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The better preserved SOBERANA-02-Plus protection can hardly be explained by past infections conferring partial immunity. Children with previous symptomatic COVID-19 were excluded from the analysis, asymptomatic infections must have affected the contrasted age groups comparably, circulation of pre-omicron variants in Cuba was below global average, and infection with such variants anyhow confers rather modest protection[33]. More importantly, a previous paediatric phase I/II clinical trial with the SOBERANA-02-Plus scheme demonstrated strong boostable neutralization of the original D614G strain ($cVNT_{50}$ 169.8) but also of the omicron BA1 ($cVNT_{50}$ 99.2) variant, and robust complementary specific T-cell immunity [11]. Together with the slow waning of the humoral immunity 6 months after the last dose of the scheme demonstrated in adults[9] this constitutes an important predictor of high effectiveness against omicron and possibly against other SARS CoV-2 variants.

The immune escape of the omicron variant is well documented for natural as well as vaccine associated immunity[34]. Since COVID-19 vaccines employ various platforms and target a plethora of differing antigens, the magnitude of escape after vaccination can differ. The immunity induced by the SOBERANA-02-Plus combination is notably dissimilar from that resulting from other COVID-19 vaccines. SOBERANA-02 is a recombinant viral protein conjugated to tetanus toxoid, a well-known protein carrier. From previous experience with the weak bacterial polysaccharide antigens of *Haemophilus influenza* type b, *Streptococcus pneumoniae* and *Neisseria meningitidis* conjugated vaccines can be expected to stimulate a strong B-cell immune response characterized by maturation, as well as vigorous T-cell specific immunity.[35] Finally, the slightly higher VE for BA.2 is related to the absence in BA.2 of two critical RBD BA.1 mutations at amino acid G446S and G496S that participate in contact with the ACE2 receptor[36].

Our favourable results in comparison to observations in previous real-world SARS-CoV-2 vaccine effectiveness studies in children can thus be explained by the vaccination strategy and by the type of immunity the SOBERANA combination induces. Whether high vaccination coverage in children can have an impact on transmission is another,

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debated, matter[37] and population level benefits may be context specific[6]. Still, all schools in Cuba reopened after the vaccination campaign in the 2 to 18 years-old, which attained more than 95% full coverage, and the COVID-19 incidence in the 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].

In any case, although a SARS-CoV-2 infection generally causes less morbidity and mortality in healthy children than in adults[1], they may need hospitalization when infected and can, although rarely, develop multi-system inflammatory syndrome and long-COVID[38]. Furthermore, absences from school or nursery due to illness or quarantine can lead to undesirable follow-on effects. This study indicates that SOBERANA-02-Plus provides a safe and effective preventive option to protect a country's child population thereof.

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, manufacturing and project administration. All authors critically reviewed the manuscript for important intellectual content and approved the final version. VVB and METR were responsible for the decision to submit the paper.

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. Disclosure forms provided by the authors are available with the full text of this article upon publication.

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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. Lastly, a data access agreement must be signed.

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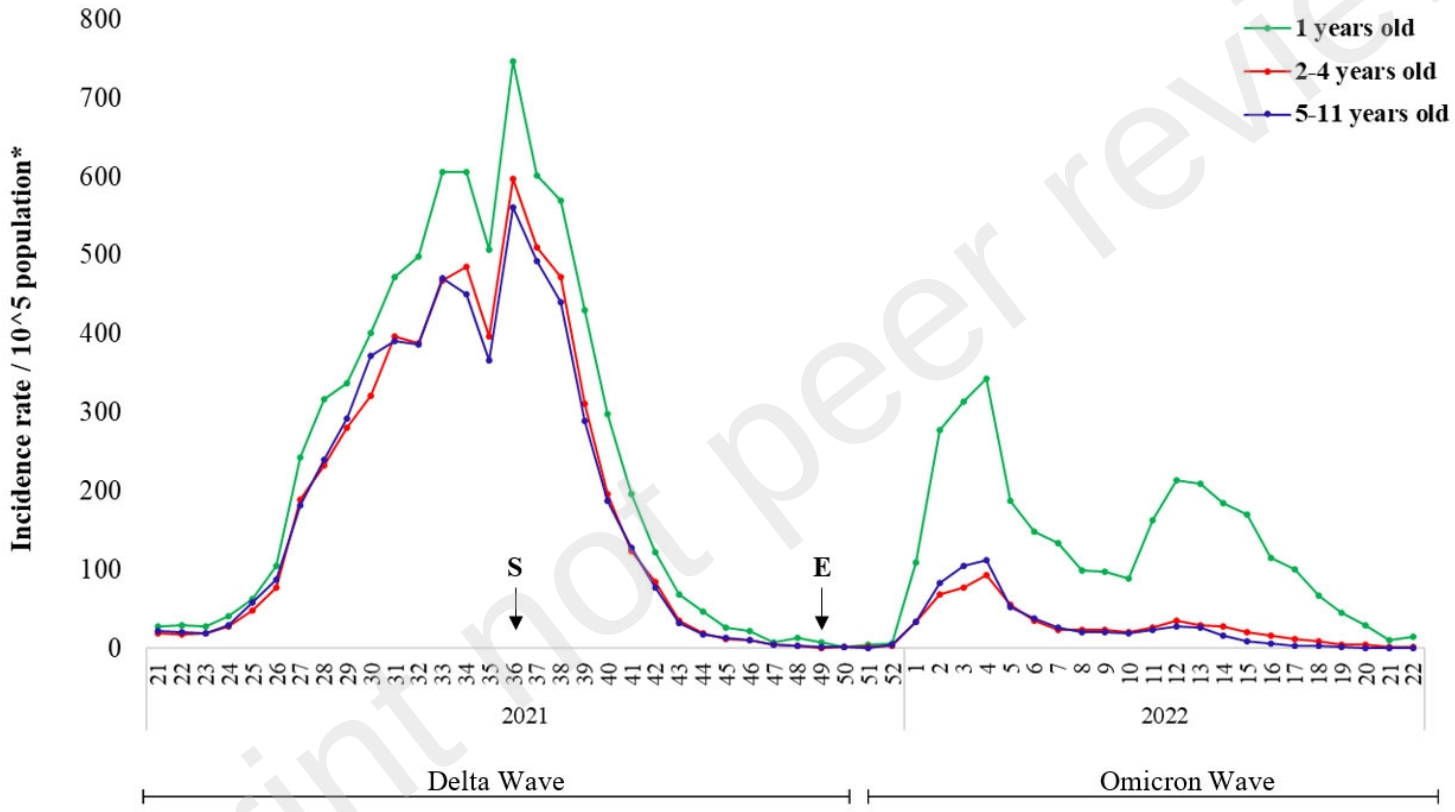
Figure 1. Delta and Omicron COVID-19 waves and timing of the national SOBERANA-02-Plus SARS-CoV-2 vaccination campaign in children 2-11 years old. Cuba, 2021-2022



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

S: Start of the vaccination campaign in children 2-11 years old

E: End of the vaccination campaign; 3 doses completed

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Figure 2. Cumulative incidence rate of symptomatic COVID-19 infection in children, by age group and municipality. Cuba, 2021-2022

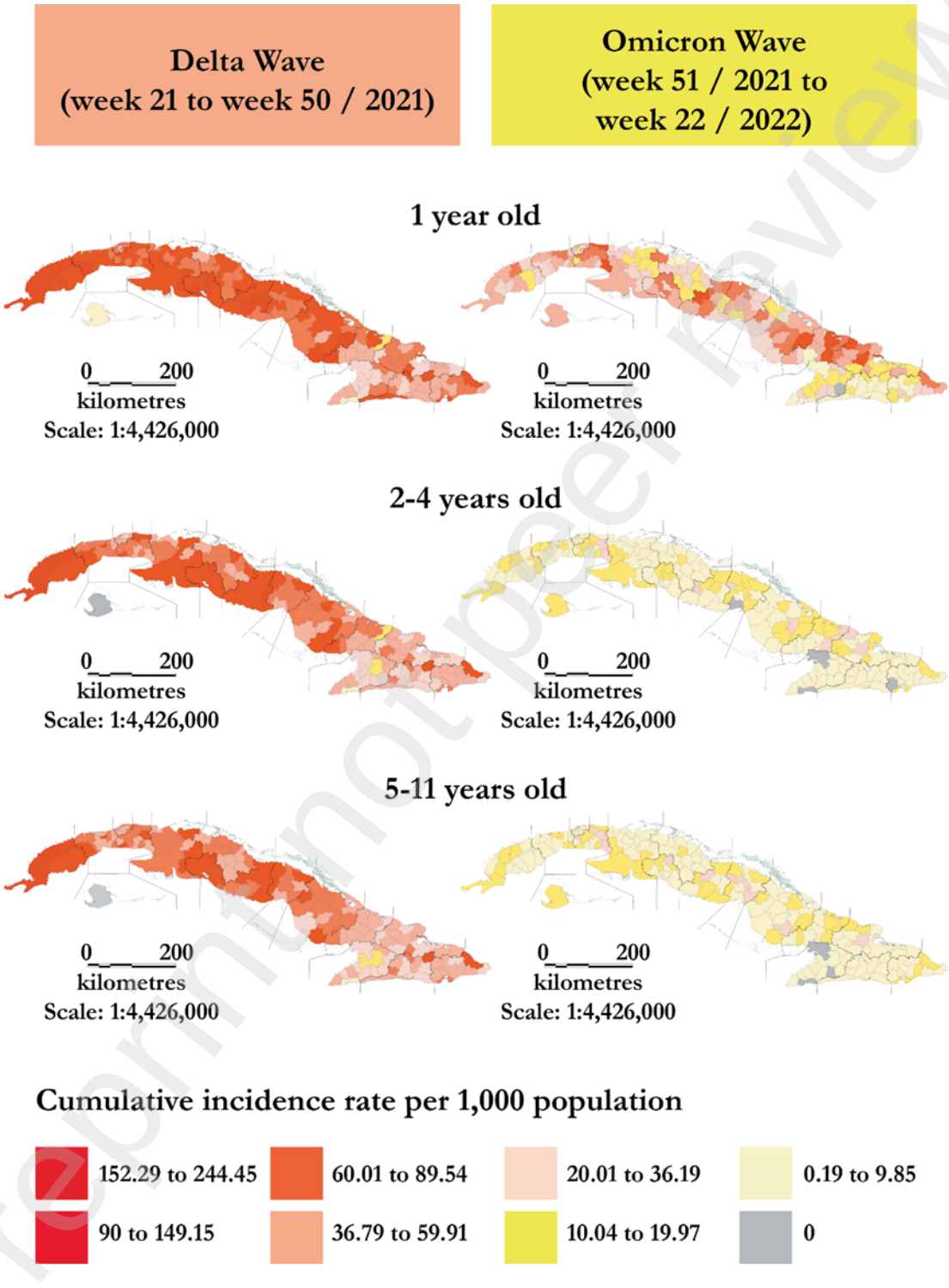

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Figure 3. Study population by eligibility for SARS-CoV-2 immunisation during the national SOBERANA-02-Plus vaccination campaign. Cuba, 2021-2022

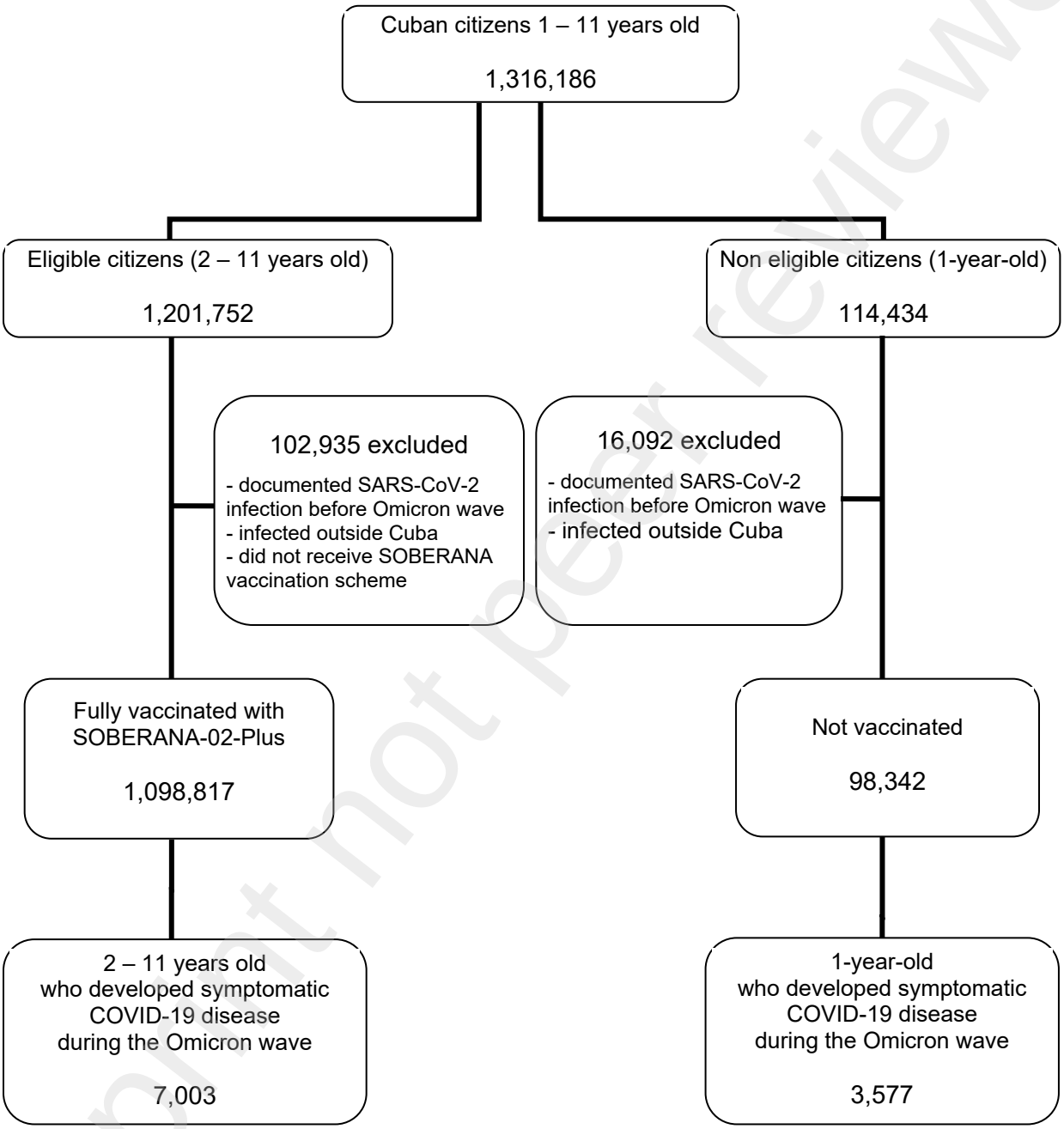

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Table 1. Effectiveness of the SOBERANA-02-Plus vaccines schedule to prevent COVID-19 symptomatic and severe disease during the Omicron variant epidemic wave. Cuba, 2021-2022

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 BA1 (week 51/2021-week 9/2022)				
1 y/o	1,070,955	1,965	183.5	
2-4 y/o	3,524,823	1,325	37.6	79.5 (78.0; 80.9)
5-11 y/o	8,528,298	4,001	46.9	74.4 (73.0; 75.8)
Omicron BA2 (week 10/2022-week 22/2022)				
1 y/o	1,241,318	1,612	129.9	
2-4 y/o	4,148,969	597	14.4	88.9 (87.8; 89.9)
5-11 y/o	10,038,383	1,080	10.8	91.7 (91.0; 92.3)
Total Omicron Wave (week 51/2021- week 22/2022)				
1 y/o	2,312,273	3,577	154.7	
2-4 y/o	7,673,793	1,922	25.0	83.8 (82.9; 84.7)
5-11 y/o	18,566,681	5,081	27.4	82.3 (81.5; 83.1)
COVID-19 severe symptomatic disease				
Total Omicron Wave (week 51/2021- week 22/2022)				
1 y/o	2,312,273	10	0.40	
2-4 y/o	7,673,793	1	0.01	97.0 (78.8; 99.9)
5-11 y/o	18,566,681	4	0.02	95.0 (82.7; 98.9)

IR: Incidence rate = new cases/person-week at risk; IRR: Incidence Rate Ratio = $IR_{vaccinated} / IR_{unvaccinated}$; VE=(1- IRR)x100%

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Table 2. Multilevel repeated measurements model of the weekly cumulative incidence rate evolution of COVID-19 symptomatic disease during the Omicron variant epidemic wave. Cuba, 2021-2022

Parameter	Estimate		CI 95 %	
			LL	UL
Fixed Part				
constant	0.391	**	0.364	0.418
$(week)$	0.751	**	0.725	0.777
$(week)^2$	-0.061	**	-0.064	-0.058
$(\text{week})^3$	0.002	**	0.0018	0.0022
$(week)^4$	-0.000040	**	-0.000044	-0.000036
$(Age_Group_{2-4\ y/o}) * (week)$	-0.055	**	-0.0554	-0.0549
$(Age_Group_{5-11\ y/o}) * (week)$	-0.061	**	-0.065	-0.057
$(Capital_Municipality) * (week)$	-0.010	*	-0.018	-0.002
Random Part				
Variance/Covariance				
Municipality level				
σ^2_{r1}	0.013	**	0.009	0.017
σ^2_{r2}	0.000020	**	0.000015	0.000025
$\sigma^2_{r_1 r_2}$	-0.0004	**	-0.0005	-0.0003
Subgroups level (Municipalities/Age_Groups)				
$\sigma^2_{u_1}$	0.013	**	0.011	0.015
$\sigma^2_{u_2}$	0.000020	**	0.000017	0.000023
$\sigma^2_{u_1 u_2}$	-0.0005	**	-0.0006	-0.0004
Residuals				
σ^2_e	0.148	**	0.144	0.152
-2*Log-lilkelihood	14170.9			

** P < 0.001; *P < 0.01

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STROBE Statement—checklist of items that should be included in reports of observational studies

Item No	Recommendation	Page
Title and abstract 1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
	(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction		
Background/rationale 2	Explain the scientific background and rationale for the investigation being reported	6
Objectives 3	State specific objectives, including any prespecified hypotheses	7
Methods		
Study design 4	Present key elements of study design early in the paper	7
Setting 5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7,8
Participants 6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	
	Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
	Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	8,9
	(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed	
	Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables 7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement 8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias 9	Describe any efforts to address potential sources of bias	9
Study size 10	Explain how the study size was arrived at	11/ Fig 3
Quantitative variables 11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9

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Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding 9,10
		(b) Describe any methods used to examine subgroups and interactions 9,10
		(c) Explain how missing data were addressed N/A
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed
		Case-control study—If applicable, explain how matching of cases and controls was addressed
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy 9
		(e) Describe any sensitivity analyses N/A
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 11/ Fig 3
		(b) Give reasons for non-participation at each stage N/A
		(c) Consider use of a flow diagram Fig 3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders N/A
		(b) Indicate number of participants with missing data for each variable of interest N/A
		(c) Cohort study—Summarise follow-up time (eg, average and total amount) 11
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure N/A
		Cross-sectional study—Report numbers of outcome events or summary measures 11/ Fig 3
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included 11/12/Table1/Table 2
		(b) Report category boundaries when continuous variables were categorized N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12/Table 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	
		Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14,15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3,10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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