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The impact of COVID-19 childhood and adolescent vaccination on mortality in Argentina

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ABSTRACT

Introduction: Argentina authorized COVID-19 vaccination for adolescents 12 years and older in August 2021, and then for children three years and older in October 2021. Children aged 6 months–2 years received a two-dose regimen beginning July 2022.
Objective: This study aims to analyze the impact of COVID-19 vaccination among children aged 0–17, considering vaccination status and mortality for the 2020–2022 period.
Methods: We conducted a population-level analysis examining all-cause mortality, COVID-19 cases, deaths, and vaccination records. We compared outcomes with child mortality for diseases for which vaccination is compulsory, before and after each vaccine rollout.
Results: A decrease in COVID-19-related deaths was observed in 2022 for pediatric age groups (3–11 and 12–17) with relatively higher vaccination coverage. However, no decrease was observed for the 0–2 year old age group, which had the longest delay in access to immunization and lowest vaccination coverage. When compared to unvaccinated populations in 2022, we observe an 8–15-fold reduction in cumulative death rates for pediatric populations vaccinated with 1 or more doses, and a 16–18-fold reduction for those vaccinated with 2 or more doses. Historical analysis shows that for diseases for which vaccination is now compulsory in many countries, pre-vaccine-rollout mortality was lower than COVID-19 deaths during 2020–2022.
Conclusions and relevance: SARS-CoV-2 immunization was associated with reduced COVID-19 deaths for children and adolescents in Argentina. Our findings suggest that greater efforts should be undertaken to ensure wider COVID-19 vaccine coverage in children and adolescents, especially infants.

1. Introduction

With the advent of vaccines to mitigate severe illness and hospitalization, health authorities have advocated for including children and adolescents among the demographic groups that should be eligible for vaccination against SARS-CoV-2. Citing the risk of reinfection, the presence of unvaccinated children in some regions, and the increasing number of cases of childhood multisystemic inflammatory syndrome (MIS-C), Plotkin and Levy have urged public health authorities to consider mandatory childhood vaccination against COVID-19 [1]. Of these factors, the mortality rate among children infected with COVID-19 has emerged as a focal point in bolstering arguments advocating for the

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vaccination of children against SARS-CoV-2, driven by pragmatic, immunological, ethical, and societal imperatives. However, since the onset of the COVID-19 pandemic, data regarding the impact of pediatric vaccination has remained limited, particularly pertaining to the mortality rates, underlying health conditions, and the vaccination status of those who have succumbed to the virus in Latin America.

Vaccination of children and adolescents has been shown to be safe and effective in preventing severe illness and death from COVID-19 disease [2–6], including in countries such as Chile, where these age groups received immunization relatively early on in the pandemic [7,8]. Retrospective population-based studies similarly show sizable differences in the risk of infection and hospitalization among vaccinated and unvaccinated children and adolescents. In New York, the risks of infection and hospitalization were elevated for unvaccinated children aged 5–11 and 12–17 years compared to their vaccinated counterparts [9].

Several important studies have produced evidence reinforcing the severity of disease in these age groups and the high incidence of hospitalization. In the United States, COVID-19 was the leading cause of death from infectious or respiratory diseases in children aged 0–19 years in 2021–2022, and it also caused more deaths annually than any other vaccine-preventable disease in recent history [10]. Infants under one year were the most vulnerable, with a mortality rate of four per 100,000 infants. Nearly one-fourth of pediatric patients with COVID-19 in Brazil in 2020 required ICU admission (23.8 %), 10.0 % required invasive ventilation, and 7.5 % died [11]. In Argentina, recent studies have shown that with the emergence of new variants, the number of severe and critical cases, as well as case fatality rates in children, have remained unchanged: children under 18 years of age represented 8.5 % of all confirmed cases, and case fatality in this age group was estimated to be 0.06 % [12].

Studies in Brazil and Mexico, which have considerably younger populations, suggest that morbidity and mortality may be substantially higher than reported among those in non-developing country settings, and rates are much higher considering income, regional and racial inequalities [11,13,14]. Furthermore, studies have documented that the complications and sequelae of COVID-19 in children and adolescents include MIS-C and long-COVID [15].

Building upon the monitoring of pediatric COVID-19 vaccination in Argentina [16], this study seeks to contribute to this discussion by presenting novel evidence on COVID-19-related mortality for children and adolescents. Argentina is one of the few countries that initiated COVID-19 vaccination of 12 year old adolescents and older in August 2021 and children aged three years and older in October 2021. In the study period, children from 6 months to 2 years old were vaccinated with a two-dose regimen starting July 2022. We leverage the gradual phasing in of vaccination to examine how COVID-19 immunization impacted mortality trends in children and adolescents using information on their vaccination status. We also contextualize COVID-19 pediatric mortality concerning other vaccine-preventable diseases.

1.1. Vaccination eligibility, surveillance, variants and non-pharmaceutical interventions in Argentina

Argentina gradually authorized vaccinating adolescents and children. Prioritization was based on the risk of disease severity, risk of exposure, and social vulnerability [13]. In August 2021, pediatric vaccination against COVID-19 began in adolescents aged 12–17 years with the vaccines mRNA-1273 (Spikevax, Moderna) and BNT162b2 (Comirnaty, Pfizer-BioNTech). For adolescents, immunization was undertaken with a two-dose regimen of mRNA1273 (Spikevax, Moderna) or BNT162b2 (Comirnaty, Pfizer-BioNTech) vaccines. In October 2021, children between 3 and 11 years of age were authorized to receive two doses of the inactivated virus vaccine BBIBP-CorV (Sinopharm). Booster doses for adolescents were authorized in February 2022. For those who received Sinopharm, a booster dose was introduced in July 2022. Children from 6 months to 2 years old were authorized to be vaccinated with two doses of mRNA1273 (Spikevax, Moderna) starting in July 2022, making Argentina the first country in Latin America to provide vaccination against COVID-19 for children as young as six months of age. Booster doses in this group were authorized in January 2023.

We identified three distinct periods for SARS-CoV-2 surveillance. From the onset of the pandemic to October 2020, there was limited testing available in Argentina due to limited testing capacity and supplies. In the second period (November 2020–April 2022), the epidemiological surveillance system monitored COVID-19 separately from other acute respiratory infections. In this period, cases were confirmed by laboratory diagnostic tests (RT-PCR and antigen tests). The preferred testing method for children under 10 years was the nasopharyngeal swab because of its reduced invasiveness compared with nasal or saliva swabs and clinical/epidemiological criteria in symptomatic cases. However, this method was used mainly during contact tracing following at least one laboratory-confirmed case. In the third period, from April 2022 to the end date of the study, testing for children and adults under 50 with no comorbidities was restricted to hospitalized cases with severe respiratory distress.

In the early pandemic phase, Argentina adopted an extensive emergency cash transfer program (March–August 2020) and reimbursed businesses that experienced hardship due to stay-at-home orders (April–December 2020). As shown in Fig. 1C, stay-at-home orders were strictly enforced from March 19 to June 7, 2020, and then gradually, different parts of the workforce were excluded from these restrictions from June to October 2020. Stay-at-home orders were replaced with social distancing policies and mandatory masking from October 2020 to August 2021. When these policies were further loosened, mask use on public transport and health facilities was maintained until September 2022. Children were schooled remotely from March 2020 to February 2021. Face masks were mandatory when on-site schooling commenced from March 2021 to April 2022. In some provinces, off-site remote schooling returned for two weeks in April 2021 due to a surge in cases. In November 2021, different districts began to abandon mandatory face-mask use, both in schools and workplace settings. The information regarding the dates for vaccination approval, SARS-CoV-2 testing regimes and non-pharmaceutical intervention (NPI) implementation is summarized in panel C of Fig. 1, and data sources are provided in Supplementary Table 6.

2. Material and methods

2.1. Data sources

We conducted a national population-level time-series, cross-sectional epidemiological analysis using several data sources. We analyzed the Yearbook of Vital Statistics of the Ministry of Health of Argentina to obtain data on mortality and cause of death for the 0–14 year old age group for the 2005–2022 period. Since publicly available datasets on COVID-19 cases and deaths, as well as cause-of-death data are anonymous and unlinked to vaccination data, we requested information on the monthly evolution of the pediatric vaccination campaign and the vaccination status of COVID-19 cases and deaths among children aged 0–17 for 2020–2022 under data transparency laws (Argentine Law 27275). Thus, in contrast to other country-specific studies of the pediatric population, our study analyzed unpublished information from Argentina's National Ministry of Health and combined this information with published records. Since the information was anonymized and publicly available, our study did not require informed consent or a research ethics committee review. All of the databases from varied sources used in this study, as well as which figures and tables they were used to produce, are summarized in Supplementary Table 5.

We also analyzed and brought together data from different sources regarding COVID-19 cases, deaths, government policies and SARS-CoV-2 variants (see Fig. 1). First, we considered the onset of vaccine

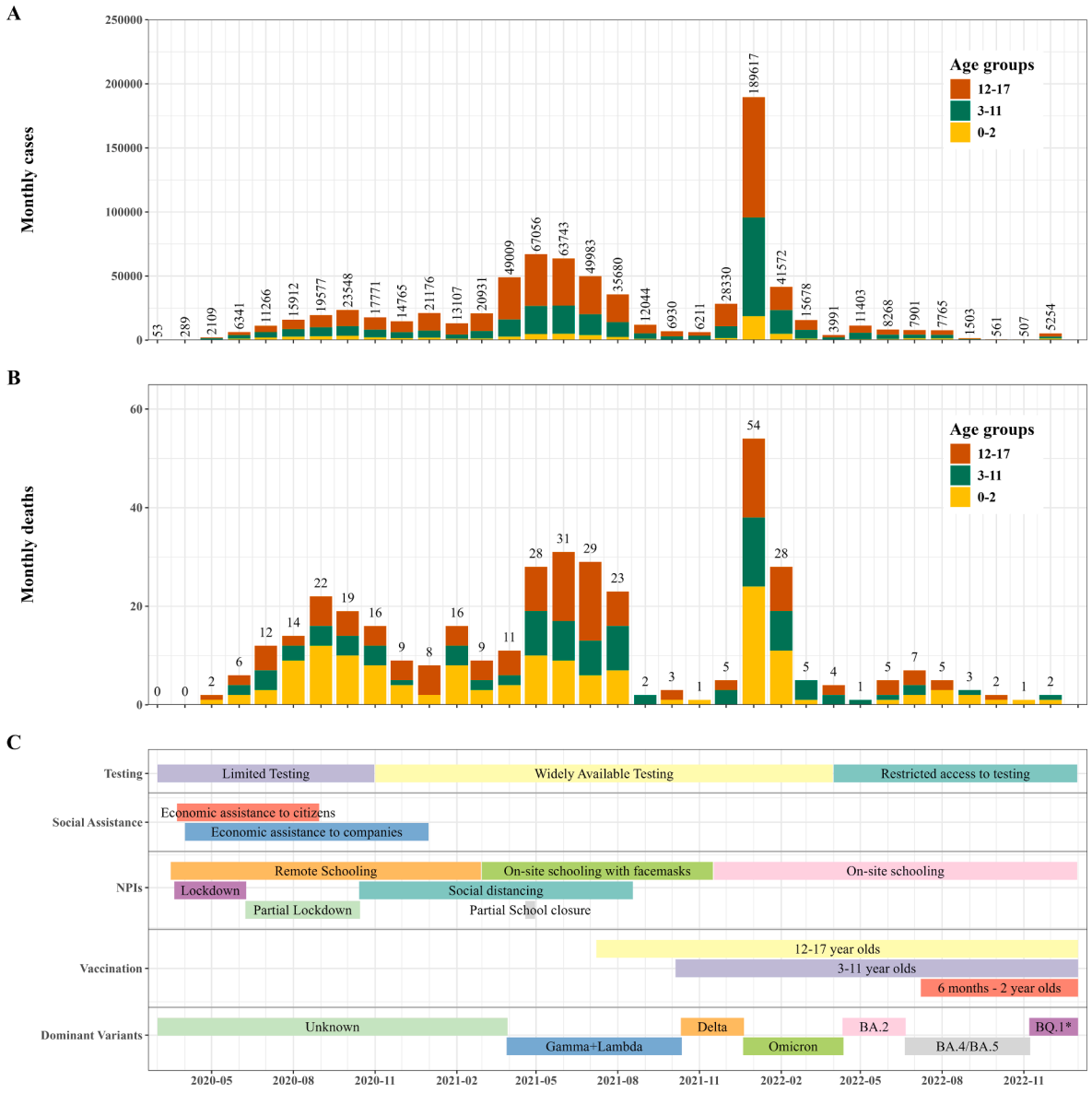

Fig. 1. Monthly COVID-19 Cases, Deaths and Public Health Policies for Children and Adolescent Age Groups in Argentina, 2020–2022. Panel A shows a stacked bar chart displaying monthly COVID-19 cases for each age group. Panel B shows monthly deaths as a stacked bar chart, where colors correspond to different age groups. For Panels A and B, yellow is used for the 0–2 age group, green for 3–11 and dark orange for the 12–17 age group. Panel C shows the main public health policies adopted in Argentina, grouped into "Testing", "Social Assistance", "NPIs" and "Vaccination" initiatives, as well as data from Covariants.org regarding dominant SARS-CoV-2 variants. Data corresponds to the period between March 2020 and December 2022. As of April 2022, due to changes in epidemiologic surveillance, the Ministry of Health warns that the number of pediatric deaths "may be underrepresented as of that date." (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

eligibility for children and adolescents. Second, we monitored Ministry of Health guidelines to assess changes in SARS-CoV-2 surveillance in Argentina. Third, we mapped the introduction and duration of non-pharmaceutical policies to reduce transmission speed, including emergency cash transfers, social assistance, school closures, and mask mandates. In addition, we also identified the start and end dates for which different SARS-CoV-2 variants were dominant (which we consider as situations in which a specific variant exceeded 50 % of sequenced samples) once genomic sequencing was systematically conducted in Argentina, using data reported in Covariants.org [17]. All these data sources are summarized, referenced and documented in panel C of Fig. 1 and Supplementary Table 6.

2.2. Cumulative death rates

We used data from the Argentina National Registry of Persons (RENAPER) to estimate the size of each of these populations for each age group. The population was estimated for the 0–2, 3–11, and 12–17 age groups based on the quinquennial age group data. Vaccination data were imported, cleaned, and aggregated to match the same time period and age groups. Cumulative counts of vaccinated individuals were calculated by month. Then, combining population size and vaccination data, we estimated the population size for each combination of age group and doses received. A limitation of this estimate is that since we lack the birth date for each vaccination record, we could only consider constant population sizes, which can lead to an overestimation of vaccination coverage. Also, since no deaths were registered for vaccinated populations in the 0–2 year old populations, for this age group we only

calculated a cumulative death rate for the non-vaccinated population. Once population sizes were established for age and vaccination status groups, we merged these data with monthly deaths classified by vaccination status, which allowed us to calculate the monthly cumulative death rate per 100,000 population for each combination of age and vaccination status group. Finally, these rates were added cumulatively for each month of 2022 to compare the annual death rates of non-vaccinated individuals and individuals that received 1 or more (1+ doses) or 2 or more doses (2+ doses) for each age group. For further information on what data sources were used to construct cumulative death rates for vaccinated and unvaccinated populations shown in panel B of Fig. 2, see Supplementary Table 5.

2.3. Yearly average mortality for COVID-19 and other diseases for which vaccination is now compulsory in Argentina

To contextualize our findings regarding COVID-19 mortality, we analyzed the mortality for other vaccine-preventable diseases affecting children and adolescents before and after mass vaccination was adopted by the Ministry of Health, using the Vital Statistics Mortality and Cause of Death database (see Table 3). We calculated the mean number of annual deaths before and after the introduction of mandatory vaccination for the 0–14 year old age group for 2005–2022 in Argentina. The number of years prior for each disease was contingent on data availability. For COVID-19 deaths by vaccination status, those with two or more doses were considered "vaccinated." For these diseases, the age groups differ from those reported for COVID-19 because of how publicly available annual mortality data are tabulated in Argentina. The statistics for the year vaccination was introduced for each disease were considered part of the pre-vaccination period.

2.4. Cause of death analysis and ranking

To contextualize COVID-19 mortality, we analyzed the Vital Statistics Mortality and Cause of Death database for the 0–14 year old age group from the Ministry of Health of Argentina. We analyzed yearly mortality by ICD-10 causes, grouped and categorized as suggested by Flaxman et al. [10]. This information was used to produce Supplementary Tables 1 and 2. A yearly rank analysis was performed for COVID-19, and other infectious and respiratory diseases as shown in supplementary Fig. 3.

2.5. Comorbidities analysis

To analyze comorbidities present in COVID-19 deaths, we analyzed the information provided by the National Ministry of Health of Argentina in response to our access-to-public-information request. We categorized and unified the information provided, finding that while some deaths were registered with a confirmation that no comorbidities were present, many deaths with no registered comorbidities had no such confirmation.

2.6. Data and code availability

All data analysis was performed using scripts written in the R programming language [17]. To improve the reproducibility of this work, all the

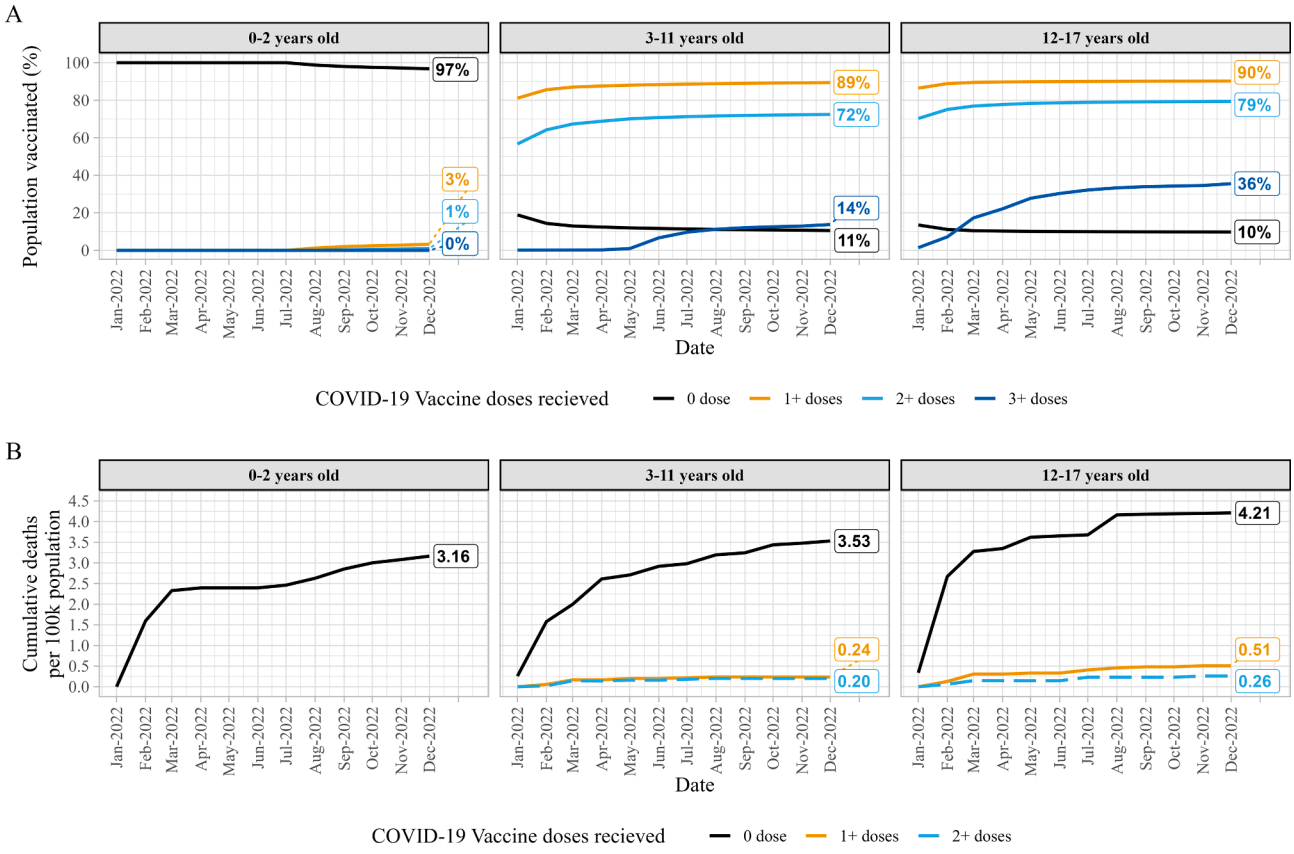

Fig. 2. Cumulative Vaccination and Incidence of COVID-19 Deaths for 0–2, 3–11 and 12–17 year olds in Argentina, 2022. Panel A shows the cumulative percentage of the 0–2, 3–11 and 12–17 year old populations with lines representing the percentage of the population that received 0 doses in black, 1 or more doses in orange, 2 doses or more in light blue, and 3 or more vaccine doses in dark blue. Panel B shows the cumulative deaths per 100,000 population for the same age groups and vaccination status. The line for 2 or more vaccine doses is shown dashed to allow proper visualization of all lines plotted. Cumulative deaths were calculated on a monthly basis as the ratio of deaths and the population having received said number of COVID-19 vaccine doses. Data corresponds to the year 2022. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

datasets and all the code used to load, clean, merge, analyze, and create tables and plots from said datasets have been made publicly available in a Github repository at: https://github.com/rquiroga7/The-Impact-of-COVID-19-Childhood-and-Adolescent-Vaccination-on-Mortality-in-Argentina.

3. Results

3.1. COVID-19 incidence and lethality in children and adolescents in the four pandemic waves observed in Argentina

There were four COVID-19 waves in Argentina from 2020 to 2022. For the first wave, before March 2021, there is limited information on dominant variants. From this month to October 2021, the Gamma and Lambda variants were the most frequently observed variants during the second wave. The original Omicron variant (BA.1) dominated until April 2022 during the third wave. Then, we identify a fourth wave during the dominance of the BA.4/BA.5 variants (June–November 2022). Each of the observed upsurge in cases was synchronously linked to the dominance of new SARS-CoV-2 variants.

Between March 1, 2020, and December 31, 2022, there were 779,851 COVID-19 cases reported for the 0–17 year old age group in Argentina. Amongst the 0–2, 3–11 and 12–17 age groups, the cumulative reported infections were higher for the 12–17 group (427,717, which represents 54.8 % of the total reported infections for the 0–17 age group). The relatively higher incidence of infections in this age group could be partly due to higher testing and reporting probability than for younger children.

The month with the highest number of pediatric cases (189,617 cases, 24.3 %) occurred with the arrival of the Omicron (BA.1*) variant in January 2022. The reduced coverage for 2nd and booster doses, the beginning of on-site schooling, and the loosening of social distancing restrictions may have contributed to this surge. Since January 2022, there has been a reduction in cases reported for these age groups.

Fig. 1 shows that 383 children and adolescents died of COVID-19 in Argentina from the start of the pandemic to December 31st, 2022. Among the deceased, 147 (38.3 %) were in the 0–2 age group, 102 (26.6 %) in the 3–11 age group and 134 (35.0 %) in the 12–17 age group. In all three age groups, the majority of deaths occurred before vaccines were available. Specifically, 65.9 % of 12–17 year olds, 63.7 % of 3–11 year olds and 98.6 % of 0–2 year olds died due to COVID-before vaccines were available to each age group.

Fig. 1 shows that the number of deaths in the 0–2 age group persisted over the entire study period, ranging from the lockdown phase to the partial lockdown, and the final phase following the lifting of NPIs. Even though there were proportionately fewer cases reported in this age group relative to children aged 3–17, it is important to point out that the 0–2 age group, which accounted for 38.3 % of the total pediatric deaths, did not have access to vaccination until August 2022 and after this period, vaccine uptake rates were low. Furthermore, the youngest children could not easily access and effectively use facemasks. Earlier studies have shown that 0–2 pediatric deaths were closely related to the contagion of the family group during the first wave in Argentina [18].

Once pediatric vaccination commenced in children aged 3–17, considerable reductions in recorded cases and deaths are observed in Fig. 1, except for a peak during the arrival of Omicron. The peak coincided with the return to on-site schooling in the context of limited mitigation measures throughout Argentina's territory. The decrease in cases and deaths observed in the periods of dominance of the BA.2 and BA.4/BA.5 variants should be considered in the context of possible underreporting of both variables since this period coincided with the onset of restrictive access to testing due to the change in the epidemiological surveillance strategy. However, it should also be added that high percentages of the 3–11 and 12–17 age groups had received 2 or more vaccine doses at the time of the arrival of BA.2 (see Fig. 2).

3.2. COVID-19 vaccination coverage

For the first two doses, the uptake for the pediatric vaccination campaign in Argentina was relatively high, reaching 79 % for adolescents and 72 % for children between 3 and 11 years old by the end of December 2022 (see Table 1). However, only 1 % of children between 6 months and 2 years had received a two-dose regimen. Furthermore, only 3 % of this age group received a single COVID-19 dose by the end of December 2022.

Booster uptake has been low for all age groups. Among children and adolescents, there has been more progress in ensuring booster coverage for adolescents since these were authorized earlier (February 2022). However, by the end of December 2022, only 36 % of Argentines 12–17 years old had received at least three doses. For those between the ages of 3 and 11, only 14 % had received a booster.

3.3. COVID-19 deaths and vaccination status

Table 2 reports the number of reported COVID-19 deaths in 2020–2022 with information on the vaccination status of the deceased. The analysis of annual registered COVID-19 deaths in Argentina by age group and vaccination status (considering those who have received 2 or more doses as vaccinated) shows that, in the 0–2 years age group, there were 147 deaths: 49 deceased in 2020, 51 in 2021 and 47 in 2022. None of the children who perished were vaccinated, and only 1 % of the population in this age group had received 2 or more vaccine doses by the end of 2022.

In the 3–11-year age group, there were 22 deaths in 2020 (a year in which school-age children were highly shielded from exposure by NPIs and remote schooling), 46 deaths in 2021, 9 deaths in vaccinated children and 25 in unvaccinated children in 2022, with 72 % of the population in this age group having received at least 2 vaccine doses by the end of 2022. In the 12–17 year age group, there were 29 deaths in 2020, 69 deaths in 2021, 9 deaths in vaccinated children and 27 deaths in unvaccinated children in 2022. In this age group, 79 % had received two doses by the end of 2022. For 2022, our findings show a decrease in the annual deaths for the two age groups with high vaccine coverage, while the number of deaths remained similar for the low vaccine coverage age group of 0–2 year olds. However, these absolute figures must be interpreted with care since, as shown in Table 1, the vaccinated population for the 3–11 and 12–17 year old age groups far exceeded the unvaccinated population. The number of vaccinated children changed dynamically throughout 2021 and 2022, as shown in panel A of Fig. 2 and in Supplementary Fig. 1A, 1B, and 1C. Panel A of Fig. 2 illustrates the proportion of the vaccinated population by 2022, disaggregated by age group. A rise in vaccinated populations was observed until April-May for the 3–11 and 12–17 age groups, which coincides with the beginning of the booster dose campaign. The figure shows that a plateau is reached for populations with 1+ and 2+ doses in both age groups, 89 % and 72 % for the 3–11 year-old group and 90 % and 79 % for the 12–17 year-old group. Regarding the 0–2 year-old group, the vaccination rollout commenced in July 2022. By the end of the year, the proportion of the population in this age group with at least one vaccine dose had reached only 3 %.

Panel B of Fig. 2 presents the cumulative mortality rate in 2022 for both vaccinated and unvaccinated population segments, stratified by

Table 1
Vaccination coverage by number of doses and age group in Argentina. For each age group, the percentage of the population receiving 1, 2, 3 or more vaccine doses is shown as of the 31st of December 2022.

Age Group (years)	0 dose	1+ doses	2+ doses	3+ doses	Population
0–2 years old	97 %	3 %	1 %	0 %	1,503,039
3–11 years old	11 %	89 %	72 %	14 %	6,162,373
12–17 years old	10 %	90 %	79 %	36 %	4,360,513

Table 2
Annual reported COVID-19 deaths by age group and vaccination status. For each year, reported COVID-19 deaths are shown for each age group. Vaccination status was considered unvaccinated for those who had received zero or one dose and vaccinated for those who had received two or more doses. Asterisks denote that for vaccinated deaths, it should be taken into account that pediatric vaccination in Argentina began in the year 2021 for the 0–2 and 3–11 age groups, and 2022 for the 0–2 year old age group (see Fig. 1 and Supplementary Fig. 1A, 1B and 1C). Additionally, vaccine uptake was very low for the 0–2 year old age group, as shown in Table 1 and Supplementary Fig. 1A.

Year	0–2 years old		3–11 years old		12–17 years old	
	Non-Vaccinated Deaths	Vaccinated Deaths	Non-Vaccinated Deaths	Vaccinated Deaths	Non-Vaccinated Deaths	Vaccinated Deaths
2020	49	0*	22	0*	29	0*
2021	51	0*	46	0*	69	0*
2022	47	0*	25	9	27	9

age group. No deaths were recorded for vaccinated 0–2 year olds. Therefore, we only calculated the cumulative death rates for the non-vaccinated population for this age group. The cumulative COVID-19 death rates for the non-vaccinated population in each age group increased at similar rates throughout 2022, with an annual cumulative rate of 3.16 deaths per 100 thousand for 0–2 year olds, 3.53 deaths per 100 thousand for 3–11 year olds and 4.21 deaths per 100 thousand for 12–17 year olds. In comparison to non-vaccinated populations, we observe a reduction in cumulative death rates for both the 3–11 and 12–17 year old age groups when 1 or more vaccine doses were received. The reduction was approximately 15-fold for 3–11 year olds and 8-fold for 12–17 year olds. We observe a greater reduction in cumulative death rates for populations with 2 or more doses received, with an approximate 18-fold reduction for 3–11 year olds and a 16-fold reduction for 12–17 year olds.

3.4. COVID-19 deaths in comparison to pediatric mortality of COVID-19 and other diseases

To put the mortality of COVID-19 into context, we used cause-of-death mortality data to calculate the annual pediatric deaths for viral hepatitis, varicella, and meningococcal disease, three diseases incorporated into the Argentina national vaccination calendar with mandatory vaccination. Annual pediatric deaths before mass vaccination for these diseases were lower (3.50 for Hepatitis A, 0.20 for Hepatitis B, 13.38 for Meningococcus and 12.45 for Varicella) than the annual deaths caused by COVID-19 in 2020–2022 in Argentina (104.00) (see Table 3). These results agree with findings reported in the U.S. [10]. We also compared the mortality ranking of different infectious and respiratory diseases for the 0–14 year old age group in Argentina between 2015 and 2022, which are shown in Supplementary Tables 1 and 2. Supplementary Fig. 3 shows that COVID-19 became the leading cause of death for the 0–14 year old age group in 2021. In 2022, with high COVID-19 pediatric vaccination coverage in children older than 3, influenza and pneumonia again became the leading cause of death, while COVID-19 dropped to third place.

Table 3
Annual pediatric mortality from COVID-19 and other diseases before and after instituting vaccination. Average annual mortality for each cause is analyzed for years before (this period includes the year each vaccine was introduced) and after these vaccines were introduced into the national vaccination calendar. Note: As detailed in this study, pediatric vaccination for COVID-19 was approved between 2021 and 2022 for different childhood age groups, although, unlike the other vaccines, COVID-19 vaccination is not mandatory for children and adolescents in Argentina. Age groups differ from those analyzed in Figs. 1 and 2 because of how publicly available annual mortality data are tabulated and grouped in the different databases used.

	Disease	Pre-vaccine period	Annual pre-vaccine deaths	Post-vaccine period	Annual post-vaccine deaths
1	Hepatitis A	2005–2006	3.50	2007–2022	0.12
2	Hepatitis B	2005–2009	0.20	2010–2022	0.15
3	Meningococcus	2005–2017	13.38	2018–2022	2.60
4	Varicella	2005–2015	12.45	2016–2022	3.29
5	Covid	2020–2022	104.00	–	–

3.5. Reported comorbidities

Amongst the reported COVID-19 deaths in the 0–17 year old age group, sixteen comorbidities are listed, including asthma, cardiac and renal immunodeficiency, chronic hepatitis, AHT, dialysis, COPD, prematurity, underweight, obesity, previous pneumonia, and bronchiolitis (see Supplementary Table 7). In 17.7 % of deaths, more than one comorbidity was reported. In 2020–2022, there were 383 total COVID-19 deaths in children and adolescents. No comorbidities were reported for 164 (43 %) deaths. Of these 164 deaths, information on comorbidities was absent in 139 cases, and 25 cases were confirmed as having no comorbidities.

4. Discussion

This study evaluated the combined effects of vaccinations and NPIs on reducing child and adolescent COVID-19 mortality in Argentina. Argentina had relatively low infant mortality rates before the COVID-19 pandemic (11th lowest amongst upper middle-income countries, according to WHO). One of the main strengths of this study is evidence showing that children who have not received immunization against SARS-CoV-2 are at increased risk of COVID-19-related death. Since the introduction of the COVID-19 vaccines, the World Health Organization (WHO) has asserted that “healthy children and adolescents aged 6 months–17 years” are “low-priority groups” for immunization [19]. By contextualizing mortality rates using the vaccination status of children who died from COVID-19 and other vaccine-preventable diseases, we present evidence showing why children and adolescents should be given high priority in COVID-19 immunization campaigns.

Our findings underscore that efforts to advance pediatric COVID-19 vaccine coverage are waning, even in countries with successful COVID-19 vaccination campaigns directed at children and adolescents, such as Argentina. Including COVID-19 vaccines in routine vaccination programs could decrease pediatric mortality, since we show that vaccinated pediatric populations display 8–18-fold reduced death rates when compared to non-vaccinated populations.

In contexts of sustained SARS-CoV-2 transmission and circulation, there are risk conditions for the vulnerable child and adolescent population. In addition to the mortality risk reported in this study, recent studies have shown that the COVID-19 pandemic has left a considerable proportion of the population experiencing long-term symptoms. Such sequelae can occur in children who have been infected, even asymptomatically. Studies, including a recent study conducted in Argentina, show that up to 30 % of children with COVID-19 have persistent symptoms for more than three months after the initial illness [2–4,20].

Our study also highlights some of the important challenges that must be addressed by governments in enacting immunization campaigns to protect children from COVID-19. Data shows that vaccination coverage varies considerably across provinces in Argentina (Supplementary

Fig. 2A, 2B and 2C). Vaccination coverage rates are lowest in provinces such as Chaco, Misiones, Chubut and Salta. Meanwhile, Formosa, La Rioja, Corrientes, Santiago del Estero, Jujuy and Catamarca are amongst the provinces with the highest vaccination coverage, whilst also being provinces with high poverty levels. Further research is needed to investigate this complex social phenomenon. A successful COVID-19 vaccination program should increase vaccine coverage to reduce mortality in the pediatric population.

To the best of our knowledge, this study is also the first to show that even for countries with low infant mortality rates, the mortality burden of COVID-19 for children under 3 years of age could continue to be high if no universal childhood vaccination program is implemented, especially when compared to pre-vaccination historical mortality for other vaccine-preventable diseases. In the last 20 years, Argentina has become an exemplary leader in childhood vaccination, requiring children to be protected from more than sixteen diseases, including tuberculosis, diphtheria, tetanus, pertussis, polio, hepatitis B, pneumococcal disease, measles, mumps and rubella. Mandatory childhood vaccination was a vital policy intervention for some of these diseases in Argentina. The evidence suggests that large reductions in pediatric deaths were observed following mass vaccination campaigns [21].

The evidence presented in this study for Argentina supports research reported for other countries. Plotkin and Levy (1) underscore that child immunization is central to effectively reducing the spread of COVID-19. They cite the success of the rubella vaccine as an example of why the protection of children is key to epidemic containment. These authors concluded that:

> "*By decreasing virus circulation in children, pediatric immunization may be our best hope to control COVID-19 and to return to normal social, educational, and economic activity. SARS-CoV-2 strain changes portend a need for continuous large-scale vaccination with updated vaccines, further underscoring the potential importance of pediatric immunization campaigns*." [1]

Universal childhood vaccination against COVID-19 could reduce the deaths of both children with comorbidities and healthy children. Between March 2020 and December 2022, 43 % of the deceased between 0 and 17 years of age had no recorded comorbidities. As has been pointed out: "No matter how low the mortality rate associated with COVID-19 in children and adolescents may be, mothers have lost their children during these politically motivated delays and interruptions in the vaccination campaign" [22]. In other words, SARS-CoV-2 immunization is an important public health policy and is especially justified considering the principle of a child's health rights as declared in Article 24 of the Convention of the Rights of the Child. Furthermore, the failure to implement successful childhood vaccination campaigns against COVID-19 could result in a form of childism, an institutional prejudice and systemic injustice against children [23–25].

There are some important limitations to this study. The number of pediatric COVID-19-related deaths may be underrepresented, especially since April 2022. Since the Ministry of Health adopted changes in the epidemiological surveillance strategy for SARS-CoV-2, post-mortem testing was limited to cases presenting with severe respiratory distress. Furthermore, this change in surveillance strategy also resulted in fewer confirmed cases in the second period, associated with its lower ascertainment rate. Another limitation concerns the inability to evaluate how the return to on-site schooling and the abandonment of mandated facemasks affected the impact of COVID-19. Since Argentina is a federal country, each subnational government had autonomy in deciding when NPIs would begin and end. Thus, although most schools across the country opened on on-site education sometime in 2021, the effect of the gradual reopening of schools for different educational levels across provinces could not be easily identified or evaluated. This relative autonomy of subnational governments regarding testing protocols and reporting may also result in heterogeneous ascertainment rates for pediatric COVID-19 cases and mortality amongst different provinces. A further limitation, which is not specific to Argentina, is that there is a reduced number of cases and deaths that are reported for those in the age 0–2 age group. Based on registered deaths, the data suggest that this was the only age group with no reduction in COVID-19 mortality between 2021 and 2022. However, given the limited available data, a more detailed analysis of COVID-19 mortality in this age group could not be undertaken.

Finally, this study has discussed the linkages between SARS-CoV-2 infection, vaccination and mortality in children. Further studies are needed to understand the impacts of SARS-CoV-2 infection on the health of children and adolescents, including on their hospitalization, a marker of severe illness. There is research that suggests that children who develop COVID-19 are also more likely to develop other serious health conditions, such as streptococcal tonsillitis, autoimmune disease, and cardiovascular disease [26,27]. A study of nearly 800,000 children under 18 found that those with COVID-19 were more likely to develop blood clots, heart problems, diabetes, and kidney failure [28]. Children with autoimmune disorders were also more likely to have adverse outcomes [29]. Furthermore, emerging evidence suggests that SARS-CoV-2, the virus that causes COVID-19, can have lasting effects on nearly every organ system of the body for weeks, months, and possibly years after infection [30].

5. Conclusions

A significant decrease in COVID-19-related deaths was observed in 2022 for pediatric age groups (3–11 and 12–17) with high vaccination coverage, while no decrease was observed for the 0–2 year old age group, which had low vaccination coverage. For the year 2022, when compared to non-vaccinated populations, cumulative COVID-19 death rates for vaccinated populations were 8–18-fold lower. Furthermore, we find COVID-19 mortality was higher than pre-vaccination periods for other diseases for which vaccination is already compulsory in many countries. Consequently, our results suggest that public health policies which do not recommend universal COVID-19 immunization for children 6 months and older should be reviewed.

Ethical approval

As this study uses anonymized and aggregated data outside of clinical settings, approval from a human subjects committee was not required.

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CRediT authorship contribution statement

Rodrigo Quiroga: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Sofía Gastellu:** Conceptualization, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Braian Fernández:** Conceptualization, Data Curation, Formal Analysis, Investigation, Resources, Validation. **Romina Ottaviani:** Data Curation, Software, Validation, Visualization, Writing – review & editing. **Johanna Romina Zuccoli:** Conceptualization, Writing – review & editing. **Pablo Daniel Vallecorsa:** Conceptualization, Writing – review & editing. **Jorge Aliaga:** Data Curation, Resources, Validation, Writing – review & editing. **Lorena Barberia:** Conceptualization, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

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.

Data availability

For raw data and the code necessary to replicate the figures and tables, please see: https://github.com/rquiroga7/The-Impact-of-COVID-19-Childhood-and-Adolescent-Vaccination-on-Mortality-in-Argentina.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.06.005.

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