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Abstract

Background: The burden of COVID-19 in the paediatric population in low- and middle-income countries is not well characterized. Understanding COVID-19 burden in Latin American (LATAM) countries is essential for implementing effective vaccination policies and strategies for children and adolescents. We aimed to describe the characteristics of COVID-19-confirmed cases, addressing the risk of disease,severity and outcomes of the disease in children and adolescents in four LATAM countries between 2021 and 2022.

Methods: We conducted a retrospective observational study utilizing national surveillance data from the four most populated countries in LATAM, Argentina, Brazil, Colombia, and Mexico, focusing on laboratory-confirmed COVID-19 cases among children and adolescents under 18 years of age between January 2021 and December 2022. We described sociodemographic characteristics of cases by age. Incidence rates per 100,000 inhabitants for confirmed COVID-19 cases were calculated. We estimated hospitalisation and mortality rates (per 100,000 inhabitants) as well as ICU admission and ventilatory support rates (per 100,000 hospitalised cases) per quartile each year, considering the predominant SARS-CoV-2 variant in each country during the specified period.

Results: In total 2,863,244 confirmed paediatric COVID-19 cases were included in the analysis: 1,553,234 (54%) from Brazil, 487,247 (17%) from Argentina, 430,131 (15%) from Colombia, and 392,632 (13%) from Mexico. Among confirmed cases, 66,029 (2%) required hospitalisation, and 3,058 (0.1%) died. Meanwhile, 16,941

(1%) cases utilised ventilatory support, and 9,997 (0.4%) were admitted to the ICU (data not available from Colombia). Regarding the risk of disease, rates of confirmed COVID-19 per 100,000 inhabitants were higher in cases aged 12-17 years (peaked at 1,856 per 100,000 inhabitants), whereas the risk of severe outcomes among cases were higher in children under 2 years (peaked at 170.22 and 7.36 per 100,000 inhabitants, respectively for hospitalisation and death). Rates of all study outcomes were higher in unvaccinated cases in Colombia and Brazil.

Conclusions: Our findings demonstrate that COVID-19 imposes a substantial burden among children and adolescents aged 0 to 17 years in LATAM countries, associated with significant rates of hospitalizations and deaths, particularly in children under 2 years of age. This situation underscores the necessity of adopting targeted vaccination strategies that address the specific needs of the region.

Keywords: Paediatric; COVID-19; Latin America; COVID-19 vaccines; Severe outcomes; Surveillance data

Background

Coronavirus disease 2019 (COVID-19) has impacted the health and well-being of children and adolescents worldwide (1). Although COVID-19 generally has a milder presentation in the paediatric population, severe outcomes, including hospitalisation and death, can still occur, especially among those with underlying health conditions (2, 3). In addition to the acute effects of infection, postinfectious conditions, such as multisystem inflammatory syndrome in children (MIS-C) and long COVID have important health implications (4). Beyond the health impacts, public health measures that were implemented in many countries, including lockdowns, mobility restrictions, and suspension of childcare and education services, also affected their well-being (1). These factors contributed to the implementation of COVID-19 vaccination strategies for the paediatric population in many countries.

Strategies implemented for COVID-19 vaccination in the paediatric population were heterogeneous across countries, especially regarding the vaccine platforms used and the age groups prioritised (5, 6). Even though COVID-19 vaccines have been proven to be safe and effective in both clinical trials and real-world studies (7-9), their implementation has faced challenges, especially in the paediatric population, where vaccine hesitancy has been more common. Factors affecting vaccination

uptake among children included parental concerns about adverse events and the perception of less severe disease effects among children (10).

Several studies have shown that COVID-19 vaccines are effective in preventing symptomatic infection and severe outcomes such as hospitalisation, ICU admission and death (8, 11-13). Despite the availability of effective vaccines, vaccination policies and uptake have varied significantly worldwide. Latin America faced pre-existing vulnerabilities intensified during the pandemic. This, combined with policies excluding younger children from vaccination strategies, may have resulted in worse outcomes in comparison with other regions. There is currently limited evidence addressing the burden of COVID-19 in children and adolescents in Latin American (LATAM) countries, especially considering the heterogenicity of vaccine platforms used, indication for primary and booster doses, and timeline for implementation. As the World Health Organization relies on each country the decision to prioritise and implement COVID-19 vaccines for children, it is imperative to understand the particularities of the COVID-19 disease burden in the four most populated LATAM countries. Thus, this study aimed to describe the characteristics and disease burden of COVID-19-confirmed cases under 18 years old in Argentina, Brazil, Colombia, and Mexico between 2021 and 2022. We estimated the rates of infection, hospitalisation, ICU admission, use of ventilatory support, and death, while considering the vaccination policies implemented for the paediatric population in each country.

Methods

Study design and participants

We conducted a retrospective study using the COVID-19 national surveillance databases of Argentina, Brazil, Colombia, and Mexico. The study included all

laboratory-confirmed COVID-19 cases, based on Reverse Transcription Polymerase Chain Reaction (RT-PCR) or antigenic test results, under 18 years old that were reported between January 2021 and December 2022.

Setting

During the study period, COVID-19 vaccination policies for the paediatric population and the circulating SARS-CoV-2 variants varied across different countries (14) (Figure 1). In Argentina and Colombia, vaccination was initiated in 2021 for adolescents aged 12-17 years and later expanded to include those aged 3-11 years (15-18). In Brazil, vaccination was implemented in children over 5 years old in 2021 (19). In 2022, vaccination expanded to children over 3 years old in Q3 and to children over 6 months old in Q4 (20, 21). Conversely, in Mexico, only children who were at least 5 years old received vaccination between 2021 and 2022 (19), with vaccine implementation for children ≥ 5 years old starting later than in the other countries, beginning in 2022 (22).

Data sources

We retrieved case-level data from de-identified, publicly available national surveillance databases from each country (23). Data were retrieved between January 2021 and December 2022 from all countries except Argentina (data available up to June 2022). We collected data on hospitalisation in the general ward, ICU admission, ventilatory support, and death in all countries. However, in Colombia, data on ICU admission and ventilatory support were not available. Other variables collected included age, sex, comorbidities, race, and vaccination status. Information about reported comorbidities varied across countries. Definitions of variables contained in each database and their availability are presented in Supplementary File 1.

For Argentina, we used the COVID-19 surveillance dataset, which compiles notifications made by healthcare providers to the National Health Surveillance System (24). This dataset includes information at the patient level on all confirmed COVID-19 cases, which are of compulsory notification in the country (25, 26). For Brazil, we obtained data from the Open DATASUS platform, which contains information about the procedures performed in the public healthcare system (27). About 71.5% of the Brazilian population, representing more than 150 million people, relies on the Unified Health System (SUS) for medical care. We used two databases within this platform: the Flu syndrome notifications database (*Sistema de Informação de Vigilância Sentinela de Sindrome Gripal, eSUS-Notifica* SG), in which cases with mild to moderate acute respiratory syndrome are notified, and the Influenza Epidemiological Surveillance Information System (*Sistema de Informação de Vigilância Epidemiológica da Gripe*, SIVEP-Flu), in which cases with severe acute respiratory syndrome are notified.

For Colombia, we used information from the COVID module in the Information System for Social Protection (*Sistema de Información para la Protección Social*, SISPRO) database, which covered approximately 99% of the Colombian population in 2021 (28). The COVID module contains patient-level information on confirmed COVID-19 cases reported by healthcare institutions and links data related to mortality and vaccination status. In Mexico, we retrieved the dataset from the Epidemiological Surveillance System for Viral Respiratory Diseases, which is responsible for consolidating COVID-19 patient-level data, receiving reports from the Viral Respiratory Disease Monitor Health Units in both the public and private health sectors (29).

Statistical methods

The databases of each country were analysed independently, without any data linking. We described the sociodemographic characteristics of the participants, presenting absolute counts and percentages for qualitative variables. For quantitative variables, we reported medians or means along with standard deviations and interquartile ranges, based on distribution. Age groups were categorised into the following groups: <2 years, 2-4 years, 5-11 years, and 12-17 years.

Rates of confirmed COVID-19 cases per 100,000 inhabitants were calculated based on the number of inhabitants reported in each country's demographic institute per year, considering age and sex. We calculated quarterly hospitalisation and mortality rates per 100,000 inhabitants, and rates of ICU admission and ventilatory support per 100,000 hospitalised cases each year. Ninety-five percent confidence intervals (95% CI) for rates were estimated. Categorical variables were compared using chi-square (χ^2) tests to assess associations between patient characteristics and study outcomes (hospitalisation, ICU admission, ventilatory support, and death). All statistical analyses were conducted using Python, version 3.8.10 (30).

Ethics statement

The study adhered to the protocol and ethical principles of the Declaration of Helsinki. According to local regulations, no ethics committee notification or approval or patient consent was required, as deidentified data from publicly available databases were utilized in alignment with local data privacy regulations. The results were presented in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (31) and the REporting

of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) statement (32).

Results

Overall, during the study period, 2,863,244 confirmed COVID-19 cases aged under 18 years were included in the analysis: 1,553,234 (54%) from Brazil, 487,247 (17%) from Argentina, 430,131 (15%) from Colombia, and 392,632 (13%) from Mexico (Supplementary Table 1). Among all confirmed cases, 66,029 (2%) required hospitalisation, and 3,058 (0.1%) died. Among those who required hospitalization, 34,215 (52%) were from Brazil, 15,665 (24%) from Mexico, 11,593 (18%) from Colombia, and 4,556 (7%) from Argentina (Table 1). Considering cases that died, 1,962 (64%) were from Brazil, 867 (28%) from Mexico, 254 (8%) from Colombia and 229 (7%) from Argentina (Supplementary Table 6). Including hospitalized cases from all countries except Colombia, 16,941 (26%) utilized ventilatory support, and 9,997 (15%) were admitted to the ICU (Table 3). Including all countries, most confirmed-COVID-19 cases were aged 12 to 17 years (47%), and 50% were female.

The highest proportion of confirmed cases, hospitalizations, and deaths, in Brazil and Colombia, occurred in those not vaccinated (Figure 2). Among confirmed cases from Brazil and Colombia, 70% were not vaccinated, 9% received one dose, and 20% received two vaccine doses, and among hospitalized cases, 87% were not vaccinated, 5% received one dose, and 8% two doses (Supplementary Table 1). Individual data on vaccination was not available in Mexico and Argentina. In Argentina, by Q3 of 2021, the mRNA-1273 vaccine was introduced for adolescents aged 12-17 years, and by Q4 of 2021 (15), the BBIBP-CorV vaccine was implemented for children aged 3-11 years (18). In Colombia, by Q3 2021, vaccine implementation started with the

BNT162b2 vaccine in adolescents aged 12-17 years (16), and by Q4 2021, the CoronaVac vaccine was used in children aged 3-11 years (17). In Brazil, by Q3 2021, adolescents aged 12 or older received the BNT162b2 vaccine or the CoronaVac vaccine and in Q4 the same vaccines were implemented in children aged 5-11 years (19). In 2022, in Brazil, the CoronaVac vaccine was introduced for children aged 3-5 years in Q3 (21). Additionally, in Q4 In Mexico, by Q3 2021, vaccination was approved for adolescents aged 12-17 years with the BNT162b2 vaccine, and by Q3 2022, it was extended to children aged 5 years or older (22).

Hospitalisation

In all countries, most hospitalised cases were male, ranging from 52% in Argentina to 59% in Colombia (Supplementary Table 2). In Brazil, Colombia, and Mexico, the highest proportion of hospitalised cases were aged under 2 years (46% in Brazil, 51% in Colombia and 31% in Mexico), whereas in Argentina, the highest proportion of hospitalised cases were aged 5 to 11 years (36%). Most hospitalised cases were unvaccinated (90% in Brazil and 77% in Colombia).

In 2021, the highest hospitalisation rates per 100,000 inhabitants were observed in children aged under 2 years in all countries, ranging from 43.10 (95% CI: 41.12 to 45.08) in Mexico to 170.22 (95% CI: 163.55 to 176.89) in Colombia (Table 2). In 2022, the highest hospitalization rates per 100,000 inhabitants were also observed in children aged under 2 years in all countries, except Argentina, where the age group between 2 and 4 years was responsible for the highest rates (rate: 23.06, 95% CI: 20.88 to 25.25)

ICU admission and ventilatory support

In Mexico and Brazil, most cases admitted to the ICU and those utilizing ventilatory support were under 2 years (ranging between 47-48% and 44-47%, respectively), whereas in Argentina, they were aged 5 to 11 years (33% and 30%, respectively) (Supplementary Tables 3 and 4). In all countries, most cases admitted to the ICU and those utilizing ventilatory support were male.

The proportion of hospitalised cases admitted to the ICU ranged from 6% in Mexico to 25% in Brazil (Table 3). Among hospitalised cases under 2 years old, 7.36% were admitted to the ICU Mexico, 11,81% in Argentina and 25% in Brazil. The percentage of hospitalized cases of indigenous ethnicity requiring ICU admission in Mexico was 26.09%, compared to 7.44% for other ethnicities. In 2021, in Mexico and Argentina, the rate of ICU admission was highest in children under 2 years: 10921 (95% CI: 10,813 to 11,029) per 100,000 hospitalised cases in Mexico and 12345 (95% CI: 12,043 to 12,648) per 100,000 hospitalised cases in Argentina (Supplementary Table 5). In 2022, the rate of ICU admission continued to be the highest in under 2 years in Mexico (7,884 [95% CI: 7,818 to 7,951] per 100,000 hospitalised cases), whereas in Argentina it was highest in 2 to 4 years (12,149 [95% CI: 11,691 to 12,607] per 100,000 hospitalised cases). In Brazil, it was the highest in those aged 12 to 17 years in both 2021 and 2022 (28,927 [95% CI: 27,488 to 30,366] and 23898 [95% CI: 21,995 to 25,801] per 100,000 hospitalised cases, respectively).

Regarding ventilatory support, 4.3% and 5% of hospitalized patients needed mechanical ventilation in Argentina and Mexico, respectively (Table 3). In Brazil, 46.7% of hospitalized patients required ventilation, including both invasive and non-invasive methods. Among hospitalized cases under 2 years old, 4.51% in Argentina, 6.8% in Mexico, and 47.78% in Brazil needed ventilation. Furthermore, in Brazil, 47.45% of unvaccinated hospitalized cases needed ventilation. In Mexico, 11.24% of

hospitalized cases of Indigenous ethnicity required ventilatory support, while "other" ethnicities registered only 4.65%. In 2021, for Argentina and Brazil, the rates of utilization of ventilatory support were the highest among hospitalised cases aged between 12 and 17 years (5585.11 [95% CI: 5324.47 to 5845.74] and 54130.61 [95% CI: 52549.00 to 55712.21], respectively). For Mexico, instead, the highest rate was found in those aged below 2 years (8218.42 [95% CI: 8110.31 to 8326.53]). In 2022, rates of ventilatory support utilisation were highest among hospitalised cases aged under 2 years in all countries during the study period (Supplementary Table 5).

Death

In all countries, a higher proportion of fatal cases were male (ranging from 51% in Argentina to 56% in Colombia), except in Mexico, where the proportion of fatal cases according to sex was equal (Supplementary Table 6). Among fatal cases in Brazil and Colombia, the highest proportion of fatal cases occurred in individuals aged under 2 years (43% and 38%, respectively), while in Argentina and Mexico, the highest proportion were aged 12 to 17 years (34% and 36%, respectively).

Mortality rates per 100,000 inhabitants in 2021 were the highest in children aged under 2 years, with Brazil being the country with the highest rate (rate: 7.36, 95% CI: 6.66 to 8.05). In 2022, the mortality rates per 100,000 inhabitants were also the highest in children aged under 2 years in all countries, except Argentina, where it was the highest in children aged between 2 and 4 years (rate: 1.02, 95% CI: 0.56-1.48) (Table 4).

Comorbidities

Considering only the comorbidities recorded in the databases analysed for each country, the proportion of hospitalized cases reporting comorbidities was 18.8% in Brazil, 2.6% in Colombia, and 20.7% in Mexico for all paediatric cases, and 11.4% in Brazil, 1.2% in Colombia and 11.6% in Mexico for cases under 2 years. In Colombia, rare diseases were present in 78% of hospitalized cases, followed by cancer, reported in 11% of hospitalized cases. In Mexico, the comorbidities recorded included immunosuppression, reported in 21% of hospitalized cases, obesity in 12%, and asthma in 10%. Brazil reported decompensated chronic respiratory diseases in 18% of cases and hepatic diseases in 17% (Supplementary Table 7). It is important to note that patients may have other comorbidities that were not recorded in these databases.

Regarding mortality, in Colombia, 66% of deceased cases with at least one surveyed comorbidity had rare diseases, and 13% had hypertension. In Brazil, the deceased cases frequently had chronic respiratory diseases (47%) and diabetes (36%). In Mexico, 18% of deaths were associated with immunosuppression and 14% with cardiovascular diseases.

Trends considering vaccination policies and SARS-CoV-2 variants

During the pre-Omicron period, in all countries, adolescents aged 12-17 years had the highest rates of laboratory-confirmed COVID-19 cases (Supplementary Figure 1). During that period, the peak incidence per 100,000 inhabitants in this age group occurred in Q2 2021 in Argentina (1,856.7) and Colombia (1,817.4), in Q2 2021 in Brazil (782.9), and in Q3 2021 in Mexico (316.3). Following the introduction of vaccines for individuals aged 12-17 years between Q3 and Q4 of 2021, these rates declined. In Argentina, the rates of hospitalisation and death in adolescents (12-17

years) decreased between Q3 and Q4 of 2021 (20J Gamma V3 and 21J Delta variant dominated, respectively) after vaccine implementation (Figure 3). In Mexico, cases aged under 2 years, who were not included in vaccination policies, had the highest rates of all severe outcomes in both the pre-Omicron period and during the Omicron period, except for Q4 of 2022, when the rates of ventilatory support were higher in cases aged 5 -11 years (Figure 4).

During the Omicron period, the highest rates of laboratory-confirmed COVID-19 cases were observed in adolescents aged 12-17 years in all countries, except for Colombia. In Colombia, after the introduction of vaccines for this group in 2021, their rates declined, and by 2022, those aged under 2 years had the highest rate of laboratory-confirmed COVID-19. In both Colombia and Brazil, hospitalisation rates increased across all age groups in 2022, when Omicron became predominant, with those under 2 years of age experiencing the highest rates. Additionally, mortality rates increased between Q3 and Q4 of 2022 (21A, Omicron variant dominated period) for all age groups in Colombia, except for those aged between 2 and 4 years, where they decreased. The age group with the highest mortality rates in Colombia between Q2 and Q4 of 2022 (21L and 22A, Omicron variants dominated) was those aged 12 to 17 years who were vaccinated earlier in Q2 of 2021. In Brazil, mortality rates had a declining trend for all age groups in 2022 (Omicron variants dominated). However, by the Q3-Q4 of 2022, the rates increased in those aged 12-17 years. Similarly, in Argentina, mortality rates declined during Q1-Q2 of 2022 (21K and 21L, Omicron variants dominated) in all age groups.

Discussion

This study highlighted the trends in severe COVID-19 outcomes in paediatric cases within the context of vaccine implementation in four LATAM countries. Paediatric cases account for 8.2% of the total, with country-specific proportions as follows: 9.3% in Colombia, 8.7% in Brazil, 7.2% in Mexico, and 6.8% in Argentina. We identified higher rates of severe outcomes of COVID-19 in the paediatric population, compared with that reported from developed countries. This is consistent with earlier reports in the region. In Brazil, in 2020, a lethality rate of 8.2% was reported in cases of paediatric COVID-19, with 42% of deaths corresponding to children under 2 years (33). In our study, in Brazil, the rates of hospitalisation ranged between 5.60 and 13.55 per 100,000 inhabitants in 2022, when the Omicron variant predominated in the country. Whereas in developed countries, such as the United States (US), hospitalisation rates ranged from 4.5 to 28.4 per 100,000 population (34).

We identified that, although most confirmed cases were aged 12 to 17 years, overall, the highest rates of severe outcomes occurred in cases aged under 2 years, in which vaccination was not yet implemented in any of the countries during the study period. These findings agree with previous research conducted in multiple countries (35-37). For instance, in Ecuador between 2020 and 2021, adolescents aged 15 to 19 years were at the highest risk of infection, and the highest mortality rate occurred in children under one year of age (36). A study conducted in the US between 2020 and 2022 reported the highest mortality rates in children under a year old, at 4.3 per 100,000 population (37).

The rates of all severe outcomes in our study were higher in unvaccinated cases, considering the effectiveness of COVID-19 vaccines for preventing severe outcomes in children and adolescents, both in clinical trials and real-world studies (7, 38-40). In our study, there was a tendency towards a reduction in the rates of severe

outcomes among the age groups where vaccination was implemented. However, this reduction was not sustained over time. Notably after some decrease in hospitalization rates in the age of 12 to 17 years following the vaccine introduction, approximately one year later and in a different variant circulation scenario the rates increased again, potentially pointing to factors that affect effectiveness like uptake, duration of protection, need for booster doses and or updated formulations as well as non-interventional policies implemented in each country (41).

Moreover, in most countries included in our study, younger children aged under 12 years were vaccinated with inactivated virus vaccines, whereas adolescents were vaccinated with mRNA vaccines. This may lead to different outcomes across groups. Previous research has indicated variations in vaccine effectiveness according to their platform, especially those related to their effectiveness against the variants of concern. For example, studies have shown that the neutralizing antibody titre of inactivated vaccines against the Delta variant is reduced compared with that of the wild-type SARS-CoV-2 (42). Conversely, mRNA vaccines exhibit higher effectiveness against a broader range of variants, including Alpha, Beta, Gamma, and Delta variants, compared with other vaccine types (13). Moreover, there is a significant waning of vaccine effectiveness against variants of concern over time (43). However, the use of new adapted COVID-19 vaccine booster doses might improve protection against SARS-CoV-2 Omicron sublineages and is important for protection against COVID-19, especially among individuals who are at increased risk for severe illness and death (44, 45).

Overall, in our study, children under 2 years old had higher rates of all severe outcomes. In general, when an increase in viral circulation occurs, all age groups are affected; however, the burden is substantially important in the population aged

below 2 years old. Despite the availability of effective vaccines for children (11, 12, 46), these younger age groups remained at a higher risk of severe outcomes potentially because of their delayed inclusion in vaccination programmes (2). COVID-19 vaccination in younger children was delayed in most LATAM countries because policies typically prioritised older age groups and adults, who were considered at higher risk of severe disease and death at the early stage of the pandemic. Even after the implementation of vaccination for younger age groups in some LATAM countries, vaccine deployment and uptake have encountered challenges. For example, in Brazil, parental hesitancy to vaccinate children is affected by factors such as caregivers' young age, the presence of multiple children in the household, caregivers' lower educational levels, and low household income (47, 48). Moreover, factors related to lower vaccine coverage among children and adolescents in Brazil include a higher social vulnerability index and lower municipal human development index (49). Similarly, a study conducted in Canada found that parents of younger children, racialized groups, and those born outside Canada were less likely to accept vaccination (50). These same hesitancy factors have also been reported for vaccines in the childhood immunisation schedule (51).

In our study, although we observed some differences in comorbidities report terms and information, most cases experiencing severe outcomes reported at least one comorbidity, such as immunosuppression, obesity, chronic respiratory diseases, hepatic diseases, rare diseases, cancer, diabetes, and cardiovascular diseases. In children and adolescents, the presence of comorbidities could be related to a higher risk of severe and critical COVID-19, and some of the key risk factors that have been reported include cardiovascular and neurological disorders, chronic pulmonary conditions, diabetes, obesity, and immunocompromise (52-54). Moreover, as the

number of comorbidities increases, so does the risk of severe COVID-19 disease (55). Therefore, vaccination strategies including children with underlying medical conditions could substantially impact COVID-19-related hospitalisations, ICU admissions and death. Notably, the majority of hospitalized cases under 2 years of age was reported in previously healthy infants, with no comorbidities in Brazil, Colombia and Mexico, respectively, reinforcing the need for a vaccination strategy that includes all young infants.

Overall, the mortality rates among COVID-19 cases in our study were low, which is consistent with previous research from multiple countries (56-58); however, the rates of hospitalisation, ICU admission, and ventilatory support were significant. This may contribute to higher healthcare-related expenses, resulting in financial strain on healthcare systems. Previous research estimated the economic burden of paediatric COVID-19 in Argentina, identifying that the costs per case vary according to severity. In their study, the costs per case of COVID-19 requiring hospitalisation were approximately four times higher than the cost per case hospitalised for influenza or chickenpox pre-vaccination periods (59).

Considering these challenges, it is crucial to prioritise COVID-19 vaccination for younger children in countries where such vaccination has not yet been implemented and to address the barriers to vaccine uptake in countries where implementation has occurred, but coverage remains inadequate. Moreover, there is a need to tailor strategies specific to patients with higher risk profiles, such as those with comorbidities (60). This may involve the implementation of annual doses to enhance immunogenicity and provide additional protection against emerging variants (44). Tailoring vaccination strategies to the specific needs and constraints of each country can optimise outcomes and help alleviate the substantial healthcare burden in

LATAM. Finally, efforts should be made to continually monitor COVID-19 outcomes in the paediatric population as vaccination policies evolve, ensuring that interventions remain effective and responsive to emerging challenges.

Our study has some limitations. The variables documented in the databases varied by country, and the differences and potential changes in SARS-CoV-2 testing strategies among countries could have influenced the reported occurrence and outcome estimates. To mitigate this limitation, we chose to focus on severe outcomes, such as hospitalisation, ICU admission, ventilatory support, and death, which are less impacted by the variability in testing. COVID-19 outcomes are influenced by many factors, some of which are not reported within each country's database. To address this issue, we included a description of the SARS-CoV-2 variants circulating in each country and vaccination policies. Nevertheless, the variant data were not case-specific and represented a description of the context within each country rather than an exact comparison of outcomes according to variant type. Moreover, the databases did not allow identification of potential readmissions, which may have led to duplicate counts of severe cases. Furthermore, cases not seeking medical attention are not captured within the databases analysed, potentially underestimating the burden of il dot moderate disease. Despite these limitations, the present study benefits from using nationwide surveillance systems to achieve a large sample size and incorporate data from multiple countries within LATAM. This contributes to the limited epidemiological data on COVID-19 in the paediatric population of the region.

Conclusions

Children and adolescents have been affected by COVID-19, facing impacts not only on their health but also their social and educational well-being (61). This study contributes to the understanding of paediatric COVID-19 in LATAM, a region with unique challenges and opportunities. Despite the availability of effective vaccines, the burden of severe COVID-19 in paediatric patients, especially those with comorbidities and younger children, highlights the importance of implementing and enhancing preventive and prompt treatment measures.

List of abbreviations

eSUS-Notifica SG: Sistema de Informação de Vigilância Sentinela de Sindrome Gripal. Flu Syndrome Notifications Database

ICU: Intensive Care Unit

LATAM: Latin america

MIS-C: Multisystem Inflammatory Syndrome in Children

RECORD: Reporting of Studies Conducted Using Observational Routinely-Collected Health Data

RT-PCR: Reverse Transcription Polymerase Chain Reaction

RWI: Real World Insights

SISPRO: Sistema de Información para la Protección Social. Information System for Social Protection

SIVEP-Flu: Sistema de Informação de Vigilância Epidemiológica da Gripe. Influenza Epidemiological Surveillance Information System

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

WHO: World Health Organization

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

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Authors' contributions

JS, MHK, and GSJ conceived the study idea and supervised the study. JS, MHK, GSJ, MD, and DB contributed to the study protocol. DB, VG, and NC conducted the statistical analysis, data verification, visualisation, and interpretation, with

significant contributions from all team members. NC wrote the first draft of the manuscript. All authors provided critical revisions to the manuscript and approved the final version.

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Tables and Figures

Table 1. Characteristics of hospitalised COVID-19 cases by country during 2021-2022.

Characteristic	Argentina		Brazil		Colombia		Mexico		Total	
	n	%	n	%	n	%	n	%	n	%
	4556	7	34215	52%	11593	18%	15665	24%	66029	100%
Age, N (%)										
< 2 years	864	19	15608	46	5924	51	4812	31	27208	41
2-4 years	983	22	6435	19	2248	19	2789	18	12455	19
5-11 years	1657	36	6430	19	1911	16	3894	25	13892	21
12-17 years	1052	23	5742	17	1510	13	4170	27	12474	19
Sex, N (%)										
Female	2080	46	15566	45	4497	39	7050	45	29193	44
Male	2377	52	18641	54	6890	59	8615	55	36523	55
Missing	99	2	8	0	206	2	0	0	313	0
Ethnicity, N (%)										
Indigenous	-	-	249	1	115	1	267	2	631	1
Other	-	-	27477	80	11478	99	14938	95	53893	88
Missing	-	-	6489	19	0	0	460	3	6949	11
Vaccination status, N (%)										
Booster dose	-	-	319	1	-	-	-	-	319	1
2 doses	-	-	1911	6	1665	14	-	-	3576	8
1 dose	-	-	1145	3	951	8	-	-	2096	5
0 doses	-	-	30840	90	8977	77	-	-	39817	87
Missing	-	-	0	0	0	0	-	-	0	0

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717 **Table 2. Hospitalization rates in paediatric confirmed-COVID-19 cases per 100,000 inhabitants,**
718 **during 2021-2022.**

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	Argentina					Brazil					Colombia					Mexico				
	2021			2022		2021		2022			2021		2022			2021		2022		
	Rates	95% CI		Rates	95% CI	Rates	95% CI	Rates	95% CI		Rates	95% CI	Rates	95% CI		Rates	95% CI	Rates	95% CI	
Age *																				
< 2 years	66.02	60.94	71.10	21.80	18.90	24.71	106.59	103.95	109.24	160.99	157.73	164.25	170.22	163.55	176.89	258.10	249.45	266.75	43.10	41.12	45.08	70.66	68.12	73.21
2-4 years	30.18	27.67	32.69	23.06	20.88	25.25	31.90	30.72	33.08	40.79	39.46	42.12	42.81	39.97	45.64	71.16	67.39	74.92	15.90	14.91	16.88	27.98	26.67	29.29
5-11 years	15.76	14.66	16.85	17.17	16.03	18.32	15.23	14.70	15.77	16.15	15.60	16.70	22.96	21.46	24.46	27.58	25.88	29.28	9.43	8.94	9.91	15.46	14.84	16.08
12-17 years	17.58	16.32	18.84	6.95	6.16	7.73	21.07	20.41	21.74	10.79	10.31	11.27	30.67	28.76	32.57	16.09	14.70	17.47	12.81	12.21	13.41	17.65	16.94	18.36
Q**																				
Q1	4.86	4.46	5.25	13.52	12.87	14.17	9.14	8.88	9.40	13.24	12.93	13.55	11.23	10.59	11.87	29.48	28.43	30.54	1.32	1.21	1.43	11.81	11.47	12.14
Q2	10.43	9.86	11.01	1.31	1.11	1.51	9.49	9.23	9.75	8.78	8.52	9.03	20.74	19.88	21.61	10.52	9.89	11.15	1.49	1.37	1.61	3.93	3.73	4.12
Q3	5.65	5.23	6.07	-			6.28	6.07	6.49	5.81	5.60	6.01	11.22	10.59	11.86	15.69	14.92	16.46	8.57	8.29	8.86	6.23	5.98	6.48

Q4	1.73	1.49	1.96	-		5.12	4.93	5.31	6.52	6.30	6.74	6.19	5.71	6.66	6.68	6.17	7.18	3.79	3.60	3.98	2.09	1.95	2.24

95% CI: 95% Confidence Interval; Q: Quarter.
** Denominator: country population per age group for the corresponding year*
*** Denominator: country population <18 years old for the corresponding year*

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723 **Table 3. Characteristics of paediatric hospitalized COVID-19 cases that were admitted to the**
724 **ICU and required ventilatory support by country during 2021-2022.**

Characteristic	ICU admissions					
	Argentina		Brazil		Mexico	
	n	%	n	%	n	%
	457	10%	8615	25%	925	6%
Age, N (%)						
< 2 years	102	11,81%	4111	26,3%	436	7,36%
2-4 years	88	8,95%	1389	21,6%	118	5,25%
5-11 years	153	9,23%	1551	24,1%	137	7,17%
12-17 years	114	10,84%	1564	27,2%	234	15,50%
Gender, N (%)						
Female	214	10,29%	3825	24,6%	418	9,30%
Male	226	9,51%	4789	25,7%	507	7,36%
Missing	17	17,17%			0	0,00%
Ethnicity, N (%)						
Indigenous	-		58	23,3%	30	26,09%
Other	-		6743	24,5%	854	7,44%
Missing	-		1814	28,0%	41	-
N of Comorbidity*						
Mean (SD)	-		2,66 (4.62)		0,34 (0.66)	
Median (IQI)	-		0 (0;0)		0 (0;0)	
Vaccination status, N (%)						
Booster dose	-		77	24,1%	-	
2 doses	-		493	25,8%	-	
1 dose	-		279	24,4%	-	
0 doses	-		7766	25,2%	-	

Missing	-		0	0,0%	-	
Ventilatory support						
Characteristic	**Argentina**		**Brazil**		**Mexico**	
	n	**%**	**n**	**%**	**n**	**%**
	197	4,3%	15994	46,7%	750	5%
Age, N (%)						
< 2 years	39	4,51%	7457	47,78%	327	6,80%
2-4 years	41	4,17%	2837	44,09%	97	3,48%
5-11 years	60	3,62%	2932	45,60%	118	3,03%
12-17 years	57	5,42%	2768	48,21%	208	4,99%
Gender, N (%)						
Female	99	4,76%	7172	46,07%	338	4,79%
Male	94	3,95%	8819	47,31%	412	4,78%
Missing	4	4,04%			0	
Ethnicity, N (%)						
Indigenous	-		102	40,96%	30	11,24%
Other	-		12978	47,23%	695	4,65%
Missing	-		2914	44,91%	25	5,43%
N of Comorbidity*						
Mean (SD)	-		2,47		0,41	
Median (IQI)	-		0		0	
Vaccination status, N (%)						
Booster dose	-		111	34,80%	-	
2 doses	-		755	39,51%	-	
1 dose	-		495	43,23%	-	
0 doses	-		14633	47,45%	-	
Missing	-		0		-	

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735 **Table 4. Mortality rate in paediatric confirmed-COVID-19 cases per 100,000 inhabitants.**

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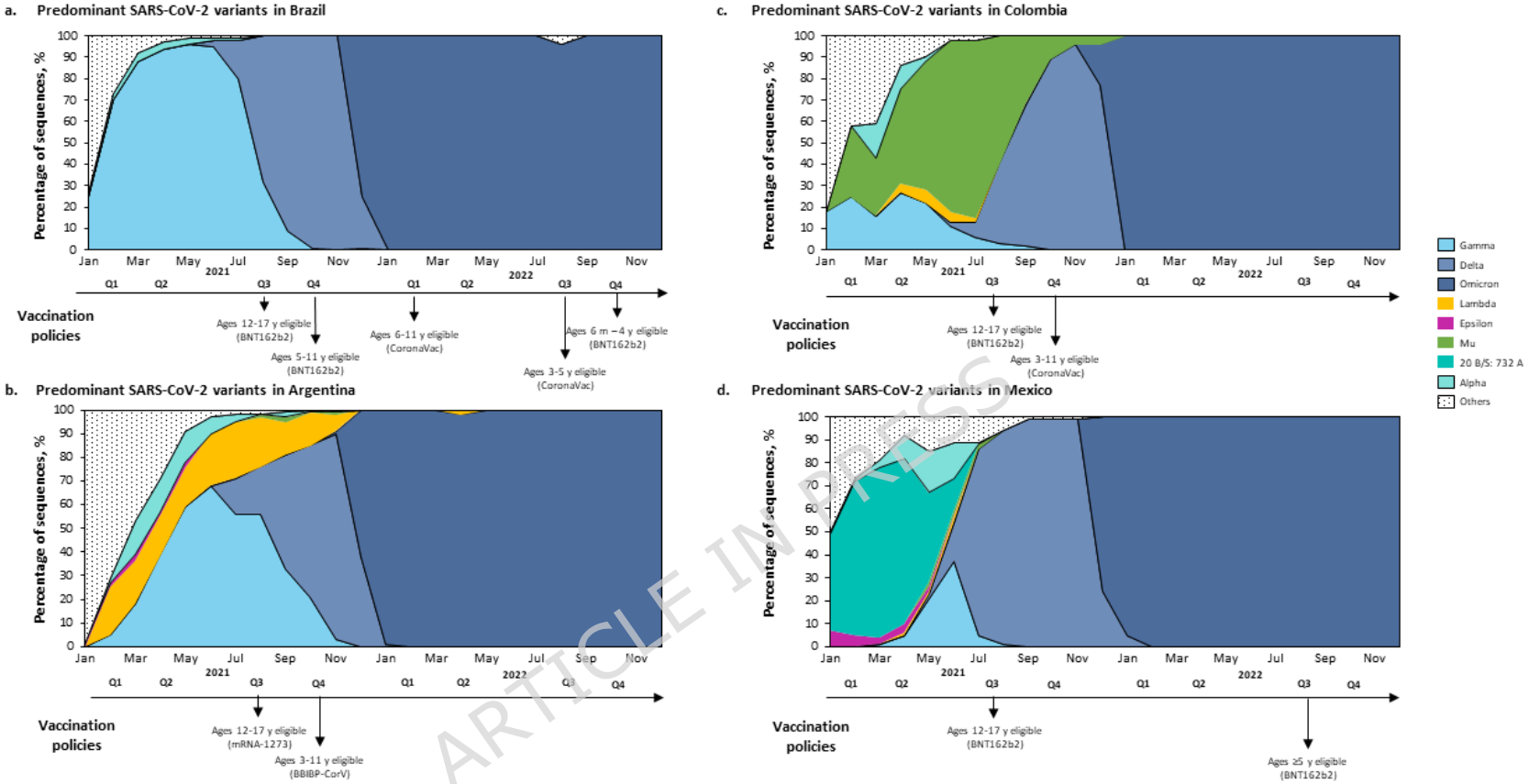
	Argentina						Brazil						Colombia						Mexico					
	2021			2022			2021			2022			2021			2022			2021			2022		
	Rates	95% CI		Rates	95% CI		Rates	95% CI		Rates	95% CI		Rates	95% CI		Rates	95% CI		Rates	95% CI		Rates	95% CI	
Age*																								
< 2 years	2.65	1.63	3.67	0.91	0.31	1.50	7.36	6.66	8.05	7.02	6.34	7.70	3.74	2.75	4.73	3.09	2.15	4.04	2.97	2.45	3.49	4.28	3.65	4.91
2-4 years	1.41	0.87	1.96	1.02	0.56	1.48	1.21	0.98	1.44	1.30	1.06	1.54	0.73	0.36	1.11	0.47	0.16	0.77	0.62	0.42	0.81	1.10	0.84	1.36
5-11 years	0.76	0.52	1.00	0.65	0.43	0.88	0.79	0.66	0.91	0.75	0.63	0.87	0.77	0.49	1.04	0.63	0.37	0.88	0.44	0.34	0.55	0.46	0.35	0.57
12-17 years	1.22	0.89	1.55	0.60	0.37	0.83	2.39	2.16	2.61	0.86	0.73	1.00	1.79	1.33	2.25	0.71	0.42	1.01	0.99	0.83	1.16	1.26	1.07	1.45
Q**																								
Q1	0.21	0.13	0.30	0.70	0.55	0.84	0.76	0.69	0.83	0.67	0.60	0.74	0.26	0.17	0.36	0.50	0.36	0.64	0.08	0.05	0.11	0.54	0.47	0.61
Q2	0.55	0.42	0.69	0.02	- 0.01	0.04	0.62	0.56	0.69	0.35	0.30	0.40	0.73	0.57	0.89	0.13	0.06	0.20	0.05	0.03	0.08	0.25	0.20	0.30
Q3	0.34	0.24	0.44	-			0.35	0.30	0.40	0.26	0.22	0.30	0.34	0.23	0.45	0.20	0.11	0.28	0.52	0.45	0.59	0.34	0.28	0.40
Q4	0.07	0.02	0.11	-			0.39	0.34	0.45	0.29	0.24	0.33	0.15	0.08	0.22	0.12	0.05	0.19	0.28	0.23	0.33	0.11	0.07	0.14

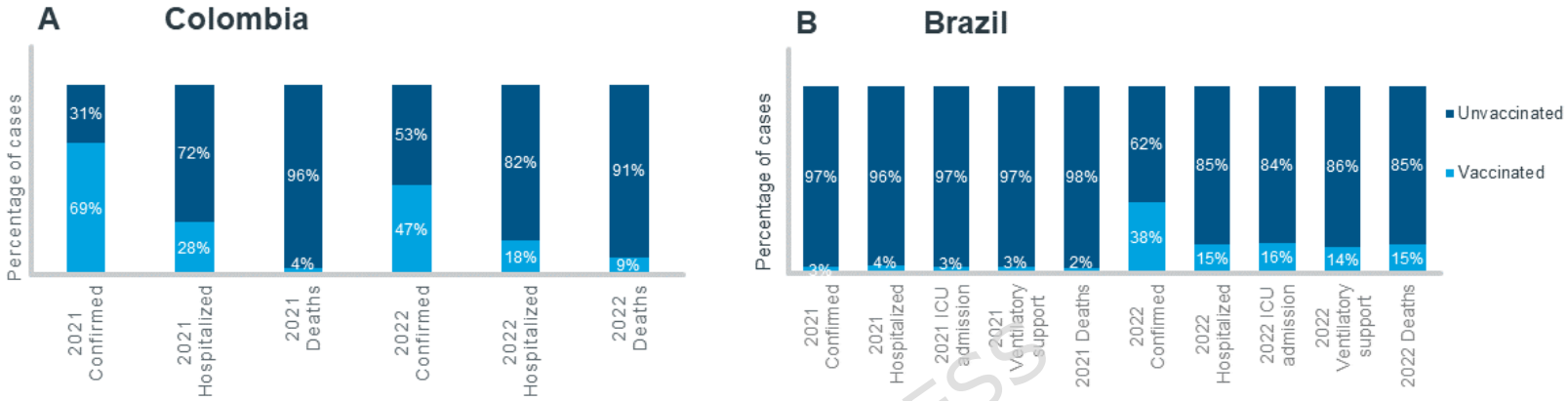
95% CI: 95% Confidence Interval; Q: Quarter.
** Denominator: country population per age group for the corresponding year*
*** Denominator: country population <18 years old for the corresponding year*

Figure 1. Timeline of predominant SARS-CoV-2 variants and vaccination policies by country during 2021-2022.



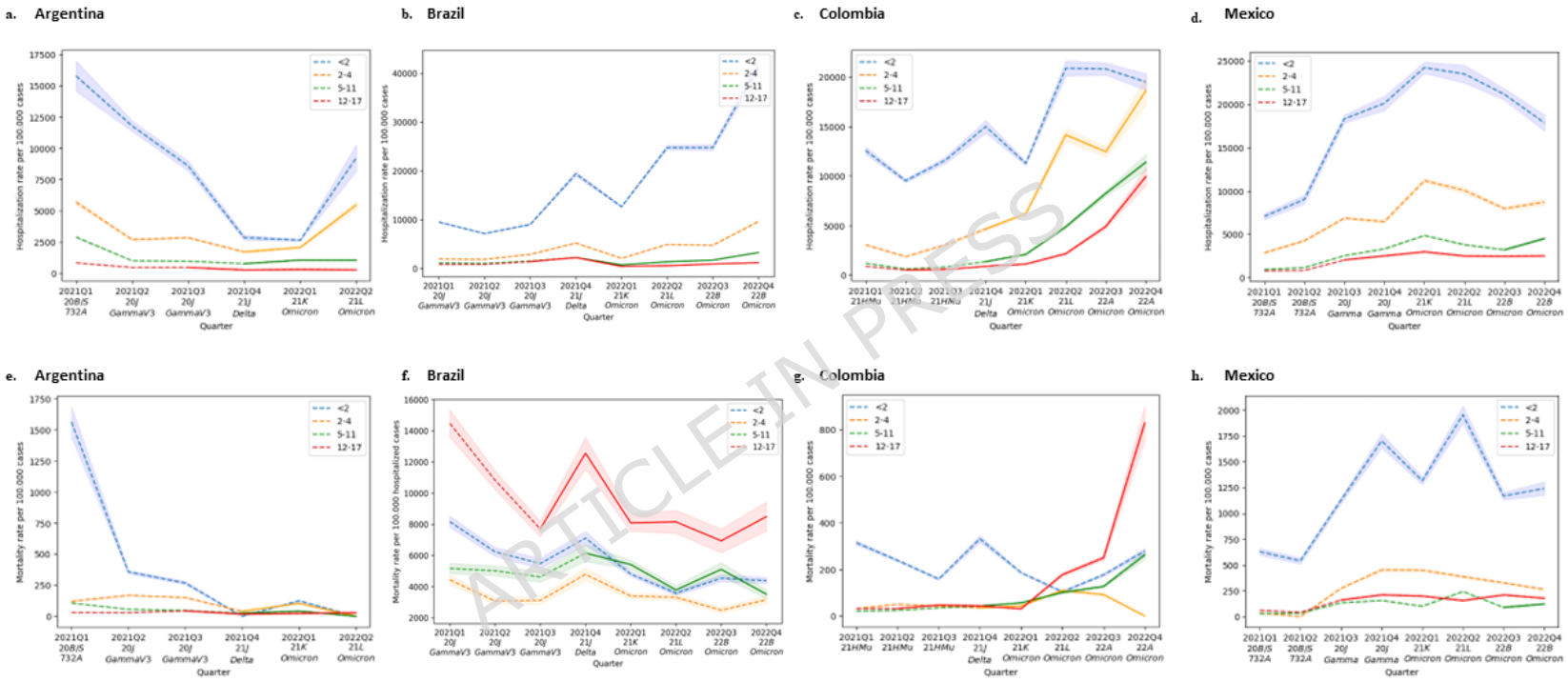
Predominant SARS-CoV-2 variants indicated as the percentage of sequences by quarter each year and time of vaccine implementation by age group along with the vaccine implemented in (a.) Brazil, (b.) Argentina, (c.) Colombia, and (d.) Mexico.

Figure 2. Proportion of vaccinated cases among each outcome group per year and country during 2021-202



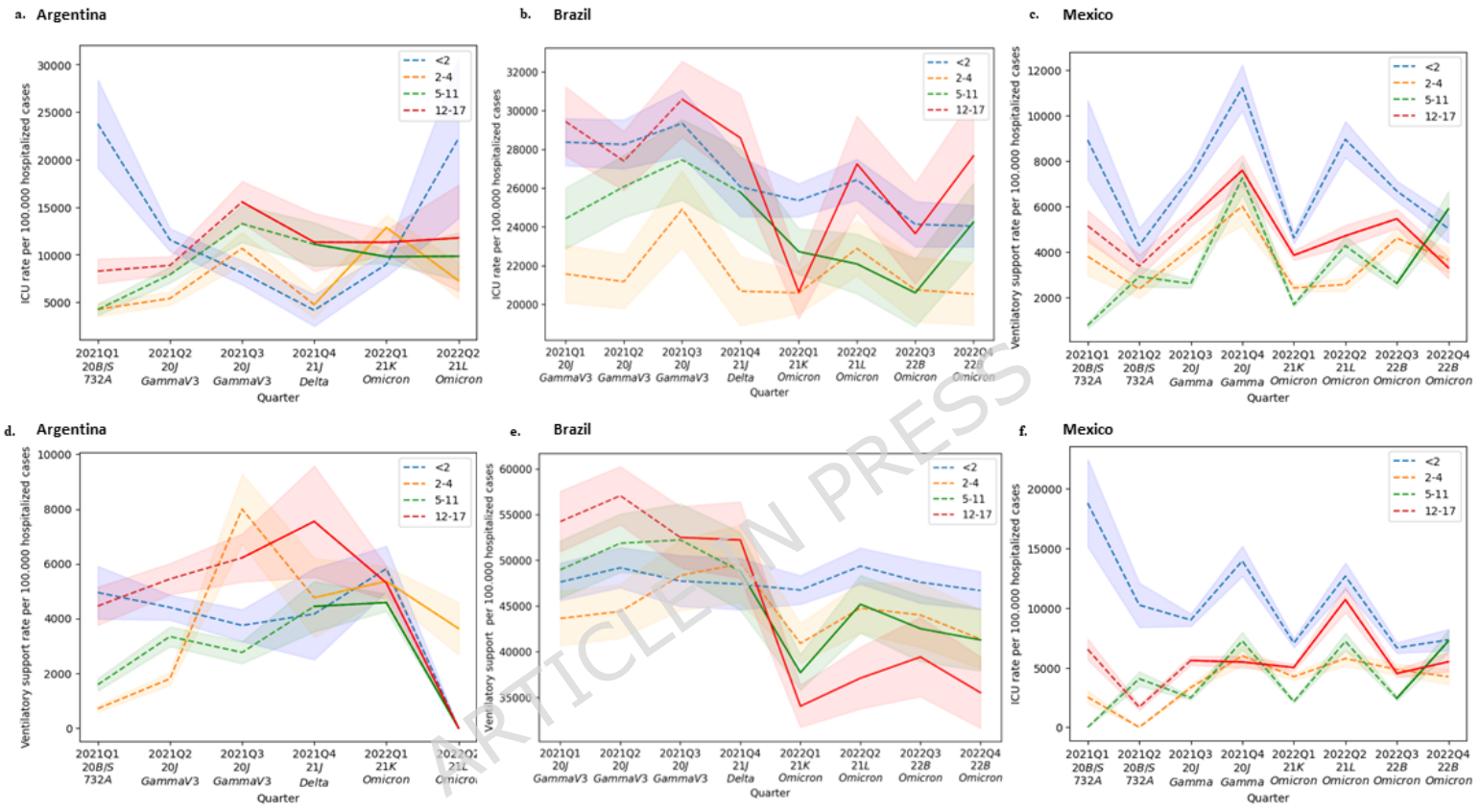
Proportion of vaccinated cases indicated as percentages among confirmed, hospitalised, deaths, ICU admissions and ventilatory support cases within 2021 and 2022 in (a) Colombia and (b) Brazil.

Figure 3. Quarterly rates of hospitalisation and death by age groups in each country.



Quarterly hospitalisation rates per 100,000 confirmed cases by age group in (a) Argentina, (b) Brazil, (c) Colombia, and (d) Mexico, and quarterly death rates per 100,000 confirmed cases by age group in (e) Argentina, (f) Brazil, (g) Colombia, and (h) Mexico. Dashed lines indicate the rates during the period preceding vaccine implementation in the age group, and continuous lines indicate the rates after vaccine implementation in the age group. Shaded areas represent the 95% Confidence Interval of the rates.

Figure 4. Quarterly rates of ICU admission and ventilatory support by age groups in each country.



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781 *Quarterly Intensive Care Unit (ICU) admission rates per 100,000 hospitalised cases by age group in (a) Argentina, (b) Brazil ,and (c) Mexico, and quarterly ventilatory support utilization*
782 *rates per 100,000 hospitalised cases by age group in (d) Argentina, (e) Brazil, and (f) Mexico. Dashed lines indicate the rates during the period preceding vaccine implementation in*
783 *the age group, and continuous lines indicate the rates after vaccine implementation in the age group. Shaded areas represent the 95% Confidence Interval of the rates*

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