



Children with influenza admitted at a children's hospital in Argentina in the 2019–2022 period: What has changed after the COVID-19 pandemic?

Ximena Juárez^a , María F. García Causarano^a, Carmen Burundarena^a, Patricia Dondoglio^a, Luciana Montoto Piazza^b, Gretel Wenk^b, Emilce Haleblian^b, María J. Rial^b, Aldo Cancellara^a 

ABSTRACT

Introduction. During 2020 and 2021, the circulation of influenza virus remained below expectations worldwide. In Argentina, in 2022, we observed an uninterrupted circulation of influenza all year round. Our objectives were to describe the circulation patterns and clinical characteristics of hospitalized children with influenza.

Population and methods. Retrospective, analytical, observational study. All children with influenza virus admitted to a children's hospital during the 2019–2022 period were included.

Results. A total of 138 patients were admitted over 4 years; in 2019, the rate of hospital discharges was 4.5/1000, compared to 15.1/1000 in 2022. No cases were recorded in 2020 and 2021. In 2019, most cases were observed in the winter; in 79%, the cause was acute lower respiratory tract infection (ALRTI); influenza A was detected in 92%. In 2022, most cases occurred in the spring; 62% developed ALRTI; and influenza A was detected in 56%. Similar rates of vaccination and comorbidities were observed in both periods.

Conclusions. In 2022, more hospitalizations due to influenza were recorded, which may have correlated with the use of more sensitive molecular diagnostic testing and a change in seasonality, with more cases observed in the spring. In 2019, influenza A predominated in lower respiratory tract infections, while in 2022, cases of influenza A and B were similar, with more extra-pulmonary forms.

Keywords: influenza; human influenza; influenza A virus; influenza B virus.

doi: <http://dx.doi.org/10.5546/aap.2023-10130.eng>

To cite: Juárez X, García Causarano MF, Burundarena C, Dondoglio P, et al. Children with influenza admitted at a children's hospital in Argentina in the 2019–2022 period: What has changed after the COVID-19 pandemic? *Arch Argent Pediatr* 2024;122(3):e202310130.

^a Department of Infectious Diseases; ^b Laboratory; Hospital General de Niños Pedro de Elizalde, City of Buenos Aires, Argentina.

Correspondence to Ximena Juárez: ximenasjuarez@gmail.com

Funding: None.

Conflict of interest: None.

Received: 6-17-2023

Accepted: 8-11-2023



This is an open access article under the Creative Commons Attribution–Noncommercial–Noderivatives license 4.0 International. Attribution - Allows reusers to copy and distribute the material in any medium or format so long as attribution is given to the creator. Noncommercial – Only noncommercial uses of the work are permitted. Noderivatives - No derivatives or adaptations of the work are permitted.

INTRODUCTION

Influenza virus causes annual epidemic outbreaks of respiratory disease in the autumn-winter season in temperate countries; children play an important role in dissemination because of the high attack rate, because they shed the virus for a longer period and have higher titers than adults.¹ While influenza may be serious at all ages, children account for a greater burden of disease: an estimated 20–45% of children become infected compared to 10–20% of adults, and each year approximately 870 000 children are hospitalized worldwide due to influenza.^{2–5} The pediatric population accounts for a significant healthcare burden and resource use for the healthcare system, both in primary care and hospital settings.^{3,6,7} The hospitalization rate and morbidity are higher in children younger than 2 years with chronic pulmonary disease, congenital heart disease, or other cardiovascular, metabolic, kidney, liver, hematological, neurological, neuromuscular, and immune diseases.⁸

Influenza virus causes a wide range of clinical manifestations, including mild symptoms, such as colds, whereas, in young children, it may cause sepsis-like symptoms, bronchiolitis, and pneumonia.⁸ Likewise, both in healthy children and those with comorbidities, it may cause complications at the respiratory system level, such as respiratory failure and death.⁹ In a smaller percentage, influenza virus causes extra-pulmonary manifestations, such as neurological, cardiac, and musculoskeletal symptoms.¹⁰

The lockdown policy implemented to reduce the dissemination of SARS-CoV-2 also impacted influenza virus transmission; during 2020 and 2021, the circulation of influenza virus remained below expectations worldwide.¹¹

In South America, the activity of respiratory viruses was also low, except for SARS-CoV-2, which remained in moderate to high levels.^{12–15} In Argentina, reports of influenza-like illness, bronchiolitis, and pneumonia in 2021 were lower than in previous years;¹⁶ in 2022, an uninterrupted circulation of influenza virus, with a large increase in cases in September–October, was observed.¹⁷

Our objective was to describe the circulation pattern and clinical characteristics of children with influenza virus hospitalized during 2019–2022.

POPULATION AND METHODS

This was an observational, analytical, and retrospective study. Children younger than 18 years old admitted to Hospital Elizalde, a

children's hospital located in the City of Buenos Aires, Argentina, between January 1st, 2019 and December 31st, 2022 were included.

A search of the records of the Laboratory of Molecular Biology and Virology was conducted for patients in whom influenza virus was detected by molecular testing, such as reverse transcription quantitative polymerase chain reaction (RT-qPCR) or direct immunofluorescence in nasopharyngeal swabs or nasopharyngeal aspirates collected within 48 hours of hospital admission or onset of symptoms in the case of children with community- or hospital-acquired infection, respectively.

During 2019, direct immunofluorescence was performed on all patients hospitalized with respiratory symptoms, whereas RT-qPCR was done only in immunocompromised patients or those admitted to the Intensive Care Unit (ICU) or the Neonatology Unit (using multiplex RT-qPCR [LightMix Modular[®]] with the Roche Cobas z480 analyzer). For patients requiring mechanical ventilation, since 2020, a multiple PCR panel (Biofire[®] FilmArray[®] Pneumonia Panel) was performed, whereas Biofire[®] Filmarray[®] Respiratory Panel was used in patients in the general hospitalization ward in patients with comorbidities, depending on resource availability. As of May 2022, an RT-qPCR was performed on all hospitalized patients with respiratory symptoms (Allplex SARS-CoV-2/FluA/FluB/RSV Assay kit with CFX96 thermal cycler).

Data from medical records were collected to assess the following variables: date of hospital admission, age, sex, comorbidities for influenza, clinical presentation, influenza vaccination status, co-infections, and course during hospitalization.

The study variables are described using proportions and their 95% confidence intervals. Continuous variables were described as average and standard deviation (SD) or as median and interquartile range (IQR), as appropriate. Ratios and their corresponding 95% confidence intervals and the χ^2 test with Yates' correction were used for categorical data. Analysis was done using the Epi Info version 7 software.

The study was approved by the hospital's Teaching and Ethics Committee.

RESULTS

During the study period, influenza was detected in 170 children; 14 were excluded because they were outpatients and 18 because of lack of data. Data from 138 patients were analyzed.

In relation to the temporal distribution of cases, 28% occurred in 2019, of which 92% corresponded to influenza A; 72% occurred in 2022, of which 56% corresponded to influenza A. No cases were recorded in 2020 and 2021. In 2019, 87% of hospitalizations occurred in autumn-winter, while in 2022, only 38% occurred in those months (*Figure 1*).

The mean age of patients was 56 months (SD: 46); 38% were younger than 2 years, with a male to female ratio of 1:1.02. Comorbidities were observed in 59% (81) of patients; the most frequent comorbidity was previous pulmonary disease in 58% (47) (*Figure 2*).

Ninety-one children were identified who had an indication for the flu vaccine as per the guidelines of the Ministry of Health. Data from the vaccination cards of 71 children were obtained; only 38% (27) of these children were vaccinated.

Ninety percent (124) of the specimens corresponded to community-acquired infections.

The annual percentage of positivity was similar in both periods, both by PCR and immunofluorescence testing. PCR testing was positive in 8% (2019) and 7% (2022), whereas

immunofluorescence testing was positive in 2% (2019) and 1% (2022) of cases. However, there was an increase in the proportion of samples that were processed with molecular methods (from 14% to 60%).

The most frequent clinical form of presentation was acute lower respiratory tract infection (ALRTI) in 67% (92). In 19% (26), the clinical form corresponded to upper respiratory tract infection and, in 14% (20), to extra-pulmonary manifestations of influenza: myositis (9), gastrointestinal (5), neurological (5), and Kawasaki disease (1) (*Table 1*).

Nine patients were hospitalized with influenza-induced myositis, with a similar distribution between both sexes and a mean age of 98 months (SD: 24). All patients had pain in the lower limbs and increased creatinine kinase (CPK) levels with a median value of 3200 U/L (IQR: 2928–6371) at the time of admission. No patient developed complications. Influenza B was detected in 8 cases.

In the gastrointestinal forms, the reason for hospitalization was oral intolerance and dehydration. Influenza A and influenza B were

FIGURE 1. Temporal distribution of cases and types of influenza virus by epidemiological week. Years 2019 and 2022

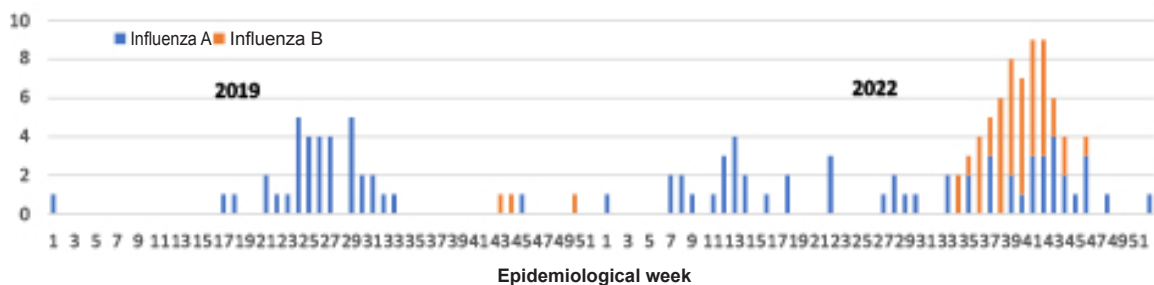
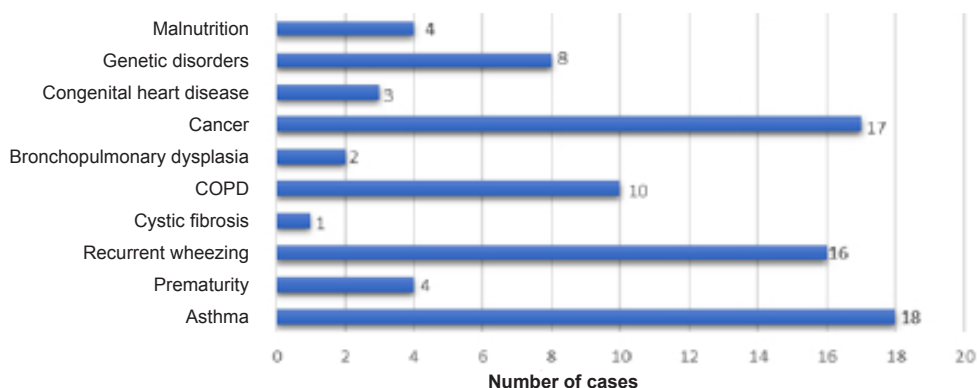


FIGURE 2. Comorbidities (n = 81)



COPD: chronic obstructive pulmonary disease.

TABLE 1. Comparison between pulmonary (n = 92) and extra-pulmonary forms (n = 46)

	Pulmonary forms (ALRTI)	Extra-pulmonary forms	p
Sex	55% males	60% females	
Average age (months)	42 (SD: 41)	84 (SD: 44)	p < 0.01
Influenza A	70 (76%)	21 (46 %)	p < 0.01 OR: 3.8 (1.8–8)
Vaccination	20 (22 %)	12 (26 %)	NS
Comorbidities	55 (60 %)	26 (56 %)	NS
Complications	17 (18 %)	7 (15 %)	NS
Oseltamivir	64 (70 %)	16 (35 %)	p < 0.01 OR: 4.2 (2-9)

ALRTI: acute lower respiratory tract infection. SD: standard deviation. NS: not significant difference.

detected in 2 and 3 specimens of respiratory tract secretions, respectively.

All neurological forms were reported in girls; 4 of them had a history of previous neurological disease (epilepsy); the average age was 60 months (SD: 46). The reason for hospitalization was the presence of seizures, 3 of them developed fever within 24 hours of the event. A cerebrospinal fluid (CSF) test was done in 1 of them due to suspected encephalitis; the CSF cytochemistry was normal and the PCR for influenza virus was negative. Four cases of influenza A and 1 case of influenza B were detected. A computed tomography (CT) scan was done in all 5 cases, which was normal.

A 5-year-old boy was admitted with fever for the past 4 days associated with bilateral conjunctival hemorrhage, measles-like rash on the trunk, and cheilitis, so multisystemic inflammatory syndrome associated with COVID-19 (MIS-C) versus Kawasaki disease was suspected. He also had upper respiratory tract catarrh. Influenza B was detected in nasopharyngeal secretions,

with a negative PCR for adenovirus, SARS-CoV-2, and respiratory syncytial virus (RSV). The viral serologies (human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus) were negative. The echocardiogram was normal. The patient received gamma globulin (IVIG) and acetylsalicylic acid (ASA) and completed a 6-month follow-up period without complications.

Admission to the pediatric intensive care unit (PICU) was required in 22% (20) of ALRTI cases, which was more common in younger children (Table 2). Mechanical ventilation was used for an average of 13.44 days (SD: 7.7). Among children who required admission to the PICU, 55% (11) had co-infections; 5 corresponded to bacterial infections; the most common microorganism was *Streptococcus pneumoniae* in 2 patients, followed by *Haemophilus influenzae* (1), *Streptococcus pyogenes* (1), and methicillin-resistant *Staphylococcus aureus* (1).

Overall, 59% of patients received oseltamivir; all children in the PICU received antiviral therapy

TABLE 2. Comparison between hospitalization in the PICU (n = 20) versus outside the PICU (n = 118)

	PICU	Outside the PICU	p
Age (months old)	17 (IQR: 7–39)	51 (IQR: 16-102)	P < 0.01
Type	Influenza A 14 Influenza B 6	Influenza A 77 Influenza B 41	NS
ALRTI	20	65	NS
Presence of co-infections	11	10	NS
Vaccination	3	29	NS
Comorbidities	11	70	NS

NS: not significant difference; ALRTI: acute lower respiratory tract infection.

for 5 days. The overall mean length of hospital stay was 9.7 days (SD: 9.9).

An 11-month-old female patient with recurrent wheezing, who had not been vaccinated, and in whom influenza A was detected, died. She also had bacteremia due to *Haemophilus influenzae*.

DISCUSSION

In our country, the near absence of viral circulation during the winter of 2020 was remarkable. According to official data, in 2021, the clinical reports of influenza-like illness, bronchiolitis, and pneumonia increased compared to 2020, but they were fewer than in previous years, with isolated cases of adenovirus, parainfluenza, metapneumovirus, and influenza.¹⁶ In our hospital, in 2020, no usual respiratory viruses were detected in children admitted with ALRTI, but more than 500 patients with SARS-CoV-2 infection were hospitalized with a seasonality similar to that of respiratory viruses, with a peak around epidemiological week (EW) 26.¹⁸

The analysis of the distribution of influenza virus during the previous years in our country shows that, for the 2015–2019 period, there was an increase in the number of cases as of EW 16–24, with a variable peak depending on the year, in winter. Since the onset of the COVID-19 pandemic, in Argentina, influenza activity has remained low. However, as of late 2021 and early 2022, the number of cases increased.¹⁹ In our series, the distribution of cases in 2019 was similar to national reports from previous years; in 2022, we observed a loss of seasonality with year-round circulation, with higher numbers of cases in the spring.

Consistent with national data, where the highest number of cases was detected in children under 5 years of age,¹⁹ the mean age in our series was 4.6 years.

In 2022, in our hospital, the incidence rate recorded was higher compared to 2019; in part, this may be due to the fact that, in this period, the use of molecular techniques with greater sensitivity has expanded, but also that national data show that there was a higher number of cases.¹⁷

In our series, 41% of patients were previously healthy, similar to what was reported in the bibliography.^{7,8}

As a consequence of the COVID-19 pandemic, 23 000 000 children did not receive the corresponding vaccines in 2020 and at least 17 000 000 children did not receive any vaccine.²⁰

According to data from the Division for the Control of Vaccine-Preventable Diseases (Dirección de Control de Enfermedades Inmunoprevenibles, DICEI), in 2019, the coverage of the first and second doses of the flu vaccine for children aged 6–24 months was 91% and 75%, respectively, with a decrease to 85% and 69% by 2020.²¹

An ALRTI was the most common manifestation in patients hospitalized with influenza and was present in 67% of cases. Also, 14% of patients developed extra-pulmonary manifestations. The most frequent manifestation was myositis, which is a benign, self-limited form of the disease that presents with functional impotence and increased serum CPK levels. Influenza B was detected in 88% of our patients, similar to what was described by Kerr J. et al.²² in a study published in 2021 that included 49 cases; 85% were due to influenza B. Gastrointestinal tract manifestations are common in children and may occur in 10–30%.²³ In our series, 5 children were admitted with diarrhea, abdominal pain, and vomiting; 3 were dehydrated. All of them had upper respiratory tract catarrh with a favorable evolution.

Influenza infection may lead to a variety of neurological manifestations, including severe and progressive forms, such as acute necrotizing encephalopathy (ANE), as well as post-infectious syndromes.¹⁰ In our study, 5 patients developed neurological manifestations, which accounts for 3.6% of hospitalized patients; such frequency was lower than the 7.6–16% frequency reported in other studies.^{24,25} Most of them had previous neurological conditions; the most common clinical manifestation was febrile seizures; influenza A was detected more frequently, as in other series.^{24,25}

In the bibliography, Banday et al.²⁶ reviewed 43 cases of influenza-associated Kawasaki disease, with a mean age of 41 months, and found a higher frequency in males, incomplete form in 60%, involvement of coronary arteries in 50%, an adequate response to IVIG, and no complications from the use of ASA. The case described in our series referred to a 5-year-old male, with an incomplete form of the disease, without cardiac manifestations or long-term complications.

Co-infections of influenza virus and other viruses and bacteria are associated with more severe forms of the disease. These have been described in 26% of hospitalized children and in 50% of those requiring intensive care,²⁷ similar to

what was reported in our study. In our series, as mentioned in the bibliography, the most frequent co-infection corresponded to *S. pneumoniae*.²⁸

Among our patients, 22% required admission to the PICU; 75% were under 3 years of age; and influenza A was detected in 80%, similar to the observations of other studies.²⁹ In our series, 1 patient died: an 11-month-old female infant with wheezing, bacteremia due to *H. influenzae*, influenza A detection, and who had not been vaccinated.

Oseltamivir is the antiviral therapy of choice for influenza A and B and should be offered early to all children hospitalized due to influenza A and B, as well as to those with complicated or progressive forms.⁸ In our series, only 59% of children received oseltamivir.

This study has limitations. Given the retrospective nature of this study, it was not possible to obtain follow-up data to assess long-term sequelae. In addition, since different diagnostic methods with a varying sensitivity were used, the number of cases may have been overestimated.

CONCLUSIONS

After the COVID-19 pandemic, the influenza virus showed a different behavior. More hospitalizations due to influenza were recorded in 2022 compared to 2019, but this could be due to a higher proportion of samples from hospitalized children being tested with more sensitive molecular methods. A different behavior was observed in the pattern of virus circulation, with most infections occurring in the winter of 2019 and in the spring of 2022. However, the studied post-pandemic period is too short to define an actual change. In 2019, most children developed ALRTI and influenza A virus was detected. In 2022, more extra-pulmonary forms and a similar frequency of influenza A and B were recorded. Vaccination coverage and comorbidities were similar in both periods. ■

REFERENCES

- Dawood F, Bresee J. *Influenza Viruses*. In Long SS, Prober CG, Fischer M (eds). *Principles and Practice of Pediatric Infectious Diseases*. 5th ed. St. Philadelphia: Elsevier; 2018:1181-90.e5.
- Sociedad Argentina de Pediatría. Gripe: actualización 2022. [Accessed on: June 12th, 2023]. Available at: https://www.sap.org.ar/uploads/documentos/documentos_gripe-actualizacion-abril-2022-296.pdf
- Ruf BR, Knuf M. The burden of seasonal and pandemic influenza in infants and children. *Eur J Pediatr*. 2014;173(3):265-76.
- Fraaij PL, Heikkinen T. Seasonal influenza: the burden of disease in children. *Vaccine*. 2011;29(43):7524-8.
- Lafond KE, Nair H, Rasooly MH, Valente F, et al. Global Role and Burden of Influenza in Pediatric Respiratory Hospitalizations, 1982-2012: A Systematic Analysis. *PLoS Med*. 2016;13(3):e1001977. Erratum in: *PLoS Med*. 2016;13(6):e1002060.
- Arostegi Kareaga N, Montes M, Pérez-Yarza EG, Sardón O, et al. Características clínicas de los niños hospitalizados por infección por virus Influenza. *An Pediatr (Barc)*. 2005;62(1):5-12.
- Munoz FM. Influenza virus infection in infancy and early childhood. *Paediatr Respir Rev*. 2003;4(2):99-104.
- American Academy of Pediatrics. *Influenza infections*. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021 Report of the Committee on Infectious Diseases*. Itasca, IL: American Academy of Pediatrics; 2021:447-57.
- Mistry RD, Fischer JB, Prasad PA, Coffin SE, Alpern ER. Severe complications in influenza-like illnesses. *Pediatrics*. 2014;134(3):e684-90.
- Sellers SA, Hagan RS, Hayden FG, Fischer WA 2nd. The hidden burden of influenza: A review of the extra-pulmonary complications of influenza infection. *Influenza Other Respir Viruses*. 2017;11(5):372-93.
- Organización Panamericana de la Salud/Organización Mundial de la Salud. Informe de situación de Influenza SE41 de 2020. Actualización Regional: Influenza y Otros virus respiratorios octubre 2020. [Accessed on: May 3rd, 2022]. Available at: <https://www.paho.org/es/documentos/actualizacion-regional-influenza-semana-epidemiologica-41-20-octubre-2020>
- Van Brusselen D, De Troeyer K, Ter Haar E, Vander Auwera A, et al. Bronchiolitis in COVID-19 times: a nearly absent disease? *Eur J Pediatr*. 2021;180(6):1969-73.
- Hills T, Kearns N, Kearns C, Beasley R. Influenza control during the COVID-19 pandemic. *Lancet*. 2020;396(10263):1633-4.
- Yeoh DK, Foley DA, Minney-Smith CA, Martin AC, et al. Impact of Coronavirus Disease 2019 Public Health Measures on Detections of Influenza and Respiratory Syncytial Virus in Children During the 2020 Australian Winter. *Clin Infect Dis*. 2021;72(12):2199-202.
- Olsen SJ, Azziz-Baumgartner E, Budd AP, Brammer L, et al. Decreased Influenza Activity During the COVID-19 Pandemic - United States, Australia, Chile, and South Africa, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(37):1305-9.
- Argentina. Ministerio de Salud. Boletín integrado de vigilancia 2021;570;SE40. [Accessed on: May 31st, 2023]. Available at: <https://bancos.salud.gob.ar/recurso/boletin-integrado-de-vigilancia-n570-se40-2021>
- Argentina. Ministerio de Salud. Comunicación epidemiológica, 18 de noviembre de 2022. Aumento de casos de influenza. [Accessed on: June 2nd, 2023]. Available at: https://bancos.salud.gob.ar/sites/default/files/2022-11/Comunicacion-epidemiologica_influenza22-11-2022.pdf
- Ferrero F, Ossorio MF. Is there a place for bronchiolitis in the COVID-19 era? Lack of hospitalizations due to common respiratory viruses during the 2020 winter. *Pediatr Pulmonol*. 2021;56(7):2372-3.
- Argentina. Ministerio de Salud. Actualización epidemiológica, 16 de marzo de 2022. Circulación de Influenza en contexto de la pandemia de COVID-19. [Accessed on: June 4th, 2023]. Available at: <https://bancos.salud.gob.ar/sites/default/files/2022-03/Actualizacion-influenza-16-03-2022.pdf>
- UNICEF. La pandemia de COVID-19 causa un importante retroceso en la vacunación infantil, según nuevos datos de la OMS y UNICEF. [Accessed on: May 28th, 2023]. Available at: <https://www.unicef.org/es/comunicados->

-
- prensa/pandemia-covid19-causa-importante-retroceso-en-vacunacion-infantil
21. Argentina. Ministerio de Salud. Dirección de Control de Enfermedades Inmunoprevenibles. Coberturas de Vacunación por Jurisdicción. Calendario Nacional de Vacunación 2009-2020. [Accessed on: May 28th, 2023]. Available at: <https://bancos.salud.gob.ar/sites/default/files/2021-12/coberturas-de-vacunacion-por-jurisdiccion-cnv-2009-2020.pdf>
 22. Kerr J, Macartney K, Britton PN. Influenza-associated myositis: a single-centre, 5-year retrospective study. *Eur J Pediatr*. 2021;180(2):577-84.
 23. Kondrich J, Rosenthal M. Influenza in children. *Curr Opin Pediatr*. 2017;29(3):297-302.
 24. Jantarabenjakul W, Paprad T, Paprad T, Anugulruengkitt S, et al. Neurological complications associated with influenza in hospitalized children. *Influenza Other Respir Viruses*. 2023;17(1):e13075.
 25. Antoon JW, Hall M, Herndon A, Johnson DP, et al. Prevalence, Risk Factors, and Outcomes of Influenza-Associated Neurologic Complications in Children. *J Pediatr*. 2021;239:32-8.e5.
 26. Banday AZ, Arul A, Vignesh P, Singh MP, et al. Kawasaki disease and influenza-new lessons from old associations. *Clin Rheumatol*. 2021;40(7):2991-9.
 27. Klein EY, Monteforte B, Gupta A, Jiang W, et al. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. *Influenza Other Respir Viruses*. 2016;10(5):394-403.
 28. Hsing TY, Lu CY, Chang LY, Liu YC, et al. Clinical characteristics of influenza with or without Streptococcus pneumoniae co-infection in children. *J Formos Med Assoc*. 2022;121(5):950-7.
 29. Shi T, Nie Z, Huang L, Fan H, et al. Mortality risk factors in children with severe influenza virus infection admitted to the pediatric intensive care unit. *Medicine (Baltimore)*. 2019;98(35):e16861.