Arch Argent Pediatr 2023;121(4):e202202805

Invasive *Haemophilus influenzae* disease: A report of 14 cases one year after the COVID-19 pandemic outbreak

Ximena Juárez[a], Rebeca Flores Yavi[a], Romina Balboa[a], Erika Matteucci[a], Carmen Burundarena[a], María F. Causarano[a], Sandra Miranda[a], Patricia Dondoglio[a], Cecilia Echave[a], Rosana Pereda[b], Aldo Cancellara[a]

ABSTRACT

Haemophilus influenzae (Hi) causes invasive disease. There are encapsulated strains, such as serotype b (Hib), and non-typeable strains (NTHi). One year after the outbreak of the COVID-19 pandemic, the number of cases increased.

In this report we describe the clinical and epidemiological characteristics of children hospitalized with invasive Hi disease (July 2021-July 2022). There were 14 cases; 12 were previously healthy children. Isolations: Hib (n = 6), Hi serotype a (n = 2), NTHi (n = 5); 1 case was not typified. Median age: 8.5 months (IQR: 4–21). Manifestations: meningitis (n = 5), pneumonia (n = 6), cellulitis (n = 2), arthritis (n = 1). Incomplete Hib immunization was observed in 9 children.

Invasive Hi disease increased 2.5 times from previous years. These data suggest the reemergence of Hib due to a decline in vaccination coverage and an increase in other non-b-type Hi serotypes.

Key words: *meningitis;* Haemophilus influenzae *type b; epidemiology.*

doi: http://dx.doi.org/10.5546/aap.2022-02805.eng

To cite: Juárez X, Flores Yavi R, Balboa R, Matteucci E, et al. *Invasive Haemophilus influenzae* disease: A report of 14 cases one year after the COVID-19 pandemic outbreak. Arch Argent Pediatr 2023;121(4):e202202805.

[a] Department of Infectious Diseases; [b] Department of Bacteriology. 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*: 8-5-2022*
Accepted*: 10-13-2022*

INTRODUCTION

There are 2 types of *Haemophilus influenzae* (Hi): encapsulated and non-encapsulated or non-typeable (NTHi). *Haemophilus influenzae* type b (Hib) is the most virulent encapsulated serotype and causes invasive disease, such as meningitis, pneumonia and epiglottitis, in areas where vaccination coverage is inadequate. Children who did not receive the Hib vaccine are at a higher risk for invasive disease, as are those with other risk factors, such as immunosuppression, tobacco exposure, lack of breastfeeding, overcrowding, attendance to a daycare center, and a low socioeconomic status.[1]

Hib was an important cause of invasive disease in children in the pre-vaccine era. In Argentina, before the introduction of Hib vaccination, it was the leading cause of documented bacterial meningitis in children under 5.[2] Since the introduction in 1998 of the Hib vaccine in the immunization schedule, the number of cases decreased significantly, with a national rate of less than 0.1 cases/100 000 inhabitants that remained stable from 1999 to 2011.[3] In areas with routine vaccination, the prevalence of Hi has decreased, and the ecological niche of NTHi has increased.[4,5] NTHi is generally less virulent and causes mild upper respiratory tract infections; occasionally, it may cause invasive disease in immunocompromised individuals.[1]

As a consequence of the COVID-19 pandemic, it has been estimated that at least 25 million children under 1 year of age did not receive their vaccines as per schedule in 2020, and at least 17 million children did not receive any vaccines at all.[6] In Argentina, in 2020, vaccination fell by 64.2%; and the administration of the first dose of the pentavalent vaccine decreased by 74.9%.[7]

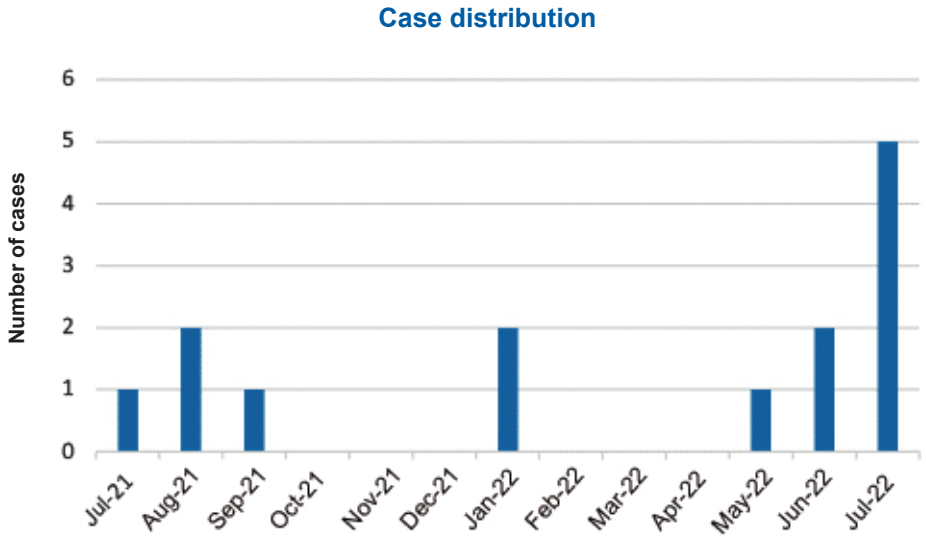
In the past year, in our hospital, we observed an increase in cases of invasive Hi disease compared to previous years. Our objective is to describe the clinical and epidemiological characteristics of 14 cases of invasive Hi disease in hospitalized children, their clinical presentation, immunization status, and course over treatment.

METHODOLOGY

This was a descriptive, cross-sectional, and retrospective study. Children under 18 years of age diagnosed with invasive Hi disease hospitalized at the Hospital General de Niños Pedro de Elizalde between July 1st, 2021 and July 31st, 2022 were included.

Patients were found using the microbiology records based on Hi isolation. The following variables were recorded: date of admission, age, sex, origin, clinical source of infection, history, vaccination, course, complications at discharge, cerebrospinal fluid (CSF) findings, and culture from other sterile sites.

Figure 1. Temporal distribution of cases of invasive diseases



Invasive disease was defined as the isolation of Hi in sterile sites (CSF, blood, joint, pleural, pericardial fluid) and complete Hib vaccination for the patient's age, as referenced.[1]

Data were analyzed using the EpiInfo software, version 7.2. The variables were described using proportions and their respective 95% confidence intervals (CIs). Continuous variables were described as average and standard deviation or as median and interquartile range, as appropriate.

Ethical considerations

A written informed consent was obtained from the parents of all patients included in the study.

CASE REPORTS

A total of 14 children were diagnosed with invasive Hi disease. Most cases occurred during the winter months (*Figure 1*). Children's median age was 8.5 months (IQR: 4–21). The following Hi strains were isolated: 6 cases of Hib, 5 cases of NTHi, 2 cases of Hi serotype a (Hia), and no typing in 1 case. Five children had been fully vaccinated for their age. *Tables 1 and 2* describe the patients' characteristics. The most frequent clinical manifestations in patients in whom Hib was isolated were meningitis and cellulitis.

Among the patients with NTHi, 4 had a pulmonary source of infection; of these, 3 had co-infections: 1 case of necrotizing pneumonia with isolation of *Streptococcus pneumoniae* and NTHi in the pleural fluid; a girl with bifocal pneumonia and co-infection with respiratory syncytial virus (RSV); and 1 neonate with co-infection with rhino/enterovirus.

Invasive Hia disease was observed in 2 cases. The first case was a healthy 4-month-old infant with severe meningitis. The other case was a child diagnosed with non-progressive encephalopathy who developed pneumonia and had a favorable course.

All patients with invasive disease underwent

Table 1. Clinical and microbiological characteristics of patients with invasive *Haemophilus influenzae* disease

Id	Sex	Age (m)	Healthy	Origin	ST	Isolation	Source	CSF cel./gluc./prot.	CO-INF.	COMPL.
1	M	4	Yes	PBA	Hia	BC and CSF	Meningitis	7300/2/2.5	No	Subdural empyema
2	F	11	Yes	PBA	Hib	BC	Arthritis	N	No	No
3	M	96	Yes	PBA	Hib	BC	Pneumonia with effusion	NR	No	No
4	F	8	Yes	PBA	Hi	CSF	Meningitis		No	Subdural empyema
5	M	21	Yes	PBA	Hib	BC	Facial cellulitis	N	No	No
6	M	7	Yes	CABA	Hib	CSF and BC	Meningitis	2200/< 2/1.3	No	Cerebral ischemia
7	M	74	NS	PBA	Hia	BC	Pneumonia with empyema	NR	No	No
8	F	5	Yes	PBA	Hib	BC	Preseptal cellulitis	N	No	No
9	M	9	Yes	PBA	NTHi	BC and CSF	Meningitis	1700/< 2/2	No	No
10	F	20	Yes	PBA	NTHi	BC	Pneumonia	10/73/0	RSV (IIF)	No
11	M	4	Yes	CABA	Hib	CSF and BC	Meningitis	4400/37/1	No	Subdural empyema
12	M	24	Yes	CABA	NTHi	PF	Necrotizing pneumonia	NR	Spn (CC)	No
13	F	0.1	DiGeorge	PBA	NTHi	BC	Pneumonia	N	No	No
14	M	0.1	Yes	PBA	NTHi	BC	Pneumonia	N	RV (PCR)	No

Id: identification, M: male, F: female, m: months,
PBA: province of Buenos Aires, CABA: the City of Buenos Aires, NS: neurological sequelae,
ST: serotype, Hia: Haemophilus influenzae a*, Hib:* Haemophilus influenzae b*, Hi:* Haemophilus influenzae*,*
NTHi: non-typeable Haemophilus influenzae*, PF: pleural fluid,*
BC: blood culture, CSF: cerebrospinal fluid, cel.: cells/mm^3, gluc.: glucose (mg/dL), prot.: proteins (g/L),
CO-INF.: co-infection, RSV: respiratory syncytial virus, Spn: Streptococcus pneumoniae*, RV: rhino/enterovirus, COMPL.: complications, NR: not reported, N: normal,*
IIF: indirect immunofluorescence,
PCR: polymerase chain reaction, CC: conventional culture.

Table 2. *Haemophilus influenzae* serotypes and relationship with Hib vaccination and source of infection

Haemophilus influenzae serotype	Hib vaccination		Sources of infection
	Complete	Incomplete	
Hib (n = 6)	1	5	Meningitis n = 2
			Cellulitis n = 2
			Arthritis n = 1
			Pneumonia n = 1
Hia (n = 2)	1	1	Meningitis n = 1
			Pneumonia n = 1
NTHi (n = 5)	3	2	Pneumonia n = 4
			Meningitis n = 1

Hib: Haemophilus influenzae *type b, Hia:* Haemophilus influenzae *type a, NTHi: non-typeable* Haemophilus influenzae.

immunological assessment that was normal for age in all patients, except in 2 of the cases in which NTHi was isolated: in 1, DiGeorge syndrome was suspected and the other case was under study.

All patients were treated with ceftriaxone; for a median of 18 days (IQR: 14–24) in the case of meningeal presentation and for 14 days (IQR: 10–22) in the rest. Children with meningitis received dexamethasone for 48 hours. Six patients required intensive care. No patient died. Of the 5 cases with meningeal forms, 4 had complications during hospitalization and are receiving follow-up for long-term neurological sequelae.

DISCUSSION

A total of 14 cases of invasive disease are described in this report; Hib was isolated in 6. The 2 cases of Hib meningitis were younger than 1 year and developed sequelae, as described in the bibliography.[1]

During 2018, 2019, and 2020, 6, 5, and 3 cases of invasive Hi disease were diagnosed in our hospital, respectively; Hib was isolated in 5, 2, and 2 cases, respectively. The 14 cases described in our study in the course of 13 months represent a 2.5-fold increase in the frequency of invasive disease from previous years.

In Argentina, the number of Hi isolations in invasive disease in the past 5 years has been decreasing: 202 cases in 2016, 151 in 2019, and 49 in 2020. The predominant serotype in children under 2 years of age is NTHi, followed by Hib and Hia.[8] In the Caucasian population of North America and Europe, *Haemophilus influenzae* serotype f (Hif) is the most common cause of invasive disease in adults. In neonates, immunocompromised and older adults, NTHi is prevalent.[4]

In our study, most children had not completed their Hib vaccination schedule. As a consequence of the COVID-19 pandemic, at least 17 million children did not receive any vaccination,[6] and the worldwide coverage with 3 doses of the Hib vaccine by 2022 was 70%.[9] According to data from the National Ministry of Health, in Argentina, during 2020, the pentavalent vaccination coverage at 6 months old dropped 10% compared to 2018.[10]

In our study, 36% (n = 5) corresponded to NTHi. As observed in other countries, the cases of invasive disease due to NTHi, have increased in Argentina. In Canada, they increased by 5.6% during 2014–2018 at the expense of NTHi in most cases, and of Hia and Hif to a lesser extent.[11] In the United States, NTHi is the most frequent cause of invasive Hi disease across all age groups.[1] In our series, NTHi was isolated in 5 patients, 2 were neonates and 2 had suspected immunodeficiency.

Hia was isolated in 2 children; this type has re-emerged as a cause of meningitis in aboriginal children in North America[12] and has replaced Hib as the major cause of invasive disease in these populations. In our series, the child with meningeal source had a severe course similar to Hib, as described by other authors.[1,4,12]

During the pandemic, many children did not receive the corresponding vaccines for their age. According to the data described here, on the one hand, Hib has reemerged as a consequence of the drop in coverage and, on the other hand, other

virulent non-b-types of Hi appear to be increasing, as has been reported in other countries.

It is worth emphasizing the importance of completing and recovering vaccination schedules to prevent the reemergence of vaccine-preventable diseases, as well as encouraging the development of new vaccines that expand coverage to other causative serotypes likely to emerge.

The importance of our study lies in alerting the medical community of the reemergence of this infection. Given the retrospective nature of our study, it limitation is that it underestimates the frequency of late detection sequelae and other immunological alterations. In addition, we did not assess demographic variables that may have impacted disease incidence.

CONCLUSIONS

A total of 14 cases of invasive disease were observed over 13 months, 5 had a meningeal source and 9 had not completed their vaccination schedule. There has been a 2.5-fold increase in invasive Hi disease compared to the years before the COVID-19 pandemic. ■

REFERENCES

1. American Academy of Pediatrics. *Haemophilus 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.Pages.345-35.
2. Vacuna anti-*Haemophilus Influenzae* B (Hib). In: Abate H, Aquino AP, Bakir J, Barcán L, et al. Recomendaciones Nacionales de Vacunación Argentina. Buenos Aires: ProNaCEI/Ministerio de Salud; 2012:236-9. [Accessed on: September 28th, 2022]. Available at: https://bancos.salud.gob.ar/recurso/recomendaciones-nacionales-de-vacunacion-argentina-2012
3. Romanin V, Chiavetta L, Salvay MC, Chiolo M, et al. Vacuna anti-*Haemophilus influenzae* de tipo b (Hib) en el Calendario Nacional de Argentina: portación nasofaríngea de Hib tras 8 años de su introducción. *Arch Argent Pediatr.* 2007; 105(6):498-505.
4. Tsang RSW, Ulanova M. The changing epidemiology of invasive *Haemophilus influenzae* disease: Emergence and global presence of serotype a strains that may require a new vaccine for control. *Vaccine*. 2017; 35(3):4270-5.
5. Collins S, Ramsay M, Campbell H, Slack MP, Ladhani SN. Invasive *Haemophilus influenzae* type b disease in England and Wales: Who is at risk after 2 decades of routine childhood vaccination? *Clin Infect Dis*. 2013; 57(12):1715-21.
6. UNICEF. La pandemia de COVID-19 causa un importante retroceso en la vacunación infantil, según nuevos datos de la OMS y UNICEF. [Accessed on: September 28th, 2022]. Available at: https://www.unicef.org/es/comunicados-prensa/pandemia-covid19-causa-importante-retroceso-en-vacunacion-infantil
7. Torres F, Domínguez P, Aruanno ME, Macherett MJ, et al. Impacto de la pandemia por SARS-CoV-2 en la administración de vacunas del Calendario Nacional de Inmunizaciones en menores de 2 años. *Arch Argent Pediatr*. 2021; 119(3):198-201.
8. Corso A, Efron A, Gagetti P, Lucero C, et al. Caracterización de los aislamientos de *Haemophilus influenzae*, Argentina, 2020. In: Informe Argentina SIREVA II 2020:14-8. [Accessed on: August 4th, 2022]. Available at: http://antimicrobianos.com.ar/ATB/wp-content/uploads/2021/12/Informe-Argentina-SIREVA-II-2020.pdf
9. World Health Organization. UNICEF and WHO warn of perfect storm of conditions for measles outbreaks, affecting children. [Accessed on: September 28th, 2022]. Available at: https://www.who.int/news/item/27-04-2022-unicef-and-who-warn-of--perfect-storm--of-conditions-for-measles-outbreaks--affecting-children
10. Dirección de Control de Enfermedades Inmunoprevenibles. Coberturas de Vacunación por Jurisdicción: Calendario Nacional de Vacunación 2009-2020. Ministerio de Salud Argentina. [Accessed on: October 13th, 2022]. Available at: https://bancos.salud.gob.ar/sites/default/files/2021-12/coberturas-de-vacunacion-por-jurisdiccion-cnv-2009-2020.pdf
11. McTaggart LR, Cronin K, Seo CY, Wilson S, et al. Increased incidence of invasive *Haemophilus influenzae* disease driven by non-type B isolates in Ontario, Canada, 2014 to 2018. *Microbiol Spectr.* 2021; 9(2):e0080321.
12. Ulanova M, Tsang RSW. *Haemophilus influenzae* serotype a as a cause of serious invasive infections. *Lancet Infect Dis*. 2014; 14(1):70-82.