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Meningococcal burden of disease in Argentina: 10 years epidemiologic review

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ABSTRACT

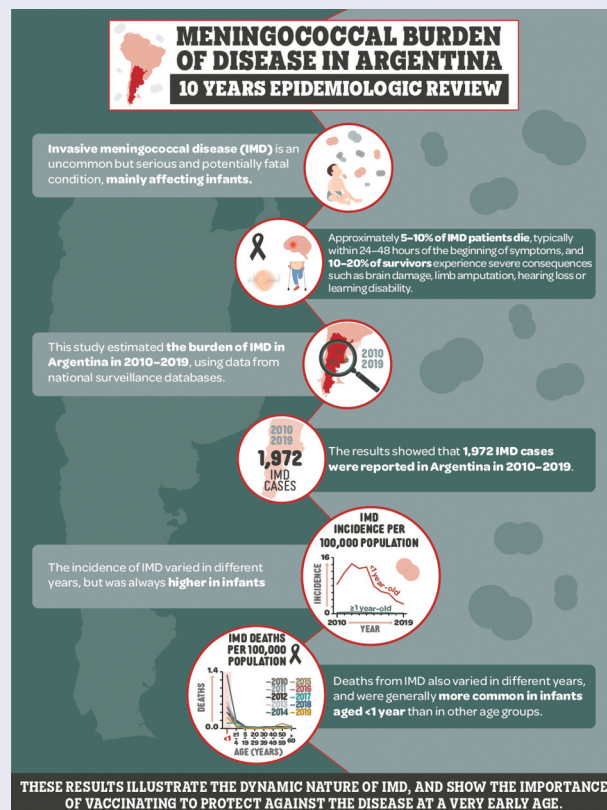
Invasive meningococcal disease (IMD) is an uncommon but serious and potentially fatal condition, mainly affecting infants. In 2017, Argentina introduced a vaccination program against serogroups A, C, W and Y (MenACWY) for infants aged 3, 5 and 15 months and adolescents aged 11 years. The objective of this study was to review the burden of IMD in Argentina in 2010–2019. Data were obtained from national surveillance databases, and the study estimated IMD incidence, mortality, case-fatality rates, and serogroup distributions across age groups. A total of 1,972 IMD cases were reported in the study period, with the highest incidence in infants aged < 1 year. Incidence peaked in 2013 and subsequently declined. Mortality rates were 18 times higher in infants than in other age groups, reflecting the high impact of IMD in this age group. The case-fatality rate was 8.5% on average and increased with age. The proportion of notified cases with serogroup identification increased over the period, reaching 91% in 2019. The most common serogroups over the study period were serogroup B (48%) and serogroup W (42%), with an increase in B relative to W since 2015. In infants aged < 1 year, the proportion of serogroup B increased in recent years, reaching around 70% of characterized cases in 2018–2019. These results show the dynamism of IMD and indicate the importance of vaccination at an early age and offering protection against predominant serogroups. These data are valuable to support evidence-based decision-making in healthcare.

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Introduction

Neisseria meningitidis can cause invasive meningococcal disease (IMD), a range of serious infections including septicemia, meningitis, arthritis and other less frequent clinical presentations.¹ Meningitis can be rapidly fatal even with prompt diagnosis and treatment; approximately 5–10% of patients die, typically within 24–48 hours of symptom onset.¹ Severe sequelae such as brain damage, hearing loss or learning disability occur in 10–20% of survivors.¹ Furthermore, reduced health-related quality of life may persist for years after infection even in IMD survivors without sequelae.² Six serogroups of *N. meningitidis* are capable of causing epidemics (A, B, C, W, X and Y).¹ Serogroup distribution varies between age groups and countries.³

Vaccines are available against serogroups A, C, W and Y, and further vaccines are available against serogroup B.⁴ In 2013,⁵ the National Immunization Program (NIP) of Argentina implemented meningococcal vaccination with MenACWY-CRM197 vaccine for high-risk groups. In 2017, the Argentine NIP implemented universal meningococcal vaccination using the MenACWY-CRM197 vaccine for infants aged 3, 5 and 15 months and adolescents aged 11 years,⁶ and since 2020 the NIP has recommended a combined vaccination strategy with MenACWY and 4CMenB for high-risk groups, including individuals with anatomical or functional asplenia, complement factor deficiency, individuals under treatment with eculizumab, children with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) infection (aged <18 years), and workers who handle or process samples with potential exposure to *N. meningitidis*.⁷

The annual incidence of IMD ranges from <1 per 100,000 population in Europe and North America to 10 per 100,000 in the ‘meningitis belt’ in sub-Saharan Africa.⁸ In Latin America, incidence of IMD has been reported to range from 0.06 per 100,000 (Mexico) to 1.9 per 100,000 (Brazil).⁹ In Argentina, 170–300 cases of IMD were reported annually in the period up to 2015, equating to an annual incidence of 0.44–0.75 cases per 100,000 inhabitants.⁶ Data from an active surveillance study conducted in hospitals in Argentina in 2012–2015 indicated that IMD cases were concentrated in infants, with 48% of cases reported in children aged <1 year.¹⁰ This pattern of peak incidence in children aged <1 year is also reported elsewhere in the Latin America region. In North America and Europe, there is typically a second peak in IMD incidence in adolescents and young adults.¹¹ In contrast, a peak in incidence in adolescents is not observed in Argentina.⁶ Surveillance data from the Directorate of Health Statistics and Information (DEIS)¹² reported 20–30 deaths annually from IMD in Argentina in the period up to 2015, with a case-fatality rate (CFR) of 10%. The reported CFR is consistent with data from active surveillance in hospitals in Argentina.¹⁰

Detailed and up-to-date epidemiologic data on the burden of IMD are needed to support evidence-based decision-making. World Health Organization (WHO) recommends that knowledge of the meningococcal disease burden is essential for making appropriate use of the available vaccines.⁴ In Latin America, data are collected by a passive surveillance network of 21

national and two regional laboratories known by its Spanish acronym SIREVA and operated by the Pan-American Health Organization (PAHO).¹³ However, passive surveillance systems tend to under-report disease cases compared with active surveillance.¹⁴ Only a limited number of countries in Latin America have implemented meningococcal disease surveillance, and the information collected is not always uniform or easily accessible.¹³ In Argentina, IMD surveillance is carried out under an integrated modality, which includes clinical and laboratory data. Meningococcal notification is performed through the National Surveillance System (SNVS),¹⁵ and laboratories complement this information through the same internet platform.

The objective of the present study was to review the burden of IMD in Argentina in the period 2010–2019 using data from the national surveillance system, estimating IMD incidence, serogroup distribution, mortality and case fatality rates across age groups in the country.

Materials and methods

This retrospective observational study used surveillance data on meningococcal disease collected in Argentina during the period from 2010 to 2019. Investigators were blind to patients’ identity information. This evaluation of public health information poses no risk to participants. Nevertheless, the protocol was approved by an independent ethics committee (Fundación de Estudios Farmacológicos y Medicamentos Luis M. Zieher) informed by 0000002138.

Case definitions

Cases of any age and sex were included if they were notified to the Argentinian National Surveillance System (versions SNVS (SIVILA-C2)/SNVS2.0)¹⁵ or to the National Reference Laboratory (NRL) as confirmed or suspicious cases of meningococcal disease with diagnosis between 2010 and 2019. Public and private effectors (hospitals) notify meningococcal cases (especially clinical and demographic data) through the National Surveillance System (SNVS) and laboratories complement this information with laboratory results through the same internet platform. Biological samples and/or *N. meningitidis* isolates are remitted from the laboratory network to the National Reference Laboratory (NRL). The NRL database is combined and compared with the SNVS database to maximize case identification.¹⁵ The case definitions were as follows:¹⁶

- Confirmed case: A clinically compatible case and isolation of *N. meningitidis* from a usually sterile site or the detection of *N. meningitidis*-specific nucleic acid in specimens obtained from a normally sterile body site.
- Suspicious case: A clinically compatible case and gram-negative diplococci in a sterile fluid or clinical purpura fulminans without a positive culture.

Outcomes

The analysis estimated the following outcomes:

- IMD cases and mean incidence (number of cases per 100,000 population) by year;
- IMD-related deaths, mortality (deaths per 100,000 population) and CFR (number of IMD-related deaths divided by number of IMD cases) by year.

Outcomes were stratified by age group: <1 year of age (in increments of 1 month); 1–4 years of age; 5–19 years of age; 20–59 years of age (in increments of 10 years); and 60 years of age or more. Outcomes were also categorized by region: North-East, North-West, Center, Cuyo and South. The analysis also estimated meningococcal serogroup proportions by age, year, and region.

National vaccination coverage data in target groups was reported as a percentage for 2017 to 2019, obtained from official data.¹⁷

Data sources and analysis

Any suspicious or confirmed case of bacterial meningoencephalitis of any etiology must be reported to the Argentine Integrated Health Information System (SISA). Data on all laboratory- or clinically-notified IMD cases between 2010 and 2019 were obtained from two databases, the SNVS and the NRL, with data from the two databases combined to avoid duplication. The SNVS system software is part of SISA, and was updated in 2018 (SNVS 2.0).¹⁵ The system covers all regions of the country and reaches the public sector, private sector and social security. For each meningococcal disease case, information was collected on age, gender, consultation date, province, type of sample, diagnostic method (culture or polymerase chain reaction [PCR]) and serogroup/genogroup. Most hospitals performed agglutination tests (serogroup) while the National Reference Laboratory (NRL) and some hospitals where PCR was available carried out this methodology. The PCR technique was used at the NRL to confirm *N. meningitidis* using specific primers for detecting *crpA* gene preserved in the species and *ctrA*, the capsular transport gene. Genogroups were determined using PCR by amplification of specific genes corresponding to serogroups A, B, C, E, W, X, Y and Z.^{18,19} Isolates negative for *ctrA* were tested for presence of the capsule null region (*cnl*).²⁰ PCR was used as a diagnostic tool when sample cultures of suspected cases were negative. Until 2012, conventional PCR was used at the NRL.^{18–20} Since 2013, real-time PCR has been implemented.²¹ Both methodologies were transferred to the laboratories of the National Network with the facilities to implement those methodologies. In this paper the term ‘serogroup’ is used to refer to both serogroup and genogroup.

IMD deaths of any age and sex were included if they were reported by DEIS as meningococcal disease (International Classification of Diseases, 10th Edition [ICD-10] A39 and subcodes used in the deaths databases) between 2010 and 2019.²² Data on deaths were available for the period 2010–2019.²³

Data on vaccination coverage since 2017 were provided by the DICEI (Directorate of Controlling Immunopreventable Diseases)¹⁷ and calculated considering the number of doses administered and the target population for each province as reported by the local Statistics Directorate.

Results

IMD incidence

A total of 1,972 cases of IMD were reported over the study period, 88% of which were confirmed cases (with the identification of *N. meningitidis*; $n = 1,735$). The remaining 237 cases were clinically suspected and diagnosed (i.e. a clinically compatible case and gram-negative diplococci in a sterile fluid, or clinical purpura fulminans without a positive culture). Of the 1,972 total cases, 55% occurred in males. Incidence by year is shown in Figure 1. Peak incidence occurred in 2013, at 0.69 per 100,000 population, with a decline after 2015 to 0.22 per 100,000 by 2018 and 0.23 per 100,000 in 2019 (Figure 1).

IMD incidence was highest in infants aged <1 year every year during the whole study period, with no secondary peak in adolescents and young adults (Figure 2). IMD cases in infants aged <1 year accounted for 33.5% of all IMD cases ($n = 661$) recorded over the study period. The average incidence rate of

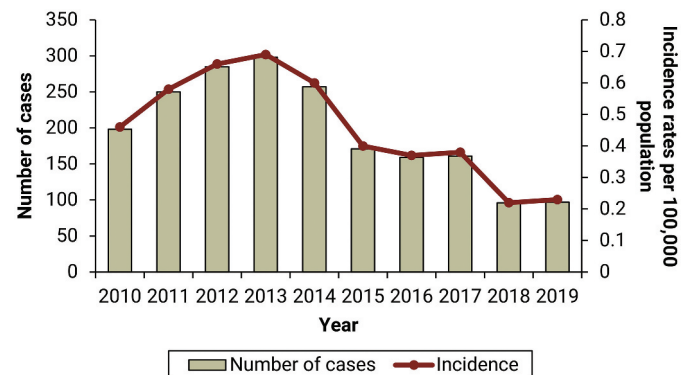


Figure 1. Number of meningococcal disease cases and incidence per year. Source: DiCEI-SISA-National Reference Laboratory. Ministry of Health.

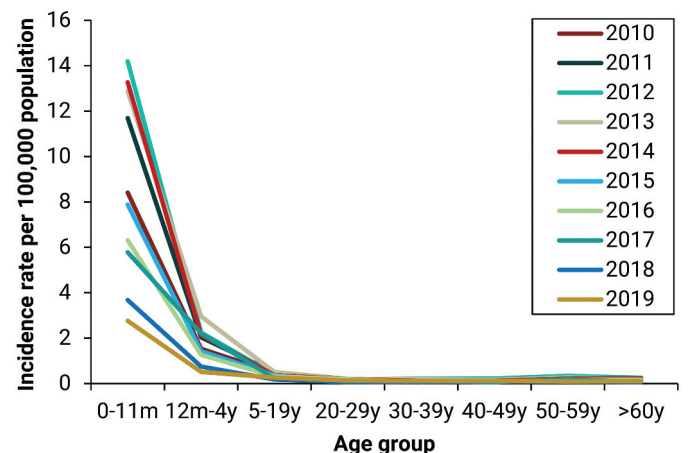


Figure 2. Meningococcal disease incidence by age group and year. Source: DiCEI-SISA-National Reference Laboratory. Ministry of Health. m, month; y, year.

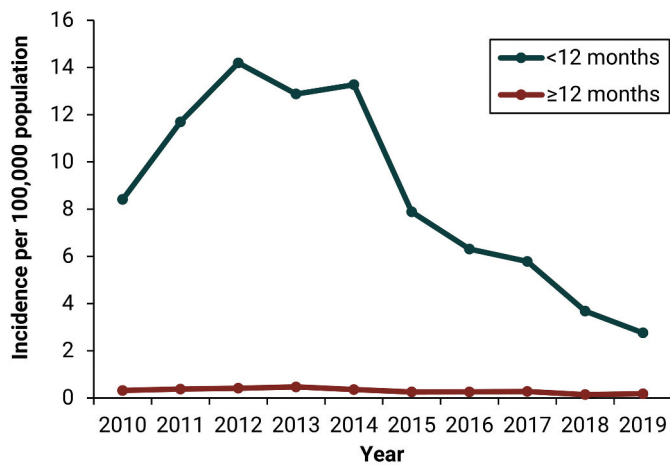


Figure 3. Meningococcal disease incidence in infants aged <12 months and in the population aged 12 months or over, by year. Source: DiCEI-SISA. National Reference Laboratory. Ministry of Health.

IMD in infants aged <1 year considering the entire period was 27.9 times higher than in all the other age groups combined (aged ≥1 year) (8.7 vs 0.3 cases/100,000 inhabitants). This ratio ranged from 15 to 33 times higher depending on the year assessed (Figure 3). The IMD incidence in infants showed a decline after 2015 (Figure 2), similar to the pattern observed in all ages (Figure 1).

Most of the cases occurred in the central region of Argentina, which is the most populated region (Supplementary Figure S1). The central region accounted for 1,562 IMD cases over the study period (79% of total cases).

IMD mortality

There were 167 IMD-related deaths recorded over the period 2010–2019, and the average CFR was 8.5% over the period. In all years, the mortality rate (deaths per 100,000 population) was highest in infants aged <1 year (Figure 4), on average 18 times higher than in all other age groups. The year 2014 had an exceptionally high mortality in infants aged <1 year (Figure 4), with 10 cases reported compared with the average of four per year across the study period. There was no obvious reason for this. Similarly, in 2015 mortality in the group aged 50–59

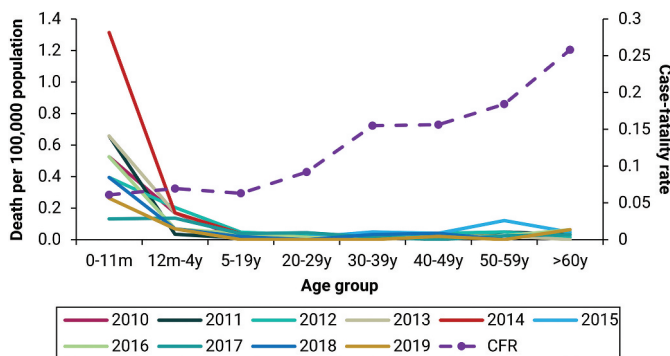


Figure 4. Meningococcal disease deaths by year and age group, and case-fatality rate by age group. Source: DEIS and SNVS. Ministry of Health. CFR, case-fatality rate; y, year.

years was above-trend (Figure 4), with five cases reported, again with no clear cause.

Although mortality was highest in infants aged <1 year, reflecting the high impact of IMD in this age group, CFR increased steadily after the age of 20 years (Figure 4), reaching over 25% in the group aged 60 years or more.

Serogroups

Serogroup identification of meningococcal samples improved over time, from 73% identified in 2010 to 91% identified in 2019 (Figure 5). The most common serogroups over the study period were B (48% of the serogrouped IMD cases) and W (42% of the serogrouped IMD cases), with an increase in B relative to W since 2015 (Figure 5), reaching 51% serogroup B and 27% serogroup W in 2019, particularly in the central region where most cases concentrate (Supplementary Figure S2). In contrast, in the north-east region there was a higher proportion of isolates corresponding to serogroup C, in the Cuyo region serogroup W predominated over the others, and in the north-west region both serogroups W and C predominated over B. The southern region showed few cases and mainly a predominance of serogroup B (Supplementary Figure S2).

In infants aged <1 year, the group in which most IMD cases were reported, serogroup B accounted for an increasing proportion of the characterized samples from 2015 onwards, reaching 70% in 2019 (Figure 6). In young children aged 1–4 years, serogroup B was also predominant, reaching over 70% of

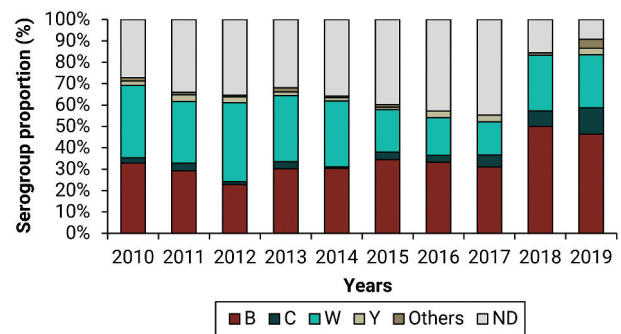


Figure 5. Meningococcal serogroups by year. Source: DiCEI-SISA-National Reference Laboratory. Ministry of Health. ND, not determined.

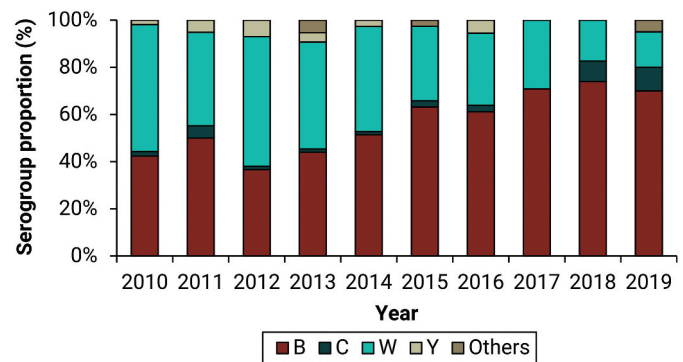


Figure 6. Meningococcal serogroups by year in infants aged <1 year (excluding cases without serogroup identification). Source: DiCEI-SISA-National Reference Laboratory Ministry of Health.

characterized samples in 2019 (Supplementary Figure S3). However, in adults aged 20 years and over, serogroup W was the most common (65% of IMD cases due to serogroup W and 24% of IMD cases due to serogroup B in the whole period) (Supplementary Figure S3).

MenACWY vaccination coverage

Since the introduction of the MenACWY vaccination program in Argentina in 2017, coverage for the first, second and third doses in infants ranged between 75–77%, 56–67% and 45–47%, respectively. There was a marked decline in coverage for the dose administered at age 11 years from 47.5% in 2017 to 38.1% in 2018 and 24.1% in 2019 (Supplementary Figure S4). This was due to a shortage of vaccine supply and the NIP authorities, in that context, suggested the prioritization of infant over adolescent vaccination during that time.

Discussion

This study used data from official sources to describe the epidemiology of IMD in Argentina between 2010 and 2019, by estimating IMD incidence rates, mortality, CFR and serogroup patterns in this period, including the reported MenACWY vaccine coverage rates (2017–2019) following the introduction of the vaccine in 2017. A total of 1,972 IMD cases were reported over the study period, concentrated in infants aged <1 year (661 cases), and with an increasing proportion of serogroup B in recent years.

Our results are consistent with publications from WHO⁴ that have also reported the highest IMD incidence in infants aged <1 year and highlight the importance of vaccination against meningococcal disease at a very early age. Our study found no second peak in IMD incidence in adolescents and young adults. This contrasts with the pattern of a second incidence peak in adolescents and young adults observed in Europe and North America and may reflect differences in adolescent/young adult lifestyles in Argentina, for example fewer individuals living in collective housing such as college accommodation.

Our results indicated a higher incidence rate of IMD in 2012–2014 with a decline after 2015 and the lowest incidence in 2018–2019. The peak in 2012–2014 could be related to the emergence of serogroup W in Chile at the end of 2011, which led to a 30% increase in IMD cases in Chile.²⁴ The lowest incidence rates for IMD were observed in 2018 and 2019 after the introduction of the MenACWY-CRM197 vaccination program in Argentina, although it is not yet possible to fully attribute this observed decrease to the vaccination strategy as the decreasing trend started earlier, in 2015. It may reflect natural variations in disease incidence, and epidemiological surveillance for a longer period will be needed to assess the impact of the vaccination program. Similarly, the IMD-related mortality rate in infants aged <1 year was lower in 2017, 2018 and 2019, with one, three and two cases reported, respectively, compared with an average of four cases per year over the study period. However, the numbers are too small to draw any firm conclusion.

Our finding that CFR increased with age is consistent with previous publications,^{25,26} and may reflect increasing prevalence

of co-morbidities among older age groups, or variations in serogroups between age groups.

Serogroup B was the most prevalent serogroup in infants aged <1 year and young children aged 1–4 years in our study, particularly since 2015, whereas serogroup W was the most prevalent type in adults aged 20 years or over. These results are broadly consistent with those reported by Guedes et al²⁶ and also ECDC,²⁷ that showed the serogroups W and Y as predominant in adults aged ≥65 years in Europe²⁷ and adults aged ≥55 years in North America and Europe.²⁶ In contrast, serogroup B was the predominant serogroup in infants aged <1 year in Europe.^{27,28} Our finding of an increasing proportion of serogroup B in young infants and children aged up to 4 years in recent years in Argentina, reaching 70% of all IMD cases serogrouped in 2019, illustrates the dynamic nature of IMD, and supports the importance of surveillance systems to help adjust prevention strategies against predominant serogroups.

The main strength of this study is that it covers data on reported IMD cases over a decade throughout Argentina in a wide range of age groups. Nevertheless, the study also had some limitations. Passive surveillance systems do not capture all cases, and therefore some under-reporting is likely.²⁹ However, this limitation does not influence our goal to describe the present epidemiology of IMD in Argentina. Meningococcal serogroups were not identified in all cases, although the proportion of cases with serogroups characterized has increased since 2018. Deaths due to IMD may be under-reported because only the primary cause of death is usually recorded in death certificates, and in addition, deaths may be mis-classified in the database despite internal quality control procedures. It was not possible for our study to identify IMD-related deaths by serogroup, due to the lack of connection between the official databases. Finally, the databases do not record sequelae resulting from IMD cases. As IMD is known to be associated with serious sequelae such as hearing loss or learning disability in 10–20% of survivors,¹ this means that the true impact of IMD will be substantially under-reported in our analysis.

The effort of the NIP to implement and sustain a universal vaccination program against meningococcus is noteworthy, considering the investment and the logistics issues involved in developing a program to cover infants, toddlers, and adolescents. Substantial heterogeneity exists in the recommendations of meningococcal vaccines included in NIPs across countries. Worldwide recommendations³⁰ are usually based on infant/toddler immunization, with some countries recommending immunization only for toddlers. Only a few countries in Latin America have developed a universal mass vaccination program for *N. meningitidis*. The NIP of Chile has implemented a universal toddler vaccination program with one dose of MenACWY vaccine for all children at 12 months of age, following an outbreak of MenW IMD that occurred between 2012 and 2014, affecting mainly children aged <5 years and adults aged over 80 years.^{24,31} More recently, the Chilean Ministry of Health announced that in 2023 the IMD vaccination strategy will be extended also to cover MenB in infants.³² In contrast, Brazil only offers vaccination against MenC in infants and toddlers, with MenACWY as a booster dose implemented in adolescents since 2020.^{33,34}

In conclusion, this study reports epidemiological data for IMD in Argentina over a ten-year period. Our findings are broadly consistent with other studies and show that IMD presents a significant public health burden, concentrated in infants aged <1 year. Serogroup B was the predominant serogroup in this age group, increasing in recent years. Our results indicate the importance of vaccination against IMD at an early age, and the need to periodically review preventive strategies in order to protect against all predominant serogroups. The dynamic behavior of IMD indicates that efficient disease surveillance systems are essential to provide timely epidemiological information on IMD in Argentina, which will help to support evidence-based decision-making.

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Disclosure statement

Maria E. Pannunzio, Maria B. Seoane, and Jorge A. Gomez are employed by GSK. Maria B. Seoane and Jorge A. Gomez hold shares in GSK. Analía Urueña's institution received funding for investigator-led studies from GSK, MSD, Seqirus, Takeda and Sanofi-Pasteur. Analía Urueña has received honoraria from Takeda and Seqirus for acting as a speaker in congresses outside the scope of the submitted work. Analía Urueña has received support for Seqirus and Pfizer for attending meetings. Analía Urueña has received honoraria from GSK, Takeda and Seqirus for taking part in advisory boards. Analía Urueña is a member of Directory board of Sociedad Argentina de Vacunología y Epidemiología (SAVE). Norberto Giglio's institution received funding for investigator-led studies from GSK, MSD, Seqirus, Takeda, Sanofi-Pasteur, FIPEC, NUTRICIA BAGO. Norberto Giglio has received honoraria from SANOFI, Seqirus, Pfizer, MSD. Norberto Giglio has received support from SANOFI, Seqirus, Pfizer for attending meetings. Norberto Giglio is a member of the Pediatric Research Board Argentina Pediatric Society and Ricardo Gutierrez Children's Hospital IRB. Analía Urueña, Maria E. Pannunzio, Maria B. Seoane, Jorge A. Gomez, and Norberto Giglio declare no other financial and non-financial relationships and activities. Silvina Neyro is a member of Directory board of Sociedad Argentina de Infectología Pediátrica (SADIP) and a member of the pediatric infectious diseases Committee of Sociedad Argentina de Infectología (SADI). Carolina Rancaño and Adriana Efron declare no financial and non-financial relationships and activities and no conflicts of interest.

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