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Original Article

Meningococcal Disease in a Pediatric Hospital in Chile: An 8 Year Review

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Abstract

Background: Epidemiology of Meningococcal Disease (MD) has changed in Chile these recent years due to the appearance of serogroup W, which led to a vaccination campaign during 2012 and the incorporation of a meningococcal vaccine in the National Immunization Program. Our aim is to describe clinical and epidemiological pediatric patients with *Neisseria meningitidis* infections in our hospital during these recent events.

Methods: Descriptive epidemiological study analyzing clinical presentation and evolution of children aged 0 to 15 years admitted to a public pediatric hospital in Santiago de Chile between 2008 and 2015 with the diagnose of meningococcal disease and their microbiological confirmation.

Results: We attended 44 patients with MD (5.5 cases per year). The average age was 31.9 months (52.3% males). Clinical presentation was: 16 meningitis with meningococcemia, 10 isolated meningococcemia, 8 bacteremia, 7 isolated meningitis and 3 septic arthritis. The predominant serogroup until 2010 was B (10/14) and since 2011 it was W (18/30). Average incidence was 2,69/100,000. Overall mortality was 13.6% (6/44).

Discussion: We observed a rising incidence of MD in our population since 2010 with a peak in 2013, given both cases of serogroup W and B. Serogroup W was predominant since 2011. Most children were under 2 years (32/44). Mortality was low (13.6%) and we didn't have higher lethality associated with serogroup W. After the vaccination campaign, we observed the absence of W cases in the vaccinated age group.

Keywords: Meningococcemia; Meningococcal; *Neisseria meningitidis*; W serogroup; Pediatric

Background

Meningococcal Disease (MD) is one of the most devastating infectious diseases, feared both for patients and for health care personnel since it tends to affect previously healthy young patients and can progress to shock and death within a few hours [1]. It is caused by the bacterium *Neisseria meningitidis*, a Gram-negative diplococcus which is divided into 13 serogroups from its polysaccharide capsule, with 5 serogroups which mainly relate to infection in humans: A, B, C, Y and W [2].

While in countries with endemic MD incidence is low (0.5-1.5 per 100,000 in the US), it has a high fatality rate, which varies between 7 and 22% [3-5], which makes it a major public health problem. The most affected patients are infants younger than 2 years, with an almost 10 times higher incidence than the rest of the population [6]. However, the disease can also present in epidemic periods, which are difficult to define. These periods are usually related to overcrowding (periods of war, natural disasters, educational institutions and student's residences) or a change in the circulating bacteria serogroup [4] and are associated with an increased lethality up to 30% [7].

In Chile, there has been a significant drop in the incidence of MD since year 2000, from 3.7/100,000 that year to less than 1 per 100,000 since 2006, maintaining lower rates than 1/100,000 until 2012 inclusive, being the lowest value in 2011 (0.4/100,000). However, there has been a significant increase of lethality from 2010 (which had been stable since the 90's close to a 10%) to 14.1%, 15.1% and 25.3% in the years 2010, 2011 and 2012 respectively [8,9]. This has coincided with a change of the circulating serogroup in the country, which until 2009 consisted mainly of serogroup B. But since 2010 there has been a rapid decline of the serogroup B with a sustained rise in cases of serogroup W [10]. Despite these events, the incidence in 2012 remained low and did not exceed 0.8 cases per 100,000 inhabitants. Even at regional level, in areas where a high number of cases were registered, the highest rates did not exceed 1.4/100,000 in the region of Valparaiso and 1.1/100,000 in the Metropolitan Region [8], which are below the definition of outbreak established by the Center for Disease Control and Prevention (10 per 100,000 inhabitants) [2].

In Latin America, an increase in the presence of serogroup W in Brazil has been documented since 2002, later in Argentina since 2006 and then in Chile since 2009, and there is a significant increase in cases between 2011 and 2012 in Chile, Argentina and Uruguay [11]. Through methods of molecular characterization and phenotyping made on samples taken in the Southern Cone countries, it has been established that the clones of the circulating serogroup W mostly correspond to the ST-11/ET-37 complex, which is related to the strain called Hajj, responsible for the outbreak of the pilgrims from

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Mecca of the year 2000 [12].

Following these changes in national epidemiology prevalence, with circulation of serogroup W and increasing lethality of MD in the country during these last years, a mass vaccination plan was conducted at the end of year 2012 for children between 9 months and 4 years 11 months and 29 days (with Menactra®, Menveo® and Mencevax® vaccines) [13] and subsequently to its incorporation as a regular vaccine of the National Immunization Program for 1 year old children, in order to prevent MD by serogroup W. In light of these facts, we wanted to review how MD has performed locally in a pediatric hospital of high complexity at the North Metropolitan Health Service (NMHS) of Santiago. For this, we evaluated all documented cases of invasive disease caused by *Neisseria meningitides* or high clinical suggestion cases, with primary emphasis on the causative serogroup, the clinical presentation, lethality and associated complications, prompt health care consult and the start of antibiotics; in order to compare the behavior of MD in our center with the national trend.

Objectives

1. Describe the clinical and epidemiological behavior of pediatric patients with infection by *Neisseria meningitidis* between the years 2008 and 2015 treated at Roberto del Río Children's Hospital, confirmed clinically or by microbiology.

2. Describe the causative serogroup of each case, the site of isolation of the infectious agent and the clinical presentation of MD.

3. Determine the incidence of MD in the NMHS, comparing the data obtained with national epidemiology these recent years.

4. Determine the lethality of meningococcal infection in patients treated in our hospital.

5. Explore eventual risk factors for severe outcome (lethality, extended stay, complications and sequels) for MD: age, gender, previous pathologies, time spent on medical care and evolution time prior to the start of antibiotics.

Materials and Methods

Study design

Descriptive epidemiological study, initially retrospective and prospective from 2012 onwards, gathering information between January 1st 2008 and December 31st 2015 at Roberto del Río Children's Hospital, which is a public pediatric hospital of high complexity with 131 basic beds and 45 critic beds and serves the population under 15 years of the northern sector of Santiago de Chile, which corresponds to approximately 185,550 children [14].

Study population

Patients whom *Neisseria meningitidis* was isolated as the causative agent of invasive infectious disease, isolated in blood, Cerebrospinal Fluid (CSF) and/or joint fluid, with serogroup confirmation at the Instituto de Salud Pública (ISP, the national reference laboratory of our country), or patients with a febrile purpura and signs of shock without identified etiologic agent.

Source of information

Patients' data was obtained from computerized hospital discharge records. The following diagnoses were sought: meningococcemia (acute, chronic and unspecified), meningococcal meningitis, meningococcal arthritis, unspecified meningococcal infections and other unspecified meningococcal infection. Patients with sterile liquid cultures in which *Neisseria meningitidis* was isolated were analyzed from the hospital's Kern Mic® microbiology laboratory records or confirmed by the ISP. We obtained demographic variables, clinical information (date and time of the first medical consultation and use of antibiotics), microbiological data (the site of isolation, serogroup of bacteria and susceptibility testing) and a history of previous vaccination. Finally, we measured the total days of hospitalization and stay in Pediatric Intensive Care Unit (PICU), hospitalization's associated comorbidities, sequels and mortality.

Definitions

Meningococcemia: Patients with hemodynamic compromise that required at least resuscitation with volume, from whom *Neisseria meningitidis* was isolated in blood cultures or presented a febrile purpura without other demonstrable cause [15].

Purpura fulminans: Cases of meningococcemia with rapidly evolving and progressive purpura [16].

Bacteremia: Patients with positive blood cultures for *Neisseria meningitidis* without meningitis, purpura or hemodynamic compromise.

Meningitis: Patients with positive CSF cultures for *Neisseria meningitidis* or those with positive blood cultures or a febrile purpura

Table 1: Clinical presentation and sequels of MD by serogroup.

Serogroup	W	B	C	Total	Sequels
Meningococcemia + meningitis	4 (1 purpura fulminans)	10 (2 purpura fulminans)	1	15	3 Deceased 2 Neurological 1 Skin necrosis
Meningococcemia	3 (1 purpura fulminans)	5 (1 purpura fulminans)	2 (2 purpura fulminans)	10	3 Deceased 1 Amputation
Bacteremia	7	1	-	8	-
Meningitis	3	3	1	7	4 Neurological
Septic arthritis	2	1	-	3	-
Total	19	20	4	43*	
Sequels	2 Deceased 3 Neurological 1 Skin necrosis	3 Deceased 3 Neurological	1 Deceased 1 Amputation		

*One patient who presented a meningococcemia with meningitis was excluded due the infectious agent could not be determined. No sequels or decease were registered.

which presented compatible CSF with bacterial meningitis, but whose CSF cultures were negative [15].

Primary meningococcal arthritis: patients with acute septic arthritis without association of meningitis or meningococcal sepsis with isolation of *Neisseria meningitidis* in inflammatory joint fluid or blood [17].

Onset of fever was considered as the initial symptom of the disease, since it is an objective symptom, readily available and common to almost all cases of the different forms of MD presentation.

Statistical analysis

Descriptive analysis based on frequencies and rates. Incidence rates were calculated from the total population of children less than 15 years old attended at the NMHS, according to the forecast of the Institute of National Statistics (INS 2005-2020), excluding cases referred to the hospital from other areas of Santiago that do not correspond to NMHS. The calculation of lethality of the local MD included all cases attended at our hospital. We explored possible risk factors for severe course of MD (complications, extended stay and sequels) and mortality, associated with age, gender, previous pathologies, time prior to medical attention and time prior to the start of antibiotics. This association was measured with Fisher test and its odds ratio; also confidence interval and *p* value were reported.

Ethical framework

Our investigation was approved by the NMHS ethics committee and research. It does not require informed consent or presence of a public notary for reviewing the clinical records, by being a non-interventional local epidemiological surveillance study and being ourselves part of the treating team directly related to the health care of the patient's included [18]. We declare to have no conflict of interest since we did not receive any kind of funding for this study.

Results

During the period between 2008 and 2015, 44 patients were treated with invasive meningococcal infections at Roberto del Río Children's Hospital, with an average of 5.5 cases per year. The average age was 31.9 months and 52.3% of them were males (23/44). Of the patients affected, 10 had previous pathologies; 4 of them being preterm infants with less than 34 weeks of gestational age.

Clinical behavior

During this period, we attended 16 cases of meningococcemia with meningitis, 10 isolated meningococcemia, 8 bacteremia, 7 isolated meningitis and 3 primary meningococcal arthritis. Among cases of meningococcemia (isolated or with meningitis) 7 were presented as purpura fulminans, of which 5 died, one ended with lower limbs amputation and the other with lower limbs skin necrosis (see Figure 1). The cases of bacteremia corresponded to benign course diseases, mostly caused by serogroup W and only 1 was handled for 48 hours in PICU as a caution because of the isolation of *Neisseria meningitidis* in blood. The time between the onset of fever and the first consultation time was on average 9.25 hours, while the average time between onset of fever and antibiotic administration was 40.33 hours.

Serogroup

The main serogroup until 2010 was B (10/14) and we observed a marked change from 2011 onwards, with serogroup W predominating (18/30) and reaching 100% of cases during 2012, until 2013 in which reappears B (see Figure 2). 4 cases of serogroup C were recorded, 2 of them were presented as purpura fulminans, of which one died and the other had lower limbs amputation. 20 cases of serogroup B and 19 cases of serogroup W were presented, with variable clinical features (see Table 1). In one case (2.27%) we were not able to isolate the agent, which clinically behaved like a meningococcemia with meningitis but whose cultures were negative. The patient survived without apparent sequels at discharge.

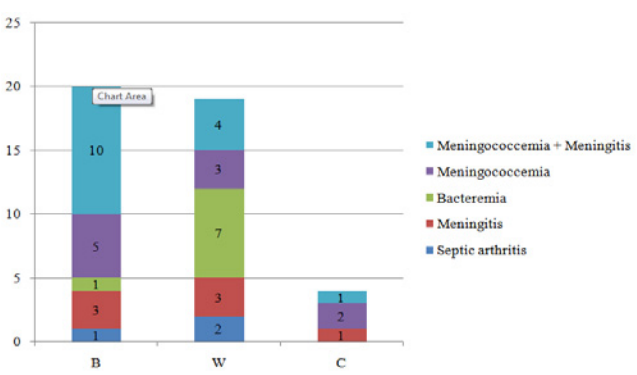

Figure 1: Clinical presentation by serogroup.

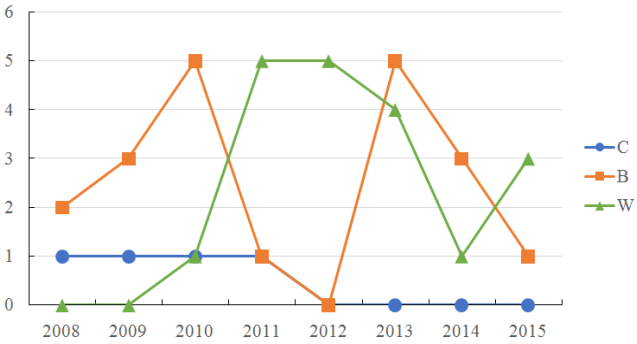

Figure 2: Annual cases of MD attended at Roberto del Río Children's Hospital by serogroup.

Treatment

On average, patients completed 8.8 days of antibiotic treatment (excluding deceased patients and 3 who completed treatment in their respective hospitals once stabilized in PICU). In about 80% of cases (35/44) treatment began with third-generation cephalosporins, mainly cefotaxime. Of these patients, 17 completed their treatment with the same antibiotic, 15 completed their treatment with penicillin once the causative agent was isolated and 3 of them died within 24 hours, reaching only one dose of antibiotic administration. Of the remaining patients, treatment began mostly with penicillin, only one of which was changed to cefotaxime because he evolved with meningitis. Only 2 patients began treatment with cloxacillin (patients with septic arthritis) but once the infectious agent was confirmed it was changed to cefotaxime and penicillin respectively. One of the patients died in the emergency room and could not receive antibiotics.

Susceptibility

We detected *Neisseria meningitidis* with intermediate resistance

Table 2: Association between possible risk factors with death, prolonged stay and sequels at discharge.

Risk factor	Death	Prolonged stay	Sequels at discharge
Age < o = 6 months	OR 2.8 IC (0.31 – 23.9) *p* 0,2	OR 1.1 IC (0.18 – 815) *p* 0,6	OR 4 IC (0.5 – 27.8) *p* 0,1
Male	OR 5.5 IC (0.5 – 275.5) *p* 0,11	OR 1.4 IC (0.28 – 71) *p* 0,4	OR 0.29 IC (0.02 – 2.04) *p* 0,1
Previous pathology	OR 1.87 IC (0.14 – 15.8) *p* 0,4	OR 0.71 IC (0.11 – 5.6) *p* 0,4	OR 3 IC (0.3 – 21.9) *p* 0,2
Time between onset of fever and first consultation > 6 hours	OR 1.3 IC (0.16 – 11.5) *p* 0,5	OR 5.8 IC (0.91 – 62,2) *p* 0,03	OR 0.7 IC (0.1 – 4.9) *p* 0,5
Time between onset of fever and antibiotic administration > 12 hours	OR 5 IC (0.47 - 248) *p* 0,13	OR 1.6 IC (0,3 – 8.3) *p* 0,3	OR 1.9 IC (0.29 – 14.29) *p* 0,3

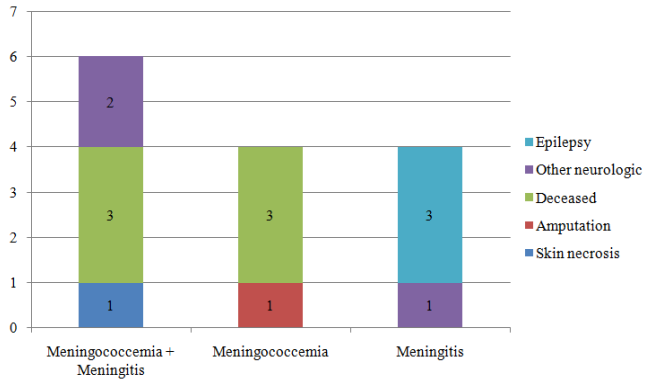

Figure 3: Sequels according to clinical presentation of MD (cases of bacteremia and septic arthritis evolved without sequels).

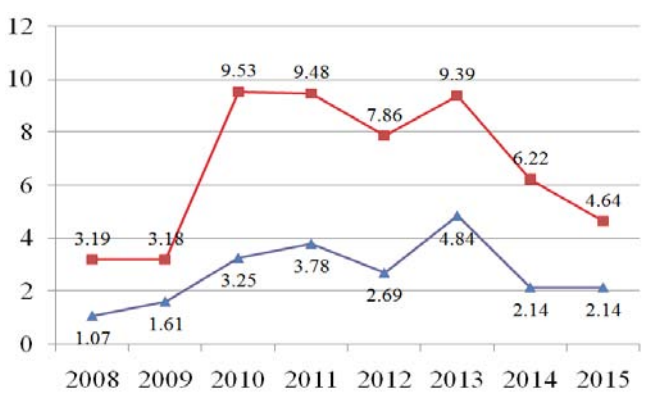

Figure 4: Cases of MD every 100.000 habitants under 5 years old (squares) and under 15 years old (triangles) residents in areas are corresponding to the NMHS.

to penicillin in only one patient, but only 25% (11/44) patients had antibiotic susceptibility testing registered on their laboratory records.

Hospitalization

Hospitalization lasted 14.17 days on average, excluding deceased patients and those transferred to their reference hospitals or private clinics. 72.7% (32/44) of the patients required hospitalization in PICU, with an average stay of 6.23 days (range 1-44), excluding 2 patients who died in PICU within the first 24 hours.

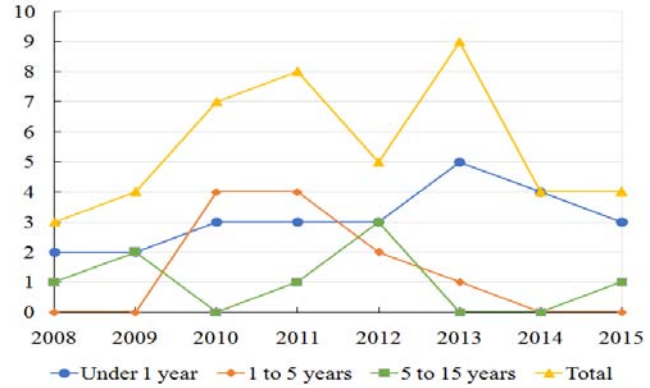

Figure 5: Annual cases of MD by age group.

Evolution

Comorbidities associated with hospitalization were presented in 16 patients (all stayed in PICU). In addition, 8 patients were discharged with sequels, mainly neurological, 2 of them were preterm infants less than 32 weeks. The 4 patients who moved to their reference hospitals once stabilized in PICU had no sequels at the time of referral, but it is unknown whether they had any at the moment of discharge. The aftermath according to each serogroup are summarized in Table 1 and Figure 3.

Incidence and cases

The average incidence rate for the analyzed period was 2.69 cases per 100,000 children under 15 years of the NMHS, ranging from 1.07/100,000 in the year of lower incidence and 4.84/100,000 in the year of more cases. An increase in the incidence of MD from 2010 is observed, coinciding with the emergence of serogroup W, being the highest incidence during 2013 given by the presence of both serogroups: W and B (which reappears this year). From 2014 a sustained drop in cases is observed (see Figure 2). The highest incidence is concentrated in patients younger than 5 years (see Figure 4), corresponding to more than 80% of cases, being the vast majority under 1 year (25/44). After the 2012 vaccination it is evidenced that most cases are concentrated in children under 1 year, corresponding to 100% of cases during 2014 (see Figure 5).

Fatality

The overall lethality of the series in our hospital during these years

was 13.63% (6/44); 3 cases by serogroup B, 2 by serogroup W and 1 by serogroup C. The annual fatality rate was 33.3% in 2008 (1/3), 0% the following years, 22.2% in 2013 (2/9), 25% in 2014 (1/4) and 50% in 2015 (2/4). Lethality was 25% for serogroup C (1/4), 15% for B (3/20) and 10.5% for W (2/19). Lethality in children under 1 year for serogroup W was 7.7% (1/13) and 25% for serogroup B (3/12). Isolated meningococcemia lethality was 30% (3/10), meningococcemia and meningitis lethality was 18, 8% (3/16).

Vaccination

None of the patients in our series was previously vaccinated for MD. No cases of serogroup W or C occurred in the age range from 1 to 5 years from 2013, after the immunization with quadrivalent vaccine started in the country.

Discussion

Meningococcal Disease (MD) remains an important cause of pediatric morbidity and mortality in our country, but there has been a significant change in the epidemiology regarding the circulating serogroup, with a significant increase in the presence of serogroup W these recent years in several countries of the Southern Cone (including ours) [11,12]. Since 2010, Chile observed the appearance of serogroup W and its predominance until 2013, mainly in the Metropolitan Region, displacing serogroup B which was the previous predominant serogroup. In our analysis, we see the same behavior in the rest of the country reflected in our local circulating serogroups. However, the predominance of W in the study population was only until 2012 and from 2013 we see the re-emergence of serogroup B, probably as a result of the intervention of the vaccination campaign implemented during 2012, dominating again with serogroup W for the following years (see Figure 2).

The main group affected by MD corresponds to children less than 5 years, concentrating most cases in infants (25/44 are under one year). More than half of the cases of the NMHS are presented as meningococcemia, either alone or accompanied by meningitis. Almost 20% of patients have sequels, mainly neurological. Striking is the high proportion of neurological sequels in patients with meningitis alone (4/7), mainly epilepsy, when classically isolated meningococcal meningitis is described to have lower incidence of focal neurological signs and seizures compared with other etiologies of meningitis (such as *Haemophilus influenzae* or *Streptococcus pneumoniae*) [19].

Serogroup C is presented in older children and corresponds to the most aggressive clinical behavior; it is the most harmful serogroup and it relates with the highest percentage of fatalities (1/4), which coincides with what is described in the literature [20,21]. Serogroup B showed a total lethality of 15% (3/20) with a 20% annual lethality during 2013, 33.3% in 2014 and 100% in 2015 (only one case of serogroup B that year). With respect to the emergence of serogroup W, we can conclude that the epidemiological behavior of our center was similar to that observed in the rest of Metropolitan Region, however, it showed a lower fatality rate compared to what is described at the national level, being 25% in 2013 (*versus* 31.7% nationally) [9] without fatalities between 2012 and 2014 and 33.3% in 2015, with an overall fatality rate of 10.5% (2/19) during the years analyzed.

Perhaps what is most surprising in our analyzed group is the high number of cases of bacteremia with benign clinical course (8/44), mainly by serogroup W (7/8). In fact, the possibility of bacteremia by serogroup W was significantly greater than by serogroups B or C (OR 14, CI [1.4 - 656.3] $p = 0.007$). This may be because in our environment and in pediatrics in general, we have a higher index of suspicion regarding meningitis and meningococcemia, unlike what happens in adults, in whom the W serogroup behaved more aggressively and with greater lethality. It also could be that occult bacteremia corresponds primarily to a pediatric presentation, however, searching in the literature we found many authors mentioning bacteremia as one of the presentations of MD but its frequency is usually not described, probably being classified as meningococcemia or other forms of clinical presentation [9].

The incidence of MD in children under 5 years in the NMHS is almost 10 times higher than the overall incidence rate, which coincides with national data [8]. In our center, a significant rise in the incidence was observed from 2010 (3.25 versus 1.07/100,000 the previous year), being even higher in 2011. It is interesting to note that during 2012 we had a slight decrease in the incidence of MD (year in which the alert is generated by the lethality associated with serogroup W), but increases again in 2013 reappearing serogroup B. Since 2013 the number of cases caused by serogroup W begins to decrease, co dominating with serogroup B during the following years (Figure 2), which could be explained by the effect of the vaccination campaign of 2012 and the subsequent incorporation of the tetravalent conjugated vaccine to the National Immunization Program. In fact, after the campaign no cases of MD by serogroups contained in the vaccine are observed in the age group included (9 months to 5 years). It is worth remembering that the vaccine used in the campaign was quadrivalent, which does not include coverage for serogroup B. Recently the FDA (US Food and Drugs Administration) approved the use of the first vaccine against serogroup B in patients from 10 to 25 years, but its use in infants is still not approved [22].

Although our study group is small and no statistically significant data was obtained, a tendency for certain risk factors that are associated with an unfavorable evolution of MD were observed (see Table 2). For example, being less than one-year-old and being a male means greater risk of death and sequels. Being a male shows tendency to be protective for sequels at discharge, which may seem contradictory, but this is probably due to when calculating such risk deceased patients are excluded (therefore, males who survived probably did so in better conditions). The start of antibiotics later than 12 hours from the onset of fever shows no tendency to increased risk for death, sequels and prolonged stay. Consultation later than 6 hours from the onset of fever also shows a risk tendency of prolonged stay, but would be protective for the risk of sequels. The latter may also seem counter intuitive, but may be because those who consult later in general will have a less severe and therefore less harmful disease.

In global, we can conclude from our analysis that MD is a low incidence infection but with high morbidity and lethality, especially for infants. Our impression is that that the vaccination campaign in 2012 with quadrivalent vaccine had a positive effect on the fall in the incidence of serogroups contained in the vaccine included age group, especially the W. It is therefore important to maintain a preventive strategy, vaccinate children at the lowest possible age and expand vaccination to achieve serogroup B protection to generate a global impact on reducing the disease.

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