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Uma década de casos de meningite no estado do Paraná, Brasil: estudo dos casos no período pré- e pós-vacinal

One decade of meningitis cases in Paraná State, Brazil: study of cases in the pre- and post-vaccinal period

RESUMO| Introdução: *A meningite é caracterizada por um processo inflamatório que acomete o sistema nervoso central e que representa um problema de saúde pública em todo o mundo.* **Objetivo:** *Esta pesquisa teve como objetivo descrever a epidemiologia das meningites no estado do Paraná, Brasil, bem como o impacto da introdução das vacinas conjugadas (pneumocócica e meningocócica) no calendário vacinal.* **Métodos:** *Foi realizado um estudo observacional, descritivo e retrospectivo dos casos notificados e confirmados de meningite no estado do Paraná. Os dados obtidos foram organizados em período pré (2007 a 2009) e pós-introdução (2010 a 2016) das vacinas meningocócica C e pneumocócica 10-valente.* **Resultados:** *Entre 2007 e 2016, foram confirmados 17.045 casos de meningite no estado do Paraná, e o ano com maior número de casos foi 2007 (3.489). A maioria dos casos notificados ocorreu em homens (59,1 %), e a faixa etária mais acometida foi de 0 a 9 anos de idade. Das meningites com etiologia definida, a meningite viral foi a mais frequente, seguida de Neisseria meningitidis, Streptococcus pneumoniae, Mycobacterium tuberculosis e Haemophilus influenzae. Neisseria meningitidis sorogrupo C foi o mais frequente, seguido do sorogrupo B. Após a implantação da vacina, houve diminuição significativa da frequência de N. meningitidis e S. pneumoniae em crianças de 1 a 4 anos.* **Conclusão:** *As meningites bacterianas imunopreveníveis têm diminuído no Paraná, especialmente com o advento das vacinas conjugadas. O conhecimento da etiologia da meningite é importante para elaborar medidas de controle e prevenção pela vigilância epidemiológica e, assim, promover melhorias na saúde pública.*

Palavras-chave| *Meningite; Meningite Pneumocócica; Meningite Meningocócica; Vacina.*

ABSTRACT| Introduction: Meningitis is an inflammatory process capable of affecting the central nervous system in humans; thus, it is a global public health issue. **Objectives:** Describing meningitis epidemiology in Paraná State, Brazil, as well as the impact of introducing conjugate vaccines (pneumococcal and meningococcal) in the immunization schedule. **Methods:** Retrospective, observational and descriptive study about notified and confirmed meningitis cases in Paraná State. Data were organized in pre- (2007 to 2009) and post-introduction (2010 to 2016) of meningococcal C and 10-valent pneumococcal vaccines. **Results:** In total, 17,045 meningitis cases were confirmed in Paraná State from 2007 to 2016 - 2007 was the year recording the largest number of cases (n=3,489). Most notified cases were diagnosed in men (59.1%) and mostly affected patients in the age group 0-to-9-years. Aseptic meningitis (viral) was the most often diagnosed type of the disease among meningitis with known etiology; it was followed by *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis* and *Haemophilus influenzae*. *Neisseria meningitidis* serogroup C was the most common type; it was followed by serogroup B. There was significant decrease in the frequency of *N. meningitidis* and *S. pneumoniae* in 1-to-4-year-old children, after vaccination. **Conclusion:** Vaccine-preventable bacterial meningitis rate has decreased in Paraná State, mainly due to the introductionof conjugate vaccines. Understanding meningitis etiology is a key factor to measuments taken by epidemiological surveillance to prevent and control the diseaseand, consequently, to help improving public health.

Keywords| Meningitis; Pneumococcal Meningitis; Meningococcal Meningitis; Vaccines.

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INTRODUCTION|

Meningitis is known for causing inflammatory process in human meninges, between the two membranes involving the brain and the spinal cord (pia mater and arachnoid). It can be caused by different infectious agents such as bacteria, viruses, fungi and parasites, as well as by non-infectious agents[1].

Although meningitis can be caused by different etiologic agents, bacterial origin meningitis is of greater concern from the epidemiological viewpoint, since it is more often diganosed, severe and can quickly evolve to death[2]. Bacterial meningitis (BM) can be treated with antimicrobials, although it remains a serious public health issue, with over 1.2 million cases estimated per year worldwide[1,3-6]. Its lethality rate can reach up to 70% when patients are not treated; it accounted for 300,000 deaths in 2015[5-7]. Approximately 20% of survivors present permanent sequelae, such as mental retardation, deafness and epilepsy, which may vary depending on invidivuals' age, geographical location and etiological agent[7,8].

Seventy-five percent (75%) of BM cases wordwide are diagnosed in children younger than 5 years, due to their immature immune system[3,4,8]. The number of confirmed BM cases in Brazil has decreased since 2013; however, 4,863 cases and 903 deaths (18.57%) were reported in 2019. Although BM lethality in Paraná State is slightly lower (12.13%), the disease accounted for 470 cases and 57 deaths in that very same year[9].

Acute BM is mainly caused by *Neisseria meningitidis* (meningococcus), which is followed by *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* serotype b (Hib)[10]. Disease control and prevention are primarily based on vaccines capable of promoting serum-specific protection to each etiological agent. Hib conjugate vaccine was implemented in Brazil in 1999, and it helped decreasing meningitis cases caused by this agent by 90%[1].

Serogroups C and B have been the most frequent meningococcal meningitis types circulating in Brazil since 1990. The number and proportion of meningitis cases attributed to serogroup C in different regions countrywide has increased after 2015.

Meningococcal C and pneumococcal 10-valent vaccines were included in the vaccine calendar set for children treated in the Brazilian public health system, in 2010. Meningococcus remains the first cause of BM in the country, although its incidence has changed in recent years - 1.54 cases per 100,000 inhabitants were recorded in 2010 and 0.53 cases per 100,000 inhabitants, in 2018[11].

Given the high morbidity and mortality rates associated with meningitis, it is essential conducting a study about the pre- and post-introduction of new vaccines to help better understanding the current status of the disease. Such a study can encourage epidemiological surveillance agencies to implement prevention and control measures.

The aims of the current research wereto describe the epidemiology of one decade of meningitis cases in Paraná State, Brazil, as well as the impact of introducing conjugate vaccines (pneumococcal and meningococcal) in the immunization schedule.

METHODS|

Retrospective, observational and descriptive study about notified and confirmed meningitis cases in Paraná State from January 2007 to December 2016. Data were extracted from *Sistema de Agravo de Notificações* (SINAN)-Tabwin 2.7 software - by the 15th Regional Health Unit of Paraná State.

Variables collected from SINAN comprised sex, age, disease signs and symptoms, pregnancy, pre-existing diseases, confirmation criteria, laboratory data, case etiology and evolution.

Data were tabulated in the pre-vaccine period (between 2007 and 2009), before the introduction of meningococcal C and 10-valent pneumococcal vaccines, as well as in the post-vaccination period (between 2010 and 2016), after these vaccines were introduced in the basic immunization schedule.

Meningitis cases reported in Paraná State, Brazil, were analyzed through Chi-square test and Odds ratio, at 5% significance level (p <0.05), in OpenEpi® software. The study was approved by the Human Research Ethics Committee of Paraná State Health Department (1.113.915).

RESULTS |

The total number of 21,649 suspected meningitis cases were notified (Supplementary material, Table S1) in all 22 Regional Health (RH) Units of Paraná State, Brazil, from 2007 to 2016 - 17,045 of them were confirmed (Table 1). Metropolitana (2nd) was the RH unit recording the largest number of absolute reported cases, whereas Cianorte RH unit (13th) recorded the smallest number of cases (Table S1). In addirion, 2007 was the year recording the largest number of confirmed cases (n=3,489) (Table 1). Most notified cases were diagnosed in men (59.1%) (Table S2). Most confirmed cases comprised children in the age group 0 to 9 years (55.8%), whereas 38.1% of cases were observed in children in the age group 0 to 4 years (Tables 1 and 2).

It was possible confirming 9,301 (54.6%) meningitis cases caused by virus throughout the 10 investigated years; 929 (5.5%) cases were caused by *N. meningitidis*,;678 (4.0%), by *S. pneumoniae;* 218 (1.3%), by *Mycobacterium tuberculosis;* and 69 (0.4%), by *H. influenzae* (Table 3).

The high annual frequency of meningitis caused by *N. meningitidis* and *S. pneumoniae* in 0-to-9-year-old children has encouraged the analysis of the number of cases caused by these two main agents in this age group (Figure 1).

Children in the age groups <1 year, 1-4 years and 5-9 years were analyzed for pneumococcal and meningococcal meningitis. The number of cases caused by *N. meningitidis* in 1-to-4-year-old children has significantly decreased

Table 1 - Confirmed cases of meningitis by age group, in Paraná state, Brazil, from January 2007 to December 2016

Age group (years old)	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
< 1	339	306	265	249	251	227	276	255	345	275	2,788
1 – 4	985	503	239	257	319	239	341	253	331	236	3,703
5 – 9	943	423	197	179	265	214	272	184	186	159	3,022
10 – 14	401	173	127	119	127	107	127	83	85	75	1,424
15 – 19	160	108	82	50	74	74	64	49	56	49	766
20 – 34	317	225	158	189	232	166	185	186	164	133	1,955
35 – 49	189	218	141	153	166	173	182	171	167	145	1,705
50 – 64	110	132	79	74	105	108	138	118	136	129	1,129
65 – 79	43	56	33	46	49	40	54	43	60	50	474
≥ 80	2	6	7	7	4	12	9	14	9	9	79
Total	3,489	2,150	1,328	1,323	1,592	1,360	1,648	1,356	1,539	1,260	17,045

Source: Sistema de Agravo de Notificações (SINAN)-Tabwin 2.7 software.

Table 2 - Cases of meningococcal disease and pneumococcal meningitis in the pre- (2007-2009) and post-vaccination (2010-2016) period, in Paraná state, Brazil in all age groups

	Meningococcal disease				Pneumococcal meningitis			
	Pre-vaccinal	Post-vaccinal			Pre-vaccinal	Post-vaccinal		
Age range (years old)	**n (%)**	**n (%)**	**OR (CI95%)**	**p**	**n (%)**	**n (%)**	**OR (CI95%)**	**p**
< 1	65 (15.4)	101 (19.9)	0.7 (0.5; 1.0)	0.094	47 (21.3)	59 (12.9)	1.8 (1.2; 2.8)	0.007*
1 – 4	130 (30.9)	120 (23.6)	1.4 (1.0; 1.9)	0.016*	39 (17.6)	52 (11.4)	1.7 (1.1; 2.6)	0.034*
5 – 9	57 (13.5)	65 (12.8)	1.1 (0.7; 1.6)	0.813	17 (7.7)	26 (5.7)	1.4 (0.7; 2.6)	0.404
10 – 14	42 (10.0)	36 (7.1)	1.5 (0.9; 2.3)	0.144	18 (8.1)	29 (6.3)	1.3 (0.7; 2.4)	0.482
≥ 15	127 (30.2)	186 (36.6)	0.8 (0.6; 0.99)	0.045*	100 (45.3)	291 (63.7)	0.5 (0.3; 0.7)	< 0.001*
Total	421 (100)	508 (100)			221 (100)	457 (100)		

*p < 0.05. Source: Sistema de Agravo de Notificações (SINAN)-Tabwin 2.7 software.

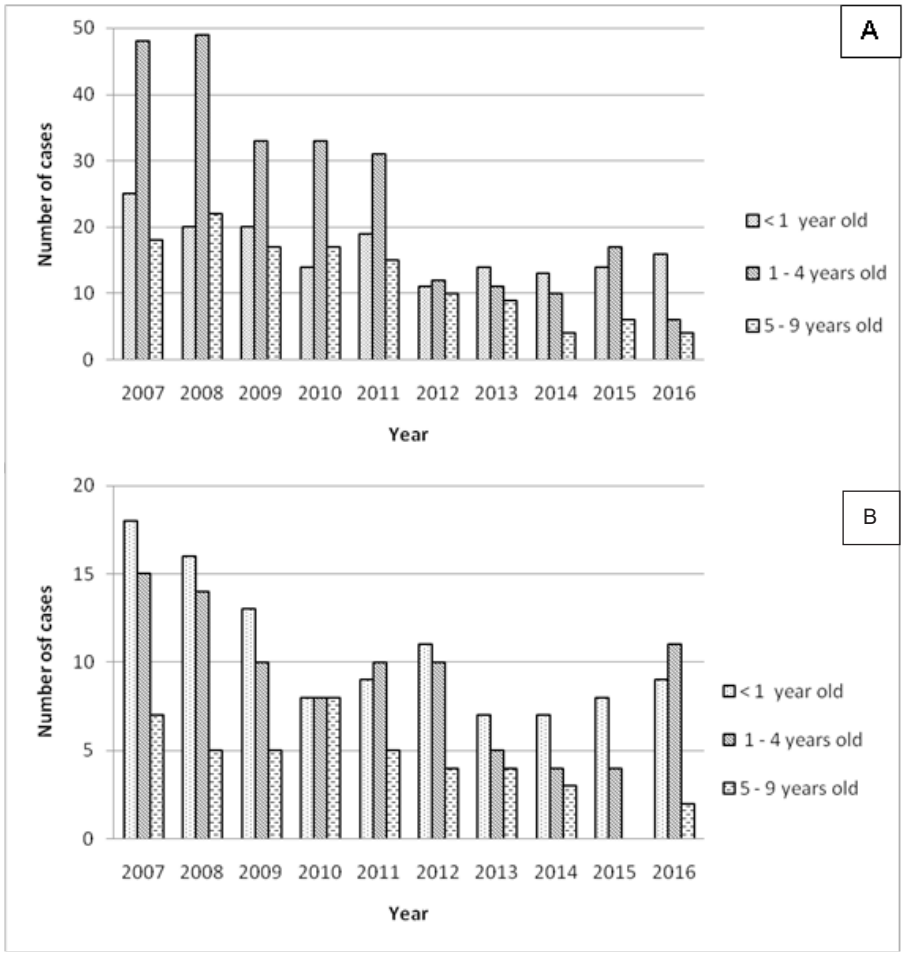
between the pre- and post-vaccinal periods (p=0.016). There was statistically significant decrease in the frequency (%) of meningitis cases caused by *S. pneumoniae* in children in the age groups <1 and 1-4 years (p=0.007 and p=0.034, respectively), after vaccination (Table 2). Both etiologies recorded significant increase in the number of cases in

Table 3 - Frequency of confirmed cases of meningitis by etiology, in Paraná state, Brazil, from January 2007 to December 2016

Etiology	Cases		Death	
	n	%	n	%
Aseptic meningitis	9,301	54.6%	131	1.4%
Bacterial, others	5,147	30.2%	396	7.7%
Meningococcal disease	929	5.5%	202	21.7%
Pneumococcal	678	4.0%	176	26.0%
Mycobacterium tuberculosis	218	1.3%	26	11.9%
***Haemophilus* spp.**	69	0.4%	4	5.8%
Others*	703	4.1%	130	18.5%
Total	17,045	100.0%	1,065	6.2%

*Not specified, other etiology and ignored. *Source: Sistema de Agravo de Notificações (SINAN)-Tabwin 2.7 software.*

Figure 1 - Distribution of cases of meningitis by Neisseria meningitidis (A) and Streptococcus pneumoniae (B), in Paraná state, Brazil, in children aged 0 to 9 years, from January 2007 to December 2016



Source: Sistema de Agravo de Notificações (SINAN)-Tabwin 2.7 software.

15-year-old (or older) individuals (p=0.404 and p=0.813) (Table 4).

Meningitis caused by *N. meningitidis* (meningitis and sepsis) comprised 929 confirmed cases between 2007 and 2016. Of this total, serologic tests (serogroup antigen detection) for *N. meningitidis* were performed in 469 patients (Table 4). *Neisseria meningitidis* serogroup C was the main BM agent in all age groups (227 cases) andit was followed by serogroup B (200 cases). Y, W135 and 29E were the other less common serogroups (42 cases, in total). There were no reports of A, D, X and Z serogroups (Table 4). The increased number of patients presenting serogroups B and C after the vaccine was introduced (in all age groups) was not statistically significant (p=0.324 and p=0.987, respectively). On the other hand, the increased number of patients presenting serogroup W135 in the post-vaccination period was statistically significant (p=0.034).

There was small decrease in the number of cases presenting serogroups C and B after vaccine implementation in the age group 0 to 4 years, but it was not statistically significant (p=0.628/p=0.620) (Table 4).

Children in the age group 0-to-4 years were mostly affected by meningitis caused by *H. influenzae*. However, Paraná State did not record any case of meningitis caused by this bacterium in 2009 (Table S3).

The main reported symptoms comprised fever (57.6%), headache (49.4%), vomit (47.3%) and neck stiffness (28.0%). The lesser common symptoms comprised convulsions (8.4%), Kernig and Brudzinski signs (4.8%), petechiae (4.6%) and bulging fontanelle (2.3%). The most prevalent pre-existing diseases associated with meningitis comprised HIV/AIDS (1,184 cases), trauma (442 cases) and tuberculosis (244 cases) (data not shown).

Confirmatory criteria based on the collected data and applied to meningitis cases have changed depending on disease etiology. Meningococcal sepsis was the most reported (67.8%) clinical/clinical-epidemiological diagnosis and microbial culture (15.2%). Culture (39.5% and 64.2%) and antigen detection (latex) (29.8% and 23.0%) were the criteria mostly applied to meningococcal and pneumococcal meningitis, respectively. Chemocytological cerebrospinal fluid analysis was mostly used for aseptic/viral meningitis (72.8%), and it was followed by clinical/clinical-epidemiological diagnosis (16.0%) (data not shown).

Aseptic/viral meningitis was the most common type of the disese diagnosed in pregnant women. Overall, 15 and 43 meningitis cases were diagnosed in this population from 2007 to 2009 and from 2010 to 2016, respectively. The first investigated period did not show any case of meningitis caused by *Haemophilus* spp. and *N. meningitidis*. However, the second period recorded one case of meningitis caused by *Haemophilus* spp. and five cases caused by *S. pneumoniae* in pregnant women (Table S4).

There were 1,065 deaths (6.2%) due to meningitis belonging to all etiologies in Paraná State. Although *N. meningitidis* was the most common etiologic BM agent in Paraná State; Pneumococcal meningitis recorded the highest mortality rate (26.0%) throughout the investigated decade (Table 3).

Table 4 - Serogroups of Neisseria meningitidis in Paraná, Brazil, from January 2007 to December 2016

Serogroup	2007 - 2009		2010 - 2016		Total
	≤ 4 years	> 4 years	≤ 4 years	> 4 years	
A	0	0	0	0	0
B	49	39	39	73	200
C	33	60	25	109	227
Y	0	5	1	6	12
W135	1	5	6	17	29
29 E	0	1	0	0	1
Total	**83**	**110**	**71**	**205**	**469**

Source: Sistema de Agravo de Notificações (SINAN)-Tabwin 2.7 software).

DISCUSSION |

Although the Brazilian Ministry of Health has introduced the meningococcal vaccine (serogroup C) in the vaccination schedule set for infants (since 2010), toddlers and preschoolers (since 2017), meningococcal disease remains a significant public health issue[12,13]. Several studies have shown decreased incidence of meningococcal disease in Brazil, but the research carried out in Paraná State still has not been reported[14]. *Neisseria meningitidis* was the main BM agent recorded in Paraná State, mainly in children, and it corroborated studies performed in other Brazilian regions[14].

Viral meningitis was the most often observed type of the disease, although it was less severe than bacterial meningitis. Enterovirus was the main agent causing meningitis; it lives in the upper respiratory and gastrointestinal tracts of infected patients[1]. Viral etiology was the one most often observed in the current study; it accounted for over 50% of cases in all investigated years. This result corroborates the study by Labiak et al.[15], who also reported aseptic meningitis as the most recurrent etiology in their research (45.6%).

Meningitis prevailed in male patients on a yearly basis from 2007 to 2016. This outcome was also observed in other studies performed in different regions countrywide and abroad[15-18]. According to Moraes and Barata[19], the male sex is mostly affected by the disease due to greater occupational exposure sources - such as construction, oil extraction and mining, among others - that enable disease transmission under confinement and agglomeration conditions.

The most affected age group comprised 1-to-4-year-old children; it was followed by age groups < 1 and 5--to--9 years. Results in other studies conducted in Paraná State recorded results similar to the current findings[15,16]. The vulnerability recorded for the age group < 1 year is justified by lack of maternal antibodies after the age of 3 months, lack of acquired immunity and lower prevalence of bactericidal antibodies, which opens room for infectious conditions[17].

The most reported signs and symptoms comprised fever (57.6%), headache (49.4%), vomit (47.3%) and neck stiffness (28.0%). The current results were similar to the ones reported by Gonçalves et al.[20] in study carried out in Curitiba City, Paraná State, Brazil, as well as by Vasconcelos et al.[21] in reseach conducted in Rio de Janeiro, Brazil, namely: fever (85.7%; 82.9%), vomit (82.7%; 62.2%), headache (60.6%; 57.7%) and neck stiffness (57.1%; 51.5%), respectively. Despite the divergent frequency of signs and symptoms, the current study has shown the same profile of classic signs and symptoms reported in other studies.

Gonçalves et al.[20], have performed antigen detection (serology) test in 82% of reported meningococcal meningitis cases to confirm meningococcal meningitis diagnosis from 2001 to 2012. Sixty percent (60%) of them belonged to serogroup B; 36%, to serogroup C; and 4%, to other serogroups. Antigen detection test in the current study was carried out in 50.5% of meningococcal diseases; serogroup C was the most detected group (52.3%). These data are in compliance with the Brazilian standard, which has been showing decrease in the number of cases with serogroup B and increase in the number of cases with serogroup C, since 2005.

A study conducted in Japan has shown significant (69%) decrease in pneumococcal meningitis incidence in 0-to-4-year-old children after vaccination; this ouctome corroborated our findings[19]. Disease incidence in the United States of America has also decreased; however, there was increase in the number of patients presenting serotypes not covered by the vaccine used in the country[17,23,24]. Vaccination against pneumococcus is of paramount importance worldwide, mainly in Paraná State, where this pathogen recorded the highest lethality rate[16]. Based on an observational retrospective study conducted in Central Europe, there has been significant decrease in the number of death cases resulting from pneumococcal meningitis in recent years (from 24.1% to 5.5%). Among the reasons for such an improvement, the authors have mentioned adjuvant dexamethasone administration as standard procedure in treatment applied to this severe disease[25].

Vaccine against *H. influenzae* serotype b (Hib) was implemented in Brazil in 1999; since then, the number of Hib meningitis cases has effectivelly decreased countrywide. The incidence of this disease, as well as its lethality rate, remains low. Castelblanco et al.[24] have performed a study in the USA and found steady decrease in the number of Hib cases after vaccine implementation. Studies have shown that other non-capped serotypes or bacteria belonging to

this genus have also caused meningitis due to the serotype replacement phenomenon.

Although meningitis notification is compulsory, there is lack (ignored) or even inconsistency of data about secondary sources based on notification systems such as SINAN. Studies carried out with such data have limitations, a fact that is well documented in the literature. It is essential properly filling all SINAN fields to enable analyzing meningitis, which requires the participation of all team members involved in the reasearch. Previous vaccination data were also collected; however, it was not possible reaching accurate results and they were not described in the current study due to limitations and likely biases.

CONCLUSION |

Significant decrease in the number of pneumococcal meningitis cases in 0-to-4-year-old children, and of meningococcal meningitis cases in 1-to-4-year-old children, has confirmed the positive effect of conjugate vaccines on disease incidence in the post-vaccination period in Paraná State. It is essential performing frequent and detailed studies about meningitis, regardless of the region, to help decision-making processes about disease control measures, such as selecting the proper vaccine to be applied based on the most frequent serotypes or serogroups of agents.

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Table S1 - Notified cases of meningitis by Regional Health in Paraná state, Brazil, from January 2007 to December 2016

Regional Health	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
01 Paranaguá	50	77	57	83	113	132	103	94	75	41	825
02 Metropolitana	1,865	1,190	653	774	875	692	803	663	700	655	8,870
03 Ponta Grossa	131	101	71	80	48	50	70	78	63	76	768
04 Irati	50	53	68	40	46	39	40	28	30	31	425
05 Guarapuava	66	56	37	29	34	18	32	27	32	35	366
06 União da Vitória	59	40	24	30	25	19	15	8	13	10	243
07 Pato Branco	57	40	42	66	45	50	65	85	58	34	542
08 Francisco Beltrão	74	48	61	63	65	46	39	22	41	55	514
09 Foz do Iguaçu	134	72	59	58	94	86	59	88	107	75	832
10 Cascavel	156	136	80	46	66	82	86	65	62	34	813
11 Campo Mourão	49	50	34	35	75	37	14	18	22	30	364
12 Umuarama	47	7	13	23	30	76	96	82	100	104	578
13 Cianorte	28	20	20	24	22	19	26	26	25	20	230
14 Paranavaí	55	32	33	34	41	25	26	16	30	28	320
15 Maringá	245	126	111	86	94	103	151	128	286	253	1,583
16 Apucarana	133	59	39	33	29	46	43	39	40	30	491
17 Londrina	594	243	162	118	234	161	220	135	143	122	2,132
18 Cornélio Procópio	95	43	24	11	18	18	22	19	34	33	317
19 Jacarezinho	50	32	18	24	30	20	10	20	20	30	254
20 Toledo	39	33	44	47	98	71	69	61	100	49	611
21 Telêmaco Borba	47	62	50	53	32	19	11	7	14	12	307
22 Ivaiporã	44	39	21	16	20	15	27	41	17	24	264
Total	4,068	2,559	1,721	1,773	2,134	1,824	2,027	1,750	2,012	1,781	21,649

Source: Sistema de Agravo de Notificações (SINAN)-Tabwin 2.7 software.

Table S2 - Notified cases of meningitis by gender in Paraná state, Brazil, from January 2007 to December 2016

Gender	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Male	2,418	1,513	1,002	1,004	1,265	1,040	1,153	1,020	1,194	1,047	12,656
Female	1,649	1,045	719	769	869	784	874	730	817	734	8,990
Ignored	1	1	0	0	0	0	0	0	1	0	3
Total	4,067	2,558	1,721	1,773	2,134	1,824	2,027	1,750	2,011	1,781	21,649

Source: Sistema de Agravo de Notificações (SINAN)-Tabwin 2.7 software.

Table S3 - Confirmed cases of meningitis by Haemophilus influenzae, in the state of Paraná, Brazil, from January 2007 to December 2016

Age group (years old)	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
< 1	5	0	0	0	3	1	3	3	2	3	20
1 – 4	6	1	0	1	5	2	0	4	1	2	22
5 – 9	0	1	0	1	0	0	2	2	1	0	7
10 – 14	1	0	0	0	0	0	2	0	0	0	3
15 – 19	2	0	0	0	0	0	0	1	0	0	3
20 – 34	0	1	0	1	0	0	0	0	0	0	2
35 – 49	1	1	0	0	2	0	0	0	0	2	6
50 – 64	1	0	0	0	0	1	0	1	0	0	3
65 – 79	0	0	0	0	1	0	1	0	1	0	3
≥ 80	0	0	0	0	0	0	0	0	0	0	0
Total	16	4	0	3	11	4	8	11	5	7	69

Source: Sistema de Agravo de Notificações (SINAN)-Tabwin 2.7 software.

Table S4 - Confirmed cases of meningitis by etiology, in pregnant women per trimester, in Paraná state, Brazil, from January 2007 to December 2016

Etiology	Trimester			Total
	1º	2 º	3º	
Aseptic Meningitis	5	6	3	14
Bacterial, others	3	5	8	16
Meningococcal disease	0	0	0	0
Pneumococcal	2	3	0	5
Mycobacterium tuberculosis	0	0	1	1
***Haemophilus* spp.**	0	1	0	1
Others	1	5	0	6
Total	11	20	12	43

*Not specified, other etiology and ignored. *Source: Sistema de Agravo de Notificações (SINAN)-Tabwin 2.7 software.*