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Pneumococcal Meningitis in Infants and Toddlers: Epidemiology and Potential Impact of a Cuban Conjugate Vaccine

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Keywords

- Pneumococcal meningitis; Infants; Toddlers; Cuban pneumococcal conjugate vaccine; Vaccination impact

Abstract

Objective: To describe pneumococcal meningitis main epidemiological features in young children, and discuss potential effect of Cuban Pneumococcal Conjugate Vaccine.

Methods: Nationwide retrospective observational study (1998-2016), in children <2 years old based on surveillance. It were estimated incidence, mortality and case-fatality rate and pneumococcal meningitis cases comprised in community acquired bacterial meningitis of unknown bacteriological etiology. Prediction of cases (2017-2020) was by time series modelling using generalized linear model methodology.

Results: 385 cases in children <2 years old, with incidence 7.8/10^5 population; in infants 9.7/10^5 population and toddlers 5.9/10^5 population. Highest overall incidence arose in 2000 (15.1/10^5 population), decreasing toward 2016. Surveillance reported 106 overall fatalities, causing mortality of 2.1/10^5 population and 27.5 % case-fatality rate, with similar figures by age groups. Biggest proportion of disease occurred at fourth (13.0 %), second (10.4 %), and sixth (10.0 %), months of birth, with topmost case-fatality rate at ninth (55.5 %), fifth (31.6 %), and tenth (30.0 %), months of birth. Adjusted sum of pneumococcal meningitis cases reached 633, with incidence of 12.8/100 000 population and descending trend. Pneumococcal meningitis prediction in children <2 years old was two cases monthly and annually around 22.

Conclusions: Pneumococcal meningitis still is the major and most lethal cause of community acquired bacterial meningitis in Cuban children. Introduction of Cuban new heptavalent PCV (serotypes 1, 5, 6B, 14, 18C, 19F, 23F) might decrease considerably Pnm and other clinical features in a near future. Surveillance must follow closely subsequent changes in epidemiological behavior.

ABBREVIATIONS

IPD: Invasive Pneumococcal Disease; Pnm: Pneumococcal Meningitis; CABM: Community-acquired Bacterial Meningitis; PCV: Pneumococcal Conjugate Vaccines; CABMNSS: Community-acquired Bacterial Meningitis Surveillance System; NPCPNIS: National Program for Control and Prevention of the Neurological Infectious Syndrome; Hib: *Haemophilus influenzae* type b; NIP: National Immunization Program; CSF: Cerebrospinal fluid; $CABM_{kbe}$: Community-acquired Bacterial Meningitis of known Bacteriological Etiology; $CABM_{ube}$: Community-acquired Bacterial Meningitis of "unknown bacteriological etiology"; IPK: Tropical Medicine Institute Pedro Kourí; CFR: Case-fatality Rate; PAHO: Pan American Health Organization; GLM: Generalized Linear Model.

INTRODUCTION

Streptococcus pneumoniae is a leading cause of severe community-acquired infections in young children [1]. Nasopharyngeal colonization is a prerequisite for the invasion of sterile sites [2]. Invasive pneumococcal disease (IPD), is a life-threatening clinical presentation including three syndromes: meningitis, pneumonia, and bacteremia [3,4].

Pneumococcal meningitis (Pnm) is one of the most severe cause of community-acquired bacterial meningitis (CABM) in children under 2 years old [5], and is estimated that pneumococcus causes globally near 900 000 fatalities, representing 15 % of all deaths in this age group [6]. On the other hand, survivors often develop permanent neurological sequels and other disabilities

[7]. The decreasing susceptibility to antibiotics is also a worrying issue [8].

The advent of pneumococcal conjugate vaccines (PCV) provided an effective approach for prevention. Available PCV can induce protection in vaccinated children [9-11], and in unvaccinated by herd immunity [12,13].

Surveillance systems are an essential tool for Public Health allowing monitoring disease behavior. Since 1961 the report of CABM is compulsory, as part of national communicable diseases surveillance [14]. In 1998, implementation of CABM Surveillance System (CABMNSS) as part of the National Program for Control and Prevention of the Neurological Infectious Syndrome (NPCPNIS) [15,16] renewed surveillance. Since then, it successfully evidenced variations in the epidemiological and microbiological behavior of these infections, contributing significantly to decision making in Cuban Public Health [17]. As well, CABMNSS shown morbidity and mortality reduction of meningococcal and *Haemophilus influenzae* type b (Hib) meningitis, as result of massive vaccinations through National Immunization Program (NIP) [18, 19]. After those interventions, *S. pneumoniae* has arisen as the leading and most lethal cause of CABM in Cuba [20].

Despite Cuban National Health System has considered the use of vaccine preventable diseases as a main Public Health priority, the high prices of commercially available PCV hamper their use in NIP. Finlay Institute for Vaccines in Havana has been developing a heptavalent PCV Cuban candidate to prevent disease in Cuba since 2006 [21].

The aim of this study was to describe main epidemiological features of Pnm in infants and toddlers, as well as to discuss the potential effect of PCV Cuban candidate on Pnm morbidity and mortality based on long-term available data.

METHODS

This is a nationwide retrospective observational study on children under 2 years old with Pnm, reported by CABMNSS from January 1, 1998 to December 31, 2016, considering the date of symptoms onset.

For the purpose of the study, a case of Pnm was defined as "a clinical meningeal syndrome, with positive identification of *Streptococcus pneumoniae* directly from blood, petecchia, cerebrospinal fluid (CSF) culture, or indirectly by polymerase chain reaction, latex test or another rapid diagnostic test" [15]. CABMSS reports meningitis cases caused by *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, other bacteria CABM of known bacteriological etiology ($CABM_{kbe}$), as well as CABM of "unknown bacteriological etiology" ($CABM_{ube}$), which includes those cases with a clinical meningeal syndrome and cyto-chemical exam of CSF suggesting bacterial infection, but a negative culture or bacteriological test for a particular bacterium [15].

Socio-demographic, clinical, epidemiological and microbiological data from nationwide standardized case-report questionnaires, was collected by provincial epidemiologists and subsequently reviewed and mended by specialists at the Tropical Medicine Institute Pedro Kourí (IPK), as part of the National Program for Control and Prevention of the Neurological Infectious Syndrome (NPCPNIS), assuring consistency of data [15-17].

Cuban population estimations from the National Statistics and Information Office allowed calculating annual and overall incidence and mortality per 10^5 population, and case-fatality rate (CFR) (fatalities/100 cases), by age group. In infants, it was also estimated specific proportion of cases and case-fatality rate by month of birth.

Use of Pan American Health Organization (PAHO) methodology [22], adjusted by authors, allowed to assess Pnm cases contained within $CABM_{ube}$, assuming that annual proportion of Pnm cases included in $CABM_{kbe}$, would be the same as those of $CABM_{ube}$. Letters α, β, γ, δ were respectively assigned for confirmed cases due to pneumococcus, meningococcus, *H. influenzae* and other bacteria respectively, while ε was assigned to $CABM_{ube}$ and α' was considered as presumed Pnm cases included in $CABM_{ube}$. It was also assumed that $\alpha / (\alpha + \beta + \gamma + \delta) + \beta / (\alpha + \beta + \gamma + \delta) + \gamma / (\alpha + \beta + \gamma + \delta) + \delta / (\alpha + \beta + \gamma + \delta) = 1$. Finally, the equation: $\alpha' = \varepsilon * \alpha / (\alpha + \beta + \gamma + \delta)$ estimate Pnm cases within $CABM_{ube}$. The adding of α and α' was interpreted as the adjusted sum of Pnm cases, assuming a full bacteria identification.

As the number of Pnm cases reported per month is, on average, small (less than 10 per month with a few months reporting no cases at all), time series was modelled as a count time series with generalized linear model (GLM) methodology. A Negative Binomial (GLM) with a log-link, was used to fit count time series of Pnm cases reported, regressing on the counts of cases from the last month (as an auto regression term) and on the conditional mean 12 months ago to account for seasonality [23].

The Scientific Board at Department of Surveillance and Epidemiological Research of IPK approved the present study. Approval of an Ethics Committee was not required since the Public Health Ministry of Cuba is the governmental organization responsible for the collection and notification of infectious diseases, hospital discharge records and population or laboratory surveillance. The management of this data for public health purposes does not require informed patient's informed consent nor does it require any authorization regarding privacy laws in Cuba. For data analysis, it were used Microsoft Excel 2010 and R version 3.4.4 (2018-03-15).

RESULTS

From 1998 to 2016 CABMSS reported 385 overall Pnm cases in children under 2 years old, with a $7.8/10^5$ population incidence, while in infants and one-year-old toddlers, occurred 237 and 148 Pnm cases, with incidences of $9.7/10^5$ population and $5.9/10^5$ population, respectively. An annual average of 20 Pnm cases were observed in children under 2 years old, while in infants were 12 and 5 in one-year-old toddlers (Data not shown). Pnm incidence contrast between 1998 and 2016, showed an overall slight increase (0.7 %), more substantial in one-year-old toddlers (30.9 %). Contrarily, incidence in infants decreased 11.2 % (Data not shown).

Highest overall incidence rate was observed in year 2000 (15.1/100 000 population), decreasing slowly toward 2016. Similar behavior occurred in infants with likewise increase in biennium 2000-2001 (incidence 23.7 and 15.9/100 000 population respectively), decreasing to 1.6/100 000 population in 2013, but increasing noteworthy in 2016 (10.6/100 000 population). Different behavior was detected among one-year-old toddlers with major peaks in 2004 (10.3/100 000 population) and 2015 (9.5/100 000 population), showing an unequal comportment along the series. In 2013 occurred the lowest overall incidence and for all the age groups (Figure 1).

During the study, surveillance reported 106 overall Pnm fatalities in children under 2 years old, for a $2.1/10^5$ population overall mortality, while infants and one-year-old toddlers accumulated 61 and 45 Pnm deaths, with overall mortality of $2.5/10^5$ population and $1.8/10^5$ population, respectively. Overall Pnm fatalities annual average was three, in infants two and five in toddlers (Data not shown). Pnm mortality, comparing the start of the study period with the end, showed an overall decrease (11.1 %), more significant in toddlers (20.0 %). In infants, mortality remained unchanged from the beginning to the end ($3.3/10^5$ population) (Data not shown).

Uppermost overall mortality occurred in years 2003 (4.7/100 000 population) and 2000 (4.5/100 000 population), declining subsequently. Comparable behavior occurred in infants and toddlers, with major peaks in 2003 (6.6/100 000 population) and 2000 (3.4/100 000 population) respectively. No fatalities occurred in infants (2008 and 2014), and toddlers during biennium 2009-2010 (Figure 2).

Overall CFR reached 27.5 % in children under 2 years of age, with similar figures in infants (25.7 %) and toddlers (30.4 %) (Data not shown). Comparison of Pnm CFR in 1998 to 2016, showed an overall slight decrease (9.2 %), more substantial in toddlers (44.3 %). In contrast, CFR in infants increased 9.7 % (Data not shown).

Highest overall CFR rate was observed in year 2003 (46.4 %) and 2012 (44.4 %), with lowest figure in 2010 (6.7 %). In infants,

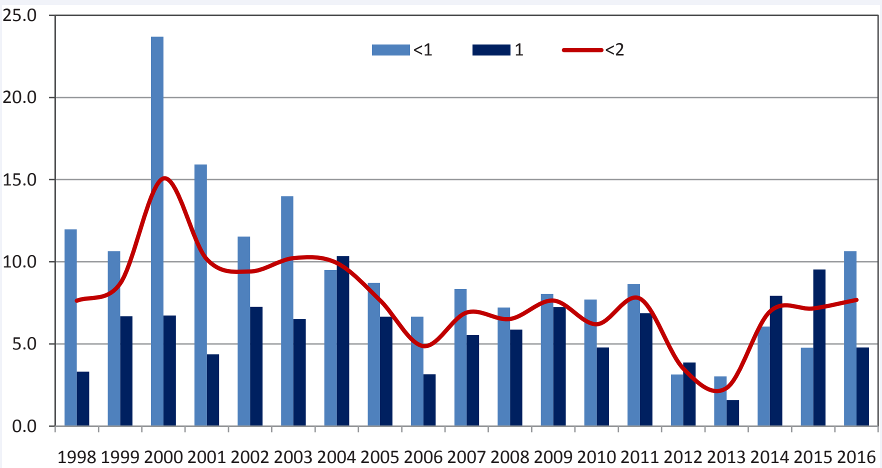

Figure 1 Annual incidence of pneumococcal meningitis in children under 2 years according to age groups. Cuba, 1998-2016.

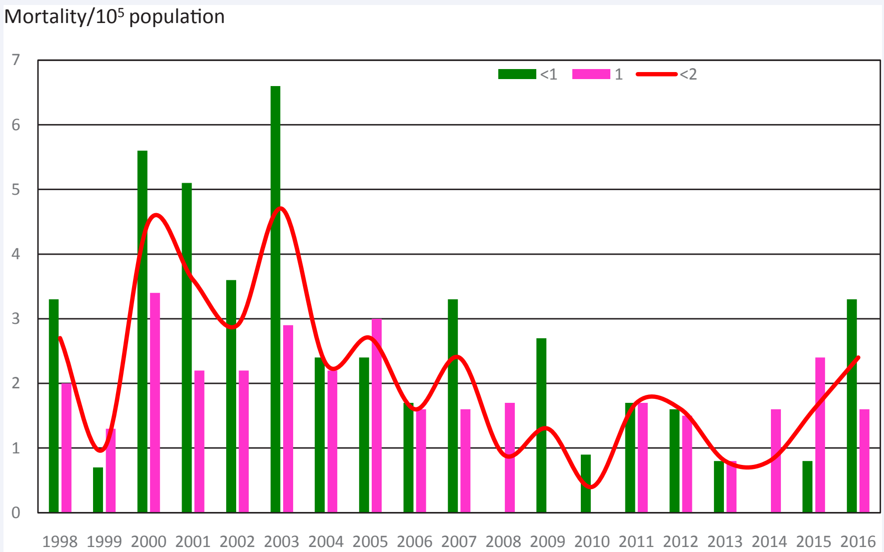

Figure 2 Annual mortality of pneumococcal meningitis in children under 2 years by age groups. Cuba, 1998-2016.

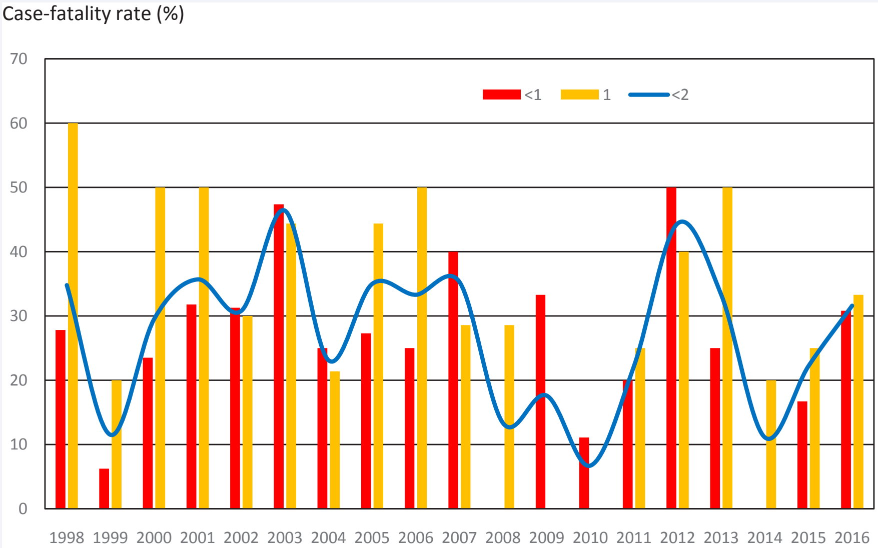

Figure 3 Annual case-fatality rate of pneumococcal meningitis in children under 2 years by age groups. Cuba, 1998-2016.

highest CFR occurred in 2012 (50.0 %) and 2003 (47.4 %), while in toddlers were registered during 1998 (60.0 %), 2000, 2001 2006 and 2013 (50.0 %) (Figure 3).

Throughout study period, CABMSS collected information about the months of birth from 231 of 237 infants (97, 5 %). Biggest number of Pnm cases occurred among infants at fourth (30), second (24) and sixth (23) months of birth, with proportions of 13.0, 10.4 and 10.0 % respectively. Topmost CFR were observed at ninth (55.5 %), fifth (31.6 %) and tenth (30.0 %) months of birth (Table 1).

Along study period, the CABMSS reported 1804 cases in children under 2 years old, caused by confirmed bacterium (pneumococcus, meningococcus, *H. influenzae* and other bacteria). As well, it reported 674 cases of $CABM_{ube}$ (Data not shown). CABMSS confirmed and reported 385 Pnm cases. As shown in Table 2, it was identified 248 Pnm cases contained within $CABM_{ube}$ by using previously described methodology. The adjusted sum of Pnm cases (assuming a full bacteria identification) was 633 along study period with resulting incidence rate of 12.8/100 000 population, exceeding significantly those confirmed from both $CABM_{kbe}$ (7.8/100 000 population) or estimated from $CABM_{ube}$ (5.0/100 000 population). In addition, highest Pnm annual incidence was observed simultaneously in 2000 for adjusted sum (25.7/100 000 population) and both, confirmed from $CABM_{kbe}$ (15.1/100 000 population) and estimated from $CABM_{ue}$ (10.6/100 000 population) (Table 2). More evident descending trend was appreciated in adjusted sum ($y = -0.3502x + 16.281$ $R^2 = 0.1729$) than confirmed from $CABM_{kbe}$ ($y = -0.2877x + 10.582$ $R^2 = 0.3476$) and estimated from $CABM_{ue}$ ($y = -0.064x + 5.714$ $R^2 = 0.0169$) (Data not shown).

CABMSS data allowed a monthly prediction between 2017 and 2020 of 2 Pnm cases in children under 2 years old with yearly overall figures around 22 cases (Figure 4).

DISCUSSION

The 19-years results presented in this paper are certainly the largest and longest epidemiological study on Pnm in young children registered in Cuba so far. They are based on a proficient nationwide surveillance [14], including a geographically well-defined population, where Public Health is free and accessible to every citizen along the country [16].

However, interpretation of the results from this study must consider that CABMSS is a passive surveillance. In addition, the full microbiological identification of causative bacteria in hospitals is not always achieved, owing to different reasons (laboratory practices, lack of supplies and/or diagnostic methods, previous antibiotic therapy), as occurs in many developing and transitional countries [14,27]. Therefore, authors attempt to overcome this limitation by using methodology for better assessment of Pnm actual incidence, which might be useful and contribute to Public Health decisions in other contexts.

Since the turn of the century, *S. pneumoniae* is the major and most lethal agent causing CABM in Cuban young children [14,16-19], as occurs in many parts of the world [3-6]. Incidence in children under 2 years old in Cuba was similar to those reported by countries before implementation of PCV vaccination [4-28].

Highest incidence in infants among children under 2 years old is coincident with other authors [5,25,28]. Major proportions of Pnm observed below sixth month of birth might be related to specific developmental demands and adaptation of the immune system [29], that may increase susceptibility to infections, as well as the non-application of PCV in Cuba so far.

Overall Pnm highest incidence rate observed in 2000 coincide with the sharp decline of Hib meningitis in children under 2 years old subsequent to Hib routine countrywide vaccination in 1999 throughout the NIP [30]. An explanation might be that vaccine intervention released a niche for pneumococci, increasing their carriage, exposure and likelihood to infection and disease [31]. Bacteria and serotypes replacement after massive vaccination are well-documented [32-34].

On the other hand, after 2000, disease showed a descending trend, overall and by age groups, along the study period, which

Table 1: Cases, proportion, fatalities and case-fatality rate pneumococcal meningitis infants, according to months of birth. Cuba, 1998-2016.

Months of birth	Cases*	Proportion	Fatalities	Case-fatality rate
<1	16	6.9	4	25.0
1	17	7.3	3	17.6
2	24	10.4	7	29.2
3	16	6.9	1	6.2
4	30	13.0	4	13.3
5	19	8.2	6	31.6
6	23	10.0	3	13.0
7	21	9.1	4	19.0
8	21	9,1	6	28.6
9	18	7.8	10	55.5
10	10	4.3	3	30.0
11	16	6.9	4	25.0

* There was omission of the information about months of birth in six infants.

Table 2: Cases and incidence of pneumococcal meningitis in children under 2 years (confirmed, estimated and totality) from community acquired bacterial meningitis surveillance system. Cuba, 1998-2016.

Year	Pneumococcal meningitis					
	Confirmed from $CABM_{ke}$		Estimated from $CABM_{ue}$		Adjusted sum	
	Cases	Incidence	Cases	Incidence	Cases	Incidence
1998	23	7.6	5	1.7	28	9.3
1999	26	8.7	13	4.3	39	13.0
2000	44	15.1	31	10.6	75	25.7
2001	28	10.2	17	6.2	45	16.3
2002	26	9.4	7	2.5	33	11.9
2003	28	10.2	11	4.0	39	14.2
2004	26	9.9	10	3.8	36	13.7
2005	20	7.7	25	9.6	45	17.2
2006	12	4.9	7	2.8	19	7.7
2007	17	6.9	21	8.5	38	15.5
2008	15	6.5	20	8.7	35	15.2
2009	17	7.6	17	7.6	34	15.3
2010	15	6.2	7	2.9	22	9.1
2011	18	7.8	12	5.2	30	12.9
2012	9	3.5	6	2.3	15	5.9
2013	6	2.3	4	1.5	10	3.9
2014	18	7.0	15	5.8	33	12.8
2015	18	7.2	9	3.6	27	10.7
2016	19	7.7	12	4.8	31	12.5
TOTAL	385	7.8	248	5.0	633	12.8

$CABM_{ke}$: Community acquired bacterial meningitis of known etiology.
$CABM_{ue}$: Community acquired bacterial meningitis of "unknown etiology".

is difficult to explain in the absence of specific vaccination. It cannot be rule out that those changes may be due to nationwide improvements within NPCPNIS [15], as well as the continuous development of national public health and other social benefits accessible to the population [16,17]. Moreover, it cannot discarded the coincidence along the study of a low incidence phase as a part of a larger cyclic variation of disease (periodical long-lasting oscillations) [17]. This behavior should require additional studies to better define.

Mortality may depends on the host response, underlying conditions, population care-seeking behavior, referral practices to hospitals, opportune diagnose, timely and quality of health care, as well as the virulence of the strains [17].

Overall mortality, among study groups, was around $2/10^5$ population and CFR nearly 27,0 %, similar to ranges reported in the United States [25], and Brazil [26], although Pavia et al. reported in Utah (United States) lower figures [24], but were much lesser than reported in low-income countries [11].

Adequate management of Pnm certainly requires timely hospitalization, and delay in treatment may increase the risk of an unfavorable outcome [17]. In Cuba, the association of delayed hospitalization and treatment with fatal outcome in small children has not been fully demonstrated [14].

Estimates of IPD burden is an important decision-making factor for policymaking and program planning, especially before

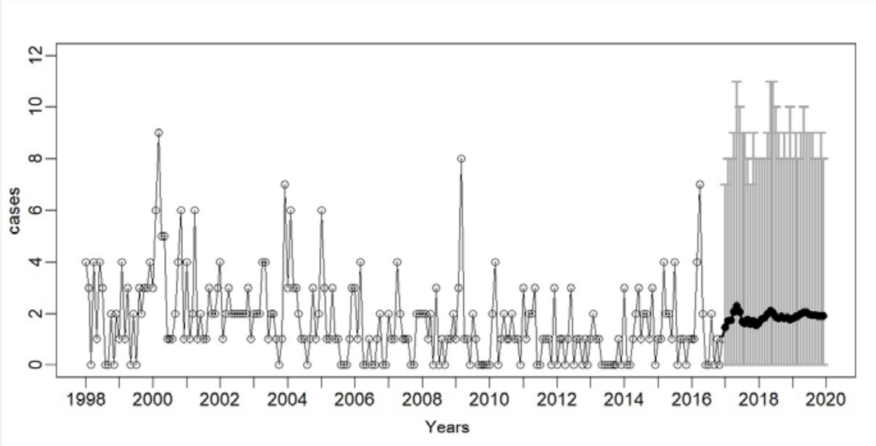

Figure 4 Monthly prediction of pneumococcal meningitis in children under 2 years old. Cuba, 1998-2016.

the introduction and sustained use of new vaccines, as well as to assess their potential impact [38].

For this purpose, Cuban Public Health Ministry, through the scientific team of Finlay Institute for Vaccines in Havana, has been reviewing extensively the body of scientific evidence on available PCV regarding safety [39], immunogenicity [40], effects on nasopharyngeal colonization [41], efficacy in reduction of IPD [42,43], as well as the indirect effect on unvaccinated population [44]. Cuban new heptavalent PCV (serotypes 1, 5, 6B, 14, 18C, 19F, 23F) is under advanced clinical development [35,36] showing a safety and immunogenicity profile not inferior to the Prevnar13® and for these reasons is an affordable and safe alternative to reduce IPD burden in Cuban children [21,36-38].

On the other hand, CABMSS inform the meningitis cases caused by different bacterium (pneumococcus, meningococcus, *H. influenzae* and other bacteria) and those considered as from bacterial origin, but with failed microbiological identification [14,15,17]. Then, it is critical to know the actual amount of CABM cases for Public Health purposes, in order to guarantee highest effectiveness of control and prevention measures. PAHO methodology adjusted by authors proved his potential to better define the totality of children that might be at risk along the study.

Technical challenges associated with observational studies base on surveillance, may require modelling to provide complementary insight into disease burden. Annual and monthly prediction of Pnm cases from 2017 to 2020 was similar to those reported by CABMSS from 1998 to 2016. Therefore, the use of Cuban PCV potentially might prevent annually nearly 40 cases of Pnm, which considerably increase by extension to other clinical features: from life-threatening diseases like bacteremia and pneumonia, to milder manifestations as otitis media, sinusitis and conjunctivitis, and could be translated to a substantial decrease in health care system costs and human suffering burden.

Finally, it should be emphasized the importance of CABMSS to achieve deeper comprehensive insights on pneumococcal epidemiology, as well as their contribution to the implementation and assessment of future immunization strategies and their impact.

CONCLUSION

S. pneumoniae is the major and most lethal agent causing CABM in Cuban children since 1998. Annual highest incidence in 2000 occurred subsequent to *Haemophilus influenzae* type countrywide vaccination. Introduction of Cuban new heptavalent PCV (serotypes 1, 5, 6B, 14, 18C, 19F, 23F) might decrease considerably Pnm and other clinical features in a near future. Surveillance must follow closely subsequent changes in epidemiological behavior.

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