Invasive Meningococcal Disease. Cuba, 1983 – 2006

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Invasive Meningococcal Disease (IMD) is a worldwide health problem. In Cuba, vaccination against meningococcal B-C has been carried out since 1989. The study aimed at describing the epidemiology of IMD in Cuba from 1983 to 2006 and at contributing to the immunization strategy. A descriptive and analytical study was carried out. Epidemiological data was obtained from the National Surveillance System at the Institute "Pedro Kourí". More than 1 000 cases were reported in 1986 and the overall incidence was above 10/100 000 inhabitants. Since 1989 a remarkable and continuous decline in the incidence was observed. In the last nine years a strong association of IMD to boarding school students (OR=9.4; confidence interval 95%: 5.1-17.4), recluses (OR=5.9; CI 95%: 1.5 -24.3) and day students (OR=3.9; CI 95%: 2.8-5.6) was observed. Housewife (OR=4.9; CI 95%: 1.9-12.4) and pensioned (OR=4.5; CI 95%: 1.2-16.8) showed association with mortality. Previous vaccination was a protective factor against morbidity (OR=0.6; CI 95%: 0.4-1.0) and mortality (OR=0.4; CI 95%: 0.2-0.9) by IMD. *Neisseria meningitidis* B4:P1.15 was the main circulating strain. Incidence of IMD declined markedly in Cuba by using group BC strain-specific meningococcal vaccine.

Keywords: Invasive Meningococcal Disease, Epidemiology, Risk factors, *Neisseria meningitidis*, Immunization.

Introduction

Invasive Meningococcal Disease (IMD) is a severe bacterial infection caused by *Neisseria meningitidis,* a leading cause of bacterial meningitis and/or septicemia. It represents a relevant worldwide health problem.

In most countries, attack rates of endemic IMD is 1 to 5/100 000 inhabitants. In the sub-Saharan African meningitis belt the endemic incidence may be over 20/100 000 population (1).

In developed countries such as the United States, a substantial proportion of cases of meningitis and sepsis are caused by *N. meningitidis* (2). The incidence of IMD was estimated to be 0.7–1.4/100 000 population, and the case-fatality rate (CFR) is approximately 10%. Both the incidence rate and CFR have been relatively constant, with no major changes observed in the past decade (3).

The most common manifestations of IMD include meningitis (50-55% of cases), septicemia (5-20%), and meningitis accompanied by septicemia (20-30%) (4).

Left untreated, the disease can lead to fatality rates greater than 50% and despite treatment 10% of patients die quickly while 10-20% survivors develop neurological sequels (5).

Cuba is among the countries that were affected by an epidemic on meningococcal disease since 1976 for what has carried out different vaccination strategies. In 1979, there was a vaccine campaign using serogroup C polysaccharide vaccine, targeting age under 19 years old. After this, *N. meningitidis* serogroup B prevailed and based on encouraging results in efficacy trials (6), the Ministry of Public Health carried out in 1989 a mass vaccination campaign of two doses of a combined serogroup C and B vaccine. This vaccine, known as VA-MENGOC-BC® (Havana, Cuba) contains purified proteins from outer-membrane of group B meningococci from strain Cu385/83; B:4;P1.15 (7).

The vaccine was administered to the high risk population below 20 years of age achieving almost 95% coverage. Later, in 1991 vaccine was added to the National Immunization Program (NIP), targeting infants at the age of 3 and 5 months with an average coverage superior to 90% (8,9). Since then, Cuba have been registered the cumulative of 10 479 779 doses up to 2006 (10).

The present paper shows the main epidemiological features of IMD in Cuba during the last 23 years including results previous and after the immunization.

Materials and Methods

Data source

This study included all confirmed and registered cases of IMD (9429) from 1983 to 2006, on the basis of the following definition: "a clinical meningeal syndrome and/or septicemia, through the identification of N. meningitidis directly by culture of the cerebrospinal fluid (CSF), blood, petecchias and by

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Gram stain results or indirectly by latex agglutination techniques" (11). In view of the severity of IMD, the National Program for Control and Prevention of the Infectious Neurological Syndrome endorse hospitalization of all IMD cases in Intensive Care Units. The conventional bacteriologic diagnosis of *N. meningitidis* is available in hospital laboratories network along the country. On the other hand, Ministry of Public Health requires the mandatory report of IMD by all health-care providers, laboratories and health-care facilities.

A database on IMD was obtained from a full-coverage nationwide Surveillance System from 1983 by an epidemiological questionnaire processed at the Institute "Pedro Kourí" (IPK). Since 1998, improvement of the existing surveillance system (12) allowed the inclusion of other pathogen causing bacterial meningitis, as well as socio-demographic data (attendance to day care centers or boarding students, worker, unemployed, housewife, pensioned, military, recluses, and previous specific vaccination status considering that all people under 37 years old may be vaccinated in campaign or by NIP).

Laboratory methods

The strains isolate recovered were sent to the National Reference Laboratory for Neisseria (NRLN), IPK for microbiological confirmation and strain typing. All *N. meningitidis* isolated from normally fluid specimens (blood, cerebrospinal CSF or both) and received at NRLN-IPK were cultured using modified Thayer Martin medium, incubated at 37 °C, in 5-10% CO_2, for 48-72 hours according to handbook of operations and proceedings on NRLN at IPK- Reference National Laboratory.

Identification of *N. meningitidis* colonies was made by glucose and maltose oxidation in cystine tripticase agar (CTA) medium base (Difco) and by the production of y-Glutamyl aminopetptidase enzymatic activity. Serogroups were determined by slide agglutination with polyclonal antiserum to serogroups A, B, C, W135, X, Y and Z (Difco, USA). Strain serosubtyping was based on the detection of outer membrane protein (porin) antigens of class 2/3 (designate serotypes) and OMP class 1 (define subtypes) using a standard set of monoclonal antibodies obtained from the National Institute for Public Health, The Netherlands (3).

Statistical methods

Based on chronological series of cases we estimated the incidence rate (/100 000 inhabitants) and CFR by age groups, per year using estimates of Cuban population data obtained from the National Office of Statistics.

Proportional differences were calculated as follows (Incidence Rate $_{Initial}$ – Incidence Rate $_{ending}$) / Incidence Rate $_{Initial}$ * 100 taking 1989 as initial period and 2006 as the ending.

In order to assess the association of IMD with socio-demographic variables, a selective prevalence study (13) was used, including 1 716 cases of bacterial meningitis registered from 1998 to 2006 (377 cases of IMD and 1 339 cases of meningitis caused by both, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b).

Associated variables (RR $\geq$ 1.5) in the bivariate analysis and the vaccination status (population under 37 years olds vaccinated with VA-MENGOC-BC® since 1989) were additionally analyzed by using multiple logistic regression model. The model was fitted including all the exploratory variables and subsequently dropped one by one until only those that were associated (OR >2).

Similarly, the association of the above mentioned factors with mortality was made by comparing deaths versus survival and also assessed by bivariate and logistic regression model.

In Addition, 95% Confidence intervals and statistically significant ($p<0.05$) were also estimated.

A sample of 314 meningococcal strains was characterized out of 1 254 strains received at NRLN-IPK from 1989 to 2006. EPIINFO 2000 version 3.3 and Excel (version 5.1) were used for statistical analysis.

Ethical considerations

The present study did not require approval from an Ethics Committee. The Cuban Ministry of Public Health is the governmental organization responsible for the collection of infectious disease notifications, hospital discharge records and population or laboratory surveillance. The management of these data for public health purposes requires neither a patient's informed consent nor any authorization regarding privacy laws in Cuba.

Results

Morbidity

IMD epidemic caused by serogroup B started in Cuba during 1980, the number of cases reached the peak in 1983 with 1420 cases registered and an incidence rate of 14.3/100 000 inhabitants. Overall, IMD decreased over time and rates were decreasing slowly before vaccination (1989).

From 1984 to 1986, more than 1000 cases (annual incidence rate >10/100000 inhabitants) were reported annually. The annual incidence rate during 1987-1988 was 8.8/100 000 inhabitants (nearly 900 cases). An important reduction (26.1%) of overall incidence was observed between 1988 and 1989 (8.8 versus 6.5/100 000 inhabitants) respectively (Table 1 and Figure 1). Since 1993 the continuous decreasing trend reached rates <1/100 000 inhabitants.

Table 1. Invasive Meningococcal Disease. Cases (C) and Incidence /100 000 inhabitants (I) by age groups. Cuba, 1983- 2006.

	Age Groups (in years)											
	<1		1 - 4		5 - 14		15 - 64		>64		Total	
Years	C	I	C	I	C	I	C	I	C	I	C	I
1983	170	102.6	209	35.6	532	25.7	479	7.6	30	4.0	1420	14.3
1984	203	123.6	249	41.2	425	21.4	481	7.4	43	5.6	1401	14.1
1985	213	113.0	260	40.2	366	19.5	482	7.2	33	3.8	1354	13.5
1986	221	134.6	205	32.3	329	19.1	344	5.2	32	3.7	1131	11.0
1987	209	117.8	193	29.9	230	14.2	245	3.5	33	3.8	911	8.8
1988	215	114.9	200	29.7	222	14.5	258	3.6	27	3.2	922	8.8
1989	184	100.5	139	20.2	167	10.7	178	2.4	15	1.7	683	6.5
1990	133	71.9	80	11.4	79	5.2	145	2.0	17	1.8	454	4.2
1991	86	45.9	54	7.6	42	2.7	61	0.8	15	1.6	258	2.4
1992	58	37.2	38	5.2	19	1.2	33	0.4	4	0.4	152	1.4
1993	34	22.5	18	2.4	13	0.8	19	0.2	10	1.0	94	0.8
1994	26	14.9	18	2.5	21	1.3	15	0.2	8	0.8	88	0.8
1995	13	7.5	8	1.1	10	0.6	27	0.3	6	0.6	64	0.5
1996	22	12.9	9	1.3	13	0.7	14	0.2	5	0.5	63	0.5
1997	10	6.8	13	2.0	13	0.8	15	0.2	6	0.6	57	0.5
1998	14	9.3	11	1.9	9	0.5	13	0.2	3	0.3	50	0.4
1999	14	9.3	5	0.8	19	1.1	26	0.3	4	0.4	68	0.6
2000	13	9.1	7	1.2	16	1.0	18	0.2	2	0.2	56	0.5
2001	16	11.6	9	1.5	8	0.5	6	0.1	3	0.2	42	0.4
2002	10	7.2	5	0.8	12	0.7	9	0.1	2	0.2	38	0.3
2003	10	7.5	4	0.7	12	0.8	7	0.1	1	0.1	34	0.3
2004	9	6.5	6	1,0	11	0.7	7	0.1	2	0.2	35	0.3
2005	3	2.3	7	1.2	7	0.5	10	0.1	1	0.1	28	0.2
2006	7	5.5	3	0.5	6	0.4	8	0.1	2	0.2	26	0.2

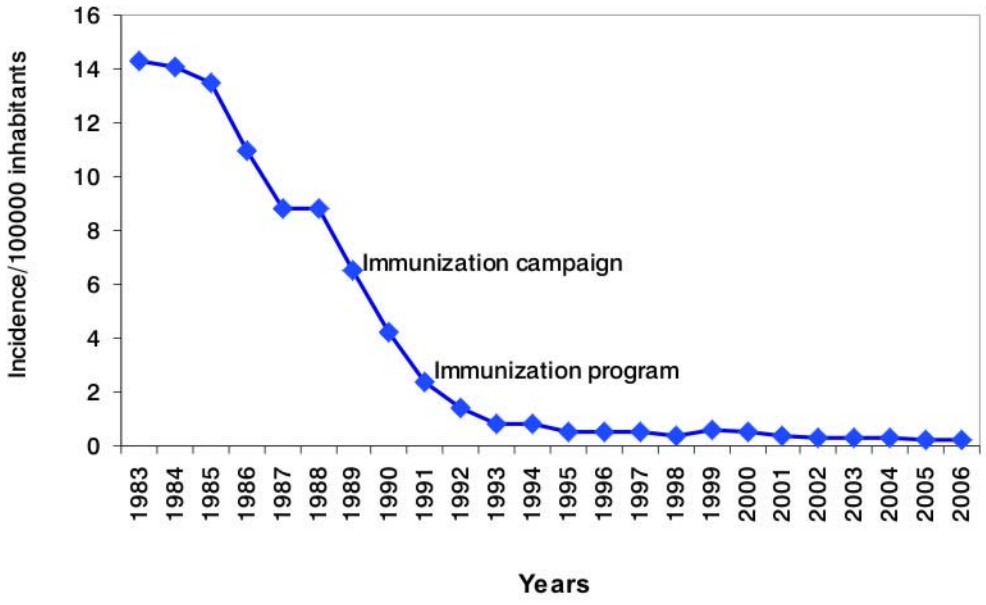

Figure 1. Meningococcal Disease. Overall incidence in Cuba 1983-2006.

Reduction of the overall incidence from 1989 to 2006 was 96.9% and the most important decrease was observed in children from 1 to 4 years (97.5%), 5 to 14 years (96.3%) and infants (94.5%).

Since 1998, infants continued with the highest rates although falling, but in 1 to 4 and 5 to 14 age groups incidence rates were nearly 1/100 000 inhabitants. The other groups had incidence rates <0.5/100 000 inhabitants (Table 1). When infants were excluded, mean age of patients was 21.9 years (standard deviation was 22.1) and the median age was 13 years.

Among infants the disease was reported more frequently at 6 months of age (13.8%) reaching 61.6% of cumulative percentage. Only two infant were less than 30 days old.

Nine socio-demographic variables were studied from 1998 to 2006. A total of 51 students attended boarding schools (IMD=34), 178 were day students (IMD=86), 8 were recluses (IMD=4), 2 military (IMD=1) and 1 041 may have received previous vaccination (IMD=292) (data not shown).

Bivariate and Multivariate analysis are shown in Table 2.

Table 2. Bivariate and Multivariate analysis of factors associated with morbidity of Invasive Meningococcal Disease. Cuba, 1998-2006.

Variables	Bivariate		Multivariate	
	Relative Risk (CI 95%)	p value*	Odds Ratio (CI 95%)	p value*
Boarding students	3.2 (2.6-4.0)	0.0000	9.4 (5.1-17.4)	0.0000
Day Students	2.5 (2.1-3.1)	0.0000	3.9 (2.8-5.6)	0.0000
Previous vaccination	2.2 (1.7-2.75)	0.0000	0.6 (0.4-1.0)	0.0565
Recluses	2.3 (1.1-4.6)	0.0555	5.9 (1.5-24.3)	0.0124
Military	1.5 (0.3-7.5)	0.6360	2.9 (0.3-33.2)	0.3780

* Significant value <0.05

Table 3. Invasive Meningococcal Disease. Deaths (D) and case fatality rate (CFR) by age groups. Cuba, 1983-2006.

Years	Age Groups (in years)											
	<1		1 - 4		5 - 14		15 - 64		>64		Total	
	D	CFR	D	CFR	D	CFR	D	CFR	D	CFR	D	CFR
1983	41	24.1	40	19.1	52	9.7	68	14.2	11	36.6	212	14.9
1984	45	22.1	49	19.6	32	7.5	77	16	17	39.5	220	15.7
1985	43	20.2	42	16.5	41	11.2	74	15.3	22	66.6	222	16.3
1986	37	16.7	44	21.4	42	12.7	56	16.2	16	50	195	17.2
1987	30	14.3	39	20.2	30	13	52	21.2	11	34.3	162	17.8
1988	32	14.8	45	22.5	28	12.6	59	22.8	12	44.4	176	19
1989	31	16.8	22	15.8	17	10.1	45	25.3	7	46.6	122	17.8
1990	24	18	18	22.5	22	27.8	33	22.7	9	52.9	106	23.3
1991	14	16.3	13	24	8	19	14	22.9	10	66.6	59	22.8
1992	6	10.3	12	31.5	2	10.5	10	30.3	3	75	33	21.7
1993	9	28.1	3	16.6	1	7.7	6	31.5	6	60	25	27.1
1994	3	11.5	3	16.6	6	28.5	7	46.6	4	50	23	26.1
1995	3	23	1	12.5	3	30	6	22.2	3	50	16	25
1996	2	9.1	2	22.2	2	15.4	2	14.3	3	60	11	17.4
1997	1	10	0	13	4	30.7	3	20	1	16.1	9	15.7
1998	0	0	1	9.1	0	0	3	23.1	2	66.7	6	12
1999	1	7.7	1	20	5	26.3	9	34.6	3	75	19	28.3
2000	2	15.4	2	28.6	3	18.7	1	5.9	0	0	8	14.5
2001	1	6.2	1	11.1	0	0	0	0	2	66.7	4	9.5
2002	0	0	0	0	1	8.3	1	11.1	2	100	4	10.5
2003	2	20	0	0	0	0	3	42.8	0	0	5	14.7
2004	0	0	1	16.7	1	9.1	3	50	1	50	6	17.6
2005	1	33.3	3	42.8	1	14.3	5	50.0	1	100	11	39.3
2006	0	0	0	0	1	14.3	3	37.5	1	50.0	5	19.2

Logistic regression analysis showed association with boarding students, day students and recluses. Patients previously vaccinated (OR=0.6; CI 95%: 0.4-1.0) showed protection to IMD (Table 2).

Mortality

It was registered nearly 200 deaths during the peak of the epidemic, decreased continuously and reaching an annual average of 6 deaths since 2000 (Table 3). The highest CFR was observed in 2005, 1999, 1993 and 1994 with 39.3%, 28.3%, 27.1% and 26.1% respectively. In general, the elderly showed the highest CFR. Since 1998 the mean age of fatality (excluding infants) was 36.8 years old and the median was 36 years old. Only 7 infants died and four of them (57.1%) were six months of age or older.

Table 4. Distribution of serogroup, serotype and subtype of *Neisseria meningitidis* strains received at the National Reference Laboratory for Neisseria IPK. Cuba, 1989-2006.

Strain types	No.	%
B4:P1.15	202	64.3
B4:P1.2,15	1	0.3
B4:P1.7,5	1	0.3
B4:P1.NT	5	1.6
B4:P1.12,15	4	1.2
B4:P1.2, 5	4	1.2
B4:P1.10,15	1	0.3
B4:P1.7,15	1	0.3
B4:P1.13,15	1	0.3
B4:P1.4	2	0.6
B4:P1.9,15	2	0.6
B4:P1.14	1	0.3
B4:P1.10,12	1	0.3
B4:P1.14,15	1	0.3
B4:NT	20	6.4
B4,17:P1.15	10	3.2
B15:P1.15	2	0.6
B15:P1.NT	1	0.3
B15:P1.16	1	0.3
B15:P1.13	2	0.6
B17:P1.14,15	1	0.3
B17:P1.15	1	0.3
B17:P1.15,16	1	0.3
B17:P1.4,15	1	0.3
BNT:P1.5,13	1	0.3
NT:P1.15	6	1.9
NT:P1.NT	2	0.6
NT:P1.4,15	2	0.6
NT	2	0.6
C *	1	0.3
Others	35	11.1
Total	314	100.0

Bivariate analysis only showed association with housewives (RR=3.8; CI 95% 2.5-5.7), pensioned (RR=3.5; CI 95% 2.0-5.9), workers (RR=1.7; CI 95% 1.0-2.9). Logistic regression analysis demonstrated association with housewives (OR=4.9; CI 95%: 1.9-12.4) and pensioned (OR=4.5; CI 95%:1.2-16.8). Previous immunization as a protective factor against mortality was also observed (OR=0.4; CI 95%: 0.2-0.9).

Laboratory surveillance

From 1989 to 2006, a sample of 314 meningococcal strains (25.0% of 1 254 strains received) was characterized at NRLN-IPK. All strains belonged to serogroup B except one (serogroup C) that was isolated in 2001 from a foreign patient. The majority of strains (64.3%) belonged to phenotype B4.P1.15. A lower frequency of strains with different serosubtypes was detected (Table 4).

Discussion

The Cuban Health System is based on a nationwide free-health service with total access and equal opportunity for every citizen to access medical care, hospitalization, vaccination, social assistance and other services (8).

Incidence of IMD decreased slowly from 1984 to 1987. The incidence stabilized during 1987 and 1988, but a subsequent and marked decline was observed from 1989 following a mass vaccination campaign in population < 20 year old, demonstrating the impact of this intervention. A continuous and high coverage vaccination through NIP allowed keeping low incidence (8). Nevertheless, we wonder what would have happened (a hyper endemic or a re-emergence epidemic) if the referred strategy with specific meningococcal vaccine under these circumstances had not been used.

In a different strategy aiming to reduce the incidence of an epidemic caused by phenotype B4:P1:15 in Sao Paulo, Brazil, only children aged from 3 months to 6 years were vaccinated (1989-1990) with the same specific vaccine used in Cuba, a little or no measurable effect on this outbreak was observed (14). Recently, the Global Advisory Committee on Vaccine Safety recognized the safety of outer membrane-vesicle meningococcal B vaccines based on their usage in Cuba, France, New Zealand and Norway (15).

In 2007, it was estimated that 1 000 cases of IMD occurred in the United States, with 130 (13%) case fatalities and equal rate of morbidity, including primarily amputations and hearing loss. It was considered that protection against IMD will require eliciting durable serum antibody present at the time of acquisition of *N. meningitidis*, and sufficient antibody to decrease colonization in adolescents and young adults, if the goal of population-based reduction in disease is to be achieved (16). Serogroup B prevails in Cuba as observed in other studies developed in the United Kingdom, where the majority of strains belong to serogroup B or C (17), and in

Germany (18), where 70% of *N. meningitidis* strains belong to serogroup B. In spite of the low incidence in Cuba, it is necessary to observe the future behavior of IMD very close, considering that the vaccination program is only addressed to serogroup B and C, and an emerging serogroup or new mutant strains may arise (19).

It has been reported that after 12 years of the immunization with VA-MENGOC-BC® (Havana, Cuba) in teenagers, only 42% had ≥ 1:4 of bactericidal antibodies titers against *N. meningitidis* B4:P1.19.15, and a booster dose response achieved 57% of seroconvertion of the antibodies titers (20). The possible association between previous vaccination and IMD found with the bivariated analysis could be explained taking into account the wide coverage of the Cuban immunization program, and that the most population has been vaccinated with VA-MENGOC-BC®. On the other hand, multivariate analysis proved protection with previous vaccination showing the real behavior of a complex phenomenon. These results permit the development of accurate and timely adjustments to both the immunization program and the policy to ensure their ultimate success.

An important and recent result of our surveillance system is the assessment of socio-demographic factors associated to IMD. Strong association with attendance to boarding school, recluse, day attending student, is coincident with reports in close settings. (21, 22). Mortality was strongly associated with housewives and retired people, which are unvaccinated and regularly older people have predisposing conditions. CFR is more related with health care and other factors beyond the purpose of this paper. Previously, we pointed out that vaccination is important to reduce mortality and severe clinical forms. High CFR observed among the elderly might be likely due to poorly recognizable clinical features in this vulnerable group (23). On the other hand, it is important to highlight that the main circulating *N. meningitidis* type B4:P1.15, belonging to the ET5 complex is characterized by a high virulence (24).

A new meningococcal B vaccine in a nationwide vaccination program was recently assessed in New Zealand, showing an effectiveness of 73%. The conclusion was that further observation is needed to determine whether the three-dose will provide longer lasting protection, although in infant a fourth dose was recommended (25).

In the United States IMD is more frequent between the ages of 2 to 18 years old, therefore meningococcal vaccine is recommended in the immunization schedules at different range of age (2 to 6 years old and 11 to 12 years old) (26). Recently the Advisory Committee on Immunization Practices (ACIP) recommends meningococcal vaccination with MCV4 at 3 years after receipt of MPSV4 for children 2-10 years who are at increased risk for IMD (27). In Cuba, the last autochthonous meningococci strains different to serogroup B (serogroups A and C) were confirmed by the NRLN in 1986. Therefore, now it is the moment to consider the use of a booster dose to provide longer lasting protection for serogroups B and C in target groups as toddlers and adolescents.

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Enfermedad meningocócica invasiva. Cuba, 1983–2006

Resumen

La enfermedad meningocócica invasiva (EMI) es un problema de salud mundial. En Cuba, la vacunación antimeningocócica BC se ha llevado a cabo desde 1989. El propósito del presente trabajo fue describir la epidemiología de la EMI entre 1983-2006 y contribuir a la estrategia de prevención. Se realizó un estudio descriptivo y analítico de todos los casos confirmados y registrados. Los datos se obtuvieron del Sistema Nacional de Vigilancia en el Instituto «Pedro Kourí». En 1986 se registraron más de 1 000 casos de EMI con una incidencia de 10/100 000 habitantes. Desde 1989 se observó un notable y continuo descenso de la incidencia. En los últimos 9 años se observó una fuerte asociación en la ocurrencia de casos con estudiantes de régimen interno (OR=9,4; Intervalo de Confianza 95%: 5,1-17,4), reclusos (OR=5,9; IC 95%: 1,5-24,3) y estudiantes externos (OR=3,9; IC 95%: 2,8-5,6). Mostraron asociación con la mortalidad las amas de casa (OR=4,9; CI 95%: 1,9-12,4) y los jubilados (OR=4,5; CI 95%: 1,2-16,8). La vacunación previa mostró ser un factor protector para la morbilidad (OR=0,6; CI 95%:0,4-1,0) y la mortalidad (OR=0,4; CI 95%: 0,2-0,9). El principal fenotipo circulante de *Neisseria meningitidis* fue B4:P1.15. La incidencia de EMI se redujo notablemente en Cuba a partir del uso de la vacuna antimeningocócica específica del grupo B.

Palabras clave: Enfermedad meningocócica invasiva, epidemiología, factores de riesgo, *Neisseria meningitidis*, inmunización.

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