# The Epidemiological Impact of Antimeningococcal B Vaccination in Cuba

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*The incidence of invasive meningococcal disease (IMD) before (1984-1988) and after (1989-1994), a nationwide intervention with VA-MENGOC-BC vaccination started in 1989, was compared. The prevaccination period incidence density (ID> 8.8/ $10^5$ year-person) was higher than the postvaccination ID (ID< 6.5/ $10^5$ year-person). The percentage proportional differences from the start to the end of each period of ID in the vaccinal period was higher (87%) than the prevaccinal (37%) with significant differences among vaccinated groups (< 25 years old). A break-point (Chow test) was confirmed by the decrease in the ID between 1989 and 1990 in children under 1 year old, 5-9, 10-14, 15-19 and 50-54 years. Comparison of ID using maps showed a decrease in IMD in all municipalities during the postvaccination period. These findings support the epidemiological impact of VA-MENGOC-BC vaccination in the reduction of IMD morbidity.*

Key words: invasive meningococcal disease - impact of vaccination - antimeningococcal B vaccine - vaccine effectiveness - control of epidemic - Cuba

Septicemia and meningitis are the most lifethreatening forms of invasive meningococcal disease (IMD) infections (De Voe 1982). This disease has become a relevant worldwide health problem because of it's high morbidity and mortality.

Thirteen serogroups have been identified based on antigenic differences in the capsular polysaccharides of the causative agents. The most common are A, B and C which are responsible for 90% of disease in the whole world (PAHO 1994, WHO 1996).

At present in Europe, Australia and America the incidence of serogroup B disease is increasing mostly in children under 5 years of age (WHO 1996). The European incidence rate in 1995 reached 1.71 cases per 100,000 inhabitants and the prevailing serogroups were B (69%) and C (27%) (Noah & Connolly 1996).

IMD was endemic in Cuba (10-41 cases per year) and was not considered a health problem. Starting from 1962, the reported incidence increased from 0.1, reaching 1.8 cases per 100,000 inhabitants in 1978, with the increased incidence mostly caused by serogroup C. The Public Health Ministry decided to carry out nationwide vaccination in 1979 with a capsular polysaccharide A-C vaccine (Merieux Laboratories) in the portion of the population ranging in age from 3 months to 19 years. A vaccination coverage of 80% was achieved, resulting in a reduction of *meningococci* C infections (Valcárcel et al. 1990). Despite this intervention, the incidence rate continued to rise and in 1980 the Public Health Ministry considered IMD as a nationwide major health problem. The prevailing serogroups were B (78.4%) and serogroup C (7.2%). The peak of the epidemic occurred in 1983, reaching a maximum incidence of 14.4 cases per 100,000 inhabitants. In the 1980s research started in Cuba on a serogroup B-C vaccine (VA-MENGOC-BC) produced from strain Cu385/83 (B:4; P1.15) which consisted of lipooligosaccharide-depleted outer membrane proteins and group C polysaccharide, enriched with envelope proteins from 65 to 95 kDa (Sierra et al. 1990). Based on encouraging results in the efficacy trials between 1987 and 1988, the Ministry of Public Health carried out a massive vaccination of the high risk population under 20 years of age, achieving 95% coverage (>3 million vaccinated) with remarkable success in the control of IMD (Almeida & Rico 1994). Starting in 1991 the vaccine was included in the National Immunization Program (NIP) for all infants (first dose at 3½ months and the second at 5½ months), and since then has achieved 89.4% of coverage (581,210 infants) (Pérez & Dickinson 1998).

The goal of the present study was to assess the impact of meningococcal vaccination against IMD serogroup B in Cuba.

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Received 9 June 1998
Accepted 10 February 1999

## MATERIALS AND METHODS

*Study population and data sources* - Cuban population data obtained from the National Center of Population and Development were used in single ages from 0 to 4 years old and quinquenial groups for the remainder.

The Cuban State Health System is based on nationwide free health service with total access and equal opportunity for every citizen to obtain medical assistance, hospitalization, vaccination, social assistance and other services. Therefore National Epidemiological Surveillance System has covered the entire country since 1962 and provided passive information data on all reported IMD (7,448 cases) in the selected period between January 1st, 1984 to December 31st, 1994. In view of the severity of IMD, all suspicious cases are always referred to hospital, where the laboratory diagnosis and notification are endorsed. In addition, an Oversight Committee in each hospital analyses all infectious neurological syndromes to ensure cases of meningococcal disease were not missed. Complementary epidemiological information about IMD cases was obtained from the National Meningococcal Survey as established the control program. The reliability and fitness of the data was assured by the above stated standarization of diagnosis, compulsory and complete reporting and registration of a systematic audited-evaluated surveillance system. This included the 1982 changeless definition which considered a confirmed case as "every patient with clinical illness consistent with IMD and *Neisseria meningitidis* isolation from blood or cerebrospinal fluid and/or a positive antigen test for meningococcus and/or a Gram stain of cerebrospinal fluid or blood showing Gram-negative *diplococci*. Exceptionally by clinical-epidemiological criteria and the advice of authorized experts".

*Analysis* - The statistical analysis involved two well defined periods in which the only difference was vaccine intervention: the first, from January 1st, 1984 to December 31st, 1988 and coincident with the decrease of the epidemic without vaccination mediation (prevaccinal period) and the other, with the mediation of VA-MENGOC-BC vaccine, from January 1st, 1989 to December 31st, 1994 (vaccinal period).

Chronological series of incidence density (ID) (Miettinen 1976, Kleinbaum et al. 1982, Rothman 1987, Jenicek & Cléroux 1993), per year allowed the descriptive analysis.

The percentage proportional differences for each period (PPD) were calculated as PPD = $(ID_{initial} - ID_{final}) / ID_{initial} \cdot 100$.

The Sign Rank Wilcoxon Test was used to calculate the respective percentage difference ID mean in each age group and period. This finally allowed a comparison of individuals under 25 and ≥ 25 years old between periods.

A Chow Test (Novales 1993) was performed which considered the hypothesis of a break point in 1989 or 1990 because of the high vaccination coverage (>80%) in the population under 25 years of age.

The ID of the prevaccinal and vaccinal periods was mapped at the municipal level in each age group in order to illustrate the reduction of this indicator all over the country. As an example, only the maps for the children under 1 year old were included in this paper.

Data processing was made using EPIINFO 6.0, EXCEL 5.1, Statistica for Windows 4.3, TSP 7.0 to run Chow Test; MAPINFO was used for making maps.

## RESULTS

From 1984 to 1994 total ID decreased from 14.1 (1401 cases) to 0.8 (88 cases) per 100,000 persons-year. In the prevaccinal period the ID reduction was from 14.1 (1401 cases), to 8.8 (922 cases) per 100,000 persons-year (reduction of 479 cases), but in the vaccinal period the reduction observed was more significant from 6.5 (683 cases) to only 0.8 (88 cases) per 100,000 persons-year (595 fewer cases). The highest risk of IMD was among infants of less than 1 year old in both periods. From 1992 the highest risk was for children under 3 years old but was lower than in the prevaccinal period. In all simple and clustered ages the ID decreased by more than 50% during the vaccinal period when compared with the prevaccinal. The overall risk of IMD was higher in the population under 20 years old in both periods and the decrease observed among this group was remarkable during the vaccinal period. Contrarily in the population ≥ 20 years old, which remained unvaccinated, ID were low even in the prevaccinal period and did not change notably when the two periods were compared (Tables I, II).

When comparing ID percentage proportional differences in both periods, the highest reduction was observed in the vaccinal period. All age groups reduced their ID in the vaccinal period, but this was particularly marked in children under 3 years old (Fig. 3). The Sign rank Wilcoxon Test confirmed the significant differences between both periods ($p<0.01$), most notably in the vaccinated population ($p=0.0019$).

The Chow Test provided evidence for a significant break point ($p<0.05$) in 1989 for groups under 1 year old, 15-19 and 50-54 years old, while in 1990 the statistical significance was only observed in 1 year old children, 5-9 and 10-14 years old age groups, coincident with the achievement of high vaccination coverage (Table III). As an example, in

TABLE I

Invasive meningococcal disease. Number of cases according to age and year of occurrence. Cuba 1984-1994

| | Prevaccinal period | | | | | Vaccinal period | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 1984 | 1985 | 1986 | 1987 | 1988 | 1989 | 1990 | 1991 | 1992 | 1993 | 1994 |
| < 1 | 203 | 213 | 221 | 209 | 215 | 184 | 133 | 86 | 58 | 34 | 26 |
| 1 | 92 | 87 | 77 | 72 | 76 | 67 | 40 | 20 | 16 | 5 | 6 |
| 2 | 49 | 75 | 59 | 56 | 45 | 23 | 18 | 11 | 9 | 8 | 4 |
| 3 | 60 | 55 | 40 | 37 | 41 | 32 | 8 | 16 | 7 | 2 | 3 |
| 4 | 48 | 43 | 29 | 28 | 38 | 17 | 14 | 7 | 6 | 3 | 5 |
| 5-9 | 189 | 161 | 136 | 99 | 98 | 89 | 40 | 27 | 16 | 9 | 15 |
| 10-14 | 236 | 205 | 193 | 131 | 124 | 77 | 39 | 15 | 3 | 4 | 6 |
| 15-19 | 170 | 179 | 114 | 94 | 66 | 50 | 39 | 11 | 7 | 2 | 2 |
| 20-24 | 76 | 62 | 52 | 32 | 46 | 30 | 17 | 5 | 3 | 2 | 0 |
| 25-29 | 37 | 49 | 32 | 14 | 30 | 14 | 11 | 8 | 2 | 3 | 4 |
| 30-34 | 30 | 32 | 26 | 15 | 21 | 13 | 12 | 9 | 1 | 3 | 0 |
| 35-39 | 35 | 41 | 24 | 8 | 14 | 10 | 12 | 5 | 7 | 0 | 1 |
| 40-44 | 39 | 29 | 22 | 29 | 23 | 15 | 10 | 9 | 2 | 2 | 1 |
| 45-49 | 29 | 26 | 21 | 13 | 19 | 17 | 14 | 4 | 0 | 2 | 2 |
| 50-54 | 28 | 23 | 19 | 15 | 10 | 12 | 14 | 3 | 4 | 4 | 2 |
| 55-59 | 22 | 19 | 20 | 13 | 15 | 11 | 10 | 4 | 5 | 1 | 3 |
| 60-64 | 15 | 22 | 14 | 13 | 14 | 6 | 6 | 3 | 2 | 0 | 0 |
| ≥65 | 43 | 33 | 32 | 33 | 27 | 16 | 17 | 15 | 4 | 10 | 8 |
| Total | 1401 | 1354 | 1131 | 911 | 922 | 683 | 454 | 258 | 152 | 94 | 88 |

TABLE II

Invasive meningococcal disease. Incidence density ($10^5$ year-person ) according to age and year of occurrence. Cuba 1984-1994

| | Prevaccinal period | | | | | Vaccinal period | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 1984 | 1985 | 1986 | 1987 | 1988 | 1989 | 1990 | 1991 | 1992 | 1993 | 1994 |
| < 1 | 123.6 | 118.6 | 134.6 | 117.7 | 115.6 | 100.5 | 71.9 | 49.9 | 37.2 | 22.5 | 14.9 |
| 1 | 56.6 | 50.1 | 42.9 | 43.9 | 42.9 | 36.0 | 21.8 | 10.8 | 9.3 | 3.2 | 3.4 |
| 2 | 31.5 | 46.7 | 36.4 | 31.6 | 27.6 | 13.0 | 9.7 | 6.0 | 4.9 | 4.6 | 2.2 |
| 3 | 45.3 | 35.2 | 22.2 | 20.6 | 25.1 | 17.3 | 4.5 | 8.6 | 3.7 | 1.0 | 1.6 |
| 4 | 36.3 | 32.4 | 18.6 | 17.4 | 23.5 | 9.6 | 8.5 | 3.9 | 3.2 | 1.6 | 2.7 |
| 5-9 | 22.0 | 20.2 | 19.2 | 14.1 | 13.6 | 11.9 | 5.3 | 3.3 | 1.9 | 1.0 | 1.7 |
| 10-14 | 20.9 | 19.0 | 18.9 | 14.0 | 14.4 | 9.6 | 4.8 | 2.1 | 0.4 | 0.5 | 0.8 |
| 15-19 | 14.6 | 15.5 | 9.8 | 8.0 | 5.7 | 4.5 | 3.4 | 1.1 | 0.7 | 0.2 | 0.2 |
| 20-24 | 7.2 | 5.6 | 4.5 | 2.7 | 3.9 | 2.6 | 1.4 | 0.4 | 0.2 | 0.1 | 0.0 |
| 25-29 | 5.2 | 6.7 | 3.9 | 1.5 | 3.0 | 1.3 | 1.0 | 0.7 | 0.1 | 0.2 | 0.3 |
| 30-34 | 4.3 | 4.6 | 3.6 | 2.1 | 3.0 | 1.9 | 1.7 | 1.1 | 0.1 | 0.3 | 0.0 |
| 35-39 | 5.4 | 6.2 | 3.5 | 1.1 | 1.9 | 1.3 | 1.5 | 0.7 | 1.0 | 0.0 | 0.1 |
| 40-44 | 6.6 | 4.8 | 3.5 | 4.6 | 3.5 | 2.3 | 1.5 | 1.3 | 0.2 | 0.2 | 0.1 |
| 45-49 | 5.7 | 4.9 | 3.9 | 2.3 | 3.3 | 2.8 | 2.3 | 0.7 | 0.0 | 0.3 | 0.3 |
| 50-54 | 6.8 | 5.5 | 4.3 | 3.4 | 2.1 | 2.5 | 2.8 | 0.5 | 0.7 | 0.7 | 0.3 |
| 55-59 | 5.9 | 5.0 | 5.3 | 3.3 | 3.7 | 2.7 | 2.4 | 0.9 | 1.1 | 0.2 | 0.6 |
| 60-64 | 4.8 | 7.0 | 4.3 | 4.0 | 4.1 | 1.7 | 1.7 | 0.8 | 0.5 | 0.0 | 0.0 |
| ≥65 | 5.6 | 4.2 | 3.7 | 3.7 | 3.0 | 1.7 | 1.8 | 1.5 | 0.4 | 1.0 | 0.8 |
| Total | 14.1 | 13.5 | 11.0 | 8.8 | 8.8 | 6.5 | 4.2 | 2.4 | 1.4 | 0.8 | 0.8 |

order to make clear the results of Chow test, Figs 1 and 2 showed that when comparing both periods the decrease was faster in the 1 year age group ($p<0.01$) than in the 3 year age group ($p> 0.05$).

The mapped data relating to children under 1 year old showed the highest ID values during the prevaccinal period in the municipalities of Cuban central region; this epidemiological situation was modified after the use of vaccination. The number of case less-municipalities increased five fold after vaccination and was reflected in the reduction of the ID in the vaccinal period (Figs 4, 5).

TABLE III

Invasive meningococcal disease. Chow test (break point) on chronological incidence density series according to group of ages. Cuba 1984-1994

| Simple and grouped ages | Chow Test | |
|---|---|---|
| | Statistic F | p-value |
| <1 | 12.4850 | 0.0049 |
| 1 | 8.0385[a] | 0.0154 |
| 2 | 3.7409 | 0.0785 |
| 3 | 1.0643 | 0.3948 |
| 4 | 1.9852 | 0.2075 |
| 5-9 | 11.5490[a] | 0.0061 |
| 10-14 | 7.1641[a] | 0.0203 |
| 15-19 | 6.0205 | 0.0282 |
| 20-24 | 1.4763 | 0.2918 |
| 25-29 | 2.1061 | 0.1923 |
| 30-34 | 0.1352 | 0.8758 |
| 35-39 | 3.6426 | 0.0824 |
| 40-44 | 0.9140 | 0.4439 |
| 45-49 | 0.4265 | 0.6687 |
| 50-54 | 6.0540 | 0.0298 |
| 55-59 | 0.3277 | 0.7310 |
| 60-64 | 1.6409 | 0.2604 |
| =65 | 3.5781 | 0.0850 |

*a*: break point in 1990.

Only 1,006 samples (58.2%) of 1,729 cases reported were classified during the vaccinal period, corresponding to 98.6% (992/1,006) serogroup B, 0.9% (9/1,006) serogroup C, and 0.5% (5/1,006) serogroup A. A number of cases (679/1,729; 39.3%) were diagnosed by Gram stain and only a few cases (44/1,729; 2.5%) using clinical-epidemiological experts criteria. The National Reference Laboratory of Tropical Medicine Institute "Pedro Kourí" received 346 strains classified 65.0% (225/346) as B4 P1.15 (vaccinal strain), 33.5% (116/346) as serogroup B and 0.3% (1/346) as serogroup B2, with only 1.2% (4/346) remaining unclassifiable.

## DISCUSSION

This investigation was based on epidemiological analysis of the IMD behavior supported by statistical tools in order to evaluate the impact of a vaccination program at the time of slow epidemic decrease which was dependent on the recent availability of a new vaccine against serogroup B which was essential to control the worrying morbidity levels seen in the population under 20 years old and especially in children under 5 years old.

The greatest reduction of IMD was evident during the vaccinal period (87.7%) compared with prevaccinal (37.6%) as shown by the chronological series supported by ID percentage proportional difference and the Chow Test. The significant break point observed for some age groups was illustrated by comparing the significant change in the reduction of morbidity which occurred in the 1 year of age group (Fig. 1) with the non significant change (Fig. 2) in the 3 years of age group. Nonstatistical significance observed with the Chow Test for some

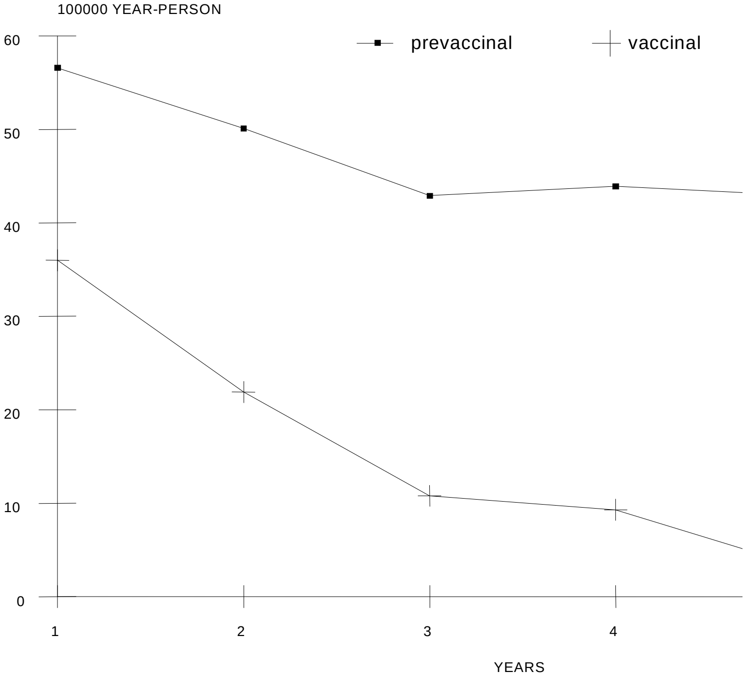

Fig. 1: invasive meningococcal disease. Incidence density in children of 1 year old during prevaccinal and vaccinal period. Cuba 1984-1988 and 1989-1994.

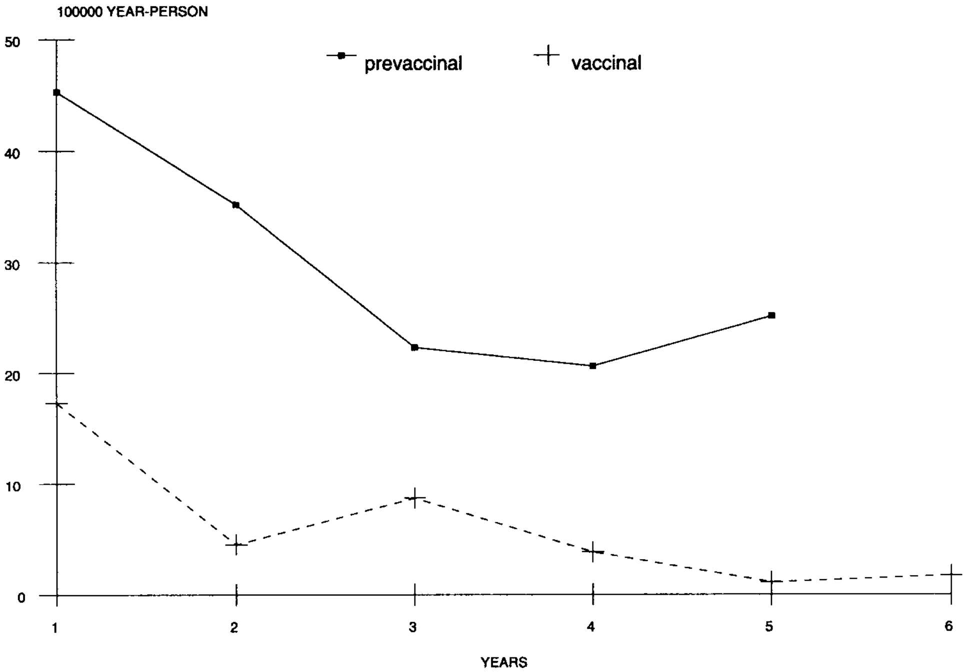

Fig. 2: invasive meningococcal disease. Incidence density in children of 3 years old during prevaccinal and vaccinal period. Cuba 1984-1988 and 1989-1994.

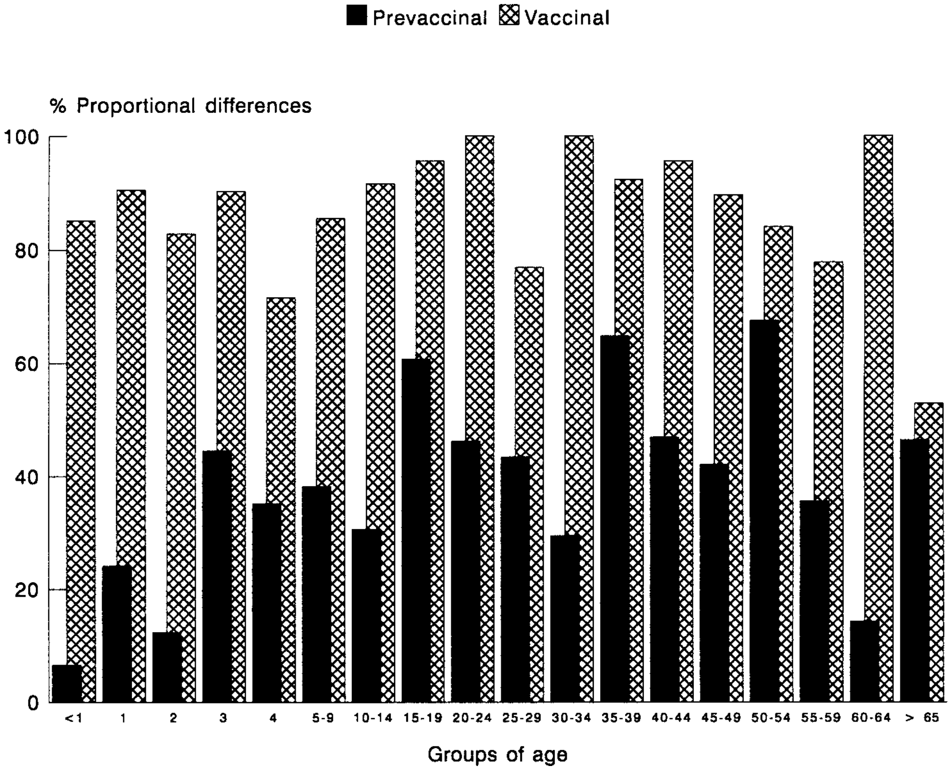

Fig. 3: invasive meningococcal disease. Percentage proportional differences from starting to end of each period of incidence density according to groups of age. Cuba 1984-1988 and 1989-1994.

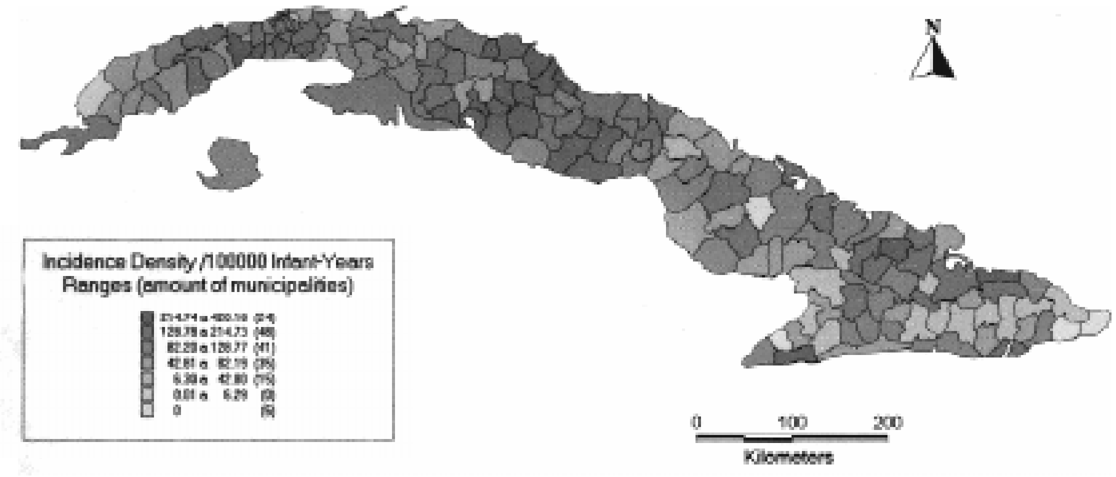

Fig. 4: invasive meningococcal disease. Incidence density in children under 1 year old according to municipalities. Cuba 1984-1988.

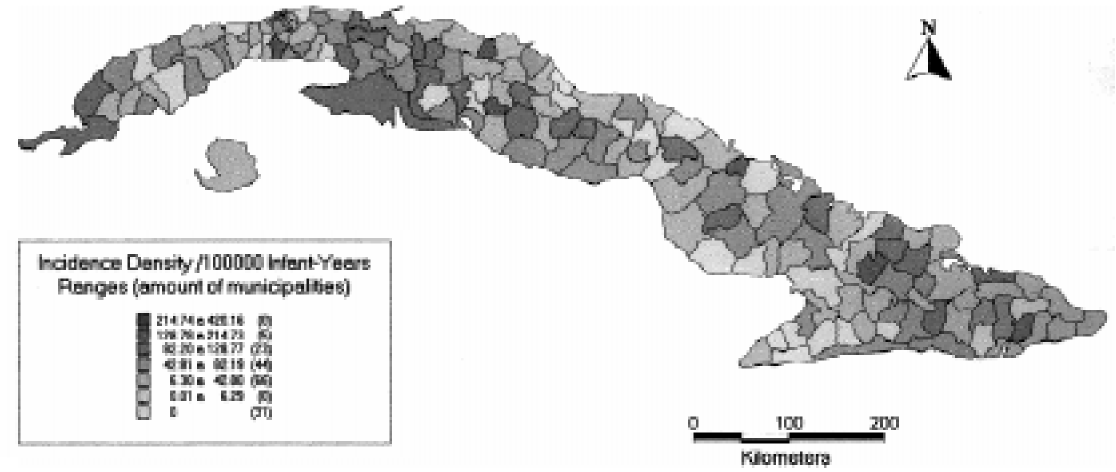

Fig. 5: invasive meningococcal disease. Incidence density in children under 1 year old according to municipalities. Cuba 1989-1994.

immunized age groups, may be related to the low number of cases which occurred in these groups at the begining of the vaccinal period (cohort effect) with a subsequently slow morbidity reduction which resulted in a low endemicity threshold, only reducible when implementing a disease elimination program. This might explain the heterogeneous Chow Test results for different age groups in the vaccination period.

Parameters for evaluating vaccine intervention programs against infections diseases must take into account the direct effects of the intervention as well as the indirect, also known as the protective effects, that are mediated by the intervention-induced changes in transmission of disease (Halloran et al. 1991).

In our study the decrease of ID observed during the vaccinal period in the unvaccinated population (≥20 years old), might be also explained by herd immunity and the other factors mentioned above. Nevertheless in some of these groups ID was already low without vaccine mediation and it may have been related to specific host susceptibility phenomenon.

The mapped data facilitated interpretation of the results, showing not only that almost all municipalities decreased their ID, but also the important increase in the number of IMD case less-municipalities after vaccination. These data represent a very useful tool for demonstrating the homogeneus nationwide impact on ID decrease, as a result of the high coverage of vaccination.

Studies of antimeningococcal BC vaccination under epidemic conditions in other countries (Boslego et al. 1995, Noronha et al. 1995) suggest low efficacy for VA-MENGOC-BC vaccine in serogroup B IMD, especially in children under 5 years of age. In contrast, our results revealed a dramatic decrease of epidemic after vaccination with a type specific vaccine (an initial mass vaccination followed by systematic immunization) which confirms that community interventions may be a reliable source of knowledge even if the findings are sometimes confusing or disappointing. We agree that "the art of epidemiologic reasoning is to draw sensible conclusions from imperfect data" (Comstock 1990). On the other hand, previous studies in Cuba endorse our results reporting an efficacy of between 93 to 98%, e.g. 98% effectiveness in Ciego de Avila province, 96% in Holguin, and 99% in Havana in children from 0 to 5 years old (Sierra et al. 1991, Almeida & Rico 1994, Rico et al. 1994). The Cuban-Brazilian Commission studied effectiveness in Brazilian children under 6 years old, observing an effectiveness between 60 and 79% (Mixed Commission Brazil-Cuba 1994). It is necessary to point out that the Ministry of Public Health preventive strategy of using VA-MENGOC-BC in children under 1 year old through NIP since 1991, was an important factor involved in maintaining the morbidity reduction even when continous circulation of the agent was confirmed. This is an important difference with regard to other countries, which only used vaccination as a punctual measure in epidemic control and could also explain differences in the results.

The prevalence of serogroup B among the cases was similar in both periods according to the National Surveillance data. In addition, previous studies indicated that VA-MENGOC-BC did not influence meningococcus B carriage (Valcárcel et al. 1990). From our point of view, desisting in the systematic vaccination strategy might result in hyperendemic behavior or epidemic reemergence of disease.

After VA-MENGOC-BC vaccination in 1988, the meningococcal B morbidity started to decrease substantially throughout the whole country in children under 1 and 1 year old in which IMD is frequently high. The greater incidence of disease between 6 months and 2 years old is probably due to catabolism of maternal antibodies in a unexperienced immunological organism (González et al. 1990, Martínez et al. 1990, Martínez 1994). Moreover in children under 2 years old antibodies may decrease three years after vaccination, and the same effect may occur in acquired disease (González et al. 1990). Studies carried out in Africa have documented that the decline of antibodies started three weeks after vaccination and a booster was not effective (Goldschneider et al. 1969, Kaythy et al. 1980, Lepow et al. 1986). According to Comstock (1994) the design of some studies on the effect of vaccination could be considered to wane with time and the immune vaccinates could subsequently become susceptible vaccinates.

The nationwide occurrence of IMD was greater among nonvaccinated populations and the absence of outbreaks in the vaccinal period is also notworthy; both facts emphasized the protective effect of mass vaccination when continued by a systematic and accesible NIP.

We conclude that the above findings largely support the hypothesis of antimeningococcal B vaccination as the only difference between the two analized periods evidenced by epidemiological analysis of reliable data and supported by statistical tools.

## ACKNOWLEDGMENTS

To Dr Cándido López Pardo for the statistical assistance, Dr Miguel Galindo for helpful discussions, Dr Isabel Martínez for laboratory surveillance, and to Mariela Otaño, Damarys Concepción, Georgina Guevara and Irene Toledo.

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