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Assessment of the Direct Effectiveness of BC Meningococcal Vaccine in Rio de Janeiro, Brazil: A Case-Control Study

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Background. Meningococcal disease is still a serious public health problem in many countries. A vaccine produced by Cuba was the first product against B meningococcus available on a large scale. In an attempt to control the increasing incidence of this serogroup in greater Rio de Janeiro, Brazil, the vaccine was used in 1990 in children aged 6 months–9 years. About 1.6 million children were vaccinated.

Methods. In order to assess the direct effectiveness of the vaccine in preventing disease, we conducted a case-control study during the first year after vaccination. Using a hospital-based census, we selected all children hospitalized with meningococcal disease and sampled the control group among children hospitalized with other types of meningitis. Vaccine effectiveness was estimated from the relationship, 1 – OR, where OR (odds ratio) was the exponential of the logistic regression coefficient for the association between meningococcal disease and previous vaccination.

Results. A total of 275 cases and 279 controls were selected between September 1990 and October 1991. The summary adjusted measure of protection against serogroup B was 54% (95% confidence interval [CI] : 20–74%). Estimated protection varied among different age strata and place of residence, being high among children aged ≥4 years, 71% (95% CI : 34–87%), and among those who lived in the City of Rio de Janeiro, 74% (95% CI : 42–89%).

Conclusions. The results suggest that the vaccine produced by Cuba may offer protection against serogroup B meningococcal disease, but its effects may not be homogeneous.

Keywords: meningococcal disease-serogroup B, Neisseria meningitidis, polysaccharide vaccine, vaccine effectiveness

Meningococcal disease (MD) is the term used to describe the various clinical syndromes that may follow infection with *Neisseria meningitidis*. Meningitis and acute meningococcaemia are the more important clinical manifestations of MD.[1] It has been a threat to many people throughout the world, especially younger children.[2–4] Type B meningococcus has affected Norway, Spain, Chile, Cuba and Brazil in recent years.[5–8] Polysaccharide vaccines offer a high protection against serogroups A and C, but B polysaccharide is poorly immunogenic in humans. Studies of the outer membrane protein (OMP) of this meningococcus have made possible the development of various vaccines against the B serogroup. However, a highly immunogenic vaccine against this serogroup is not yet available.[9–11]

The vaccine produced by Cuba against B meningococcus is composed of the OMP from strain B:4:P1.15, about 1% of lipopolysaccharide and phospholipids, added to serogroup C capsular polysaccharide and aluminium hydroxide. The addition of polysaccharide C affords protection against C serogroups. It covers the major portion of MD serogroups in many countries. Randomized double-blind trials and observational studies carried out in Cuba demonstrated greater than 80% protection against serogroup B MD with this vaccine.[8,12] An estimate of the efficacy of this vaccine against serogroup B in greater São Paulo, Brazil, by means of a case-control study matched by age and neighbourhood demonstrated a variable protection by age. This protection was high and statistically significant only for children of age ≥4 years.[13]

In an attempt to control the increasing incidence levels of MD of serogroup B in the metropolitan region of Rio de Janeiro (MRRJ), this vaccine was given to children 6 months–9 years old during a campaign in 1990. About 1.6 million children were vaccinated with two doses.

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Among the identified meningococcus in this region during 1989/90, the strain B:4:P1.15 has appeared in 38% of serogroup B isolates from patients. Our study estimated the protective effect of the vaccine produced by Cuba among the children who lived in the metropolitan region of Rio de Janeiro, Brazil, stratified by age at time of the first dose and place of residence. We also evaluated the relationship between the protective effect of the vaccine and the clinical manifestation of the MD, in search of any possible modification of the clinical expression of meningococcal infection by the vaccine. In addition, we studied the effect of the time elapsed since the vaccination on protection, as well as the dependence of the estimates of vaccine protection on increasing levels of MD incidence.

METHODOLOGY

Study Design

We conducted a hospital-based unmatched case-control study to estimate the direct effectiveness of the vaccine produced by Cuba against MD of serogroup B.[14,15] The incident cases of MD were collected longitudinally during the first year beginning 4 weeks after the administration of the second dose of the campaign. The control group was collected concomitantly from the same catchment population. In this design the incident cases reflect the experience of the referent population regarding the occurrence of MD after vaccination, and the controls are supposed to reflect the experience of the same referent population regarding vaccine intake.[16–18]

Catchment Population and Study Base

This study was carried out in the Sao Sebastiao State Infectology Institute (IEISS), located in the metropolitan region of Rio de Janeiro (MRRJ). A population of more than 10 million inhabitants live in this region, and more than half of them live in the city of Rio de Janeiro (Capital). Annually, about 67% of all cases of meningitis of known aetiology occurring in this region are referred from many emergency public health services of IEISS for diagnosis and treatment. The remaining 33% are distributed among various hospitals (unpublished observation). In 1991, 1350 patients with meningitis entered IEISS, MD being responsible for 44% of those admissions. The case series covered almost the totality of case serogroups. However, only 46% of the deaths from MD occurred in IEISS. The case-fatality rate of MD in all other hospitals pooled together was 39%, while in the IEISS, the case-fatality rate of MD was only 9% in this year. The yearly accumulated incidence of MD in MRRJ increased progressively after 1982, increasing from one case per 100 000 inhabitants to seven cases per 100 000 inhabitants in 1990. The proportion of serogroup B among the meningococci isolated from patients also increased in the same period. Younger children were the most affected group, especially those aged ≤12 months. The average incidence rate of MD in the MRRJ varied from city to city, ranging from 3.5 to 7.9 cases per 100 000 inhabitants in 1988/91 for all ages. Immunization with the vaccine produced by Cuba was carried out in May and July 1990 in the majority of the cities enrolled. The first dose was offered during 2 weeks in May and the second dose was offered during 2 weeks in July, at all public health services. The target group for vaccination was children aged 6 months–9 years. The estimated coverage with two doses varied from city to city, with a mean of 74%.

Selection of Subjects

We interviewed all children admitted to IEISS between September 1990 and October 1991 who satisfied the following criteria: (1) they belonged to the cohort born between June 1980 and November 1989, i.e. children between 6 months and 9 years old in May 1990 when the first dose of the vaccine was given; and (2) they lived in any of the cities of MRRJ in 1990 that were included in the vaccination campaign.

Cases of MD were defined by the presence of one or more of the following criteria: (1) *N. meningitidis* isolated from a culture of cerebrospinal fluid (CSF) belonging to serogroup B or C; (2) meningococcal antigens of serogroup B or C demonstrated in CSF with latex agglutination; (3) gram-negative diplococci identified by gram stain of CSF; (4) abnormal CSF cytopathological findings in a patient with acute haemorrhagic skin lesions; or (5) symptoms of bacterial meningitis and haemorrhagic skin lesions with either normal CSF or no CSF data available.

Controls were defined by the following criteria: (1) meningitis caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, or any bacteria other than *N. meningitidis* isolated from a culture or latex agglutination of CSF; (2) meningitis caused by virus without other specification or meningitis post-mumps in a patient with aseptic meningitis who recovered without antibiotic treatment; (3) meningitis caused by tuberculosis in a patient with clinical and epidemiological findings of tuberculosis meningitis who was cured with appropriate treatment for this disease; and (4) other diagnoses for patients who were initially suspected of having meningitis. Children admitted to the hospital with bacterial meningitis of unknown aetiology were excluded from the study.

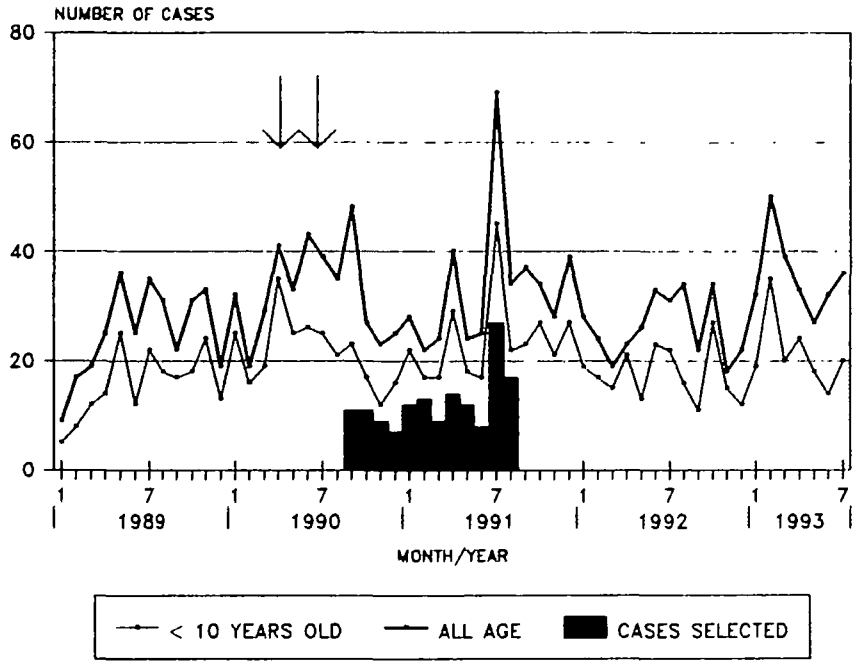

FIGURE 1 *Incident cases of meningococcal disease by month, in all ages and in children <10 years old, in the city of Rio de Janeiro, Brazil, between 1989 and 1993. The bars show the number of cases selected for the study in the city and the arrows show when the vaccination campaigns were carried out*

Data Collection and Ascertainment of Vaccination Status

The data were collected concomitantly with admission to IEISS from 1 September 1990 to 31 August 1991. The selection of controls lasted until 15 October 1991 in order to reach the same number of cases (Figure 1). Questionnaire interviews were carried out daily in private with a parent or other adult responsible for the child. Clinical and laboratory data were collected from hospital records.

Vaccination status was determined by oral reports and inspection of a child's vaccination card. The children were assigned to one of four vaccination categories; (1) completely vaccinated if they had received two doses of the vaccine; (2) incompletely vaccinated if they had received only one dose of the vaccine; (3) unvaccinated if they had not received any dose; and (4) unknown vaccination status if the parents were absent or information on the vaccine intake was missing for any other reason. In estimating the direct effectiveness of the two doses of the vaccine, we denoted as the exposed group children who were completely vaccinated, and as unexposed, children who were unvaccinated.

Statistical Analysis

Ordinary logistic regression was carried out using the program LR from the BMDP statistical package[19] and the OR (odds ratio) was estimated directly from the regression parameters. In the regression model, MD was used as the dependent variable.[20,21] Vaccine effectiveness was estimated from the relationship 1 – OR, where OR was the exponential of the regression coefficient for the association between MD and previous vaccination with the Cuban vaccine and presented with approximate 95% confidence intervals.[22] The OR was used as the estimate of the cumulative risk ratio of MD between vaccinated and unvaccinated children. To evaluate potential confounding and effect modification, we adjusted our estimates of the OR by including the following variables in the regression model: age at time of the first dose, sex, place of residence, number of people living in the household, day-care attendance, and elapsed time since 4 weeks after administration of the second dose. The model building strategy considered vaccination status as the exposure variable of interest. The remaining covariates entered the model as discrete variables. Place of residence was dichotomized into residents of the city of Rio de Janeiro (Capital) and

residents of the other cities pooled together; number of people living in the household was dichotomized into smaller or greater than five; and elapsed time since 4 weeks after administration of the second dose was dichotomized at first or second half-year. Age at time of the first dose was dichotomized into less or more than 4 years old when presenting summary measures of protection adjusted for age, but stratified in three categories (<24 months, 24–47 months, and ≥48 months) when presenting vaccine effectiveness stratified by age, for the sake of comparison with other studies. When the analysis was carried out only for children who lived in the city of Rio de Janeiro, the point estimate was adjusted by level of incidence rate (low, average, high) by dividing the 24 geographical regions of residence into three categories according to previous level of MD incidence during 1988/90, i.e. yearly accumulated average incidence rate per 100 000 inhabitants <5 cases (low incidence); incidence rate 5–7.5 cases (average incidence); and incidence rate >7.5 cases (high incidence). Model checking was performed by visual analysis of the residuals and the use of Hosmer and Lemeshow statistics of goodness-of-fit.[21]

TABLE 1 *Characteristics of the children studied*

Characteristics	Cases[a]			Controls
	B (n = 157)	C (n = 19)	all (n = 275)	(n = 279)
Mean age at time of first dose (months)	52	56	54	53
Mean no. people living in residence[b]	6	6	6	4
Male sex (%)	62	63	60	66
Day-care attendance (%)	11	10	13	7
Residence in Capital (%)	60	42	56	59
Completely vaccinated (%)	62	68	61	71
Incompletely vaccinated (%)	10	16	11	8
Unvaccinated (%)	22	16	22	12
Vaccine status unknown (%)	6	0	6	9

[a] Cases B = cases of serogroup B; C = cases of serogroup C; all = cases defined by all criteria.
[b] Except for four cases who lived in an orphanage.

RESULTS

We selected 275 cases of MD and 279 controls by the criteria defined above. Of the total cases, 57% belonged to serogroup B and 7% to serogroup C. The remaining cases were defined by criteria (3) to (5) above. The majority of the case serogroups were confirmed by isolation of the infectious agent from a CSF culture and were identified by antisera produced at the Adolfo Lutz Institute (National Reference Center for Meningitis). In this group, 29% exhibited manifestations of meningococcal meningitis, 52% exhibited meningococcal meningitis with haemorrhagic skin lesions and 19% exhibited acute meningococcaemia. Meningococcus of serogroup B was the major infectious agent among cases who exhibited meningitis. The majority of cases who exhibited acute meningococcaemia were defined by criteria (4) and (5) above. Of the cases with acute meningococcaemia, 14 were confirmed as belonging to serogroup B, 13 by culture and one by latex agglutination in CSF, and none as serogroup C. The case-fatality rate among the cases selected was 11%. Of the 279 controls, 46% were related to viral meningitis, 34% related to meningitis caused by other bacteria than *N. meningitis*, 13% related to post-mumps meningitis, 5% related to tuberculosis meningitis, and 2% related to other diseases.

Most of the meningococcus isolates from patients enrolled in the study were not serotyped and subtyped due to lyophylization problems. These data are available for only 10 out of the 157 positive cultures for serogroup B. Among these 10, four belonged to strain B:4:P1.P15, two to type B:4, one to type B:8 (both not subtypable) and the remaining three cultures positive for serogroup B were not typable, or subtypable.

The majority of children enrolled in the study lived in the capital, the city of Rio de Janeiro. The distribution of the various covariates among cases and controls is shown in Table 1. Of all the cases, 61% and 71% of the controls were completely vaccinated, 11% of the cases and 8% of the controls were incompletely vaccinated, 22% of the cases and 12% of the controls were not vaccinated, and 6% of the cases and 9% of the controls had unknown vaccination status. As a result, 230 cases and 232 controls entered the analysis. Of the children whose parents reported complete vaccination, 61% of the cases and 48% of the controls were confirmed with vaccination cards. The smaller proportion of children with confirmed vaccination status among the controls might have been due to the shorter time of stay at the hospital of the children with viral meningitis. Excluding children with viral meningitis from the control group increased to 57% the proportion of the control group completely vaccinated with confirmed vaccination status. The covariates, number of people living in the residence and day-care attendance behaved neither as a confounder nor as an effect modifier of vaccine effectiveness. Nevertheless, both are plausible risk factors for exposure to infection with meningococcus and remained in the model (Table 1).

TABLE 2 *Estimates of vaccine effectiveness by study group*

Group	Cases	Controls	VE[a]	95% confidence interval	Goodness of fit[b]
Serogroup B	133	232	54	(20, 74)	0.712
Serogroup C	16	232	24	(<−100, 80)	0.527
Other criteria[c]	81	232	63	(31, 80)	0.431
Meningitis	67	232	53	(7, 76)	0.968
Meningitis with haemorrhagic skin lesions	123	232	54	(19, 74)	0.340
Acute meningococcaemia	40	232	67	(28, 85)	0.669
Total	230	232	58	(31, 74)	0.663

[a] VE = Vaccine Effectiveness (%) adjusted by age at time of first dose, sex, place of residence, elapsed time since the vaccination, number of people living in the household, and day-care attendance.
[b] Hosmer and Lemeshow goodness of fit (*P*-value).
[c] In this category we grouped the cases defined by the following criteria: gram-negative diplococci identified by gram strain of cerebrospinal fluid (CSF); abnormal CSF cytopathological findings in a patient with acute haemorrhagic skin lesions; or symptoms of bacterial meningitis and haemorrhagic skin lesions with either normal CSF or no CSF data available.

The summary estimate of vaccine effectiveness varied according to the definition criteria of MD and the clinical manifestation. The measure of protection estimated by the analysis with cases defined by criteria (3) to (5) was higher than with case serogroups. The protection against confirmed serogroup B was approximately the same for cases defined by all criteria. The point estimate of protection against serogroup C was low and its 95% CI was wide due to the small number of children in this analysis (Table 2). When clinical manifestation was used as the classification criterion independent of the confirmation of serogroups, the protection was higher for cases who exhibited acute meningococcaemia than for those who exhibited meningitis. The protection estimated for incomplete vaccination (one dose) was low, approximately 31%, and not statistically significant.

When stratified by age, the effectiveness varied significantly, being low among children aged <4 years and high among children aged ≥4 years (Table 3). Another important source of heterogeneity was place of residence. Children who lived in the Capital had a positive estimate of protection, while children who lived in other cities demonstrated no significant protection. This heterogeneity on age and place of residence persisted when the analysis was restricted to cases of serogroup B.

In the Capital, estimated effectiveness varied by time elapsed since the second dose and age at time of the first dose. Protection was higher in the first half-year, decreasing later on, more noticeably among children aged <4 years old. When geographical region of residence in the Capital is stratified according to previous level of MD incidence during 1988/90, vaccine effectiveness showed important variation (Table 4). This pattern persisted when the analysis was limited to cases of serogroup B.

DISCUSSION

Vaccination programmes with a serogroup B meningococcal vaccine aiming at widespread coverage of the target population were uncommon before the use, in Brazil, of the vaccine produced by Cuba. Our hospital-based case-control study was the first assessment of the direct effectiveness of this vaccine in Rio de Janeiro, Brazil. The results have shown that protection varied across different epidemiological categories. The summary measure of protection was 58% (95% CI : 31–74%), but in children with severe clinical manifestation of MD, direct effectiveness was 67% (95% CI : 28–85%). The protection also varied by age and place of residence. It was higher among older children, 70% (95% CI : 38–85%) and among the children who lived in the city of Rio de Janeiro, 74% (95% CI : 46–88%). However, among the children who lived in the city of Rio de Janeiro, protection also varied in relation to time elapsed since vaccination and place of residence when stratified according to previous level of MD incidence. The estimate was higher in the first half-year after the vaccination, 89% (95% CI : 61–97%) and among the children who lived in the regions more affected by MD, 92% (95% CI : 58–98%).

The disparity between the protection in children who lived in the Capital and those who lived in other cities pooled together in the same group is difficult to explain. Estimates also varied significantly when the analysis was performed on a city by city basis (data not shown). Differences in vaccine conservation (cold chain) or vaccine administration practices among the various public health services in the Capital and in the cities situated on the periphery could explain that variability. Alternatively, differences in the levels of disease transmission or in the profile of serotypes and subtypes of B meningococcus could have produced the differences. Unfortunately we do not have sufficient information about the strains of B meningococcus isolated from the cases that occurred in these two areas.

Our estimates of vaccine protection, when broken down by age, fall within a similar range of those

TABLE 3 *Estimates of vaccine effectiveness by age and residence*

Group	Subset[a]	Cases	Controls	Vaccine effectiveness (%)	95% confidence interval	Goodness of fit[b]
Age (months)						
6–23	B	26	57	41[c]	(–96, 82)	0.178
	all	46	57	23[c]	(–119, 73)	0.360
24–47	B	38	50	14[c]	(–165, 72)	0.130
	all	65	50	42[c]	(–47, 77)	0.189
⩾48	B	69	125	71[c]	(34, 87)	0.633
	all	119	125	70[c]	(38, 85)	0.764
Capital	B	80	137	74[d]	(42, 89)	0.815
	all	127	137	74[d]	(46, 88)	0.977
Other cities	B	53	95	–7[d]	(<–100, 58)	0.533
	all	103	95	19[d]	(–74, 62)	0.979

[a] Subset B = cases of B serogroup; Subset all = cases defined by all criteria.
[b] Hosmer and Lemeshow goodness of fit (*P*-value).
[c] Vaccine effectiveness adjusted by sex, place of residence, elapsed time since the vaccination, number of people living in the household, and day-care attendance.
[d] Vaccine effectiveness adjusted by age at time of first dose, sex, elapsed time since the vaccination, number of people living in the household, and day-care attendance.

TABLE 4 *Estimates of vaccine effectiveness by age, time and region of residence according to incidence of meningococcal disease for the children who lived in the Capital*

Group	Subset[a]	Cases	Controls	Vaccine effectiveness (%)	95% confidence interval	Goodness of fit[b]
Age (months)						
6–23	B	13	34	47[c]	(<–100, 89)	0.977
	all	23	34	53[c]	(<–100, 90)	0.367
24–47	B	24	31	69[c]	(–45, 94)	0.465
	all	37	31	77[c]	(9, 94)	0.824
⩾48	B	43	72	82[c]	(40, 95)	0.190
	all	67	72	80[c]	(41, 93)	0.693
First half-year	B	33	53	91[d]	(62, 98)	0.511
	all	53	53	89[d]	(61, 97)	0.691
Second half-year	B	47	84	60[d]	(–17, 86)	0.195
	all	74	84	63[d]	(7, 85)	0.487
Incidence[f]						
Low	B	26	40	52[e]	(<–100, 93)	0.686
	all	41	40	57[e]	(<–100, 92)	0.892
Average	B	36	62	71[e]	(11, 91)	0.208
	all	60	62	74[e]	(27, 91)	0.144
High	B	18	35	89[e]	(40, 98)	0.571
	all	26	35	92[e]	(58, 98)	0.657

[a] Subset B = cases of B serogroup; Subset all = cases defined by all criteria.
[b] Hosmer and Lemeshow goodness of fit (*P*-value).
[c] Vaccine effectiveness adjusted by sex, number of people living in the household, day-care attendance, elapsed time since the vaccination, and place of residence according to incidence of meningococcal disease.
[d] Vaccine effectiveness adjusted by age at time of first dose, sex, number of people living in the household, day-care attendance, and place of residence according to incidence of meningococcal disease.
[e] Vaccine effectiveness adjusted by age at time of first dose, sex, number of people living in the household, day-care attendance, and elapsed time since the vaccination.
[f] Low, Average and High incidence = yearly accumulated average incidence rate during 1988/90 <5, 5–7.5, and >7.5 cases per 100 000 inhabitants, respectively.

presented by Moraes *et al.*[13] when evaluating the same vaccine in São Paulo, Brazil using a case-control study matched on age and neighbourhood. The estimate of protection in São Paulo was 74% (95% CI : 16–92%) in children aged ≥4 years. In Cuba, a trial among teenagers aged 11–16 years showed a protection of 81% (95% CI : 44–93%) and in the field assessment of vaccine efficacy in children <6 years old, the estimated protection was 93%.[12]

The pattern observed for decreasing estimates of vaccine protection in the second half-year after vaccination suggests that protection could be of short duration. Sierra *et al.*[12] did not observe such a pattern even in a follow-up period of 1–3 years in Cuba. We have observed that this decrease in protection was more important in children <4 years old. Further studies are necessary to corroborate this assumption, as well as to evaluate the effect of administering a third dose of vaccine 6 months after the second dose.

Orenstein *et al.* and Smith *et al.*[23,24] have argued favourably for the use of case-control studies to assess vaccine efficacy in the field. The validity of measures of vaccine protection requires comparability of the vaccinated and unvaccinated populations.[25–27] However, comparability between vaccinated and non-vaccinated groups is difficult to control in a field assessment of vaccine efficacy due to the potential heterogeneity in the previous level of susceptibility to disease and in the level of exposure to infection after vaccination.

In addition, case-control studies are susceptible to bias, especially selection bias and recall bias, which affect the estimation of the epidemiological measure of interest.[16,20,28] In our study, the major potential sources of bias are vaccine status ascertainment (or misclassification of vaccine status), differential accrual of severe cases, and non-random selection of controls. Bias related to ascertainment of vaccine status by oral report could have happened in this study. Random (non-differential) misclassification of vaccine status among the study participants has been shown to bias the estimate of the OR towards the null and consequently underestimate the true value of vaccine effectiveness.

The parameter of interest could also be underestimated if differential accrual of cases were related to severity of the cases of MD and vaccination had modified the clinical manifestation of infection. Children with severe MD could die within a short period of time without being included in the study and potentially leading to differential accrual of study participants. This is consistent with the higher protection observed against acute meningococcaemia. Differential accrual of severe cases could also result in an underestimate of the direct protection, mainly in younger children, because this age group is more frequently affected by severe clinical manifestation of serogroup B. Nevertheless, we did not observe an association between the case-fatality rate and vaccination status.

Controls were not drawn randomly from the catchment population which raises the issue of bias in the estimation of the ratio of exposure (vaccination) to non-exposure in the referent population. In the study design we adopted, controls are supposed to reflect the experience of the referent population regarding vaccine intake.[16,17] This goal can only be achieved if there were no association between the disease included in the control group and the factor under study, and if admission to the hospital is independent of exposure.[14,18,29] In this study, the clinical criteria used to define controls come close to this ideal situation. Although cases and controls were ascertained at the time of accrual of incident cases, the study population is close to a fixed cohort. Thus, the OR can be regarded as an estimator of the cumulative risk ratio (or attack rate ratio) and the measure of vaccine protection, 1 – OR, as an estimator of 1 – (ARv/ARu), where ARv and ARu are the attack rates among vaccinated and unvaccinated, respectively. Smith *et al.*[24] showed that, under the assumption of a 0/1 vaccine, 1 – (ARv/ARu) estimates the fraction of the population rendered completely protected by the vaccine, which is actually a summary measure under heterogeneity.[30] However, under the assumption of a leaky vaccine,[24] 1 – (ARv/ARu) underestimates the direct protection conferred by the vaccine. Since MD is rare, the estimates would be similar under the two mechanisms.

Our estimate of vaccine protection allows us to estimate the number of cases prevented among vaccinated children and the fraction of cases prevented in the entire population. According to our results, about 200 cases of MD would have been prevented in this age group in the first year after vaccination. This estimate permits us to say that the incidence of MD would have been reduced by 23% for all ages in the same period. If all children were vaccinated, i.e. if the coverage was 100% and no indirect effects are taken into account, about 282 cases would have been prevented in this age group in the first year after the vaccination.

Our study corroborates the results of Moraes *et al.*[13] and points to other problems for future investigations. It also supports use of the vaccine produced by Cuba in outbreaks of serogroup B meningococcal disease in the absence of other products conferring better protection. Although the estimated summary protection was neither high nor homogeneous, the level of protection observed against the more severe manifestations of meningococcal infection and the high protection estimated in children who lived in the city of Rio de Janeiro are

important positive findings. These results could justify the use of this vaccine, especially in older children, in future situations of increased incidence of serogroup B meningococcal disease.

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