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Protective efficacy of a serogroup B meningococcal vaccine in Sao Paulo, Brazil

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Serogroup B *Neisseria meningitidis* is the most common cause of epidemic meningococcal disease in developed countries. Until recently no vaccine has been available for prevention of infection with this organism. In an attempt to control epidemic serogroup B meningococcal disease in greater Sao Paulo, Brazil, during 1989 and 1990, a Cuban-produced outer-membrane-protein-based serogroup B meningococcal vaccine was given to about 2·4 million children aged from 3 months to 6 years.

We have done a case-control study to estimate the efficacy of the vaccine in greater Sao Paulo. Microbiologically confirmed cases of serogroup B meningococcal disease were identified through hospital-based surveillance. Controls were matched by neighbourhood and age. Vaccination status was confirmed by inspection of vaccination cards. Between June, 1990, and June, 1991, 112 patients and 409 matched controls with confirmed vaccine status were enrolled. Estimated vaccine efficacy varied by age: 48 months or older = 74% (95% CI 16 to 92%), 24 to 47 months = 47% (−72 to 84%), and less than 24 months = −37% (< −100 to 73%).

Our results suggest that the Cuban-produced vaccine may be effective for prevention of serogroup B meningococcal disease in older children and adults.

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Introduction

During the past 20 years, serogroup B *Neisseria meningitidis* has become the most common cause of epidemic meningococcal disease in developed countries.[1] Effective polysaccharide vaccines are available for control of serogroups A and C meningococci,[1-4] but the serogroup B polysaccharide is poorly immunogenic in humans and has not been useful for development of a vaccine.[4] Instead, investigators have focused on the use of serogroup B meningococcal outer membrane proteins (OMP) to stimulate protective immunity.[4,5] An OMP-based serogroup B vaccine has been developed in Cuba and is reported to be safe and protective.[6-8]

The Cuban vaccine is based on OMP from a Cuban epidemic serogroup B *N meningitidis* strain (B:4:P1.15) with serogroup C meningococcal capsular polysaccharide added to solubilise the preparation. Every dose contains 50 μg of serogroup B proteins, 50 μg of serogroup C meningococcal capsular polysaccharide, and 2 mg of aluminium hydroxide. The recommended vaccination regimen consists of two intramuscular doses given at an interval of 6 to 8 weeks.[6] In 1987–1989, the vaccine was evaluated in a double-blind, placebo-controlled efficacy trial in which 106 252 Cuban children aged 10 to 16 years were randomised to receive either the vaccine or a placebo preparation. After 16 months of follow-up, the estimated vaccine efficacy was 83% (95% CI 42–95%).[6]

In an attempt to control an epidemic of serogroup B meningococcal disease in greater Sao Paulo, Brazil, the Cuban-produced vaccine was given to about 2·4 million children aged from 3 months to 6 years during 1989 and 1990.[9] Two major immunization campaigns were conducted. In the first, completed in September, 1989, about 300 000 children attending day-care centres were vaccinated (12% of the estimated 2·7 million children in the target age range). The second vaccination campaign was started in regional health clinics in April, 1990, and by the end of May, 1990, about 2·4 million children (92% of children in the target age range) had received two doses of

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vaccine. Some children received a second dose of vaccine during an additional campaign in August, 1990, but most vaccine doses were distributed in April and May, 1990.

In June, 1990, we began a case-control study designed to estimate the protective efficacy of the vaccine against serogroup B meningococcal disease in Sao Paulo.

Subjects and methods

Selection of cases

Cases of serogroup B meningococcal disease occurring in greater Sao Paulo (estimated population 15·2 million) were identified through a hospital-based system for surveillance of notifiable diseases maintained by the Epidemiologic Surveillance Center, Sao Paulo Department of Health. Cases of bacterial meningitis and suspected meningococcaemia are voluntarily reported and are classified as meningococcal disease when one or more of the following criteria are met: (1) *N meningitidis* isolated from a culture of cerebrospinal fluid (CSF) or blood; (2) meningococcal antigens demonstrated in CSF or serum with counterimmunoelectrophoresis or latex agglutination; (3) gram-negative diplococci identified by gram stain of CSF or serum; (4) abnormal CSF cytopathologic findings in a patient who has acute haemorrhagic skin lesions; or (5) symptoms of bacterial meningitis and haemorrhagic skin lesions with either normal CSF or no CSF data available.

The study was started in June, 1990. Cases occurring between October 1, 1989, and March 31, 1990, were enrolled retrospectively. Cases occurring between June 9, 1990, and June 30, 1991, were enrolled prospectively. For the purposes of enrolment a definite case of serogroup B meningococcal disease was defined as isolation of serogroup B *N meningitidis* from the blood or CSF culture of a child aged 3 to 83 months (6 years, 11 months) who lived in greater Sao Paulo during the vaccination period. A probable case of serogroup B meningococcal disease was defined as serogroup B *N meningitidis* antigens detected by counterimmunoelectrophoresis in CSF or sera samples from a child with the same age and residency restriction as above.

Bacterial isolates from blood and CSF cultures we identified as *N meningitidis* in greater Sao Paulo hospital laboratories and/or the Adolfo Lutz Institute (National Reference Center for Meningitis). Serotyping of *N meningitidis* isolates was also done at the Adolfo Lutz Institute.[9] Technical assistance and reagents for serotype and subtype classification were provided by Dr Carl Frasch, US Food and Drug Administration. Antisera to serogroups A, B, C, Y, and W135 *N meningitidis* were produced at the Adolfo Lutz Institute. During counterimmunoelectrophoresis, clinical specimens were run with positive controls for each antisera.

Selection of controls

For every definite and probable case of serogroup B meningococcal disease enrolled in the study, 4 controls residing in greater Sao Paulo during the vaccination period were selected randomly. Controls were matched for age (± 6 months for case patients aged 24 months or less, but not less than 3 or more than 23 months old; ± 1 year for case patients older than 24 months, but not less than 24 or more than 83 months old) and neighbourhood.

Controls were identified from among children in the neighbourhood by questioning responsible persons in households, starting at the first house to the left of the case residence. Each consecutive household to the left was questioned until the end of the block was reached. The interviewer then returned to the case residence and went to the right. If 4 age-matched controls were not identified on the same street and block as the case residence, the interviewer proceeded around the block in a anticlockwise direction. A similar system, but by floors instead of blocks, was used to identify controls in apartment buildings. If 4 controls were not identified on the same block or floor as the case residence, other blocks or floors surrounding the case residence were systematically investigated until 4 children of the appropriate age were identified. If no one was at home at a particular residence, neighbours were questioned about the ages of children living in the house. Using this method we were able consistently to determine if children of an appropriate age resided in a particular house or apartment.

Data collection and ascertainment of vaccination status

A parent (usually the mother) or other adult responsible for each case and control was interviewed in the home with a standardised questionnaire. Information was collected about the child's age, sex, duration of residence, serogroup B meningococcal vaccination status, and other potential risk factors for meningococcal diseases, such as day-care attendance, household crowding, education, and indicators of socioeconomic status. Age was calculated as the age at time of the first dose of vaccine. For cases who had not been vaccinated, the "potential time" of vaccination was calculated from the date of vaccination of the first matched control who had been vaccinated. If a control had not been vaccinated but the matched patient had, the date of vaccination of the patient was used as the date for estimating the age at vaccination of the control. There were no concordant nonvaccinated case and control sets.

Vaccination status was determined by inspection of a child's vaccination card. During the serogroup B meningococcal vaccine campaigns in 1989 and 1990, an adhesive stamp with the vaccine name and date of injection was placed on the record card every time a dose of vaccine was given. A patient or control was considered to have been vaccinated with the serogroup B meningococcal vaccine if the card showed that two doses had been injected at an interval of between 40 days and 12 weeks, and that 21 days had elapsed between the second dose and onset of disease in the reference patient. Children were considered to be nonvaccinated if they had not received any doses of vaccine, as determined by inspection of their vaccination card with verbal confirmation. Only children documented as fully vaccinated or completely nonvaccinated were considered to have a definite vaccination status and were included in the analysis of vaccine efficacy.

Children without a vaccination card or evidence of vaccination on the vaccination card (even if said to be vaccinated), children vaccinated at an inappropriate interval, and those who received, or had evidence of, only one dose of vaccine on the record card were considered to have an indefinite vaccination status; these children were excluded from analyses of vaccine efficacy.

Statistical analysis

Data were analysed with EpiInfo (Centers for Disease Control, Atlanta) and SAS (SAS, Cary, North Carolina) statistical software. Univariate matched conditional logistic regression was used to determine two-tailed p values for comparisons between case and control groups; Fisher's exact test was used to compare groups in our evaluation for possible bias in case-patient selection. Maximum-likelihood estimates of odds ratios for the association between serogroup B meningococcal disease and previous vaccination with serogroup B meningococcal vaccine were calculated from analyses of matched data with conditional multiple logistic regression, and are shown with approximate 95% confidence intervals.[10] Vaccine efficacy was estimated as: (1 − odds ratio for vaccination) × 100.

TABLE I—SEROTYPE AND SUBTYPE CLASSIFICATION OF SEROGROUP B *N MENINGITIDIS* ISOLATED FROM 93 STUDY PATIENTS

Serotype: subtype	No *(%)* of cases
4:P1.15	39 *(42)*
4:NT	16 *(17)*
NT:NT	7 *(8)*
8:NT	4 *(4)*
NT:P1.15	3 *(3)*
2b:NT	2 *(2)*
15:P1.15	2 *(2)*
2b:P1.2	1 *(1)*
4:P1.2	1 *(1)*
8:P1.15	1 *(1)*
15:NT	1 *(1)*
Unknown	16 *(17)*

NT = nontypable.

To control for and to evaluate potential risk factors other than vaccination status, effect modifiers, and confounding variables, conditional multiple logistic regression was used to estimate odds ratios before and after adjusting for other variables. In addition to vaccination status, factors that were significant in univariate matched analysis and other variables that have been shown to be definite or possible risk factors for meningococcal disease were evaluated separately for possible inclusion in our conditional logistic regression model. These factors included age, sex, duration of residence in greater Sao Paulo, day-care attendance, number of minimum monthly salary units per household member, number of persons living in the residence, number of persons sleeping in the same bedroom, and maternal education.

Results

Enrolment

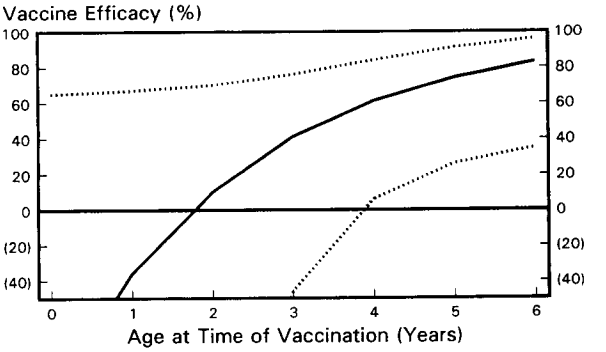
During the retrospective and prospective periods of study enrolment, 799 cases of meningococcal disease were reported from greater Sao Paulo among children aged from 3 to 83 months. 137 cases (17%) met the diagnostic criteria for a definite or probable case of serogroup B meningococcal disease. Complete sets of case and control information were obtained for 127 (93%) of these 137 cases. The remaining 10 patients were not enrolled because their addresses were unknown (4), they resided outside or had left greater Sao Paulo (5), or because we could not identify controls (1).

112 (88%) of 127 patients had a definite vaccination status and were included in analyses to estimate vaccine efficacy; 35 patients were enrolled in the retrospective part of the study and 77 in the prospective part. Of the 15 patients who did not have a definite vaccination status, 6 had received only one dose of vaccine, 5 had had an interval of greater than 12 weeks between vaccine doses, and 4 did not have written confirmation of vaccination status. 93 cases were confirmed by isolation of serogroup B *N meningitidis*, all from a CSF culture; no study patients had positive blood cultures. Blood cultures are not routinely obtained from all patients with suspected meningococcal disease in greater Sao Paulo. This is the most probable explanation for the lack of blood-culture-confirmed cases in our study population, although other causes cannot be excluded. *N meningitidis* B:4:P1.15 was the most frequently identified strain (table I), representing 51% of all strains that were completely typed; this is the same serologic classification as the type-strain used to produce the serogroup B meningococcal vaccine.

TABLE II—CHARACTERISTICS OF THE CHILDREN STUDIED

Characteristic	Patients (n=112)	Controls (n=409)
Mean age (months)	36	37
Mean duration of residency in greater Sao Paulo (months)	31	32
Male sex (%)	58 *(52)*	207 *(51)*
*Day care attendance (%)**	25 *(22)*	88 *(22)*
Number (range) minimum monthly salary units per household member†	1·3 (0·1–13)	1·3 (0–9)
Mean (range) persons living in residence‡	5·6 (2–12)	5·1 (2–17)§
Mean (range) persons sleeping in same room‡	4·2 (1–9)	3·8 (1–11)‖
Number (%) mothers with education beyond primary school	54 *(48)*	193 *(47)*
Number vaccinated with serogroup B meningococcal vaccine		
Retrospective *(%)*	2 *(6)*	7 *(5)*
Prospective *(%)*	66 *(86)*	253 *(93)*

*Day-care attendance in 3 months before date of case-patient hospital admission.
†The minimum monthly salary unit takes into account inflation during the study, although its correlation with inflation is not exact.
‡In addition to the patient or control.
§p=0·002 and ‖p=0·003 patients *vs* controls by univariate matched conditional logistic regression.



Vaccine efficacy by age as a continuous variable.

——— = estimated vaccine efficacy, - - - - - - - - = 95% CI.

19 patients were enrolled on the basis of a positive counterimmunoelectrophoresis test: 10 with a positive CSF specimen, 8 with a positive serum specimen, and 1 who had positive serum and CSF specimens.

509 control subjects were enrolled, of whom 465 (91%) had a definite vaccine status. Of these 465, 409 were matched to the 112 patients (mean of 3·7 controls per patient) who had definite vaccine status and who were included in primary analyses of vaccine efficacy. Of the 44 controls who did not have a definite vaccine status, 17 had received only one dose of vaccine, 1 had had an interval less than 6 weeks between vaccinations, 10 had had an interval greater than 12 weeks between vaccine doses, and 16 did not have written confirmation of vaccination status. There were no refusals to participate in the study amongst controls.

Patients differed significantly from controls in their characteristics only in the mean number of persons living in the residence and mean number of persons sleeping in the same room (table II). Of 35 patients enrolled in the retrospective part of the study, 2 (6%) had received the serogroup B meningococcal vaccine compared with 7 of 138 (5%) controls. Among the 77 patients enrolled during the prospective portion, 66 (86%) had been vaccinated compared with 253 of 271 (93%) controls.

Protective efficacy

With the exception of age, factors that were significant in univariate matched analysis and other variables that have been shown to be definite or possible risk factors for meningococcal disease did not substantially alter estimates of vaccine efficacy. The conditional logistic regression model used to estimate vaccine efficacy included vaccination

TABLE III—ESTIMATES OF VACCINE EFFICACY BY STUDY AND AGE GROUPS

Study groups by age (months)	Case-control sets	Protective efficacy (%) (95% CI)
*All case-patients**		
<24	34	−37 (< −100, 73)
24–47	43	47 (−72, 84)
>47	35	74 (16, 92)
Definite cases only		
<24	27	5 (< −100, 83)
24–47	38	53 (−79, 88)
>47	28	73 (2, 93)
B:4:P1.15 N meningitidis only		
<24	13	−56 (< 100, 86)
24–47	18	47 (< −100, 97)
>47	8	..†

*Retrospective and prospective study periods.
†Could not be estimated.

status and age as main effects and as an interaction term. The change in the log odds ratio for vaccination by age (expressed as a continuous variable) was linear ($p = 0.057$). The figure shows the effect of age on vaccine efficacy (after conversion from the log odds ratio for vaccination).

Estimates of age-specific vaccine efficacy for the age groups less than 24 months, 24 to 47 months, and older than 48 months were similar for all cases, all definite cases of serogroup B meningococcal disease, and all definite cases of confirmed B:4:P1.15 meningococcal disease (table III). Estimates of vaccine efficacy that used age as a continuous variable, and estimates by age group, were not substantially altered when: they were limited to the prospective study period; patients and controls with either a single dose of vaccine or two doses at any interval were included in the analysis; or patients and controls who did not have written confirmation of vaccine status but who were said to have been vaccinated were included in the analysis.

Possible case-selection bias

Two sources for possible case-selection bias with regard to vaccine status were examined. The first was the small proportion (17%) of reported patients with meningococcal disease caused by any serogroup who met the minimum diagnostic criteria for study enrolment—ie, identification of *N meningitidis* by culture or antigen detection. The second was the high proportion of cases meeting our study case definition reported from the Emilio Ribas Hospital (25%), a large tertiary infectious disease referral hospital in greater Sao Paulo, relative to all other greater Sao Paulo hospitals as a group (14%).

565 cases meeting at least one of the surveillance criteria for meningococcal disease were reported among persons in the study age range during the prospective portion of the study. We used these to determine if vaccinated patients were more likely to meet the minimum diagnostic criteria for study enrolment than nonvaccinated patients, and if vaccinated patients were more likely to be reported from Emilio Ribas Hospital than from other hospitals as a group. A definite vaccine status could be determined for 276 (49%) of 565 patients; the others either had an indefinite vaccine status or could not be contacted. Among the 102 reported patients who had *N meningitidis* infection confirmed by culture or antigen detection (including all meningococcal serogroups, although only serogroup B meningococcus would be eligible for our study), 74% has been vaccinated. By comparison, among the 174 reported patients who did not meet the minimum diagnostic criteria for our study, 78% were vaccinated. These proportions were not significantly different. Similarly, the proportion of these patients who were vaccinated and reported from the Emilio Ribas Hospital was not significantly different from the proportion reported from all other hospitals as a group (77% [125/163] and 75% [85/113], respectively). Although it would be preferable to have similar data for appropriate controls populations, the similarity of vaccination rates in these groups suggest that selection bias did not occur.

Discussion

Before this study, the only systematic estimate of protective vaccine efficacy for the Cuban-produced serogroup B meningococcal vaccine was from a trial done among children aged 10 to 16 in Cuba.[6] The vaccination campaign in greater Sao Paulo among children aged 3 months to 6 years provided an opportunity to evaluate the vaccine in a younger population and under different epidemiologic circumstances. Estimates of vaccine efficacy in greater Sao Paulo varied by age. Among children over 4 years old, the point estimate of vaccine efficacy (74%) was similar to that reported from the Cuban trial (83%), suggesting that the vaccine may be effective in older children and adults. In younger children, however, our estimates of vaccine performance were substantially lower than reported for older children in the trial in Cuba, and it is possible that the vaccine was ineffective in younger children. Although the Cuban trial did not address efficacy in children aged less than 10 years, over 850 000 Cuban children under 6 years old have been vaccinated: the estimated overall protective efficacy based on vaccine coverage and incidence of disease in this population was reported as 93%.[6] Further studies will be needed to resolve the apparent differences between our estimates of vaccine efficacy in young children and the overall estimates among children less than 6 years old in Cuba.

When an epidemic of serogroup B meningococcal disease was identified in greater Sao Paulo and use of the Cuban vaccine was considered, it was decided that a randomised trial to estimate vaccine efficacy would be unethical. However, the vaccine campaign provided the opportunity to evaluate vaccine efficacy by a case-control study. The case-control study design allowed concentration of available resources on a small number of patients and controls for assessment of vaccination status and other possible risk factor for disease or confounding variables.[11] It also provided an opportunity to identify the effect of age on vaccine efficacy.[12] Given the rates of serogroup B meningococcal disease and the resources available to evaluate this vaccine in greater Sao Paulo, it is unlikely that the age-specific differences in vaccine efficacy suggested by our study would have been detected in a controlled trial.

Bactericidal assays on sera from Brazilian children who received two doses of vaccine also reveal age-dependent differences in serologic response (unpublished observations). Among 120 children from 3 to 23 months of age at the time of vaccination, only about 25% had a greater than twofold increase in bactericidal antibody titre, whereas 48% of 80 children aged from 24 to 83 months had a greater than twofold rise in bactericidal titre. The complete results of these and further immunogenicity studies with the Cuban vaccine will be needed to better interpret our findings in younger children. One possible explanation for the apparently poor performance of the vaccine in younger children is that additional boosting may be needed to reach protective levels of immunity. Indeed, many of the protein vaccines used in infancy require more than two doses.[13] A randomised, double-blind immunogenicity trial evaluating additional vaccine doses in young children might be useful in resolving this question.

Despite the potential protective value of the Cuban vaccine in older age groups, surveillance data from greater Sao Paulo suggest that the public health impact of the vaccination campaign was disappointing (unpublished observations). Rates of serogroup B meningococcal disease in children aged from 1 to 6 years for the last 6 months of 1989 and of 1990 (before and after the principal vaccination campaign in April and May, 1990) were 2·07/100 000 and 2·30/100 000, respectively. Among greater Sao Paulo residents aged more than 10 years (older than the vaccine target age range) rates of serogroup B meningococcal disease for the same periods as above were 0·43/100 000 and 0·34/100 000, respectively.

Use of single strain of serogroup B *N meningitidis* to produce a vaccine has led to concern that the protection elicited might be serotype, subtype, or strain specific.[4] The producers of the Cuban vaccine have reported that the vaccine elicits bactericidal activity to a broad spectrum of serogroup B meningococcal isolates.[6] We did not find evidence for serotype, subtype, or strain specific protection in our study; the estimated protective efficacy of the vaccine among patients whose *N meningitidis* isolate had the same serotype and subtype classification as the vaccine type-strain was similar to the protective efficacy among patients with serologically different isolates, although numbers of cases were small. A greater range of isolates of serogroup B meningococci were found in greater Sao Paulo during our study than reported previously from Cuba. In greater Sao Paulo, only 44% of serogroup B meningococcal isolates matched the vaccine type-strain, although many isolates had serotype or subtype antigens in common with the vaccine type-strain, whereas in Cuba over 95% of serogroup B strains were B:4:P1.15.[6] This finding suggests that the vaccine can provide protection against some serogroup B meningococcal strains other than the vaccine type-strain.

Several OMP-based serogroup B meningococcal vaccines have been developed and evaluated in randomised clinical trials.[14-16] The only vaccine apart from the Cuban one to demonstrate protective efficacy was developed and tested in Norway.[16] The Norwegian vaccine consists of OMP from a B:15:P1.7,16 *N meningitidis* strain prepared by deoxycholate extraction. It contains class 1, 3, 4, and 5 proteins, lipopolysaccharide, and outer membrane vesicles that are absorbed on aluminium hydroxide. Each dose contains 25 μg of protein. The Norwegian vaccine does not contain substantial amounts of meningococcal polysaccharide. A placebo-controlled, randomised, double-blind trial among children aged 12 to 16 years in Norway produced an estimate of vaccine efficacy of 57% (lower 95% CI = 27%).[16] On the basis of this trial, it was concluded that the vaccine was not sufficiently efficacious to be considered for general use.

Our study indicates that the Cuban-produced vaccine may be effective in preventing serogroup B meningococcal disease in older children and adults. Thus, this vaccine may provide a new option for control of outbreaks of serogroup B meningococcal disease. At present, however, the usefulness of this vaccine to prevent endemic serogroup B meningococcal disease (less than 1 case per 100 000 persons per year in the USA) is questionable; this is particularly true if it is ineffective in young children in whom rates of serogroup B meningococcal disease are highest.[17] Although the results of our study with the Cuban vaccine are encouraging, further studies of this and other candidate serogroup B meningococcal vaccines are needed.

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REFERENCES

1. Schwartz B, Moore PS, Broome CV. Global epidemiology of meningococcal disease. *Clin Microbiol Rev* 1989; **2** (suppl 1): S118–24.
2. Peltola H. Meningococcal disease: still with us. *Rev Infect Dis* 1983; **5**: 71–91.
3. Advisory Committee on Immunisation Practices. Meningococcal vaccines. *MMWR* 1985; **34**: 255–59.
4. Frasch CE. Vaccines for prevention of meningococcal disease. *Clin Microbiol Rev* 1989; **2** (suppl 1): S134–38.
5. Frasch CE. Immunization against *Neisseria meningitidis*. In: Easmon CSF, Jeljaszewicz J, eds. Immunization against bacterial disease, vol 2. London: Academic Press, 1983: 115–44.
6. Sierra GVG, Campa HC, Varcacel NW, et al. Vaccine against group B *Neisseria meningitidis*: protection trial and mass vaccination results in Cuba. *NIPH Ann* 1991; **14**: 195–207.
7. Novo MV, Cruz RR, Molinert HT, eds. La enfermedad meningococica en Cuba: cronologia de una epidemia. La Habana: Editorial Ciencias Medicas, 1991.
8. Sierra VG, Campa HC, Garcia IL, et al. Efficacy evaluation of the Cuban vaccine VA-MENGOC-BC against disease caused by serogroup B *Neisseria meningitidis*. In: Achtman P, Kohl P, Matchal C, Morelli G, Seiler A, Thiesen B, eds. Proceedings of the Seventh International Pathogenic Neisseria Conference. Berlin: Walter de Gruyter, 1991.
9. Sacchi CT, Pessoa LL, Ramos SR, et al. Ongoing group B *Neisseria meningitidis* epidemic in Sao Paulo, Brazil, due to increased prevalence of a single clone of the ET-5 complex. *J Clin Microbiol* 1992; **30**: 1734–58.
10. Kleinbaum DG, Kupper LL, Morgenstern H, eds. Epidemiologic research. Principles and quantitative methods. New York: Van Nostrand Reinhold, 1982.
11. Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field. *Epidemiol Rev* 1988; **10**: 212–41.
12. Broome CV, Breiman RF. Pneumococcal vaccine—past, present, and future. *N Engl J Med* 1991; **325**: 1506–08.
13. Advisory Committee on Immunisation Practices. General recommendations on immunizations. Recommendations of the advisory committee on immunisation practices. *MMWR* 1989; **38**: 205–14, 219–27.
14. Frasch CE, Coetzee GJ, Zahradnik JM, Feldman HA, Koornhof HJ. Development and evaluation of a group B serotype 2 protein vaccine: report of a group B field trial. *Med Trop* 1983; **43**: 177–83.
15. Zollinger WD, Boslego J, Moran E, et al. Meningococcal serogroup B vaccine protection trial and follow-up studies in Chile. *NIPH Ann* 1991; **14**: 211–13.
16. Bjune G, Hiby EA, Grnnesby JK, Arnesen O. Effect of an outer membrane vesicle vaccine against group B meningococcal disease in Norway. *Lancet* 1991; **338**: 1093–96.
17. Pinner RW, Gellin BG, Bibb WF, et al. Meningococcal disease in the United States—1986. *J Infect Dis* 1991; **164**: 368–74.

From The Lancet

Death of Faraday

On Sunday last, in his 76th year, at his house at Hampton, died Michael Faraday. He was born in the neighbourhood of Newington Butts, his father being a blacksmith of that locality. Michael was early apprenticed to a bookbinder of the name of Rebean, of Blandford Street .... Owing to the kindness of Mr Dance, a neighbour of Mr Rebean, Faraday obtained tickets for some lectures on Chemistry, which were being delivered at the Royal Institution by Sir Humphry Davy. Of these lectures he took copious notes, which, having fairly transcribed, he sent to Davy, with an earnest appeal to him to engage him in some scientific employment. The post of assistant to the laboratory in the Royal Institution becoming vacant, Faraday was appointed to it. This was in 1813 .... In 1823 he demonstrated the possibility of condensing chlorine into a liquid, and thus established the identity of gases and vapours .... His subsequent investigations on electricity, which are a masterpiece of inductive philosophy, were published in three volumes. In these volumes, which contain the result of many years' laborious research, he demonstrated "the identity of the forces manifested in the phenomena known as electrical, galvanic, and magnetic; he ascertained with exactness the laws of its action; he determined its correlation with other primal forces of the natural world" .... Michael Faraday stands foremost in the list of philosophers of the age; his reputation is universal. He was a splendid type of the Baconian philosopher. No man ever exhibited a more profound regard for, or carried out more fully, the principles of inductive reasoning; no man ever achieved so many important results from the pursuit of that mode of investigation. He was simple, unpretending, and modest. He was singularly unselfish. He was always ready to do honour, even to his rivals, when they deserved it. He had a kind word and a helping hand for those young aspirants to fame who sought his advice and assistance .... On the most abstruse subject, the development of intricate theories or facts, he was singularly clear, simple, and convincing .... He has gone to the grave full of years and of honour.

(Aug 31, 1867)