

On the Controversy about the Efficacy of the Antimeningococcal B Vaccine: Methodological Pitfalls

Nota Sobre a Controvérsia Acerca da Eficácia da Vacina Anti-Menigocócica B: Ciladas Metodológicas

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The present communication analyses methodological problems related to evaluating the protection given by the anti-meningococcal B vaccine to children under four years of age in a case-control study carried out in Sao Paulo, Brazil. Detection of a hospital selection bias, among other disturbing features of the study, suggests that the efficacy of the vaccine was underestimated. Altogether, data presented support a wider use of the Cuban-produced vaccine to reduce morbidity and mortality from serogroup B meningococcal disease.

Key words: Meningococcal Disease; Case-selection Bias; Anti-meningococcal B Vaccine; Vaccine Efficacy; *Neisseria meningitidis*

INTRODUCTION

The rising incidence of serogroup B meningococcal disease in Latin America, its severity (with a case-fatality ratio of 5:1), and the lack of parameters from immunological tests for relating results to field protection (Costa, 1994a) call for a careful evaluation of the only published paper on the subject – "Protective efficacy of a serogroup B meningococcal vaccine in São Paulo, Brazil" (Moraes et al., 1992) – which found no protection in children under four years of age. In fact, a fierce controversy in Brazil has arisen concerning the public health use of the Cuban-produced vaccine as a consequence of the findings reported in the above-mentioned paper. The present communication analyzes the case-control study by Moraes et al. in light of findings from more recent studies on the use of the

vaccine in Brazil in 1989-1990 (Comissão Mista Brasil – Cuba, 1993) and draws attention to a methodological problem – a case selection bias – not described previously in the literature on communicable diseases (Costa, 1994b).

REFERENCE DATA

Table 1 summarises results from seroconversion in vaccinated children in Sao Paulo, two case-control studies, (both of which based on data collected during the first year after vaccination), and a follow-up study covering a three-year period after vaccination in twenty municipalities from the State of Santa Catarina.

This table suggests that a rise equal to or greater than twofold in titres best resembles the field estimates. Incidentally, to support the low efficacy found in the São Paulo case-control study, the authors present incorrect figures on these serological findings (p. 1077), where they state that the twofold results are the figures presented here as a fourfold increase.

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TABLE 1. Percentage Increase in Bactericidal Power and Protective Efficacy (1-RR)(%) of the Cuban-Produced Vaccine Against Serogroup B Meningococcal Disease in Brazil.

Agegroup (months)	Sero-Conversion ¹ (pairs)			Vaccine Efficacy (95% c.i.)		
	4-fold	2-fold	(n)	São Paulo ²	Rio de Janeiro ³	Santa Catarina ⁴
< 24	22%	49%	(122)	5%(-426;83%)	47%(-145;89%)	55%(-16;83%)
24 – 47	45%	64%	(44)	53%(-79;88%)	69%(-45;94%)	62%(+14;83%)
48+	52%	7096	(44)	73%(+2;93%)	82%(+40;95%)	78%(+54;90%)

- 1 Taken from Melles (s/d): percentage increase in bactericidal power following vaccination in São Paulo. Age group limits: 3 and 83 months.
- 2 Taken from Moraes et al. (1992): case-control study in São Paulo. Cases from the Emilio Ribas Hospital and controls from the neighbourhood of cases residing in Greater São Paulo. Results in this table are for “definite cases” of serogroup B. Age group limits: 3 and 83 months.
- 3 Taken from Noronha (1993): case-control study in Rio de Janeiro. Cases (serogroup B) and controls (other meningitis) from São Sebastião Hospital, residing in the municipality of Rio de Janeiro. Age group limits: 6 and 119 months. Results controlled for sex, age, area of residency, time since vaccination, and number of persons living in the same household.
- 4 Taken from Costa (1994a): follow-up of twenty vaccinated municipalities in the State of Santa Catarina. Results in this table refer to all cases recorded at the Epidemiological Surveillance Unit of the Secretariat of Health and confirmed by laboratory tests as meningococcal disease. A small proportion was serogrouped, but 90% of these were B. Age group limits: 5 and 95 months.

Based on the table, three main observations related to estimated efficacy in the epidemiological studies emerge. First, in children ³ 4 years old, estimates for all studies are similarly high and significant. The values are close to that found in the controlled trial among students aged 10-16 years carried out in Cuba (efficacy of 83%; CI 95%: 42; 95%) (Sierra et al., 1991). Second, for children 2-3 years old, efficacy values are similar, but lower; and, for the case-control studies, the estimates are not significant, in fact, because both had insufficient power to detect a significant result at the 5% level if, for example, the efficacy was 70%. Third, findings for children < 2 years old were dissimilar, low, and not significant.

DISCUSSION

These results have generated a controversy in Brazil about the use of this vaccine. Some people, basing their argument on the findings from São Paulo, considered it inappropriate to vaccinate in the “hyperendemic” stage of the disease (incidence rates from 5 to 10/100,000

for the total population), since the failure rate among children < 4 years old would be high, and it is in this age group that 40-50% of the cases occur. Others hold the view that there is nothing better at present, that the vaccine would avoid at least one third of the deaths occurring in children < 4 years of age, and that older children also have the right to protection.

I recently concluded a full analysis of the data from Santa Catarina and came across a particularly important finding which is unifying opinion in favour of the application of the vaccine: both case-control studies failed to fully consider hospital selection bias for a disease which kills 20% of those affected, half of whom in the first 24 hours following onset of symptoms.

Data from the Santa Catarina study show that if all confirmed cases, that is, including those cases of meningococemia confirmed only clinically (often terminating in death before laboratory diagnosis and effective hospital treatment are considered), then efficacy in the 5-to-47-month-old group increases to 68% (c.i. 95%: +42; 82%). Also, for children < 4 years, if the analysis is restricted to the cases of

meningococcemia, efficacy of the vaccine is 64% (CI 95%: +32; 81%), but for laboratory-confirmed cases efficacy was -48%. This "fall" in protection for cases of meningococcal meningitis confirmed by laboratory is lower, but also present, in the same age group: efficacy was 71% (CI 95%: +48; 84%) for all cases and 66% (CI 95%: +34; 83%) for cases confirmed by laboratory.

The high lethality (100/case-fatality ratio), particularly in children < 4 years of age (23.8%), has brought our attention to the protective efficacy based on mortality rates from the disease: the estimate for this age group was 76% (CI 95%: +41; 91%).

These findings suggest that exclusion from the study of those cases not confirmed by laboratory analysis decreases the efficacy of the vaccine because severe cases occur in non-vaccinated children, who die before reaching the hospital. Vaccinated children who contract the illness present an attenuated clinical picture and even those who die survive longer, making it possible for them to reach the hospital, where laboratory diagnosis is possible.

In Santa Catarina, for cases of meningococcemia the lethality in non-vaccinated children was 42.1% and in vaccinated children 26.3%, while for cases of meningococcal meningitis these figures were 5.6% and 2.6%, respectively.

Furthermore, data from Rio de Janeiro show that the mean time from the onset of disease to death in vaccinated children was 3.4 days, while for non-vaccinated children it was 1.7 days. In addition, the mean length of hospital stay for survivors was 10.2 days for vaccinated patients and 12.2 days for non-vaccinated patients.

Thus, the lower protective efficacy for children aged < 4 years, as observed in the study published by Moraes et al., in which only laboratory-confirmed cases were analyzed, is partially due to a selective effect of this procedure. Moreover, the lower estimates for this study, as compared with the other two studies, are also apparently related to methodological problems. The decision to adopt retrospective and prospective

enrollment of cases to increase the sample size has probably biased the results. In fact, although the authors say (p. 1077) that the inclusion or exclusion of several data sets, like those from the retrospective part of the study, did not substantially alter the efficacy, this was not the case. For the retrospective part of the study (35 sets), the estimated vaccine coverage was only 5% (and the overall efficacy was -23%) (p. 1076, Table II), but the actual vaccination coverage of the population was 12% (p. 1074). On the other hand, for the prospective part (77 sets), the estimated and actual coverage were 93% and 92%, respectively (and efficacy was +55%). In other words, for the retrospective part, data for the controls underestimates vaccine coverage. Although it could have arisen by chance, it is more likely that community controls were inadequate, since data collected referred to a period of time when only interneers and day care attendants had been vaccinated. It is not necessary to go deeper into this matter, but clearly, unless there were no discordant sets, mixing the retrospective part with the prospective one affected the results in many ways, including lowering efficacy estimates.

Finally, it is of interest to point out that in Santa Catarina there was no evidence of decreasing protective efficacy in the three-year follow-up, as shown by the yearly estimates. Also, a revision of routine data for six Brazilian states following the 1989/90 vaccination campaign, including Rio, Sao Paulo, and Santa Catarina, was conducted by a Cuban-Brazilian commission nominated by the Brazilian Ministry of Health: reported efficacy for the 6-to-83-month age group for serogroup B confirmed cases was 72% (c.i. 95% = +63; 80%).

FINAL REMARKS

Further studies on anti-meningococcal vaccines should carefully consider the case selection bias described in this paper. The same effect was probably present in the evaluation of the efficacy of the polysaccharide C vaccine in young children in the seventies (Taunay et al., 1978).

Meanwhile, even if protection in children under the age of 7 years were only 55% (the overall estimate of the São Paulo case-control study – the lowest found in Brazil), and the duration of the immunity were no more than two years, who would hesitate to give a one-in-two chance of preventing a case of a disease which kills one in five of those affected?

It is clear that from the public health point of view, this decision also depends on an evaluation of the local individual risk of getting the disease.

RESUMO

COSTA, E. A. Nota Sobre a Controvérsia Acerca da Eficácia da Vacina AntiMeningocócica B: Ciladas Metodológicas. Cad. Saúde Publ., Rio de Janeiro, 11 (2): 332-335, abr/jun, 1995.

A presente comunicação analisa problemas metodológicos relacionados à avaliação da proteção conferida pela vacina antimeningocócica B em crianças menores de quatro anos no Brasil em artigo utilizado como referência sobre o assunto. A identificação de sério viés na seleção dos casos, não só sugere que a eficácia da vacina é superior à encontrada, tornando seu uso a melhor arma disponível para reduzir a morbimortalidade da doença meningocócica, como coloca novos parâmetros para futuros estudos epidemiológicos sobre essa dramática doença.

Palavras-Chave: Doença Meningocócica; Viés de Seleção de Casos; Vacina Anti-Meningocócica B; Eficácia Vacinal; *Neisseria meningitidis*

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