Child mortality after high-titre measles vaccines in Senegal: the complete data set

Sir,—The Scientific Working Group concerned with the trial of high-titre measles vaccines (Oct 12, p 903) decided in February, 1991, that long-term mortality would best be analysed and reported after all 24 monthly cohorts of children had reached 36 months of age in February, 1992. Therefore, we, were disturbed when this report was published, for it is biased to the high mortality found in the first 16 cohorts, whereas the latter recruits, who to date have a lower mortality when vaccinated with a high-titre vaccine, have been excluded. We do not think that the study design legitimises the exclusion of the last 8 cohorts. Because of a chance only one high-titre vaccine for the last 8 cohorts was based exclusively on the unsatisfactory antibody response to vaccination with high-titre Schwarz vaccine.

The study in Niakhar, Senegal, included children born during the months February, 1987, to January, 1989, who attended a vaccination session at 5 months of age. The first 16 monthly cohorts were randomised to high-titre Edmonston-Zagreb (EZ), high-titre Schwarz (SW-HT), or placebo at 5 months and Schwarz standard (SW-std) at 10 months (controls). Because of an unsatisfactory serological response after SW-HT, the study design was changed to EZ or placebo/SW-std for the last 8 monthly cohorts. Between September and November, 1990, all children were visited at home (K. S., P. A.) survival information was also obtained on children who had moved out of the study area. This mid-term assessment was undertaken because preliminary results from Guinea-Bissau had suggested higher mortality for EZ vaccinees, especially girls, compared with controls.1 The number of children included in the different groups in the Senegal study, person-years-at-risk (PYR) and the number of deaths observed between the first vaccination at 5 months and the evaluation in the autumn of 1990 are indicated in the table.

<table>
<thead>
<tr>
<th>PERSON-YEARS-AT-RISK (PYR) AND DEATHS ACCORDING TO TYPE OF MEASLES VACCINATION AND COHORT: FOLLOW-UP SEPTEMBER TO NOVEMBER, 1990 (NIAXHAR, SENEGAL, 1987-90)</th>
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<td>Type of vaccine</td>
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<tr>
<td>EZ</td>
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<td>SW-HT</td>
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<td>Controls*</td>
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Compared with controls, EZ children had a relative risk (RR) of dying of 1.23 (95% confidence interval [CI] 0.86-1.77) (p = 0.297). The RR was the same if both high-titre vaccines were considered together. None of the children in the study died from measles. As in the Bissau study the excess mortality occurred among females; female recipients of high-titre vaccines had a RR of 1.51 (CI 0.86-2.45) compared with female controls whereas there was no difference for the males (RR = 0.99). The survival results were unchanged when a Cox regression model was used to adjust for age, season, and length of follow-up, the mortality ratio (MR) being 1.24 (0.86-1.77) (p = 0.245) for EZ vaccines compared with controls. The tendency towards higher mortality for the recipients of high-titre vaccines was marked for the first 16 monthly cohorts (MR = 1.75 [1.12-2.73] for EZ [p = 0.014] and MR = 1.46 [0.92-2.33] for SW-HT [p = 0.111]) but went in the opposite direction for the last 8 cohorts (MR = 0.59 [0.31-1.22], p = 0.105).

Interpretation of data from the first 16 cohorts is also complicated by divergent mortality in the control group who received standard measles vaccine; control girls had low mortality (about 7%) compared with control boys (about 12%) at 40 months of age (p = 0.18). Only longer follow-up in Niakhar and other areas can clarify the sex-specific impact of measles immunisation on mortality.

Routine use of high-titre vaccines has been suspended in the study area, and study children are being investigated for possible immunological problems.

There is room for concern about the long-term safety of high-titre measles vaccine, based on studies from Guinea-Bissau and Senegal.1 However, these concerns do not justify the premature and selective publication of data on this important matter.

The study was organised by the Ministry of Public Health, Senegal, and has been supported financially by the Task Force for Child Survival, Atlanta, USA, and the WHO Expanded Programme on Immunisation.

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** This letter has been shown to Dr Garenne and his colleagues, whose reply follows.—P.r. L.

Sir,—Mr Aaby and his colleagues argue that, in the comparison between treatment and control groups in the Senegal study, differences in morality after high-titre measles vaccines are not significant when crude death rates for all 24 cohorts are combined and that the differences were inconsistent by sex. They conclude that the publication of the results was premature. We found an excess mortality after vaccination with high-titre measles vaccines over a 3-year follow-up. There was significantly higher probability of death within 3 years of vaccination. The only proper way to estimate this probability is the life-table method, and failure to use this procedure may lead to false interpretations and can even reverse the risk ratio. An example is a comparison of mortality of two countries with different age structures: in 1983, Sao Tome and Principe
We hope to learn more about the excess mortality after HT measles vaccines in the near future. We may learn more when all cohorts vaccinated with HT vaccines in Senegal, the 24 cohorts randomised and the 15 not randomised, reach 41 months. After extensive discussion and after sharing our data with many of our peers, we deemed it important to publish the results as they were and to alert the scientific community of our findings. Unfortunately four of the investigators in the Senegal study, who spent four years of their life on the project (two full-time, two part-time) were excluded from the Data Monitoring and Safety Committee as soon as the excess mortality became significant statistically, in April, 1990.

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Unusual presentation of Mycoplasma pneumoniae infection

Situation-Mycoplasma pneumoniae is a well-known cause of community-acquired pneumonia, the most common cause of community-acquired pneumonia is now held to be pneumococcus. We report two such cases.

An 11-year-old girl was admitted for the first time to the hospital on July 29, 1991, with a 7-day history of fever and cough and of being unwell. She was sent to the emergency ward with a 4-day history of cough and respiratory symptoms. A younger brother had had a cough which had cleared 7 days before the onset of the patient's symptoms, and her father had had a dry cough 2 days before her admission. On clinical examination bilateral cervical lymphadenopathy and an acute inflammation of the right tympanic membrane were noticed. There was no neck stiffness. Chest X-ray was normal.

Blood and urine cultures were negative. The patient was treated with co-trimoxazole but she became more easy and began to drool. She was discharged after 10 days. The patient's meningitis was confirmed by the detection of specific CSF was negative. Intravenous therapy was therefore continued for 10 days. The patient responded to chloramphenicol and was discharged after 10 days. She had no history of fever and pain in the right ear. The patient was treated with chloramphenicol and was discharged after 10 days. The patient responded to chloramphenicol and was discharged after 10 days. She had no history of fever and pain in the right ear. The patient was treated with chloramphenicol and was discharged after 10 days. The patient responded to chloramphenicol and was discharged after 10 days. She had no history of fever and pain in the right ear. The patient was treated with chloramphenicol and was discharged after 10 days. 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