LETTERS to the EDITOR

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 later 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. The change to 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 24 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 (B. 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.

PERSON-YEARS-AT-RISK (PYR) AND DEATHS ACCORDING TO TYPE OF MEASLES VACCINATION AND COHORT: FOLLOW-UP SEPTEMBER TO NOVEMBER, 1990 (NIAKHAR, SENEGAL, 1987–90)

Type of vaccine	Deaths/children at risk (%) *(PYR)*		
	Cohort 1–16†	Cohort 17–24‡	Total
EZ	51/335 (15·2%) *(824·5)*	15/293 (5·1%) *(458·6)*	66/628 (10·5%) *(1283·1)*
SW-HT	41/322 (12·7%) *(790·1)*	..	..
Controls*	32/358 (8·9%) *(906·2)*	24/280 (8·6%) *(430·9)*	56/638 (8·8%) *(1337·1)*

*Placebo at 5 months of age and Schwarz standard measles vaccine at 10 months of age. †Children born February, 1987, to May, 1988. ‡Children born June, 1988, to January, 1989.

Compared with controls, EZ children had a relative risk (RR) of dying of 1·23 (95% confidence interval [CI] 0·86–1·75) (p = 0·257). 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[1] the excess mortality occurred among females; female recipients of high-titre vaccines had a RR of 1·51 (CI 0·93–2·45) 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 vaccinees 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 [0·31–1·12], 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 reason 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 UR Population et Santé, ORSTOM, Dakar, and 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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1. Expanded Programme on Immunization. Safety and efficacy of high titre measles vaccine at 6 months of age. *Wkly Epidemiol Rec* 1991; 66: 249–51.

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

SIR,—Mr Aaby and his colleagues argue that, in the comparison between treatment and control groups in the Senegal study, differences in mortality 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 had the same crude death rate as Norway (10·2 per 1000) even though life expectancy there was 29·5 years less (50·0 *vs* 79·5). In the high titre measles vaccines study, mortality was falling rapidly with age and the cohorts were not exposed to the same duration, so the use of crude rates is incorrect and misleading. The statistical evidence was clear with life-table estimates, but inconclusive with crude rates:

Comparison*	RR (and 95% CI) Crude	Life table
5 mo, cohorts 1–16		
EZ-HT/S	1·70 (1·12–2·58)	1·80 (1·18–2·74)
SW-HT/S	1·42 (0·92–2·21)	1·53 (0·99–2·37)
5 mo, cohorts 1–24		
EZ-HT/S	1·23 (0·86–1·75)	1·41 (0·97–2·05)
10 mo, cohorts 1–16		
EZ-HT/S	2·32 (1·42–3·81)	2·50 (1·52–4·13)
SW-HT/S	1·64 (0·96–2·80)	1·73 (1·00–2·98)
10 mo, cohorts 1–24		
EZ-HT/S	1·54 (1·05–2·26)	1·94 (1·26–2·99)

RR = relative risk of death; CI = confidence interval.
*EZ-HT = high titre Edmonston-Zagreb vaccine, given at 5 months; SW-HT = high titre Schwarz vaccine, given at 5 months; S = standard, low-titre Schwarz vaccine, given at 10 months.

Furthermore, the most appropriate approach to study the long-term safety of these vaccines may be to compare mortality after 10 not 5 months, the period during which both treatments and controls were at equal risk (both were vaccinated against measles). For mortality restricted to this period risk ratios (RR) are even higher (see above). For the first 16 cohorts RR = 2·50 (95% CI = 1·52–4·13) for EZ-HT and 1·73 (1·00–2·98) for SW-HT; for the 24 cohorts, RR = 1·94 (1·26–2·99) for EZ-HT.[1] Including the last 8 cohorts, and combining the two HT vaccines did not change the results, mainly because the last 8 cohorts were exposed only for a short period to the risk of death and because most of the excess mortality was in the second and third year of life. In our paper we were conservative in presenting the data after 5 months, showing the balance of risks and benefits of vaccinating at 5 months with HT vaccines, and we showed that the risks exceeded by far the expected benefits. The absolute differences in mortality after 10 months are so large (8·9% for EZ-HT and 4·6% for SW-HT) that there was little doubt that the use of HT vaccines had to be stopped.

Mortality after HT vaccines was monitored every week for the 4 years of the trial and an independent check was made annually at the time of the census. Mortality data were presented to the Ministry of Public Health of Senegal about twice a year at meetings of the Data Monitoring and Safety Committee until the end of the study. The excess mortality did not exist in the first year of follow-up; it became significant only during the third year, and that is when the health authorities of Senegal decided to stop using the vaccine.

Mortality in the controls and in the non-participant group was described in detail in the paper. It is not usual to have a precise estimate of a long-term trend in age-specific mortality available. This was possible only because of the continuous demographic surveillance system in the study area. The level of mortality in the groups that did not receive the HT vaccine was clearly consistent with the trends previously noted.

The issue of sex differences is more complex. Since 1963 there was no evidence of sex differences in mortality from 5 to 41 months in this population. It is statistically correct to say that the differences between treatments and controls were significant for girls and not for boys. However, the difference was in the same direction and it was highly significant for both sexes combined. In statistical terms, this is best explained by considering the sex allocation of deaths as a random process in each group, as is done routinely for the study of sex ratios in the birth process. When this approach is adopted none of the differences by sex was significant in any of the vaccinated or unvaccinated groups, as expected.

Measles is one of the rare diseases for which there is a consistent excess in female mortality (about 20%).[2] The fact that, in both groups receiving the HT vaccines, females had a 14–20% higher mortality (non-significant) than males could be taken as an indication that the measles virus was operating here. To use the argument that the difference is only significant for females to justify continuing use of the vaccine is unacceptable.

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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2. Garenne M. Variations in the age pattern of infant and child mortality with special reference to a case-study in Ngayokheme (rural Senegal). PhD dissertation, University of Pennsylvania, 1982.

Unusual presentation of *Mycoplasma pneumoniae* infection

SIR,—*Mycoplasma pneumoniae* is a well-known cause of community-acquired pneumonia; the number of cases now being seen in the UK is higher than usual due to the four-year epidemic cycle. Occasionally, infection presents in non-respiratory forms. We report two such cases.

An 11-year-old girl was admitted on July 29, 1991, with a 7-day history of fever and pain in the right ear. She did not have a cough or 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 acutely inflamed and bulging 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 drowsy and began vomiting. Lumbar puncture yielded clear CSF with 200 WBC/μl and 40 RBC/μl; protein 0·92 g/l; glucose 2·5 mmol/l. A 'Wellcogen' test for haemophilus type b, meningococcal, and group B streptococcal antigens was negative. Gram stain and culture of the CSF were negative. A brain scan was negative. Treatment was changed to intravenous cefuroxime and acyclovir.

A serum taken on admission had a titre of 160 for *M pneumoniae* antibody (gel particle agglutination); 3 days later the titre was 640. Intravenous erythromycin was therefore added but an immediate generalised rash developed after the first dose. Her treatment was then changed to chloramphenicol, penicillin, and acyclovir. *M pneumoniae* infection was confirmed by the detection of specific IgM at a titre of 16 (Norwich Public Health Laboratory). CSF and throat swab culture for *M pneumoniae* was negative. The patient responded to chloramphenicol and was discharged after 10 days. The father's *M pneumoniae* titre rose from 160 on Aug 2 to 640 on Sept 7; IgM weakly positive (titre).

A 10-year-old boy was admitted on July 23 with shortness of breath, dry cough, and fever of 5 days duration. He had also complained of a sore mouth for 2 days. He had conjunctivitis, swollen lips, infected gums, and small vesicles on both cheeks. An X-ray showed bilateral bronchial thickening consistent with infection. Blood and urine cultures were negative. Intravenous amoxycillin was given but his respiration and the conjunctivitis, stomatitis, and rash worsened. There was pain on micturition, with bullae and ulcers at the urethral meatus. Urinary retention necessitated catheterisation.

An admission serum sample was positive for *M pneumoniae* antibody at a titre of 160; 7 days later the titre was 1280. His IgM antibody titre was 16. Amoxycillin was replaced by erythromycin plus steroids and betamethasone eye-drops. He was discharged