Sex-specific differences in mortality after high-titre measles immunization in rural Senegal

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Administration of high-titre measles vaccine (Edmonston–Zagreb (EZ) at >10^5 plaque-forming units (PFU) per dose) before the age of 9 months has been recommended in areas with high measles mortality before the routine age of immunization after 9 months. The study compares the long-term survival after high-titre measles immunization at 5 months of age with that following routine immunization with standard-titre vaccine at 10 months of age. At 5 months of age the high-titre group received Edmonston–Zagreb (EZ-HT, 5 months) or Schwarz (SW-HT, 5 months) at titres >10^5 PFU per dose, while the standard-titre group received placebo at 5 months of age and <10^4 PFU per dose of Schwarz vaccine at 10 months (SW-std, 10 months). All the children were followed up to at least 36 months of age. The mortality ratio (MR) for infants in the EZ-HT, 5 months and SW-HT, 5 months groups was 1.32 (P = 0.089) and 1.45 (P = 0.092), respectively, which did not differ significantly from that of recipients of the SW-std, 10 months. The higher MR among recipients of the high-titre vaccines was due to the significantly lower survival among females compared with the females who received SW-std vaccine (EZ-HT, 5 months MR = 1.76, P = 0.013; SW-HT, 5 months MR = 2.14, P = 0.017). For children aged 5–10 months the high-titre measles vaccine did not increase mortality relative to unvaccinated children who had received placebo.

Introduction

Several studies have shown that Edmonston–Zagreb high-titre (EZ-HT) measles vaccine administered before 9 months of age is as immunogenic as Schwarz standard measles vaccine (SW-std) given at 9 months of age, even with the greater levels of maternal antibodies that are present (*1–4*). In 1990 WHO recommended that EZ-HT measles vaccine be used from the age of 6 months in areas where the incidence of and mortality from measles were high among under-9-month-olds to control the detrimental impact of measles early in life (*5–11*). Measles infection before 9 months of age has a high case fatality rate (CFR) (*11–13*) and an important delayed mortality (*12, 14*).

It had been assumed that this new policy would reduce overall mortality. Initial reports from Guinea-Bissau and Gambia supported this idea, even though significant reductions in mortality were not demonstrated (*4, 6*). However, a second trial in Guinea-Bissau, which had longer follow-up, indicated that girls who received EZ had significantly lower survival rates than the female recipients of SW-std (*15–16*). We therefore carried out an assessment of the impact on mortality in a trial that used two high-titre vaccines. An interim report based on two-thirds of the study cohort has appeared previously (*17–19*). The present article is based on a follow-up of all children to at least 3 years of age.

Subjects and methods

Study area and population

The study was carried out in Niakhar, Senegal, a rural area with a population of around 26 000 (March 1991), which has been under demographic surveillance since 1983. Niakhar is inhabited by the Sereer ethnic group, who live in large compounds (mean size = 14.8 persons) in scattered hamlets (*20*). The population, the demographic surveillance system (*20, 21*), and the epidemiology of measles in the area (*12*) have all been described in detail elsewhere. Briefly, during the period of the measles vaccine

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study, the surveillance system was based on a weekly visit by 12 field workers to all compounds in the study area in order to obtain information on births, deaths, marriages, migration, weaning, and any infections (measles and pertussis). The work of the field workers was monitored by two supervisors who contacted each assistant at least twice a week.

High-titre measles vaccines

Study design. The study was designed to investigate the immunogenicity, safety, and protective efficacy of two high-titre vaccines, particularly for children aged 5–10 months. All children born to mothers resident in the study area between 1 February 1987 and 31 January 1989 were included in the study, provided that they satisfied the following criteria: they were present at the 5-month vaccination session; there was no contraindication to measles vaccination; and their parents agreed to samples of blood being collected. Parents were advised to bring their children to one of the monthly vaccination sessions at the nearest health centre during the third, fifth and tenth month after birth. Those who did not were visited and transport to the centre was offered to allow the children to be vaccinated. At 3 months of age, children received BCG and diphtheria–tetanus–pertussis/inactivated poliomyelitis (DTP/IPV), at 5 months the second dose of DTP/IPV, and at 10 months the third dose of DTP/IPV and yellow fever vaccine (Table 1). Children of resident mothers were randomly assigned to receive either EZ-HT, SW-HT or placebo (standard group) at the 5-month vaccination session (median age, 5.1 months). The study was "blind" to the field workers and the mothers. The children in the standard group as well as those who had not been present at 5 months of age were offered the SW-std vaccine at 10 months of age (median age, 10.1 months). Hence, from 10 months of age the study was not blind since the identity of those children who had received a high-titre vaccine or a standard measles vaccine was known to the field workers. The weight, height, and arm-circumference of children who participated in the vaccination sessions at 3, 5, and 10 months of age were measured. The children were also examined by a physician before each of the vaccinations, and given treatment if necessary, and chloroquine tablets for weekly malaria prophylaxis, normally for 2 months; their parents were also given nutritional advice.

Blood samples were only collected from the children at 5 and 10 months of age. Analyses of the samples from the first group of vaccinated children indicated that the seroconversion rate for SW-HT was lower than that for EZ-HT (H. Whittle et al., unpublished observations, 1988). Thus, after the first 16 monthly cohorts, vaccination with SW-HT was stopped and the last eight cohorts (those born between 1 June 1988 and 31 January 1989) were randomly assigned to receive either EZ-HT or placebo. In consequence, there were fewer children in the SW-HT group than in the other two groups.

Table 1: **Outline of the study design for administration of vaccines, Niakhar, Senegal, 1987–89**

Age at immunization (months)	Vaccines administered:[a]		
	EZ-HT, 5 months	SW-HT, 5 months	SW-std, 10 months
3	BCG, DTP/IPV[b]	BCG, DTP/IPV	BCG, DTP/IPV
5	EZ-HT, DTP/IPV	SW-HT, DTP/IPV	Placebo, DTP/IPV
10	YF,[c] DTP/IPV	YF, DTP/IPV	SW-std, YF, DTP/IPV

[a] EZ-HT, 5 months = Edmonton–Zagreb high-titre vaccine administered at 5 months of age; SW-HT, 5 months = Schwarz high-titre vaccine administered at 5 months of age; SW-std, 10 months = Schwarz standard vaccine administered at 10 months of age.
[b] DTP/IPV = diphtheria–tetanus–pertussis/inactivated poliomyelitis vaccine.
[c] YF = yellow fever vaccine.

The study children who remained unvaccinated were offered measles vaccination in the course of three special campaigns during the study. After the study had been completed in July 1989, administration of EZ-HT at 5–7 months of age became routine in the surveillance area. The use of this vaccine was discontinued in November 1990 and was replaced by SW-std administered from 9 months of age.

Potential sources of bias. Since the trial was not designed to study long-term mortality, the way in which the study was conducted could have introduced a systematic bias in the comparison between recipients of high-titre vaccines and placebo/SW-std. Most importantly, participation at the 10-months vaccination session was higher for the standard group (81%) than for the EZ-HT (74%) or SW-HT (73%) groups, since providing measles vaccine to children in the placebo group was emphasized when those who had not appeared for vaccination were contacted. Only in the high-titre groups was seroconversion tested and the seronegative children were revaccinated. Furthermore, 30 unimmunized children in the placebo group were vaccinated with EZ-HT when this became the routine vaccine used in the area. We attempted to control for these potential sources of bias by both including and excluding the relevant groups.

Vaccines

Whereas standard measles vaccines have a titre of $<10^{4.0}$ plaque-forming units (PFU), high-titre measles vaccine has a titre of $\geq 10^{5.0}$ PFU. The measles vaccines used in the present study were kindly provided by the Institute of Immunology, Zagreb,[a] and by the Institut Mérieux, Lyon.[b] Tests of potency were carried out at the MRC Laboratories in the Gambia. The placebo was a standard vaccine preparation without virus (Institut Mérieux).

Measles surveillance

In the study area, measles cases were found through the weekly visit by assistants to all compounds or through follow-up of the contacts of known cases. Compounds with suspected measles cases were visited at least twice a week by the project physician. All clinical cases among children in the cohort had a typical rash and/or typical desquamation.

Death ascertainment

Most deaths among study children were identified through the weekly demographic surveillance system. Furthermore, all children in the study who still lived in the area were followed up individually in a nutritional survey in January 1992 and during the annual census in February 1992. At this time the children were aged 36–60 months.

Information on the causes of deaths were obtained through verbal autopsy questionnaires (*22*), which were reviewed by two physicians who were blind to the vaccine group of the dead children.

Background factors

The following biological, cultural and socioeconomic factors were examined: sex, twinning, age of mother, birth order, birth spacing to the preceding and subsequent child, age at vaccination (days), nutrition status at vaccination (weight, height, arm-circumference) (analysed using the WHO ANTHRO program), pre-vaccination antibody level, length of breast-feeding, literacy of mother, marital status of mother, death of mother, season (rainy/dry), measles infection, distance to health centre, number of households in the compound, number of persons in the compound, and previous under–5-year-old mortality (1983–86) among children in the same compound. Death of mother, breast-feeding, birth spacing to the subsequent child, measles infection, and season were used as time-dependent covariates. Other background factors were assessed at birth or on the date of the 5-month session.

Statistics

Children were included in the survival analysis from the date of their vaccination at 5 months of age until death, migration, or follow-up in February 1992. Children who migrated and then returned to the study area were only counted from the date of re-entry when they again came under surveillance for mortality. All children in the SW-HT group had reached 44 months of age, since this vaccine was only given at the beginning of the study, whereas children in the EZ-HT and standard groups were at least 36 months of age.

The study compares total mortality from the age at first vaccination (5 months). Crude death rates based on numbers of deaths in relation to the person-years-at-risk were assessed in the different vaccine groups. Since the difference in participation in the 10-months vaccination session could have introduced a systematic bias, all estimates have been adjusted for participation/non-participation at this session. Pooled estimates were obtained using the method of maximum likelihood (*23*). Cumulative mortality risk at specific ages were also calculated.

Multivariate Cox's regression analyses were carried out to control for age and the effects of background factors (*24*). Age was used as the time scale in the Cox's regression model. Effects are expressed as mortality ratios (MRs). Children born in the same month were vaccinated in the same month. It was therefore not possible to distinguish the effect of season at birth from the season at vaccination. Since analyses using the season-at-risk or monthly birth cohort gave similar results, only the season was used. In both the crude and the multivariate analyses, recipients of SW-HT were compared with children in the standard group from the first 16 monthly birth cohorts only, and the recipients of EZ-HT with all 24 cohorts. Hence, though there was only one standard group, the mortality levels were not identical in the two comparisons between high-titre vaccine and standard groups (Tables 2–5; Fig. 1 and 2).

Study approval

The study was approved by the Ministère de la Santé Publique, Dakar, Senegal; by ORSTOM (Institut Français de Recherche pour le Développement en Coopération, Paris); and by the Ethical and Scientific Committees of the United Kingdom Medical Research

[a] Edmonston–Zagreb: lot 81/3; titre: $10^{5.5}$ PFU (7 tests); lot 137; titre: $10^{5.0}$ PFU (1 test).

[b] Schwarz high-titre: lot 09830; titre: $10^{5.1}$ PFU; Schwarz standard: titre: $10^{3.7}$ PFU.

Council, Fajara, Gambia. Information meetings were held in the villages prior to initiating the study. Consent for blood sampling was obtained from the children's parents at each vaccination session.

Results

Study children, vaccine coverage, measles infection and vaccine efficacy. During the study period, 2467 children were born to mothers residing in the area. A total of 26 of these children were registered only after 5 months of age and were thus not eligible for the study. Before the 5-month vaccination session, 198 of the children had died and 66 had migrated out of the area, leaving 2177 children for inclusion in the study. Of these eligible children, 72.9% (1588/2177) were vaccinated at 5 months of age as follows: 624 received EZ-HT, 321 SW-HT, and 634 placebo (see Tables 2–5). The 9 children who received an unassigned vaccine were excluded from the analysis. Of the children who entered the study, 8.8% left the area during the follow-up period. Information on survival was also obtained for all 139 migrants by visiting their last compound of residence; seven of these children had died—five from the EZ-HT and two from the standard groups. Data for these children were not included in the main analysis.

There were no differences between the three groups with respect to the background factors examined (data available on request).

In the placebo group, 78.7% (480/610) of those still living in the study area received SW-std at the 10-month vaccination session. Because of subsequent vaccination campaigns, coverage for measles vaccination increased to 86.8% in the standard group at 2 years of age and to 90.4% at 3 years of age. As described elsewhere, 20 children in the study contracted measles; five in the SW-HT, six in the EZ-HT, and nine in the standard group (*25*). Four cases occurred before the children had received the vaccine at 5 months of age (1 in the EZ-HT and 3 in the standard group), a further four cases among children aged 5–10 months (1 in the EZ-HT and 3 in the placebo/standard group), and 12 cases after 10 months of age (4 in the EZ-HT, 5 in the SW-HT, and 3 in placebo/standard group). Two of these children (in the EZ-HT and the standard group) died later. Both had had measles prior to being vaccinated. The efficacy (VE) of the high-titre vaccines after exposure at home was greater than 85% and after SW-std vaccination, 100% (*25*). Since there were few cases of measles and the case fatality was low, a large beneficial impact on survival was not to be expected.

A total of 5 (1%) children in the EZ-HT group and 31 (10%) in the SW-HT group who were seronegative were revaccinated with either EZ-HT or SW-std. Furthermore, 30 unimmunized children in the placebo group were vaccinated with EZ-HT when this became the routine vaccine used in the area.

Total mortality and mortality by sex and age

Schwarz high-titre vaccine. Table 2 shows the annual mortality rates and mortality ratios by age and sex for the SW-HT and standard groups. The mortality rates for children who did or did not attend the vaccination session at 10 months of age were not significantly different (Table 3). Survival curves are shown in Fig. 1. The recipients of SW-HT tended to have higher mortality than the standard group, though this difference was not statistically significant (MR = 1.45 (95% confidence interval (CI) = 0.94–2.23), $P = 0.092$). Overall, female recipients of SW-HT had a higher mortality rate than the standard group (MR = 2.14 (95% CI = 1.12–4.09), $P = 0.017$) (Table 3), although a test for interaction between sex and vaccine was not significant ($P = 0.095$). There were no differences among boys.

For SW-HT, the mortality ratio was 1.43 (95% CI = 0.64–3.14) for children aged 5–10 months, when the standard group had not yet received measles vaccine. If the analysis is restricted to children who were present at both the 5- and 10-month vaccination sessions, the mortality ratio compares the high-titre vaccines at 5 months with the placebo at 5 months plus standard-titre vaccine at 10 months (MR = 1.35 (95% CI = 0.85–2.14), $P = 0.25$); for females only: MR = 2.14 (95% CI = 1.09–4.18), $P = 0.03$).

The above differences in mortality remained unaltered if revaccinated children were excluded from the SW-HT group or if children in the standard group who were vaccinated late with high-titre vaccine or if migrants were included in the analysis. We assessed the effects on mortality of the biological, cultural, and socioeconomic background factors independently of vaccination group. The only factors significantly associated with mortality were season, height, weight, and the death of the mother. Adjustment for these factors as well as for age and sex in a Cox's model had no effect on the mortality ratio of all recipients of SW-HT compared with the standard group (MR = 1.46 (95% CI = 0.95–2.25), $P = 0.087$).

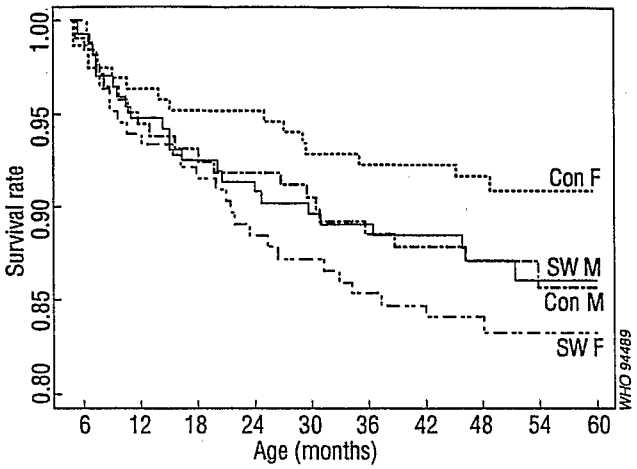
Edmonston–Zagreb high-titre vaccine. Table 4 shows the annual mortality rates and mortality ratios by age and sex for the EZ-HT and standard groups. Mortality rates for children who did or did not attend the 10-month session were not significantly different (Table 5). The survival curves are shown in Fig. 2. Recipients of EZ-HT tended to have higher mortality than the standard group, although this difference was

not statistically significant (MR = 1.32 (95% CI = 0.96–1.82), $P = 0.089$). A test for interaction between sex and vaccine type was not statistically significant ($P = 0.074$), but females in the EZ-HT group had a significantly higher mortality rate than those in the standard group, both overall ($P = 0.013$) and after 10 months of age, irrespective of whether they had attended the 10-month vaccination session. There were no differences for boys. If the analysis is restricted to children who were present at both the 5- and 10-month vaccination sessions, the mortality ratio compares high-titre vaccine at 5 months with placebo at 5 months plus standard-titre vaccine at 10 months (MR = 1.14 (95% CI = 0.80–1.63), $P = 0.48$; for females only: MR = 1.56 (95% CI = 0.94–2.57), $P = 0.080$).

For EZ-HT, the mortality ratio was 0.60 (95% CI = 0.27–1.31) between 5 and 10 months, when the standard group had not yet received measles vaccine. The corresponding values were 1.57 (1.09–2.24) from 10 months, when standardized for participation, and 2.02 (95% CI = 1.17–3.47) from 2 years of age, indicating an interaction with the time since vaccination ($P = 0.039$).

Control of the potential sources of bias did not change the mortality ratios, nor did adjustment for significant background factors modify the mortality estimate for recipients of EZ-HT compared with the standard group (MR = 1.33 (95% CI = 0.96–1.83), $P = 0.083$). The last three monthly cohorts did not receive the same lot of EZ-HT vaccine (lot 137) as the first 21 cohorts (lot 81/3). There was no difference in mortality between the two lots at 3 years of age (MR (lot 137 versus 81/3) = 1.16 (95% CI = 0.67–2.02)).

Fig. 1. **Survival rates, by sex, for recipients of Schwarz (SW) high-titre measles vaccine and standard vaccine (Con).** Data are for children born from February 1987 to May 1988, Niakhar, Senegal (M = males; F = females).



For the standard group who received SW-std at 10 months of age, as opposed to recipients of EZ-HT and SW-HT at 5 months of age, females had a lower mortality (MR = 0.57 (95% CI = 0.31–1.06)). Among the unimmunized children in the standard group who died, there was no difference in the sex ratio (MR = 1.08); 10 girls and 7 boys died aged

Table 2: **Number of deaths, person-years-at-risk (PYR) and annual mortality rate, up to February 1992, according to sex, age, and period, for recipients of Schwarz high-titre (SW-HT) and standard measles vaccine**[a]

Vaccination group	No. of deaths/PYR (annual mortality rate)			Mortality ratio (females/males)
	Males	Females	Total	
5–10 months				
SW-HT	6/61.3 (0.098); $n = 152$	8/67.3 (0.119); $n = 169$	14/128.6 (0.109); $n = 321$	1.21; *0.42–3.47*[b]
Standard	7/72.4 (0.097); $n = 180$	4/71.1 (0.056); $n = 175$	11/143.6 (0.077); $n = 355$	0.58; *0.17–1.99*
Mortality ratio[c]	1.01; *0.34–3.01*	2.11; *0.64–7.02*	1.43; *0.64–3.14*	
After 10 months				
SW-HT	14/471.4 (0.030); $n = 146$	19/492.4 (0.039); $n = 159$	33/963.8 (0.034); $n = 305$	1.30; *0.65–2.59*
Standard	16/531.5 (0.030); $n = 172$	10/556.3 (0.018); $n = 171$	26/1087.7 (0.024); $n = 343$	0.60; *0.27–1.32*
Mortality ratio[c]	0.99; *0.48–2.02*	2.15 ; *1.00–4.62*	1.43; *0.86–2.39*	
Total				
SW-HT	20/532.6 (0.038); $n = 152$	27/559.8 (0.048); $n = 169$	47/1092.3 (0.043); $n = 321$	1.28; *0.72–2.28*
Standard	23/603.8 (0.038); $n = 180$	14/627.4 (0.022); $n = 175$	37/1231.2 (0.030); $n = 355$	0.59; *0.30–1.14*
Mortality ratio[c]	0.99; *0.54–1.81*	2.14; *1.12–4.09*	1.45; *0.94–2.23*	

[a] Data apply only to the first 16 monthly birth cohorts. All children entered at 5 months and had reached at least 44 months of age; the mortality risk ratio at 44 months was 1.48 (95% confidence interval = 0.96–2.28); $P = 0.074$.
[b] Figures in italics are the 95% confidence intervals.
[c] Mortality ratio for SW-HT/standard group.

Table 3: **Number of deaths, person-years-at-risk (PYR), and annual mortality rate from 10 months of age, up to February 1992, according to sex and presence at the 10-month vaccination session for recipients of Schwarz high-titre (SW-HT) and standard measles vaccine**[a]

Vaccination group	No. of deaths/PYR (annual mortality rate)			Mortality ratio (females/males)
	Males	Females	Total	
Present at 10-month vaccination				
SW-HT	8/321.6 (0.025); *n* = 100	17/377.9 (0.045); *n* = 124	25/699.5 (0.036); *n* = 224	1.80; *0.78–4.18*[b]
Standard	14/414.3 (0.034); *n* = 133	9/429.7 (0.021); *n* = 132	23/844.0 (0.027); *n* = 265	0.62; *0.27–1.43*
Mortality ratio[c]	0.74; *0.31–1.75*	2.15; *0.96–4.82*	1.31; *0.74–2.31*	
Not present at 10-month vaccination				
SW-HT	6/149.8 (0.040); *n* = 46	2/114.5 (0.018); *n* = 35	8/264.3 (0.030); *n* = 81	0.44; *0.09–2.19*
Standard	2/117.2 (0.017); *n* = 39	1/126.6 (0.008); *n* = 39	3/243.7 (0.012); *n* = 78	0.46; *0.04–5.10*
Mortality ratio[c]	2.35; *0.47–11.62*	2.21; *0.20–24.38*	2.46; *0.65–9.27*	

[a] Data apply only to the first 16 monthly birth cohorts.
[b] Figures in italics are the 95% confidence intervals.
[c] Mortality ratio for SW-HT/standard group.

5–10 months and 3 girls and 5 boys after 10 months of age.

Causes of deaths

Analysis of the causes of death (Table 6) indicated no clear difference by sex or type of vaccine. There were more female deaths in the high-titre groups, but the distribution of causes of death did not differ significantly. These conclusions were not changed when the distribution was analysed by age.

Nutritional status

There were no significant differences in nutritional status between the three groups at the 5- or 10-month vaccination sessions. However, boys had significantly lower height-for-age (H/A) than girls at both sessions ($P < 0.05$). In addition they had lower weight-for-age (W/A) and weight-for-height (W/H) at the 10-month examination ($P < 0.05$).

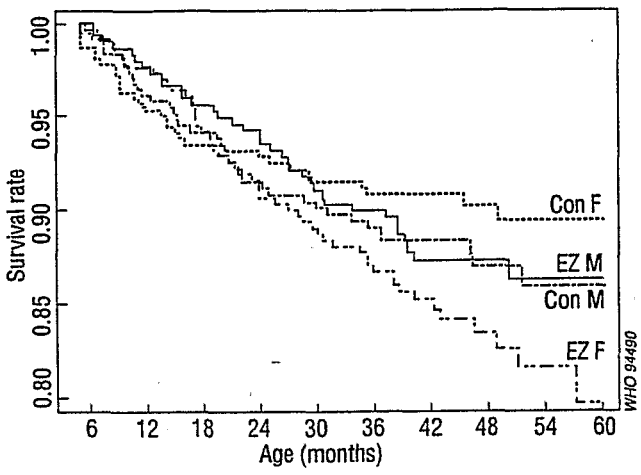
In a survey conducted in November-December 1990, when the children were 2–4 years of age, boys

Table 4: **Number of deaths, person-years-at-risk (PYR), and annual mortality rate, up to February 1992, according to sex, age, and period for recipients of Edmonston–Zagreb high-titre (EZ-HT) and standard measles vaccine**[a]

	No. of deaths/PYR (annual mortality rate)			Mortality ratio (females/males)
	Males	Females	Total	
5–10 months				
EZ-HT	4/120.4 (0.033); *n* = 298	6/132.6 (0.045); *n* = 326	10/252.9 (0.040); *n* = 624	1.36; *0.38–4.81*[b]
Standard	7/127.0 (0.055); *n* = 313	10/130.9 (0.076); *n* = 321	17/257.9 (0.066); *n* = 634	1.38; *0.53–3.62*
Mortality ratio[c]	0.60; *0.18–2.06*	0.59; *0.22–1.63*	0.60; *0.27–1.30*	
After 10 months				
EZ-HT	32/783.9 (0.041); *n* = 288	45/849.8 (0.053); *n* = 315	77/1633.7 (0.047); *n* = 603	1.30; *0.82–2.04*
Standard	31/818.1 (0.038); *n* = 301	19/863.3 (0.022); *n* = 311	50/1681.4 (0.030); *n* = 612	0.58; *0.33–1.03*
Mortality ratio[c]	1.08; *0.66–1.77*	2.41; *1.41–4.11*	1.59; *1.11–2.26*	
Total				
EZ-HT	36/904.3 (0.040); *n* = 298	51/982.4 (0.052); *n* = 326	87/1886.6 (0.046); *n* = 624	1.30; *0.85–1.99*
Standard	38/945.1 (0.040); *n* = 313	29/994.2 (0.029); *n* = 321	67/1939.3 (0.035); *n* = 634	0.73; *0.45–1.18*
Mortality ratio[c]	0.97; *0.62–1.54*	1.76; *1.12–2.79*	1.32; *0.96–1.82*	

[a] Data are for all 24 monthly birth cohorts. All children entered at 5 months and had reached at least 36 months of age; the mortality risk ratio at 36 months was 1.17 (95% confidence interval = 0.84–1.62); $P = 0.348$.
[b] Figures in italics are the 95% confidence intervals.
[c] Mortality ratio for EZ-HT/standard group.

Fig. 2. **Survival rates, by sex, for recipients of Edmonston–Zagreb (EZ) high-titre measles vaccine and standard vaccine (Con).** Data are for children born from February 1987 to January 1989, Niakhar, Senegal (M = males; F = females).



still had lower W/A and H/A values than girls (P <0.05 in each case). There were significantly more girls in the EZ-HT than in the standard group who had z-scores of –3 or lower for W/A (14/249 versus 6/269); P = 0.045) and H/A (34/251 versus 21/269); P = 0.033).[c]

[c] Data available on request.

Discussion

Although our results suggest that survival may be lower following administration of EZ and SW high-titre measles vaccines at 5 months of age than that associated with administration of standard Schwarz measles vaccine at 9–10 months of age, the differences were not statistically significant. At 36 months, an age reached by all the children, the mortality risk ratio was only 1.17 for the EZ-HT group (0.91 for boys and 1.44 for girls). Hence, our observations contrast with a preliminary communication of this data, which reported a risk ratio of 1.80 (at 41 months of age) and no sex difference (*17*). As noted previously (*18*), for children enrolled during the last third of the study there was no increased mortality among those who received the high-titre EZ vaccine. The major cause for concern is therefore the possible interactions between high-titre vaccines and sex and the time since vaccination. Female recipients of both EZ-HT and SW-HT vaccines had significantly lower survival than females in the standard group; however, this occurred only after 10 months of age, when most children in the comparison group had received SW-std vaccine. Thus, the present study reproduced patterns seen in Bissau (*15*, *16*).

The present study was not designed to examine a difference in morbidity or mortality beyond 10 months of age and bias could have been introduced as discussed below. First, participation at the 10-month vaccination session was higher in the standard group. Since the children were examined clinically at

Table 5: **Number of deaths, person-years-at-risk (PYR), and annual mortality rate from 10 months of age, up to February 1992, according to sex, age, and presence at the 10-month vaccination session for recipients of Edmonston–Zagreb high-titre (EZ-HT) and standard measles vaccine**[a]

	No. of deaths/PYR (annual mortality rate)			Mortality ratio (females/males)
	Males	Females	Total	
Present at 10-month vaccination				
EZ-HT	20/579.9 (0.035); n = 213	31/615.6 (0.050); n = 230	51/1195.5 (0.043); n = 443	1.46; *0.83–2.56*[b]
Standard	27/675.6 (0.040); n = 248	16/698.4 (0.023); n = 248	43/1374.0 (0.031); n = 496	0.57; *0.31–1.06*
Mortality ratio[c]	0.86; *0.48–1.54*	2.20; *1.20–4.02*	1.36; *0.91–2.05*	
Not present at 10-month vaccination				
EZ-HT	12/204.0 (0.059); n = 75	14/234.2 (0.060); n = 85	26/438.2 (0.059); n = 160	1.02; *0.47–2.19*
Standard	4/142.5 (0.028); n = 53	3/164.9 (0.018); n = 63	7/307.4 (0.023); n = 116	0.65; *0.15–2.89*
Mortality ratio[c]	2.10; *0.68–6.50*	3.29; *0.94–11.44*	2.61; *1.13–6.00*	

[a] Data are for all 24 monthly birth cohorts.
[b] Figures in italics are the 95% confidence interval.
[c] Mortality ratio for EZ-HT/standard group.

Table 6: **Causes of death, according to sex and vaccine group, Niakhar, Senegal, 1987–92**

Cause of death	No. of deaths among girls[a]			No. of deaths among boys[a]		
	EZ-HT	SW-HT	Standard	EZ-HT	SW-HT	Standard
Diarrhoea	11 (22)[b]	5 (19)	7 (24)	15 (42)	5 (25)	9 (24)
Malaria	11 (23)	5 (19)	6 (21)	5 (14)	2 (10)	10 (26)
Malnutrition	14 (27)	5 (19)	6 (21)	7 (19)	4 (20)	5 (13)
Pneumonia	3 (6)	5 (19)	2 (7)	1 (3)	3 (15)	2 (5)
Other specific	5 (10)	3 (11)	0 (0)	2 (6)	1 (5)	1 (3)
Unknown	7 (14)	4 (15)	8 (28)	6 (17)	5 (25)	11 (29)
Total	51 (100)	27 (100)	29 (100)	36 (100)	20 (100)	38 (100)

[a] EZ-HT = Edmonston–Zagreb high-titre; SW-HT = Schwarz high-titre.
[b] Figures in parentheses are percentages.

all vaccination sessions, the medication they received could have affected their survival. However, the mortality ratios were unaffected when adjusted for participation. For girls, mortality was higher both among participants and those who did not attend the 10-month vaccination session. Second, seronegative children in the two high-titre groups were revaccinated with another measles vaccine. Exclusion of the revaccinated children did not affect the mortality estimates. Third, some children in the standard group were vaccinated with EZ-HT when this became the routine vaccine used in the study area. Censoring at the time of vaccination eliminated a group of non-attenders from the standard group. However, inclusion of these children in the standard group would not have affected the mortality ratios.

Special efforts were made to trace all the study children. Hence, there was no loss to follow-up that altered the observed tendencies. We were unable to identify any other methodological or randomization problem to indicate that our conclusions are biased.

One of the reasons for the sex-specific differences that we have reported was the low mortality among girls in the standard group (Tables 2 and 4). Although unexpected, this lower mortality (MR (F/M) = 0.57) reflects that found in the preceding and succeeding 2-year periods (MR = 0.63 and 0.73, resp.) (*26*).

Since significantly lower female survival has not been observed in trials using medium-titre EZ vaccine (< 50 000 PFU) (*4, 6*), the dose of vaccine might be important in determining long-term mortality, which increased after intensive exposure to the wild virus (*11, 12, 14*). If high-titre or standard measles vaccines affect females differently, the reasons for this are not clear. A low efficacy of high-titre vaccines for girls could have led to lower survival; however, the incidence of measles was low and the vaccine efficacy was good (*25*). There was no indication that boys received better care, which could influence the relative mortality for girls if high-titre vaccines were likely to increase the morbidity of all children. The length of breast-feeding was the same for boys and girls. Infection with human immunodeficiency virus (HIV), which could interact with a high-titre measles vaccine, is uncommon in the study area (*17*). A number of host characteristics are currently under investigations, including antibody levels and state of nutrition at the time of vaccination. Although sex-specific differences have been observed in antibody levels and state of nutrition, these are unlikely to explain fully the mortality pattern after high-titre immunization.

In Niakhar, the reduced survival of girls in the high-titre group was observed only after children in the comparison group had received SW-std (Tables 2–5). Also, EZ vaccine has not been associated with increased mortality in areas with low mortality (*4, 27*). Since SW-std measles vaccine reduces mortality more than can be accounted for by simply preventing acute measles infection (*10, 11*), this vaccine may produce beneficial effects that are not generated by the high-titre vaccines.

No estimates have appeared of the expected increase in survival brought about by switching from SW-std vaccine at 9 months to EZ-HT at 6 months in areas where the incidence and mortality from measles are high before 9 months of age (*5*). However, such benefits are unlikely to outweigh the 20% higher mortality in high-titre recipients found in both Bissau (*15, 16*) and Niakhar. Since there is no obvious explanation for the delayed mortality or for the sex-specific effects of measles vaccine, concern has been raised about the general validity of our observations (*15*), which have not been noted in other areas where the general mortality is lower than in Senegal and Guinea-Bissau (*4, 27*). However, the sex-specific tendency has been reported in several studies (*16, 28*, and P. Aaby unpublished data, 1992). Further research to define the biological basis of these epidemiological findings is therefore needed. In view of the consistency of the results in three study areas, the

EPI Global Advisory Group has recently recommended that high-titre measles vaccines should no longer be used in routine immunization programmes (*28*).

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Résumé

Différences de mortalité liées au sexe après administration de vaccin antirougeoleux à titre élevé dans des régions rurales du Sénégal

L'administration d'un vaccin antirougeoleux à titre élevé (Edmonston-Zagreb (EZ) à >10^5 unités formatrices de plage (UFP) par dose) avant l'âge de 9 mois a été recommandée dans les régions où la mortalité rougeoleuse est forte chez les enfants n'ayant pas encore atteint l'âge normal de la vaccination. Dans la présente étude, réalisée dans des régions rurales du Sénégal, nous avons comparé la survie à long terme après vaccination à 5 mois avec un vaccin antirougeoleux à titre élevé et après vaccination selon le schéma habituel à l'âge de 10 mois avec un vaccin à titre standard. Les enfants du groupe "titre élevé" ont reçu à l'âge de 5 mois le vaccin Edmonston-Zagreb (EZ-HT) ou Schwarz (SW-HT) à un titre >10^5 UFP par dose, tandis que ceux du groupe "titre standard" ont reçu un placebo à l'âge de 5 mois et une dose <10^4 UFP de vaccin Schwarz à l'âge de 10 mois (SW-std). Tous les enfants ont été suivis au moins jusqu'à l'âge de 36 mois. Le taux de mortalité (MR) chez les enfants ayant reçu le EZ-HT ou le SW-HT à 5 mois était, respectivement, de 1,32 (intervalle de confiance (CI) à 95%: 0,96–1,82) (P = 0,089) et 1,45 (CI 95%: 0,94–2,23) (P = 0,092), et ne différait pas significativement du taux observé chez les enfants ayant reçu le SW-std à 10 mois. La tendance à une mortalité plus forte chez les enfants ayant reçu le vaccin à titre élevé résultait du taux significativement plus faible de survie chez les filles de ce groupe par rapport aux filles ayant reçu le vaccin standard (EZ-HT: MR = 1,76 (CI 95% = 1,12–2,79), P = 0,013; SW-HT: MR = 2,14 (CI 95% = 1,12–4,09), P = 0,017). Par rapport aux garçons, cette différence était due non seulement au plus faible taux de survie dans les groupes SW-HT et EZ-HT mais aussi à une augmentation inattendue de la survie dans le groupe SW-std. Chez les garçons, on n'observait pas de différence significative de mortalité. De plus, chez les enfants âgés de 5 à 10 mois, le vaccin à titre élevé augmentait la mortalité par rapport aux enfants non vaccinés ayant reçu un placebo. Ces données, jointes à celles d'autres études, ont conduit le groupe consultatif mondial du PEV à recommander l'arrêt de l'emploi des vaccins à titre élevé dans les programmes de vaccination.

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