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# A comparison of vaccine efficacy and mortality during routine use of high-titre Edmonston–Zagreb and Schwarz standard measles vaccines in rural Senegal

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**Abstract**

Vaccine efficacy and mortality in successive cohorts of children who routinely received either Edmonston–Zagreb high-titre (EZ–HT) or Schwarz standard (SW–STD) measles vaccines have been examined in a rural area of Senegal. The 2 vaccines were equally protective against measles infection (vaccination efficacy: EZ–HT 94%; SW–STD 93%). Children who did not attend a scheduled session to receive measles vaccine had a higher mortality rate between 9 months and 2 years of age than did children receiving either EZ–HT (mortality ratio [MR] = 1·81, 95% confidence interval [CI] 1·06–3·08) or SW–STD measles vaccine (MR=1·74, 95% CI 0·95–3·21). Children of either sex vaccinated with EZ–HT had lower mortality than their equivalents who had not received any measles vaccine. There was no difference in overall mortality between recipients of EZ–HT and SW–STD (MR=0·96, 95% CI 0·70–1·30). Using a Cox regression analysis to adjust for sex, age and significant background factors (season and death of mother), mortality rates tended to be lower for male recipients of EZ–HT than for boys receiving SW–STD (MR=0·73, 95% CI 0·50–1·11) and higher for girls receiving EZ–HT than for girls receiving SW–STD (MR=1·30, 95% CI 0·81–2·09) (test of interaction between sex and vaccine, $P=0·067$). The tendency to reduced survival benefit for girls following receipt of high-titre measles vaccines substantiated observations from randomized trials in Guinea-Bissau, Senegal and Haiti. Existing data provide little support for the notion that high-titre vaccine is deleterious but it may not have the same beneficial effects as standard-titre measles vaccine.

**Keywords:** measles, vaccines, Edmonston–Zagreb, Schwarz standard, Senegal

## Introduction

Recent randomized vaccine trials in Guinea-Bissau (AABY *et al.*, 1993a) and Senegal (AABY *et al.*, 1991, 1994) have identified lower survival rates due to increased non-measles mortality in females receiving high-titre ($\geqslant 10^{4·7}$ infectious particles/dose) Edmonston–Zagreb (EZ–HT) and Schwarz (SW–HT) vaccines at less than 9 months of age, compared to those receiving standard titre (approximately $10^{4·0}$ infectious particles/dose) Schwarz (SW–STD) measles vaccine at 9–10 months of age. Studies in Haiti have similarly suggested that high-titre vaccines were associated with higher mortality among girls than medium-titre vaccines (HOLT *et al.*, 1993). Since the observation of decreased survival among female recipients of high-titre measles vaccines in the randomized trials was highly unexpected and has implications for immunization policies (EPI, 1990, 1992), we have further examined mortality patterns for girls and boys who received EZ–HT or SW–STD vaccines in a routine immunization programme in a rural area of Senegal where we have previously conducted a trial of high-titre measles vaccines (AABY *et al.*, 1991, 1994).

## Subjects and Methods

*Background*

The Sereer population of Niakhar in Senegal, the demographic surveillance system (GARENNE *et al.*, 1987), and the epidemiology of measles in the study area (GARENNE & AABY, 1990; SAMB *et al.*, 1993), have been described in detail elsewhere. Since 1987, the demographic monitoring system has been based on annual censuses and weekly surveillance visits to all compounds during which information has been collected on migration, marriages, births, deaths, vaccinations, breast feeding, and infections.

A trial with high-titre measles vaccine was carried out in the Naikhar area between 1987 and 1989. This trial included children born from February 1987 to January 1989 (AABY *et al.*, 1991, 1994; SAMB *et al.*, 1993).

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*Post-trial period: use of measles vaccines*

The present study included all 2396 children born to resident mothers in the 2 years following the completion of the high-titre trial; i.e., children born from February 1989 through to January 1991. After the high-titre study, EZ–HT was used as the routine measles vaccine in the study area, except for children born in February 1989 who did not receive EZ–HT due to its unavailability (Table 1). The first monthly cohort received EZ–HT at 5 months of age. Subsequently, children were vaccinated with EZ–HT at 6–7 months of age as part of a pertussis vaccine trial conducted in the area. EZ–HT was administered together with diptheria–tetanus–pertussis/inactivated poliovirus vaccine (DTP–IPV), usually the third dose, and yellow fever vaccine. Some children received the 3 doses of DTP–IPV at 2, 4 and 6 months of age, whereas others missed one session and received the third dose at 7 months. Throughout the entire EZ–HT period, children who did not attend when first called for measles immunization were subsequently offered EZ–HT (41%) or SW–STD (59%) measles vaccines. When EZ–HT vaccine was discontinued in November 1990, after 14 months of total use, SW–STD administered at 9–10

**Table 1. Routine measles immunization in Niakhar, Senegal, 1989–1991**

| Date of birth | Type of vaccine[b] | Age at immunization[a] (months) |
|---|---|---|
| February 1989 | SW–STD, YF, DTP–IPV | 9–10 |
| March–June 1989 | EZ–HT, DTP–IPV | 5 |
| July 1989–April 1990 | EZ–HT, YF, DTP–IPV | 6–7 |
| May 1990–January 1991 | SW–STD, YF, DTP–IPV | 9–10 |

[a]All groups were followed until February 1994.
[b]DTP=diphtheria–tetanus–pertussis; EZ–HT=Edmonston–Zagreb high-titre; IPV=inactivated poliovirus; SW–STD=Schwarz standard; YF=yellow fever.

months of age was reintroduced as the routine measles vaccine in the study area (Table 1), and was used for the remaining 9 monthly cohorts encompassed in the follow-up.

Mothers of children living in the study area were advised by field assistants to attend the monthly vaccination session in their district when their children reached the appropriate age. Those who followed the invitation and received measles vaccine and those who did not come have been called attenders and non-attenders, respectively. Many of the non-attenders received measles immunization during subsequent vaccination campaigns in the study area.

*Vaccine efficacy*

Efficacy of both EZ–HT and SW–STD after 9 months of age was assessed by comparing secondary attack rates among children exposed to measles infection within their compound of residence who had not had measles previously. As in previous studies from the Niakhar area (GARENNE & AABY, 1990; SAMB *et al.*, 1993), we adjusted the analysis for intensity of exposure; i.e., exposure within the same hut, within the same household, or within the same compound. Information on exposure was obtained through the measles surveillance system in the study area. Previous studies have found that most cases of measles not detected by this system occurred outside the study area (SAMB *et al.*, 1993).

**Table 2. Secondary attack rates and vaccine efficacy among children according to intensity of exposure and type of measles vaccine; Niakhar, Senegal, 1989–1993**

| | Secondary attack rates | | |
|---|---|---|---|
| Exposure | EZ–HT[a] | SW–STD[a] | No vaccine |
| Compound | 5% (1/20) | 0% (0/18) | 42% (5/12) |
| Household | 4% (1/23) | 3% (1/30) | 46% (6/13) |
| Hut | 2% (1/53) | 6% (2/32) | 63% (15/24) |
| Total | 3% (3/96) | 4% (3/80) | 53% (26/49) |
| Vaccine efficacy | 94% (81–98%) | 93% (77–98%) | – |

[a]EZ–HT=Edmondston-Zagreb high-titre measles vaccine; SW–STD=Schwarz standard measles vaccine.

*Survival analyses*

Mortality rates, calculated as deaths in relation to person–years at risk (PYR), were compared for attenders and non-attenders. In this analysis, non-attenders later immunized against measles were excluded from the analysis from the time of measles immunization. Mortality was also compared for attenders who received, respectively, EZ–HT at 5-7 months and SW–STD at 9–10 months. Though not allocated at random to the 2 groups, these children shared the selection bias of having attended and received measles vaccine.

Since SW–STD was administered only from 9 months of age, the comparison was based on follow-up after each child reached 9 months (>273 d) of age. Children who died or migrated before reaching the recommended age for vaccination were not considered. Children resident at the time of planned measles immunization were followed to death, migration, or 10 February 1994, the first date of the annual census in 1994. The survival status of all children still living in the study area was examined individually at the annual follow-up in February 1994. Pooled estimates were obtained using the method of maximum likelihood (ROTHMAN, 1986). Variation in sex mortality ratios was assessed by a likelihood ratio test.

In the comparison of children receiving EZ–HT and SW–STD, a Cox regression model (COX, 1972) was used to adjust for possible confounding background factors such as age, season at risk (rainy/dry), and death of mother. Age was used as the time scale in the model. Effects are expressed as mortality ratios (MR) with appropriate 95% confidence intervals (95% CI), based on maximum likelihood estimation.

## Results

*Study children, coverage and measles infection*

When called for EZ–HT vaccination (5–7 months), 72·1% of the eligible children (928/1287) received vaccine. A similar proportion, 73·0% (609/834), received SW–STD when first called (9–10 months). Mean age at attendance was the same for boys and girls: 193 d for those who received EZ–HT and 295 d for recipients of SW–STD. Forty-four unvaccinated and 6 vaccinated children in this cohort contracted measles; 2 of the unvaccinated children died in the acute phase.

**Table 3. Deaths per 1000 person–years at risk for vaccinated attenders and unvaccinated non-attenders according to type of measles vaccine[a]**

| Type of vaccine | Deaths/1000 PYR[b] | | Mortality ratio[c] |
|---|---|---|---|
| and period evaluated | Vaccinated | Unvaccinated | (unvaccinated/vaccinated) |
| EZ–HT[d] | ($n$=928) | ($n$=359) | |
| 9–23 months | 44·3 (48/1084·1) | 80·2 (19/237·0) | 1·81 (1·06–3·08) |
| 24–35 months | 45·0 (36/799·6) | 31·3 (5/159·8) | 0·70 (0·27–1·77) |
| 36–59 months | 26·4 (27/1021·4) | 38·5 (8/207·7) | 1·46 (0·66–3·21) |
| Total | 38·2 (111/2905·1) | 52·9 (32/604·5) | 1·38 (0·93–2·04)[e] |
| SW–STD[f] | ($n$=609) | ($n$=225) | |
| 9–23 months | 47·6 (33/693·0) | 83·0 (15/180·8) | 1·74 (0·95–3·21) |
| 24–35 months | 44·7 (24/537·4) | 69·0 (8/116·0) | 1·54 (0·69–3·44) |
| 36–59 months | 28·9 (8/276·7) | 17·0 (1/58·9) | 0·59 (0·07–4·70) |
| Total | 43·1 (65/1507·1) | 67·5 (24/355·7) | 1·54 (0·97–2·47)[e] |

[a]Children born in Niakhar, Senegal, between February 1989 and January 1991.
[b]PYR=person–years at risk.
[c]95% confidence interval in parentheses.
[d]Edmonston–Zagreb high-titre, given at 5–7 months.
[e]Estimate adjusted for age groups.
[f]Schwarz standard, given at 9–10 months.

*Vaccine efficacy*

There was no difference in secondary attack rates after 9 months of age among recipients of EZ–HT and SW–STD vaccines (Table 2). Compared with unimmunized children from the same cohort exposed at home, the vaccines had similar efficacy, EZ–HT 94% (95% CI 81–98) and SW–STD 93% (95% CI 77–98). Efficacy did not differ by gender; for boys receiving EZ–HT it was

**Table 4. Deaths per 1000 person–years at risk according to sex, age and vaccine type[a]**

| Type of vaccine and age (months) | Deaths/1000 PYR[b] Males | Deaths/1000 PYR[b] Females | Mortality ratio[c] (female/male) |
|---|---|---|---|
| EZ–HT[d] | ($n$=470) | ($n$=458) | |
| 9–23[e] | 38·4 (21/546·2) | 50·2 (27/537·9) | 1·31 (0·74–2·31) |
| 24–35 | 47·0 (19/403·9) | 43·0 (17/395·7) | 0·91 (0·47–1·76) |
| 36–59 | 21·2 (11/517·9) | 31·8 (16/503·4) | 1·50 (0·69–3·22) |
| Total | 34·7 (51/1468·0) | 41·8 (60/1437·0) | 1·20 (0·83–1·74)[f] |
| SW–STD[g] | ($n$=317) | ($n$=292) | |
| 9–23 | 58·2 (21/361·0) | 36·1 (12/332·0) | 0·62 (0·31–1·26) |
| 24–35 | 54·7 (15/274·3) | 34·2 (9/263·1) | 0·63 (0·27–1·43) |
| 36–59 | 28·4 (4/140·9) | 29·5 (4/135·7) | 1·04 (0·26–4·15) |
| Total | 51·5 (40/776·2) | 34·2 (25/730·8) | 0·67 (0·40–1·10)[f] |
| Mortality ratio (EZ/SW–STD) | | | |
| Crude[f] | 0·74 (0·49–1·13) | 1·28 (0·80–2·06) | |
| Adjusted[h] | 0·73 (0·50–1·11) | 1·30 (0·81–2·09) | |

[a]Children born in Niakhar, Senegal, between February 1989 and January 1991.
[b]PYR=person–years at risk.
[c]95% confidence interval in parentheses.
[d]Edmonston–Zagreb high-titre, given at 5–7 months.
[e]Between 5 and 8 months of age, the mortality rates were 0·0694 (7/100·9) for males and 0·0797 (8/100·4) for females receiving EZ–HT.
[f]Estimate adjusted for age groups.
[g]Schwarz standard, given at 9–10 months.
[h]Estimate adjusted for age, season and death of mother.

96% (95% CI 70–99) vs. SW–STD 96% (95% CI 65–100), and for girls EZ–HT 91% (95% CI 69–98) and SW–STD 88% (95% CI 57–97).

*Mortality of attenders and non-attenders*

All surviving children were at least 3 years old at follow-up in February 1994. Non-attenders who were unvaccinated tended to have higher age-adjusted mortality rates than those who received measles vaccination, irrespective of whether the attenders were vaccinated with EZ–HT at 5–7 months (Table 3). The tendency was the same for boys and girls (data not shown). Most of the effect occurred between 9 and 23 months of age (Table 3).

There was no difference in mortality after 9 months of age between non-attending children from the periods where EZ–HT and SW–STD were used routinely (adjusted for age, MR=0·87, 95% CI 0·51–1·49) or between recipients of EZ–HT and SW–STD (MR=0·96, 95% CI 0·70–1·30) (Table 3).

When analysed by sex of the child (Table 4), mortality rates after 9 months of age tended to be lower among male recipients of EZ–HT than among recipients of SW–STD (MR=0·74, 95% CI 0·49–1·13), while female recipients of EZ–HT tended to have a higher mortality rate than did female recipients of SW–STD (MR=1·28, 95% CI 0·80–2·04).

Tendencies were unchanged when a Cox regression model was used to adjust for sex, age and significant background factors, season ($P$=0·000), and death of mother ($P$=0·0067). Mortality of female recipients of EZ–HT was 1·30 (95% CI 0·81–2·09) times higher than that for girls receiving SW–STD, whereas there was a tendency in the other direction for boys (MR=0·73, 95% CI 0·50–1·11) (test of interaction between sex and vaccine: $\chi^2$=3·34, 1 degree of freedom, $P$=0·067).

## Discussion

Following the completion of several studies of high-titre vaccines (WHITTLE *et al.*, 1988; TIDJANI *et al.*, 1989; MARKOWITZ *et al.*, 1990) and the trial in Niakhar, EZ–HT was introduced as the routine measles vaccine in the study area from mid-1989. In November 1990, EZ–HT was replaced by SW–STD. Even though it was not a randomized study, we tried to analyse the vaccine efficacy and the mortality pattern associated with these vaccines.

There was little measles in the post-trial cohort of children, as in the previous trials (AABY *et al.*, 1991, 1993a, 1994; SAMB *et al.*, 1993), and no important difference in vaccine efficacy was observed in any of these trials. Hence, lower efficacy of high-titre vaccines does not explain the higher mortality among girl recipients of such vaccines.

We compared mortality of attenders coming for measles vaccination when first called; these 2 vaccine groups presumably had common socio-economic and cultural characteristics. With non-attending children there was no significant difference in mortality between the periods when EZ–HT and SW–STD were used.

Both the EZ–HT and SW–STD groups had lower mortality rates than unvaccinated children. This difference could reflect an inherent selection bias between attenders and non-attenders. However, during the previous trial (AABY *et al.*, 1994), 638 attenders who received DTP–IPV or placebo, but no measles vaccine, at 5 months of age tended to have a higher mortality rate between 5 and 10 months of age than did 607 non-attenders (MR=1·60, 95% CI 0·76–3·37) (AABY *et al.*, 1995). Hence the markedly improved survival of recipients of EZ–HT compared with non-attenders is unlikely to reflect simple selection bias and suggests that EZ–HT is better than no measles vaccine. This interpretation is also supported by the observation that the recipients of EZ–HT did not have a higher mortality rate between 5 and 10 months of age than controls who had received a placebo but no measles vaccine (AABY *et al.*, 1994).

In the post-trial period, EZ–HT was not associated with an increase in mortality compared with SW–STD. The data suggested, but did not prove, an interaction between titre of measles vaccine and the sex-specific mortality pattern; girls receiving high-titre vaccine tended to have a higher mortality rate than those receiving standard doses, while boys receiving high-titre vaccine had reduced mortality compared with those receiving standard doses. A similar pattern of less survival benefit among female recipients of high-titre

Schwarz and Edmonston-Zagreb vaccines was found consistently in the randomized trials (AABY *et al.*, 1991, 1993a, 1994; HOLT *et al.*, 1993); survival of boys was remarkably similar after both high-titre and lower doses of measles vaccine.

The difference in mortality rates between recipients of high-titre and standard-titre vaccines may be related to non-specific effects of measles vaccine, since there was no difference in vaccine efficacy. It has therefore been suggested that high-titre vaccines were associated with deleterious effects (HALSEY, 1993). Retrospective studies in both Bissau (LISSE *et al.*, 1994) and Niakhar (SAMB *et al.*, 1995) have found no sign of any major persistent immunosuppression among recipients of EZ–HT which could explain differences in mortality. There was no indication of continuing excess mortality after 3–4 years of age in either Bissau (LISSE *et al.*, 1994) or Senegal (AABY *et al.*, in press). The theory of a deleterious effect of high-titre vaccines (HOLT *et al.*, 1993; GARENNE, 1994) is also contradicted by the facts that high-titre vaccines were not associated with lower survival in areas with low childhood mortality (WHITTLE *et al.*, 1990; DIAZ-ORTEGA *et al.*, 1992; LEÓN *et al.*, 1993) and that recipients of high-titre vaccine did not have higher mortality rates than control children before the latter received standard Schwarz measles vaccine (AABY *et al.*, 1993a, 1994).

Though the mechanism is not known, several studies have suggested that standard measles vaccine reduces morbidity and mortality more than would be expected from the prevention of acute measles cases (AABY *et al.*, 1993b, 1995; DESGRÉES DU LOÛ *et al.*, 1995). These studies have also suggested that the impact of measles immunization in reducing overall mortality is temporary, and varies by gender. The temporary character of the effect on mortality, also found in the present study (Table 3), supports the notion that measles immunization has important non-specific beneficial effects. A beneficial effect of standard vaccine, rather than a deleterious effect of high-titre vaccine, would explain the lack of difference in mortality between recipients of high-titre and standard-titre vaccines in areas with low childhood mortality, and the absence of excess mortality among children receiving high-titre vaccine compared with unimmunized control children in areas with high childhood mortality. A beneficial effect of standard-titre vaccine for girls (AABY *et al.*, 1993c; DESGRÉES DU LOÛ *et al.*, 1995) may be one reason that female recipients of high-titre measles vaccines had lower survival rates than recipients of standard vaccine.

The Global Advisory Group of the Expanded Programme on Immunization no longer recommends that high-titre measles vaccine be used in routine immunization programmes (EPI, 1992). Further studies into possible mechanisms are clearly warranted (EPI, 1992) and as the same pattern was noted for girls receiving EZ–HT and SW–HT in both Senegal (AABY *et al.*, 1994) and Haiti (HOLT *et al.*, 1993), it appears that investigations should focus on the amount, rather than the type, of vaccine. Future trials of measles vaccine should consider the possibility of sex-specific and non-specific effects of vaccination.

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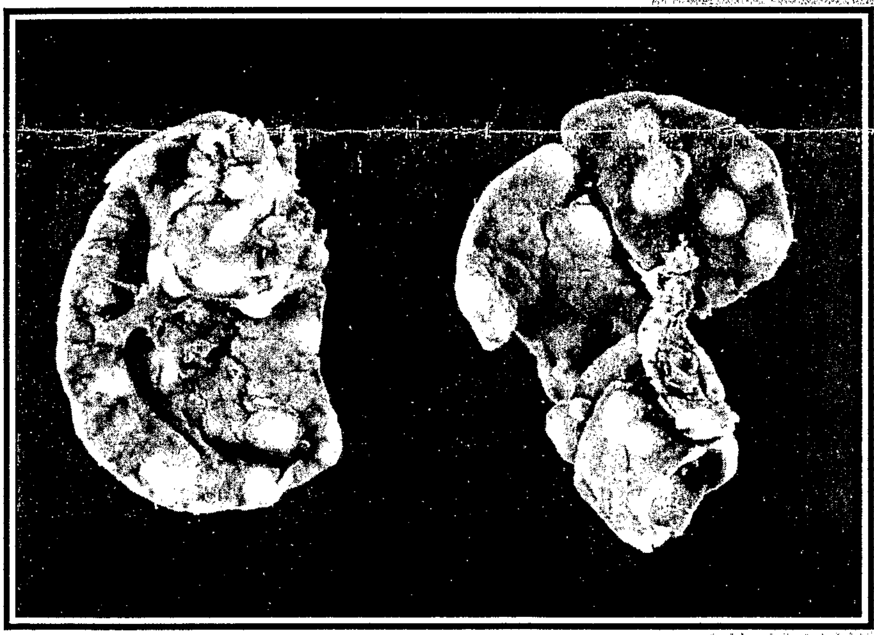

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