Child Mortality Following Standard, Medium or High Titre Measles Immunization in West Africa

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Background. The World Health Organization (WHO) recommended the use of high titre measles vaccine in 1989. Subsequent long term follow-up of several trials yielded results suggesting higher mortality among children inoculated with medium and high titre vaccines compared to standard titre vaccines, although none of the individual trials found significant differences in mortality.

Methods. Long term survival after standard, medium and high titre measles vaccines has been investigated in a combined analysis of all West African trials with mortality data. In trials from Guinea-Bissau, The Gambia and Senegal, children received medium or high titre vaccines from 4 months of age and were compared to control groups recruited at the same time later receiving standard titre vaccine from 9 months of age. All children were followed up to at least 3 years old.

Results. Combining trials of high titre vaccines showed higher mortality among the high titre group compared to the standard group: mortality ratio (MR) = 1.33 (95% CI : 1.02–1.73). Mortality among recipients of medium titre vaccines was not different from that in the standard vaccine group, MR = 1.11 (95% CI : 0.54–2.27). In a combined analysis by sex, the adjusted mortality ratios comparing high titre vaccine with standard vaccine were 1.86 (95% CI : 1.28–2.70) for females and 0.91 (95% CI : 0.61–1.35) for males. The trials were not designed to study long term mortality. Adjustments for several possible sources of bias did not alter the results.

Conclusions. The combined analysis showed a decreased survival related to high titre measles vaccine compared with standard titre vaccines, though solely among females. As a result of these studies from West Africa and a study from Haiti, WHO has recommended that high titre measles vaccine no longer be used.

Keywords: measles, high titre measles vaccines, childhood mortality, sex-specific mortality, combined analysis, vaccine safety

Measles is recognized as an important cause of both acute and delayed mortality in areas with high incidence of measles infection among infants and very young children. Although the standard Schwarz vaccine administered from 9 months of age has been successful in reducing both morbidity and mortality, a considerable number of infants contract measles within their first 9 months, especially in African countries, where

cumulative incidences of up to 15% by one year of age have been reported.[1] The use of vaccines of increased titre was proposed in the early 1980s as a strategy to induce protective immunity in the presence of maternal antibodies, and thereby to minimize the period of susceptibility between loss of maternal antibody and immunization.[2–6] Several studies evaluating Edmonston-Zagreb (EZ) medium or high titre measles vaccine in infants as young as 4–6 months showed good seroconversion rates,[2–6] and in 1989 the Global Advisory Group of the Expanded Programme on Immunization (EPI) of the World Health Organization (WHO) recommended that high titre EZ vaccine be used in areas where measles in young infants is a major health problem.[7]

As measles mortality is high in West Africa, controlled trials of medium and high titre measles vaccines were undertaken in Guinea-Bissau,[8,9] The Gambia[2,5]

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and Senegal[10–13] starting in 1985. These trials contributed to the decision to recommend high titre vaccines. However, subsequent long term follow-up of the trial populations yielded results suggesting higher mortality among children inoculated with medium and high titre vaccines compared to those who had received standard titre vaccines. Reports from the studies in Guinea-Bissau and The Gambia were submitted to EPI in January 1990. In February 1991 an EPI advisory committee met to evaluate the unexpected findings. The advisory committee recommended that the use of high titre EZ vaccine should be continued, but noted that long term follow-up in future studies of measles vaccines was essential.[13] After longer follow-up in the West African studies and with further data from a trial in Haiti[14,15] comparing high and medium titre measles vaccines, the results from these studies were presented at a consultation in Atlanta in June 1992 which led the EPI to withdraw its recommendation for the use of high titre measles vaccine.[16]

This paper presents an updated combined analysis of data relating to long term mortality in medium and high titre measles vaccine trials in West Africa. The present analysis includes an additional 2-year follow-up of the trials in Guinea-Bissau. Though one preliminary analysis reported significant increased mortality,[10] none of the individual trials have found significant differences in mortality. Using data from all these studies, we have tried to assess whether the results are sufficiently consistent to warrant a firm conclusion on the value of these vaccines. Combining the studies has also allowed us to provide more accurate estimates of the sex-specific effects of these vaccines. The combined results indicate an excess mortality among high titre girl recipients compared to girls who received a standard titre vaccine. The results of a combined analysis comparing high and medium titre measles vaccine to standard titre vaccine have not been published previously.

TRIALS AND METHODS
In this report we define standard titre as 3–4 $\log_{10}$ PFU, medium titre as 4–5 $\log_{10}$ PFU and high titre as $\log_{10}$ PFU ≥ 5. The WHO/EPI defined high titre vaccines as >5.0 $\log_{10}$ PFU in 1989, but revised the criterion to 4.7 $\log_{10}$ PFU in 1991.[17] The abbreviations EZS, EZM, EZH, SWS, SWM, SWH refer to standard, medium and high titre Edmonston-Zagreb or Schwarz vaccines, respectively.

Trials
Bandim, Guinea-Bissau. The two trials in Guinea-Bissau were carried out in Bandim, a semi-urban part of

the capital city, Bissau. The first trial was a randomized comparison of EZM with SWS vaccine.[8–18] Children born between 1 August 1984 and 31 September 1985 received either EZM vaccine lot 529 at 4.6 $\log_{10}$ PFU or an inactivated polio vaccine (IPV) at 4 months of age, or soon thereafter. At 9 months of age, or soon thereafter, the EZM group received IPV, while the standard group received SWS.

The second trial was carried out using the same design among children being born during the period 1 May 1986 to 30 April 1987.[9] The first one-third of the EZ group received the same lot of EZM vaccine as in the first trial, but the latter two-thirds received an EZH vaccine, lot 81/3 at 5.2 $\log_{10}$ PFU. Whereas previous studies followed the children only to June 1990,[9,18] the present assessment is based on a follow-up survey of all children carried out in May–August 1992.

Sukuta, The Gambia. Two trials were conducted in the Sukuta village area, 16 km from the capital Banjul.[2,5] The first trial recruited children born 2–6 January 1986. They were randomized to receive either EZM, lot 529 at 4.6 $\log_{10}$ PFU, SWM at 4.6 $\log_{10}$ PFU, or no measles vaccination at age 4 months. At 9 months, the unvaccinated group received SWS in addition to their yellow fever vaccination. Mortality data were collected at follow-up in January 1989 when children had reached 3 years of age. Since there were no deaths among recipients of medium titre vaccines and only one death among recipients of SWS, the mortality ratio between vaccination groups cannot be estimated using data from the first Gambia trial.

The second trial in Sukuta consisted of children born April 1989–January 1990. The trial had four arms. The first three arms received EZH, lot 81/3 at >5 $\log_{10}$ PFU, and the fourth arm received IPV at 5 months of age. At 9 months of age children of the first arm received IPV, the second arm EZH again, and the third and fourth arms received EZS vaccine, lot 122/6 at <4 $\log_{10}$ PFU. This trial contributes comparative data for the age interval of 5–9 months (between first and second vaccination) comparing the IPV group with the three EZH groups. Only the first and last of the four arms in the second Gambia trial were not revaccinated with measles vaccine and could be included in the combined analysis of high titre compared with standard titre vaccine.

Niakhar, Senegal. This trial was carried out in a rural area of Senegal and included all children born 1 February 1987–31 January 1989.[10–13] The children were invited to attend vaccination sessions at 5 and 10 months of age. Initially, the study had three arms of the same

TABLE 1 *Summary of studies evaluating medium and high titre measles in West Africa*

Country	Location	Name	Birth cohorts	EZ vaccines titre (lot)	Vaccines compared	Age at vaccination (months)	Children	Deaths	Child-years	Follow-up (median age)
Guinea-Bissau	Bandim	Bandim 1	1 August 1984– 31 September 1985	4.6 (529)	EZM SWS	4 9	234 236	24 30	888.3 902.0	May–June 1992 (87 months)
		Bandim 2	1 May 1986– 30 April 1987	4.6 (529) 5.2 (81/3)	EZM EZH SWS	4 4 9	77 124 183	18 23 28	225.2 319.2 568.6	May–June 1992 (67 months)
Senegal	Niakhar	Niakhar 1–24	1 February 1987– 31 January 1989	5.4 (81/3)	EZH SWH SWS	5 5 10	624 321 634	87 47 67	1886.6 1092.4 1939.3	February 1992 (48 months)
The Gambia	Sukuta	Gambia 1	2 January 1985– 6 January 1986	4.6 (529)	EZM SWM SWS	4 4 9	119 43 119	0 0 1	375.5 135.7 324 5	January 1989 (42 months)
		Gambia 2	April 1989– January 1990	5.0 (81) 4.0 (122/6)	EZH-IPV EZH-EZH EZH-EZS IPV-EZS	5, 9 5, 9 5, 9 5, 9	90 89 91 89	3 0 3 1	133.6 135.2 133.8 129.0	February 1992 (30 months)

size. At 5 months, the children received diphtheria-tetanus-pertussis-polio quadrivalent vaccine (DTP-IPV) and were given either an EZH vaccine, lot 81/3 at 5.5 $\log_{10}$ PFU, an SWH vaccine, lot 0980 at 5.1 $\log_{10}$ PFU, or a placebo in the standard group. At 10 months, all children received yellow fever and DTP-IPV vaccine, and the initial placebo group received an SWS vaccine of 3.7 $\log_{10}$ PFU as well. Seroconversion rates after SWH were found to be lower than after EZH, and thus it was decided to discontinue the SWH vaccinations in late 1988. Children born from 1 June 1988 were randomized to either the EZH or SWS trial arm.[11-13] Child mortality in this trial is based on a census and a follow-up survey carried out in February 1992.[13]

After the trial was conducted, EZH was used as the routine measles vaccine in the study area, and children born from 1 March 1989 were administered EZH at 5–7 months of age. Following interruption of the use of EZH, children born from 1 May 1990 received SWS at 9 months of age. A follow-up of mortality among all these children was performed in May 1992.

Other studies. Studies of seroconversion after high titre measles vaccine have also been undertaken in Togo,[3] Ivory Coast, Zaire, Sudan, Haiti,[15,16] Peru,[19] Mexico,[4] Thailand, New Guinea, The Philippines and USA, but most study designs did not allow for adequate follow-up of childhood mortality or results were not available for inclusion in the combined analysis. A study comparing medium and high titre measles vaccines was conducted in Haiti,[16] but as medium and high titre

vaccines were compared this trial cannot add to our comparison between standard and higher titre vaccines. The studies included in the present analysis are from neighbouring countries in West Africa with several similar design features, which provide some justification for assuming common vaccine effects in this combined analysis.

A summary of locations, vaccine types and designs of the West African medium and high titre measles vaccine studies described in this paper is given in Table 1. Methods and results of these studies are described in more detail elsewhere.[2,5,6,8-13,20]

Methods

Because the trials in Guinea-Bissau, Senegal and partly The Gambia had similar experimental designs with exact dates of recruitment, follow-up and death recorded, an identical analysis using a proportional hazards model for survival data[21] could be performed within each trial and the results from all trials could be combined. Children were included from the time of their first vaccination, regardless of whether they had received a measles vaccine or a placebo, and followed until death, migration or follow-up. The previous studies of the two trials in Guinea-Bissau had monitored child survival after migration by interviewing relatives and neighbours. Here, we have stopped follow-up at migration in all trials. Mortality rates decline rapidly with age during the first 3 years of life, and the variation in age at first vaccination was considerable between studies. For this reason, age has been used as the underlying time scale in a proportional hazards model.

Children have thus been compared from age at first vaccination until age at death or censoring. Potential confounders, e.g. sex, seasonality, measles infection, separation from mother and presence at second vaccination session, were controlled using a multivariable survival analysis. Effects are given as mortality rate ratios for recipients of high or medium titre vaccines against the standard group assigned to receive the standard titre Schwarz vaccine (SWS) after 9 months of age.

A combined mortality ratio (MR) was derived by pooling log mortality ratios of each trial in a random effects model which incorporates both sampling variation within each trial and variation between trials.[22] Because the two high titre vaccine groups had a common standard group in the Niakhar trial, the vaccine effect estimates are not independent and can therefore not be included separately in a combined analysis. The common mortality ratio in the Niakhar study was derived using a stratified proportional hazards analysis, such that recipients of SWH have been compared only with the standard group born in the same 16-month period, and recipients of EZH with all the standard group born during the entire 2-year period. In the second Bandim trial, recipients of medium titre vaccine have been compared to children from the standard group who were immunized at the same time, i.e. the first one-third of the group, while recipients of high titre vaccine have been compared to the last two-thirds of the standard vaccine group. Mortality ratios are calculated for medium and high titre vaccines separately. In the Gambia trials the number of deaths was small and only crude analyses could be performed.

The main survival analyses are based on deaths reported for residents in the study areas. Thus, follow-up is discontinued at emigration, but the analysis allows for possible re-entry into the study area. Analyses were also performed censoring at the time of measles infection, if any, and for the subgroup of children who received their first injection before the age of 9 months, the earliest recommended age for the Schwarz standard vaccine. Crude analyses are controlled for age, while the adjusted analyses control for age, sex, season (rainy or dry) and measles infection. The Niakhar data are adjusted also for presence at the 10-months medical examination and separation from mother. Mortality ratios are calculated from two ages: (i) the complete trial period, which is from first vaccination to follow-up, and (ii) from the second vaccination for the subgroup receiving both injections. In addition, mortality has been compared for the period from first to second vaccination, or to 10 months of age, whichever occurs first.

TABLE 2 *Relative mortality during the interval between first and second vaccinations among recipients of medium or high titre vaccines, compared to controls who had not yet received standard titre vaccine, for each of the West African trials, separately and combined*

Individual trials	Crude mortality ratio	95% confidence interval
Medium titre		
Bandim 1 EZ[a]	0.56	(0.13–2.35)
Bandim 2 EZ	1.80	(0.46–6.96)
High titre		
Bandim 2 EZ	1 17	(0.31–4.35)
Gambia 2 EZ	0.33	(0.02–5 20)
Niakhar EZ	0 52	(0.18–1.52)
Niakhar SW[b]	2.23	(0.76–6 53)
Combined results		
Medium titre trials	1.03	(0.33–3 22)
High titre trials	0.96	(0.49–1.87)
All trials	1.00	(0 58–1.74)

[a] Edmonston-Zagreb
[b] Schwarz.

RESULTS
The numbers of children under study and the numbers of deaths in each vaccine group for the different trials are presented in Table 1. The randomized trials with detail mortality data from Guinea-Bissau, Senegal and The Gambia involved 3073 children, with a total of 339 deaths in 11 129 child-years of follow-up.

Mortality Between First and Second Vaccination
Table 2 shows mortality ratios for the period between the first vaccination and either the second vaccination or 10 months, whichever occurs first i.e. the time before the control group had received measles vaccine. Although mortality ratios varied widely between studies, combined mortality ratios were similar for medium and high titre recipients compared to the standard group; medium titre: MR = 1.03 (95% CI : 0.33–3.22); high titre: MR = 0.96 (95% CI : 0.49–1.87). Note that because of the small numbers of deaths occurring in the interval between first and second vaccinations confidence intervals are wide.

Overall Mortality
The estimated mortality ratios comparing high or medium titre vaccines against placebo/Schwarz standard are listed in Table 3. Both crude and adjusted mortality ratios are given. Considering individual trials separately, no differences in mortality between medium or high titre and standard vaccine were significant at

TABLE 3 *Relative mortality among recipients of medium or high titre vaccines, compared to recipients of standard titre vaccines, dating from the first or second vaccination. Crude and adjusted mortality ratios (and 95% confidence interval) are given for each of the studies separately and combined*

Individual trials		From first vaccination	From second vaccination
Medium titre			
Bandim 1 EZM[a]	crude	0.81 (0.47–1.38)	0.94 (0.51–1.75)
	adjusted	0.87 (0.50–1.50)	1.06 (0.56–2.00)
Bandim 2 EZM	crude	1.69 (0.78–3.67)	1.72 (0.63–4 74)
	adjusted	1.68 (0.77–3.64)	1.70 (0.62–4.69)
High titre			
Bandim 2 EZH[b]	crude	1.35 (0.73–2.51)	1 24 (0.61–2.55)
	adjusted	1.50 (0.80–2.79)	1.38 (0 67–2.86)
Gambia 2	crude	2.89 (0.30–27.82)	†
Niakhar EZH	crude	1.33 (0 96–1.83)	1.56 (1.09–2.55)
	adjusted	1.33 (0.96–1.83)	1.57 (1.09–2.86)
Niakhar SWH[c]	crude	1.43 (0.93–2.21)	1 43 (0.86–2.40)
	adjusted	1.42 (0.93–2.19)	1.43 (0.86–2.39)
Combined results			
Medium titre	crude	1.11 (0.54–2.27)	1.11 (0.65–1.89)
	adjusted	1.14 (0.96–2.14)	1.21 (0.71–2.07)
High titre	crude	1 33 (1.02–1.73)	1.41 (1.04–1.92)
	adjusted	1.34 (1.02–1.75)	1.44 (1.06–1 96)

[a] Edmonston-Zagreb medium titre

[b] Edmonston-Zagreb high titre.

[c] Schwarz high titre.

† No deaths were recorded in the last arm of the second Gambia trial after the second vaccination so a mortality ratio could not be calculated.

the conventional 5% level for the crude age-adjusted comparisons.

Table 3 also shows results of the combined analyses. Combining the results of the different trials, the recipients of medium titre vaccines exhibited no significant difference in mortality, MR = 1.11 (95% CI : 0.54–2.27), whereas recipients of high titre vaccines had significantly higher mortality than the standard group, MR = 1.33 (95% CI : 1.02–1.73). If the comparison is limited to trials using Schwarz as standard titre vaccine, i.e. excluding the Gambia 2 trial, MR = 1.31 (95% CI : 1.01–1.71). Combining both medium and high titre vaccine trials, the MR was 1.22 (95% CI : 0.88–1.71) compared with the standard group. The results of the adjusted analyses were virtually identical. The crude results are shown graphically in Figure 1, in which the mortality ratios and 95% confidence intervals of each study are portrayed together with the joint estimates. Homogeneity of the vaccine effects could be assumed

within the high titre trials (test for homogeneity: $\chi^2 = 0.68$, 1 d.f., $P = 0.41$) and within the medium titre trials (test for homogeneity: $\chi^2 = 2.36$, 1 d.f., $P = 0.07$), although the latter difference approaches statistical significance. Since few trials are combined in both the medium and high titre groups, the power of this test to detect any differences is low.

Considering survival from the second vaccination, when children in the standard group had also received measles vaccine, recipients of high titre vaccine had an MR of 1.41 (95% CI : 1.04–1.92), whereas it was 1.11 (95% CI : 0.65–1.89) for recipients of medium titre vaccines. Again results were very similar in the adjusted analyses. Results of the individual trials and the combined results on survival from the second vaccination are shown in Table 3.

The estimated mortality ratios are unaltered if censoring is performed at onset of measles illness. Restricting the analysis to children who received their first injection before 9 months of age, the recommended age of standard Schwarz, the combined adjusted mortality ratio is MR = 1.23 (95% CI : 0.97–1.55), which is similar to the combined estimate of all children in the medium and high titre trials.

Mortality by Sex

No interactions have been identified in the individual trials apart from an interaction between vaccine type and sex. Excess mortality among female EZH recipients was noted initially in the Bissau trials[9] and reported to WHO.[11] Interactions of vaccine effect with sex adjusted for other factors are summarized in Table 4. The divergence between medium or high titre vaccine recipients and the standard group was greater in females than males in all but the first Bandim trial. In the medium titre trials combined, no interaction between sex and vaccine type was found, $\chi^2 = 3.132$, d.f. = 2, $P = 0.209$. The high titre trials display a significant vaccine-sex interaction, even after controlling for other factors, $\chi^2 = 8.508$, d.f. = 2, $P = 0.014$. Sex-specific estimates are shown in Table 4. In a combined analysis, the adjusted sex-specific mortality ratio comprising female high titre recipients with female recipients of SWS is 1.86 (95% CI : 1.28–2.70) whereas there was no difference for male recipients of high titre vaccine compared to the standard group, MR = 0.91 (95% CI : 0.61–1.35).

Mortality by Age

Since interaction between age and vaccine type was suggested in the Niakhar trial,[10] this interaction was examined in the combined analysis. It was not found to be significant ($\chi^2 = 6.319$, d.f. = 3, $P = 0.097$). However, there was some evidence for a lag in the
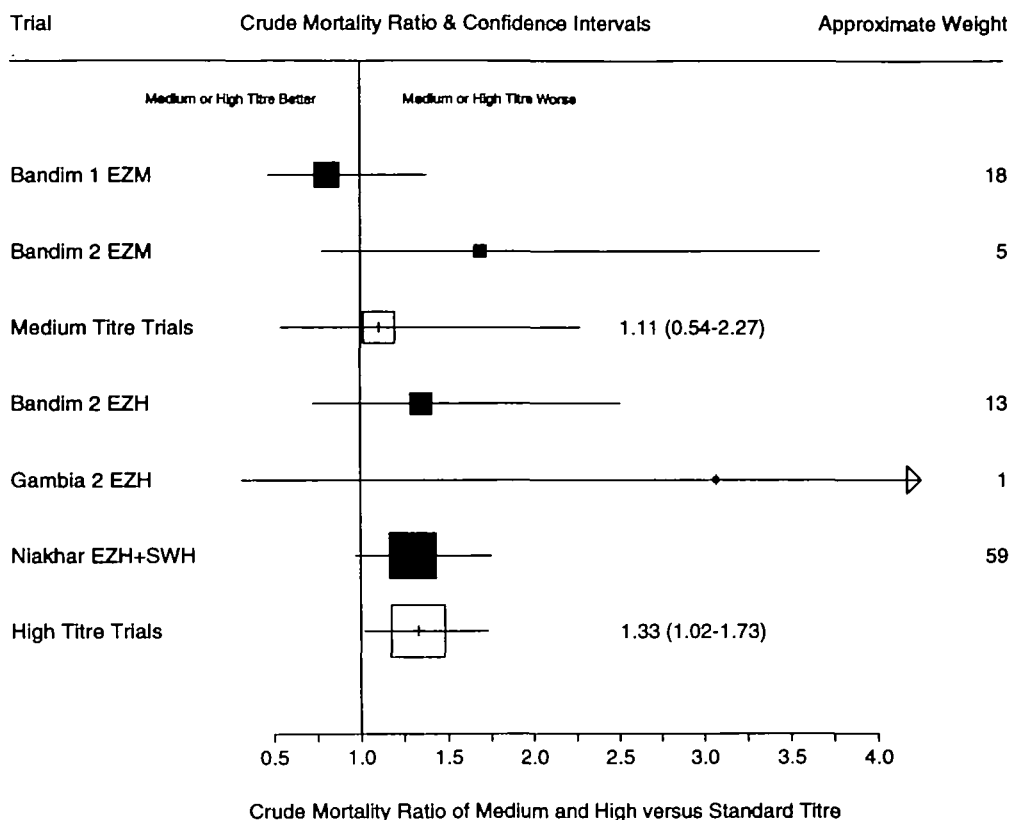
FIGURE 1 *Combined crude analysis of West African medium and high titre vaccine trials from first vaccination. Solid squares represent the rate ratios of mortality in the individual trials and empty squares represent the combined estimates. The sizes of the squares are proportional to the amount of 'information' contributed by that study, also given by the approximate weights. The 95% confidence intervals are denoted by lines*
EZM Edmonston-Zagreb medium titre
EZH Edmonston-Zagreb high titre
SWH Schwarz high titre

TABLE 4 *Mortality ratios by sex for recipients of medium and high titre vaccines compared to recipients of the standard vaccine of the same gender. Adjusted estimates (95% confidence interval) and tests for interaction controlling for age, season, measles infection and, for the Niakhar trial, presence at 10 months*

	Males	Females	Test for interaction
Individual trials			
Medium titre			
Bandim 1 EZM[a]	1.30 (0.62–2.72)	0.52 (0.22–1.23)	$\chi_{(1)}^2 = 2.583$, $P = 0.108$
Bandim 2 EZM	1.25 (0.42–3.72)	2.26 (0.72–7.11)	$\chi_{(1)}^2 = 0.549$, $P = 0.459$
High titre			
Bandim 2 EZH[b]	0.50 (0.15–1.71)	2.31 (1.09–4.88)	$\chi_{(1)}^2 = 4.832$, $P = 0.028$
Niakhar EZH+SWH[c]	0 97 (0.64–1.47)	1.73 (1.13–2.66)	$\chi_{(1)}^2 = 3.676$, $P = 0.055$
Combined results			
Medium titre	1.28 (0.70–2.37)	0.88 (0.45–1.74)	$\chi_{(2)}^2 = 3.132$, $P = 0.209$
High titre	0.91 (0.61–1.35)	1.86 (1.28–2.70)	$\chi_{(2)}^2 = 8.508$, $P = 0.014$

[a] EZM Edmonston-Zagreb medium titre.
[b] EZH Edmonston-Zagreb high titre.
[c] SWH Schwarz high titre.

differential mortality between higher titre and Schwarz standard titre recipients. In their first year of life, no excess mortality occurred: crude MR = 1.00 (95% CI : 0.66–1.52). From one to 2 years of age, the mortality ratio was 1.06 (95% CI : 0.71–1.58) increasing to MR = 2.12 (95% CI : 1.28–3.51) in the age interval from 2 to 3 years and after 3 years of age falling to MR = 1.14 (95% CI : 0.66–1.95). These estimates reflect solely differences in female mortality.

DISCUSSION

The West African studies discussed here were designed to measure immunogenicity and clinical protection as the main outcomes for comparing high or medium titre measles vaccines given at an earlier age with standard titre Schwarz given at 9–10 months of age. Although the trial protocols mention safety, sample size considerations did not include the question of adverse mortality effects of the introduction of a new vaccine policy. Since the trials in Guinea-Bissau, Senegal and The Gambia were part of the demographic surveillance systems monitoring child morbidity, immunizations, mortality and movements, it was possible to carry out detailed survival analysis of the trial populations. Because the trials were not carried out or designed for an analysis of long term mortality, but for evaluating measles morbidity, significance of test results at a 5% level should not be interpreted too literally, as these trials were addressing mortality as the secondary outcome, not the primary outcome.

The excess mortality discussed in this paper was not statistically significant in any of the individual trials when evaluated from the first vaccination and was only statistically significant in one comparison after the second vaccination (EZH versus SWS, Table 3). Combination of all the West African trials of medium and high titre vaccines resulted in a mortality ratio of 1.21 (95% CI : 0.89–1.63). The excess mortality reached conventional levels of statistical significance only when analyses were restricted to combined analyses of all high titre vaccine recipients, compared with standard titre recipients, MR = 1.33 (95% CI : 1.02–1.73). All analyses, crude and adjusted, as well as those including follow-up after migration and excluding time after measles infection, showed similar mortality ratio point estimates. The consistency in the estimates of reduced survival in connection with high titre vaccines is evidence that the result is robust with respect to possible confounders. Because the observed mortality ratios of the high titre trials are close, the random effects model delivers the same result as a fixed effect model. It should be noted that we have used recipients of both standard

titre EZ and standard titre Schwarz as the control group since this is currently the recommended dose of measles vaccine. Even if the recipients of EZS were excluded from the standard group, we obtained similar estimates of the difference between high and standard titre.

In addition to the overall difference in mortality, there are particular aspects of the combined analysis that may be indicative. First, no difference was observed in mortality between medium or high titre recipients and children who had not yet received measles vaccine (Table 2). The entire difference in mortality was found after the children in the control group had received standard Schwarz vaccine, MR = 1.41 (95% CI : 1.04–1.92).

Second, the excess mortality in the high titre group was restricted to females. The mortality was significantly greater among high titre female vaccinees compared with standard titre female vaccinees, but there was no difference between mortality in medium or high titre male recipients and SWS males. The interaction between vaccine type and sex was the only significant interaction found in the combined analysis. Given that this sex effect was unexpected, it should be viewed with caution. On the other hand, it gains credence by its consistency, having been observed in three trials (Guinea-Bissau,[9] Senegal[13] and Haiti[15]) as well as in post-trial data from Senegal (authors' unpublished data).

What are the possible explanations for these unexpected findings? All the trials compared different vaccines at different ages. Analysis of the Bandim trials, where there was a large variation in the age at vaccination, found no evidence that age at measles vaccination was responsible for the effect. A difference in vaccine response could influence vaccine-inducing protection, but differences in protection were not found[8,12] and the known cases of measles cannot explain the excess deaths among recipients of high titre vaccine. A specific batch of high titre measles vaccine does not appear to be responsible for the excess deaths, as both high titre EZ and high titre Schwarz vaccines showed similar associations with higher mortality. Since there was no overall evidence for a difference in mortality in the medium titre trials, a simple explanation for the increased mortality in the high titre trials is that the high dose of vaccine was responsible for the differences. However, this inference is weak, as only a small number of children were included in the medium titre studies.[19]

The results from Guinea-Bissau, Senegal and Haiti, all with high background child mortality, showed an association between high dose measles vaccines and decreased survival, especially among females, while studies from The Gambia[5] and Mexico,[23] where there

was low background infant mortality, displayed no difference in mortality. This suggests that the medium and high titre vaccines do not cause excess mortality by themselves, and have been interpreted as evidence that any high dose vaccine attributable effect on mortality is multiplicative rather than additive.[17] It has also been suggested that the impact of the vaccine may correspond to the delayed excess mortality reported after measles infection.[16] However, even in areas with high mortality, medium and high titre vaccines were not associated with increased mortality between 5 and 10 months of age, when the standard group were still not immunized against measles. Since the difference is only found after the standard group have received SWS and in areas with high background mortality, the observed mortality differences may be attributable to beneficial effects of SWS vaccines, particularly for girls, which are not reproduced by the high titre vaccines.[24] In this context it is notable that studies in Bissau,[25] Senegal[24] and Haiti,[26] have shown greater reductions in all cause mortality among recipients of standard measles vaccines, than could be explained by the prevention of acute measles deaths alone. In conclusion, there is no conclusive evidence that high titre vaccines are deleterious and it remains possible that they are just less beneficial than standard titre vaccines.

The findings from the these studies in West Africa and Haiti led the WHO/EPI to recommend that the use of high titre measles vaccine be stopped.[17] In addition, the EPI now recommends that post licensure field studies of new measles vaccines be designed so that late mortality can be evaluated. Given the evidence that the excess mortality was restricted to females, community studies of measles-related morbidity and mortality should be analysed for differential effect by sex. The interaction between sex and vaccine type requires further study. Despite the disappointment associated with the discontinuation of what had been considered a promising tool for measles control, the unexpected results from these studies should encourage further research towards more effective vaccination strategies against measles.

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