Child mortality after high-titre measles vaccines: prospective study in Senegal

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The use of Edmonston-Zagreb high-titre (EZ-HT) vaccine at age 6 months has been recommended for countries in which measles before the age of 9 months is a substantial cause of death, but little is known about the long-term effects of high-titre live measles vaccines given early in life. In a randomised vaccine trial in a rural area of Senegal, children were randomly assigned at birth to three vaccine groups: EZ-HT at 5 months (n = 336); Schwarz high-titre (SW-HT) at 5 months (n = 321); and placebo at 5 months followed by standard low-titre Schwarz vaccine at 10 months (standard: n = 358). All children were prospectively followed for 24-39 months in a well-established demographic surveillance system. Child mortality after immunisation was significantly higher in the two groups which received high-titre vaccines than in the group given the standard vaccine. The relative risk of death was 1.80 (95% confidence interval [CI] 1.18-2.74; p = 0.007) in the EZ-HT group and 1.81 (0.97-2.34; p = 0.07) in the SW-HT group compared with the standard group. The three vaccine groups were comparable as regards various social, family, and health characteristics, and there was no difference in mortality between children who received the standard vaccine and those who were eligible for the trial but did not take part for various reasons. The higher risk of death in the two high-titre vaccine groups remained significant in multivariate analyses. These findings suggest a need to reconsider the use of high-titre measles vaccines early in life in less developed countries.


Introduction

Measles is a leading cause of child mortality and morbidity in less developed countries.1-5 It is rare in infants of standard vaccines. Several vaccine trials have compared the immunological responses and adverse reactions after Edmonston-Zagreb vaccines of low, medium, and high titres with those of other measles vaccines of the same titres in children younger than 9 months.1-16

The use of Edmonston-Zagreb high-titre vaccine has been recommended "at age 6 months in countries in which measles before the age of 9 months is a significant cause of death"17 However, little is known about the long-term effects of high-titre live measles vaccines given early in life.

Subjects and methods

The study area was located near Niakhar, in the department of Fatick in central Senegal. It included 30 villages, inhabited by about 25,000 people of Serer origin. A comprehensive demographic surveillance system based on yearly censuses and weekly visits to households to register vital events was in progress before the study started and has been maintained since.

A randomised vaccine trial of the efficacy, safety, and immunogenicity of two high-titre live measles vaccines, Edmonston-Zagreb (EZ-HT) and Schwarz (SW-HT), was carried out in 1987-89.18 Although the primary objective of the study was clinical efficacy, a mortality surveillance was set up both to check safety and to evaluate the vaccination strategy. In addition to the routine surveillance system, independent checks on child deaths were made in October, 1990, and February, 1991. More details on the study area and on the data collection system can be found elsewhere.19-21

The study was approved by the Ministère de la Santé Publique, Dakar, Senegal; by ORSTOM authorities (Institut Français de Recherche pour le Développement en Coopération, Paris); and by the ethical committee of the British Medical Research Council, Fajarah, The Gambia. Oral informed consent was obtained from the parents of the participants; 20% of parents refused to allow their children to participate. During the 3 years of the project, vaccination was available to everyone, and free drugs and medical services were provided to all children and adults of the study population. As a consequence, overall mortality was substantially lower than during the 3 preceding years (1984-86).

Three measles vaccines were supplied by the manufacturers: EZ-HT (batch 81/3; titre 5.4 log<sub>10</sub> plaque-forming units [pfu]); Institute of Immunology, Zagreb, Yugoslavia; SW-HT (batch 081/8; titre 5.4 log<sub>10</sub> pfu; Institut Mérieux, Lyon, France), and a
TABLE I—ENROLMENT, DURATION OF FOLLOW-UP, LOSS TO FOLLOW-UP, AND MORTALITY IN STUDY POPULATION

<table>
<thead>
<tr>
<th>Trial participants</th>
<th>EZ-HT</th>
<th>SW-HT</th>
<th>Standard</th>
<th>Non-participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>No assigned at birth</td>
<td>526</td>
<td>527</td>
<td>539</td>
<td>(189)*</td>
</tr>
<tr>
<td>No enrolled at 5 mo</td>
<td>336</td>
<td>331</td>
<td>398</td>
<td>381</td>
</tr>
<tr>
<td>Person-months of follow-up</td>
<td>9522</td>
<td>9288</td>
<td>10 416</td>
<td>10 551</td>
</tr>
<tr>
<td>Mean (SD) duration of follow-up (mo)</td>
<td>28.3 (9.7)</td>
<td>28.6 (9.9)</td>
<td>29.1 (9.3)</td>
<td>27.2 (9.6)</td>
</tr>
<tr>
<td>No of non-accidental deaths during follow-up</td>
<td>50</td>
<td>42</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>No lost to follow-up</td>
<td>22</td>
<td>15</td>
<td>23</td>
<td>43</td>
</tr>
</tbody>
</table>

*Deaths and outmigrants before 5 mo.

Table II—SURVIVAL AFTER 5 mo BY VACCINE GROUP

<table>
<thead>
<tr>
<th>Months of follow-up after vaccination (age)</th>
<th>Survival (SE) per 1000 survivors at 5 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial participants</td>
<td>EZ-HT</td>
</tr>
<tr>
<td>0 (5)</td>
<td>1000 0</td>
</tr>
<tr>
<td>6 (11)</td>
<td>969.9 (9.4)</td>
</tr>
<tr>
<td>12 (17)</td>
<td>932.8 (13.6)</td>
</tr>
<tr>
<td>18 (23)</td>
<td>904.7 (16.3)</td>
</tr>
<tr>
<td>24 (29)</td>
<td>876.3 (18.3)*</td>
</tr>
<tr>
<td>30 (35)</td>
<td>859.8 (19.4)*</td>
</tr>
<tr>
<td>36 (41)</td>
<td>831.8 (22.5)*</td>
</tr>
</tbody>
</table>

Significance of difference from standard group: *p<0.05, **p<0.01 (both two-tailed).

sessions were completely vaccinated. Children who missed a session could come later to complete their vaccination series.

At birth, children were randomly assigned by means of a computer random generator to one of three vaccine groups: EZ-HT vaccine at 5 months; SW-HT vaccine at 5 months; or placebo at 5 months and standard measles vaccine at 10 months (standard schedule). Some children born during the study period did not take part in the study because the parents refused, the 5 months vaccination was missed, or vaccination was contraindicated. These non-participants were eligible for regular vaccinations, including measles at 9–10 months, and were included in the surveillance for survival in the same way as the participants.

Criteria for inclusion in the study were: birth to a resident mother between Feb 1, 1987, and May 31, 1988; clinic attendance at 5 months for vaccination and parental agreement to participation; absence of any contraindication to measles vaccination (evolving infectious disease, history of convulsion, previous measles infection, or previous measles vaccination); and no revaccination with another measles vaccine between 5 and 10 months of age.

Investigators and field workers were unaware which type of vaccine children had received.

Fig 1—Cumulative mortality from 5 to 41 months, according to vaccine group.

1989. Furthermore, the code was not revealed to the field workers who routinely recorded deaths or to the two physicians who reviewed the verbal autopsy questionnaires until the review was completed. Physicians and nurses who were treating patients in the local dispensaries knew nothing about vaccine assignment, because there was no mention of the type of measles vaccine on the health cards or on the dispensary register.

Survival of children was analysed in a monthly life-table (Kaplan-Meier product limit estimates). Multivariate analyses were carried out with linear logistic regressions on age-specific death rates. Proportional hazard models were also tried, but they did not fit the situation well, because of the very strong seasonal pattern of mortality among children. Standard testing procedures were applied, and two-tailed tests were used.

Results

1015 children were included in the vaccinetrial: 336 in the EZ-HT group, 321 in the SW-HT group, and 358 in the standard group; 388 children assigned at birth did not take part in the study (table I). By October, 1990, there was an excess of non-accidental deaths in both groups vaccinated with the high-titre vaccines (table I). There was only 1 accidental death—among the non-participants.

In a life-table analysis, children who received the EZ-HT vaccine at 5 months had significantly higher mortality at 41 months than children in the standard group (table II, fig 1): the relative risk of death was 1.80 (95% confidence interval [CI] 1.18–2.74; p=0.007). Children who received the SW-HT vaccine at 5 months also had a higher mortality than children in the standard group (relative risk 1.51 [95% CI 1.01–2.25]; p=0.04).
in cumulative mortality at 41 months between the EZ-HT and SW-HT groups (168 vs 141 per 1000 between 5 and 41 months) or between the standard group and the non-participant group (93 vs 99 per 1000).

Analyses to determine whether the vaccine groups were comparable showed that they were similar for the variables listed in table III and mortality in the randomised groups from birth to 4 months. Children in the non-participant group were also from families with a similar background. Children in the three vaccine groups were similar at 5 months in average age at vaccination, weight, height, and arm circumference (table III).

To exclude the possibility that mortality in the standard vaccine group was abnormally low, the mortality rates in the vaccine groups were compared with the rate predicted from trends in mortality since 1982 (fig 2). Extension of the trends predicts a mortality of 91 per 1000 during the study period compared with the 93 per 1000 found in the standard group.

There was no significant difference within the study groups in mortality between children in the same birth cohort.

The finding of excess mortality in the vaccinated groups (relative risks) remained stable with control for all other variables that were available: age, sex, age at vaccination, season, season of vaccination, measles antibody titre at 5 months, and seroconversion between 5 and 10 months of age. Odds ratios associated with high-titre vaccines remained stable in the various multivariate analyses. In the final model, the odds ratios were 1.71 (p=0.019) for EZ-HT and 1.49 (p=0.039) for SW-HT (table IV). The coefficient of the rainy season was always high and significant and was greater in the two HT-vaccinated groups than in the standard group. Sex, titre of antibodies at 5 months, and seroconversion between 5 and 10 months of age were not significant variables in any group.

The same multivariate analyses by vaccine group showed that the coefficient of age in the EZ-HT group was close to zero; this finding shows that mortality remained consistently high in the second and third year after the EZ-HT vaccine, whereas in other groups death rates declined substantially with age as would be expected (fig 3). The lack of decline in mortality rates with age of children is a cause for concern.

The finding of excess mortality in the vaccinated groups was possible for two reasons: the incidence of measles was low during the study period (69 cases among the study children), therefore there might have been a decline in the hot). Separate models were tested for each vaccine group. Results of the effects of the vaccines (relative risks) remained stable with control for all other variables that were available: age, sex, age at vaccination, season, season of vaccination, measles antibody titre at 5 months, and seroconversion between 5 and 10 months of age. Odds ratios associated with high-titre vaccines remained stable in the various multivariate analyses. In the final model, the odds ratios were 1.71 (p=0.019) for EZ-HT and 1.49 (p=0.039) for SW-HT (table IV). The coefficient of the rainy season was always high and significant and was greater in the two HT-vaccinated groups than in the standard group. Sex, titre of antibodies at 5 months, and seroconversion between 5 and 10 months of age were not significant variables in any group.

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death and the only death attributed to measles were among
the non-participants. The frequency of other diseases and
unknown causes of death was similar in the four groups.

Discussion

The demographic surveillance system developed in
Niakhar is an unusually reliable system of data collection
that is unique in tropical Africa. Weekly visits to households
ensure accuracy of dates of births and deaths, and yearly
updating of maternity histories and full-scale census taking
by roll call from computer printouts guarantees the
complete recording of vital events.

Differences in mortality among the groups were tested by
eight statistical procedures (life-table, death rate, probability
of death, age-standardised death rates, linear logistic
regression, proportional hazards, log-rank tests, and
simulations). They showed a consistent level of significance
of mortality differences from the standard vaccine group
(p = 0.007 to 0.024 for the EZ-HT group and p = 0.041 to
0.102 for the SW-HT group).

The consistency of the data, both in the groups vaccinated
with high-titre vaccines and in the groups not given the
high-titre vaccines, was striking. The probability of
concurrent occurrence of at least 50 deaths in the EZ-HT
group and at least 42 deaths in the SW-HT group was very
low (p < 0.0001).

Since the goal of the study was to compare two
strategies—vaccination at 5 months with high-titre vaccines
versus vaccination at 10 months with a standard vaccine—
substantial differences after 10 months was also investigated. The two
groups receiving the high-titre vaccines at 5 months had a
similar excess mortality between 10 and 41 months over that
in the standard vaccine group. Relative risks of deaths were
2.50 (95% CI 1.52-4.13; p = 0.0004) in the EZ-HT group
and 1.73 (1.00-2.98; p = 0.05) in the SW-HT group.

The fact that children who migrated out of the study area
were removed (censored) at the time of their move did not
affect the results. An attempt to find those who died after
outmigration showed that their inclusion would not have
affected the results. There were 11 deaths—3 in the EZ-HT
group, 1 in the standard group, and 7 in the non-participant
group, which included most of the outmigrants. The
difference between the EZ-HT and the standard group
would have been even larger (20 deaths) if deaths among
immunity have been observed. In a study in the Niakhar
area, a low response to yellow fever vaccination was found
when it was given in association with the EZ-HT vaccine
(personal communication, Dr J-P. Gonzalez). The wild
measles virus has severe adverse short-term effects on
immunity and nutritional status of children, in particular on
nitrogen metabolism and vitamin A. In addition, the wild
measles virus can have long-term effects, such as subacute
cerebellar ataxia.

There was no reason to suspect excess mortality after
measles vaccines in the study area: earlier findings there and
in a nearby area showed that survival was better among
children vaccinated with a standard measles vaccine, even
when it was given before 6 months of age. This finding
suggests that the high titre may be the main cause of the
effect.

Excess mortality became significant for the first time in
the spring of 1990, several months after the last child
completed the vaccination series. This effect is partly due to
the sample size, because the number of deaths was too small
before that time for a significant relative risk to show, and
partly because most excess deaths were concentrated in the
high mortality age group, which lies from 18 to 41 months in
this population.

A quick cost-benefit analysis suggests that the strategy of
using high-titre vaccines early in life is not worth while:

between 48 (SW-HT) and 75 deaths (EZ-HT) per 1000
children reaching age 5 months seemed to be associated
with the use of high-titre vaccines. This number exceeds by far
the reduction in mortality expected from the early
vaccination, estimated to be 4 per 1000 children reaching age
5 months (incidence of 42/1000 between 5 and 10 months
multiplied by case-fatality rate of 10%).

If these findings are confirmed in other settings, other
strategies to reduce mortality from early measles should be
developed. The low titre AIK-C vaccine seemed to produce
a good immunogenic response at 6 months among Togolese
children. In Niakhar, the standard measles vaccines were
safe, even when given at 4-6 months, and may well prevent
deaths from measles. Since most complications of measles
occur during the second and third weeks after onset, early
treatment is possible. A systematic treatment of
complications in the Niakhar study reduced the case-fatality
rate among children below 3 years of age by 78%.
The study revealed persistent abnormalities in the intestinal mucosa, which were associated with long-term intestinal lesions. Abnormalities in intestinal permeability, mucosal injury, and growth are monitored over a mean of 7.5 months. The focus is on the rapid catch-up growth that cannot be expected until the mucosal injury has healed. Little is known about the time taken for restoration of intestinal function after a mucosal injury, which is a crucial concern in developing countries where diarrhoea is a common issue.

What is accepted is that episodes of diarrhoea cause short-term faltering in both height and weight development. Diarrhoea affects approximately 70% of children in the first two years of life, and between 5% and 10% of children suffer from severe diarrhoea. Infants in developing countries are most affected, with the highest rates of diarrhoea observed in infants in developing countries. In the Gambia, diarrhoea in infants is strongly debated as a significant issue.

The impact of diarrhoea on growth is significant. It is estimated that 43% of observed growth faltering is associated with diarrhoea. Growth faltering is monitored using the actulose:mannitol permeability test, which is done regularly on children aged 2-15 months. This invasive test of intestinal integrity measures the permeability of the intestinal mucosa, which is crucial for assessing the impact of diarrhoea on growth.

The association between diarrhoea and growth faltering is significant, with diarrhoea affecting both height and weight development. The impact of diarrhoea on growth is not only immediate but also long-term, with persistent abnormalities in intestinal permeability and mucosal injury. These findings highlight the importance of addressing diarrhoea as a significant health issue in developing countries, where it affects the growth and development of children.