Protective efficacy of high-titre measles vaccines administered from the age of five months: a community study in rural Senegal

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Abstract
Using data on incidence and secondary attack rates, we examined the protective efficacy of high-titre Edmonston-Zagreb (EZ) and Schwarz (SW-HT) measles vaccines administered at 5 months. Control children were assigned to placebo at age 5 months and standard Schwarz (SW-std) measles vaccine at 9–10 months of age. A large proportion of measles cases was verified serologically. Though high-titre vaccines seemed to be protective before 10 months of age, a significant reduction in disease could not be demonstrated due to low incidence of measles. After 10 months of age, SW-std given at 10 months gave a vaccine efficacy of 100% and induced better protection than SW-HT (P=0.0128) administered at 5 months.

In studies of secondary attack rates in the compound, vaccine efficacy was 91% (75%–97%) for EZ-HT, 85% (40%–96%) for SW-HT, and 100% for SW-std. Attack rates were correlated with intensity of exposure (P=0.0006), being much higher for children exposed in the same hut than for those living in the same compound but in a different household (relative risk=2.36 [1.32–8.57]). The attack rate was significantly lower among high-titre vaccinated than unvaccinated children with no detectable measles antibody (relative risk=0.41 [0.18–0.93]). In rural areas with a high coverage in the surrounding community, a single dose at 9–10 months may provide sufficient protection. Since high-titre vaccines have been associated with higher mortality than SW-std, further improvements in measles control before 9 months may require two-dose strategies with standard vaccines.

Introduction
There has been increasing concern about measles infection before the normal age of vaccination (Aaby & Clements, 1989; Aaby et al., 1990; Dabis et al., 1988; Liening & Coovadia, 1985; Taylor et al., 1988). Measles before 9 months of age is connected with a high case fatality ratio (CFR) and it seems also to be connected with a significant delayed mortality (Aaby et al., 1986, 1990b; Garenne & Aaby, 1990). Several studies have shown that high-titre Edmonston-Zagreb measles vaccine (EZ) is capable of inducing measles antibodies even in the presence of maternal antibodies (Markowitz et al., 1990; Tidiani et al., 1989; Whittle et al., 1988a, 1990). Since seroconversion is usually considered to be equivalent to protection, the World Health Organization (WHO) has recommended the use of EZ from the age of 6 months in areas with a high incidence before 9 months of age (WHO, 1990). However, there have been few studies of the protective efficacy of early measles vaccination with high-titre vaccines (Aaby et al., 1988).

The present study in rural Senegal compared high-titre EZ and high-titre Schwarz vaccine (SW-HT) given at 5 months of age with standard Schwarz measles vaccine (SW-std) administered at the age of 10 months (WHO, 1990). EZ was initially recommended for use in urban areas with a high incidence before 9 months of age. However, a uniform vaccination policy would clearly be an advantage from an administrative point of view. We therefore wanted to examine whether these high-titre vaccines could contribute to improved control of measles also in rural areas which have a lower incidence before 9 months of age than urban areas.

After completion of the study, long-term follow-up of study children demonstrated increased mortality for recipients of high-titre vaccines. It has therefore been recommended that high-titre measles vaccines should no longer be used (EPI [Expanded Programme on Immunization], 1992). However, we thought it worthwhile to document the vaccine efficacy (VE) of high-titre measles vaccines and SW-std.

Subjects and Methods
The study was carried out in Niakhar, Senegal, in a rural area with a population of about 25 000 which had been under demographic surveillance since 1983 (Cantrelle, 1969). The area is inhabited by Serer who live in large compounds. The population, the demographic surveillance system (Garenne et al., 1987), and the epidemiology of measles there (Garenne & Aaby, 1990) have been described in detail elsewhere. The surveillance system was based on a weekly visit by field assistants to all compounds in the study area to get information on births, migrations, deaths, and infections (measles and whooping cough).

Study of high-titre measles vaccines
All children born of mothers resident in the study area between 1 February 1987 and 31 January 1990 were included in the study. Children were allocated at random to receive either EZ, SW-HT or placebo at 5 months of age. Parents were advised to bring their children for one of the monthly vaccination sessions at the nearest of the 3 health centres in the study area in the 3rd, 5th and 10th months after birth. At 5 months of age, children received bacillus Calmette-Guérin (BCG) and diphtheria, tetanus, pertussis and polio (DTP-IPV), at 9 months the second dose of DPT-IPV, and at 10 months the third dose of DPT-IPV and yellow fever vaccine. At the 5 months vaccination (mean age 5.1 months) children received EZ, SW-HT or placebo. The study was "blind" between 5 and 10 months of age. Children in the placebo group as well as children who had not previously attended for vaccination were offered vaccination with SW-std when they were 10 months old (mean age 10.1 months). Children belonging to the study cohort who did not attend for vaccination at 5 months also remained under surveillance although they had not entered the study. Children who remained vaccinated were called for vaccination at a health centre during 2 campaigns, and at the end of the study period (September–December 1990) all children were visited at home by a physician. Measles vaccination was offered to those who had still not received measles vaccine; 55% (138/248) accepted.

Blood samples were collected at 5 and 10 months of age from children included in the study. Recipients of high-titre vaccine found to be serologically negative at 10 months of age were offered revaccination against measles; 5 children (1%) in the EZ and 31 (10%) in the SW-HT thus received a second vaccination with either EZ or SW-std. Revaccinated children were excluded from the analysis of VE from the time of revaccination. Blood samples were not collected from the children who had received SW-std.

When blood samples from the first vaccinated children were analysed, it became clear that SW-HT gave lower...
Measles surveillance and clinical examination

As soon as a field assistant was informed of a case of suspected measles in the weekly visit to all compounds, the project physician was called to examine the children. At the first visit, a census was made of all children under 15 years of age in the compound. Whether children lived in the same hut as the index case, in the same household but not in the same compound but not in the same household, or not at all, was recorded (GARENNE et al., 1990). If the parents consented, a blood sample was taken from all cases and from exposed children without a parental history of measles infection. Convalescence samples were collected about 4–5 weeks after the beginning of symptoms from children who developed measles.

All 55 cases with a clinical diagnosis were seen by a project physician and had a typical rash and/or typical desquamation. Eleven further cases were reported by parents, usually the mother. Previous studies in this area have shown maternal diagnoses of measles to be very reliable (AABY, 1992). Most of these cases had occurred outside the study area.

Serology

Blood samples were analysed for measles haemagglutination inhibition (HAI) antibodies at the MRC Laboratories in The Gambia (WHITTLE et al., 1988b). The sensitivity of this test is 62.5 milli-international units (miu). Since the test starts with a 1:2 dilution, the minimum detectable level is 125 miu. A four-fold increase in paired samples was considered proof of acute measles infection. Protection in relation to antibody level was assessed for children who had a blood sample collected within 10 d of the onset of symptoms in the index case in the compound.

Vaccine efficacy

The protective efficacy against measles infection was examined by comparing incidence of measles in the different groups and by determining protection against infection after known exposure at home to an index case of measles. Children were considered to be vaccinated from the day of death, the day of migration, the day of measles infection, or the date of receiving a second dose of measles vaccine, whichever came first. Since study design was different for the first 16 and the last 8 months cohorts, the calculation of incidence has been standardized for these 2 periods.

The secondary attack rate (SAR) following exposure was assessed for different study groups taking intensity of exposure into consideration (GARENNE & AABY, 1990). All exposed children who developed measles experienced the onset of symptoms within an interval of 8–19 d if they belonged to the first generation of cases infected in the compound. Cases occurring in later generations within the compound were also counted as secondary cases. Cases were classified according to the closest exposure. Two children exposed twice with an interval of 6–12 months were counted only the first time they were exposed.

In the analysis of incidence, we used only the unvaccinated children in the placebo group as controls, since there could be an association between not attending for vaccination and being exposed outside the study area. In the study of secondary attack rates, however, we also used the unvaccinated children in the group which had not entered the study. There is no reason to believe that susceptibility to measles is either higher or lower when exposed at home for children who did not receive the first vaccination than for other children in the community.

Statistics

Relative risk (RR) and Greenland-Robins approximate 95% confidence interval (CI) were calculated using the EpiInfo program (Version 5.01a).

Results

Study children and vaccine coverage

During the study period 2467 children were born in the area. At the 5 months vaccination, 2177 children were eligible for inclusion in the study. Of these children, 72.9% received a vaccine at 5 months: 624 received EZ, 321 SW-HT and 634 the placebo. Nine received the wrong vaccine and were excluded from the study. Of the control children still in the study at the 10 months vaccination, 78.7% (480/610) received SW-std. At 2 and 3 years of age, coverage in the control group had increased to 86.6% and 90.4%, respectively.

Table 1. Incidence of measles per 1000 person-years-at-risk according to age and vaccine group; children with a clinical diagnosis of measles only. Niakhar, Senegal, 1987–1990

<table>
<thead>
<tr>
<th>Vaccine by time of exposure</th>
<th>No. of cases per 1000 PYR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SW-std</td>
<td>5–9 months</td>
</tr>
<tr>
<td>Placebo</td>
<td>11.7 (3/255:5)</td>
</tr>
<tr>
<td>Placebo/SW-std</td>
<td>0.0 (0/826:5)</td>
</tr>
<tr>
<td>Not in study</td>
<td>16.4 (4/244:6)</td>
</tr>
<tr>
<td>Not in study/SW-std</td>
<td>0.0 (0/239:7)</td>
</tr>
</tbody>
</table>

*As only the first 16 of the 24 monthly birth cohorts in the study received SW-HT (see note c), the analyses of vaccine efficacy have been adjusted according to whether the child belonged to cohorts 1–16 or 17–24. Hence, some vaccine efficacies cited in the text are not directly deducible from the Table. The calculation of vaccine efficacy has been standardized for the 2 age intervals in the Table. Four measles cases occurred before the children received measles vaccination; 2 cases occurred among 12 children excluded because they received the wrong vaccine or were vaccinated at an incorrect age, and one case was excluded because it had received 2 measles vaccines.

Vaccine = person-years-at-risk.

EZ=Edmonston-Zagreb vaccine; SW-HT=Schwarz high-titre vaccine; SW-std=standard Schwarz vaccine.

Children not immunized against measles.

Children immunized with the SW-std measles vaccine.
Measles cases

Fifty-five of the study children were diagnosed with clinical measles between the beginning of the study in July 1987 and the autumn of 1990, most of them during an epidemic between September 1989 and May 1990. Four cases were infected before they had received their 5 months vaccination. After 5 months of age, 5 children in the EZ group (2, 1, 1, 1 and 0-6 years old) and 5 in the SW-HT group (2, 1, 1, 1, 1 years old) caught measles, whereas none of the recipients of SW-std were diagnosed with measles. None of these children died of acute measles. One vaccinated case was excluded from the analysis because the child apparently had received 2 measles vaccines. The remaining 40 cases occurred among unvaccinated children. Of the 55 cases, 28 had 2 blood samples collected in the acute and convalescence phase of the disease, the rest had only one blood sample (20) or refused to give a blood sample (7). Of the 28 children with 2 blood samples, 24 (86%) had a four-fold increase in the HAI titre; these included 2 of the 3 children in the EZ group and all 3 children in the SW-HT groups with 2 samples. Three cases had the same log2 titre in both samples (3.5-3.5, 5-5) and one had no antibody in either sample. With 3 of the 4 cases without an increase in titre, there were other verified cases in the compound. The case who had no antibody has been maintained in the analysis since not all cases were examined by haemagglutination inhibition assay and the condition for inclusion was a clinical diagnosis.

Vaccine efficacy based on incidence of measles

The incidence in the different age and vaccine groups is shown in Table 1. The unvaccinated children who did not enter the study had a higher risk of contracting infection than children in the placebo group who never received measles vaccine (RR=2.4, CI=1.0-6.1). If children with a parental diagnosis of measles were included, the difference in incidence was even greater (RR=2.7, CI=1.2-5.9).

Comparison of recipients of high-titre vaccines and unvaccinated children. There were too few cases between 5 and 10 months of age to determine VE confidently. Considering both high-titre groups together compared with the placebo group, VE was 71% (95%-114% to 96%) (P<0.049). Compared with recipients of placebo who had not been vaccinated against measles, EZ had a protective efficacy of 75% (10%-93%) (P=0.055) and SW-HT one of 11% (88%-99% to +92%) (P=0.720), if the periods both before and after 10 months of age were considered.

Comparison of recipients of high-titre vaccines and SW-std vaccinated children

Compared from 10 months of age, SW-std had a VE of 100% (P=0.003) (Fisher's exact test) compared with the unvaccinated children. SW-std given at 10 months of age also provided significantly better protection than SW-HT administered at 5 months of age (P=0.030, Fisher's exact test) and tended to be better than EZ administered at 5 months of age (P=0.128). The protective efficacy remained essentially unchanged when cases with a parental diagnosis only were included (data not shown).

Vaccine efficacy based on the secondary attack rate

There was a highly significant tendency towards increasing SIR with immunity of exposure in the unvaccinated group (P=0.0006; t for linear trend=11.9) (Table 2). Children exposed in the same hut had a 3.36 times higher risk (1.32-8.57) (P=0.002) of developing measles than did children living in the same compound but in a different household. The VE standardized for age and intensity of exposure was 91% (75%-97%) (P=0.0001) for recipients of EZ administered at 5 months of age, 85% (40%-96%) (P=0.0002) for SW-HT administered at 5 months of age, and 100% (P=0.0001) for SW-std given at 10 months of age (Table 2). In compounds with at least one case confirmed serologically, the attack rate among unvaccinated children in the same household was 95% (19.20). The only child who did not develop measles had a titre of 4000 miu 3 d after exposure, even though the child had no history of measles infection or vaccination against measles.

After 10 months of age, when the different measles vaccines could be compared, recipients of SW-std tended to have better protection than those who had received SW-HT (P=0.104, Fisher's exact test) or EZ vaccine (P=0.109, Fisher's exact test).

Antibody levels and protective efficacy

Of the 169 study children exposed after the age of 5 months, 111 (66%) had provided a blood sample within 10 d of exposure (date of first symptom in the index case in the compound). All except one of the children who developed measles were negative in the initial HAI test. One child in the EZ group, who was a secondary case in the household, had a titre of 500 miu 9 d after exposure and 10 d before the child developed the first symptoms of clinical measles. In the convalescence phase, the child had a titre >256 0000 miu.

The attack rate was significantly lower among vaccinated children with no detectable antibody (4/12) than among unvaccinated children with <125 miu antibodies (18/22) (RR=0.41, CI=0.18-0.93), P=0.008, Fisher's exact test).

Discussion

One of the major objectives of this study was to assess the protective efficacy of high-titre measles vaccine between 5 months and the normal age of vaccination. The observed measles incidence of 5%-5% between 5 and 10 months of age was clearly lower than the incidence of 2%-5% expected from previous data (GARENNE & AABY, 1990), probably due to the effect of vaccination campaigns launched by the Ministry of Health and UNICEF in 1987 and the herd immunity provided by the higher vaccination coverage (AABY et al., 1990a) resulting from the project. The reduced rate of measles at 5-10 months of age among recipients of high-titre measles vaccine (2/61000 PYR), as compared with those immunized only after 10 months of age (167/1000 PYR) also contributed to this effect, though statistically significant protection could not be shown. Thus the study had no power (13%) to demonstrate the expected VE (85%) of high-titre vaccines between 5 and 10 months of age. However, both high-titre measles vaccines provided a reasonable VE in the secondary attack rate studies. Thus there is reason to think that these vaccines provide clinical protection before the normal age of vaccination, as was found in Guinea-Bissau (AABY et al., 1988).

The evaluation of high-titre vaccines, in particular of SW-HT, may well have been too favourable because several of the children with unmeasurable antibodies were revaccinated and in the exposure study children without

Table 1. Secondary attack rates after exposure in the compound according to age, intensity of exposure and vaccine group; only children with a clinical diagnosis. Niakhar, Senegal, 1987-1990

<table>
<thead>
<tr>
<th>Age and place of exposure</th>
<th>Attack rate (%) (no. of cases/no. exposed)</th>
<th>Placebo and unvaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-9 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>0 (0/5)</td>
<td>0 (0/6)</td>
</tr>
<tr>
<td>Household</td>
<td>0 (0/2) (211)</td>
<td>17 (160)</td>
</tr>
<tr>
<td>House</td>
<td>6 (6-0 (20)</td>
<td>14 (12)</td>
</tr>
</tbody>
</table>

EZ = Edmonton-Zagreb vaccine; SW-HT = Schwarz high-titre vaccine; SW-std = standard Schwarz vaccine.
antibodies were clearly more likely to contract measles. Furthermore, the higher age at vaccination after 10 months of age the recipients of high-titre vaccines were compared with children who had not been vaccinated with SW-std and these children may have had a higher risk of contracting measles. Since EZ provided a better antibody response than SW-HT (unpublished observations), the EZ is more likely to improve control of measles infection than high-titre Schwarz vaccine. No other community study from Africa has provided serological confirmation of a large number of cases, presumably due to the difficulties in timing when the first sample is taken late in the acute phase. In the present study, in which most of the exposed children provided a blood sample before exposure, significant increases in titre could be demonstrated in most paired samples. The one child vaccinated with EZ whose clinical diagnosis was not confirmed serologically was a case who infected no one and the exclusion of this case would not affect the results obtained for protection after exposure at home.

The recipients of SW-std tended to be better protected after 10 months of age than the recipients of high-titre vaccines, though the difference was not statistically significant in the comparison between EZ and SW-std. This result is consistent with the studies in which children in the control group reached SW-std at 10-1 instead of 9 months may have improved the performance of the standard vaccine in the present study. The potential benefits of early measles vaccine with high-titre vaccines are related both to protection before the normal age of vaccination and to the possibility of better protection than with SW-std after 9 months of age (AABY et al., 1990b). The consequence of the low incidence before 10 months of age and of the better protection in the SW-std group was that high-titre vaccines prevented few cases compared with the placebo/SW-std group in spite of the lower measles immunization coverage in this group. In the present study, the interval between giving the high-titre vaccine and the standard vaccine was 5 months, whereas it would be only 3 months in the normal situation when a change is made from vaccination at 9 months to 10 months of age. (WHO, 1990). However, such situations, the benefits of high-titre vaccine may be less. In areas with a low incidence of measles, and as long as a single dose strategy is maintained, good coverage with the standard vaccine at 10 months may be as effective for measles control as the introduction of early vaccination or even if SW-std has a better VE after 9 months of age. Thus the crucial issue for measles vaccine strategy is the relative VE after 9 months of age for SW-std and high-titre vaccines.

Since high-titre vaccines have been protective before 9 months of age (AABY et al., 1990a) and SW-std was better than high-titre vaccines after 10 months of age in the present study, two-dose strategies need to be considered. However, such strategies presuppose that the second dose can stimulate protective immunity equivalent to that obtained by vaccination for the first time with SW-std at 9 months.

In this rural area the incidence before 10 months of age was low. Hence, the major arguments for introduction of high-titre measles vaccines in rural areas also may be the simplification of vaccine policy and the possibility of obtaining better coverage at 6 months of age than at 9 months. However, since high-titre vaccines have been found to be associated with higher mortality than SW-std vaccine (Gamze-Bissett et al., in press; EPI, 1991) and Senegal (AABY et al.; 1991; GARENNE et al., 1991) it has been recommended that high-titre measles vaccines no longer be used (EPI, 1992). It may require two-dose strategies with standard vaccines to improve the control of measles after 9 months of age.

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