Early two-dose measles vaccination schedule in Guinea-Bissau: good protection and coverage in infancy

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Background Previous studies from Africa have suggested that there is little benefit to be gained from early two-dose measles vaccination schedules. Two-dose schedules have been associated with no improvement in coverage due to immunization of the same individuals on both occasions, low return rate, high refusal rate, low vaccine efficacy, and fear of blunting of the antibody response. Because of the poor results achieved previously with two-dose measles vaccination schedules, we studied patterns of participation, reasons for non-participation, vaccination coverage and relative efficacy of a one-dose versus a two-dose schedule in connection with the implementation of an early two-dose trial in Guinea-Bissau.

Methods Children born from September 1994 to January 1996 were randomized into two groups receiving either two doses of measles vaccine at 6 and 9 months or one dose of inactivated polio vaccine (IPV) at 6 months and measles vaccine at 9 months.

Results At 6 months of age 86% (1869/2181) of the children participated, and at 9 months of age participation was 87% (1775/2035). The return rate for obtaining a second dose of vaccine was 93% (1647/1773). The main reason for not participating was travelling (78%). Around 50% of those who did not take part in one vaccination took part in the other. When only children participating the first time they were called for a measles vaccination were included, the measles vaccination coverage in the one-dose group was 59% versus 80% in the two-dose group, i.e. a 50% reduction in the risk of not being vaccinated (relative risk [RR] 0.50; confidence interval [CI] : 0.43–0.57). Few measles cases have occurred in the study area since the implementation of the trial making precise estimation of the relative efficacy of the two vaccine strategies difficult, but all seven clinically diagnosed measles cases occurred in the one-dose group making the relative efficacy for the two-dose group compared with the one-dose group 100% (95% CI : 35%–100%; two-tailed P = 0.016). When including maternal reports, the relative efficacy was 90% (95% exact confidence interval; two-tailed P = 25%–97%, P = 0.022).

Conclusion In this study of a two-dose measles immunization schedule at 6 and 9 months of age there was no sign of low participation or poor return rates. The risk of not being vaccinated was lower in the two-dose group than in the one-dose group, and the relative efficacy of a two-dose versus a one-dose schedule was high. Although our results were obtained within a trial where dedicated personnel informed every participant personally about the study, we believe our results indicate that with thorough information about the population it may be possible...
to achieve a higher coverage with a two-dose measles vaccination schedule than a one-dose schedule. A two-dose schedule may be a feasible way to resolve the problems of low coverage and severe measles infection among infants.

Keywords Measles vaccine, two-dose policy, participation rate, attack rate, measles, ‘catch-up’ vaccination campaigns

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Although a preventable disease, measles is still responsible for a considerable part of childhood morbidity and mortality in developing countries. In settings with high measles-transmission rates, many children below the age of vaccination contract measles, and in this age group the case-fatality rate is especially high.

Measles vaccine was introduced in Africa in campaigns in the mid-1960s, and was initially administered at 6 months of age to prevent early cases. When it became clear that measles was not controlled, a second dose of vaccine at 9 or 12 months of age was added. Early two-dose schedules were implemented in Congo, Ivory Coast and Zaire in the 1970s. If the measles vaccine was given before 9 months of age, a second dose was also given after 12 months of age. If the first vaccine was given after 9 months of age no further doses were added. Thus the measles vaccination policy was dependent on whether the mothers came for the first dose before or after their children were 9 months of age. However, few children vaccinated before 9 months of age came back for a second dose. Thus the return rates were very low, in the range of 3%-33% and as a result of this the two-dose strategies were abandoned.

Administration of a single standard measles vaccine before the age of 9 months is associated with decreased vaccine efficacy because of persisting maternal antibodies neutralizing the vaccine leading to primary vaccine failure. Early vaccination may also lead to a blunted antibody response which is not greatly boosted by additional doses of vaccine.

With the development of the high-titre Edmonston-Zagreb measles vaccine it was hoped that the problem of low vaccine efficacy in young infants would be overcome. The vaccine which was given at 6 months of age was highly immunogenic but unfortunately long-term follow-up showed that the vaccine was associated with reduced survival in female recipients of high-titre vaccines compared with female recipients of the standard-titre Schwarz vaccine.

The combination of low vaccine efficacy, poor compliance, fear of blunting the immune response by early immunization, and the failure of the high-titre Edmonston-Zagreb vaccine has led to the continued recommendation of a one-dose at 9 months strategy for Africa. This still leaves the continent with a high measles attack rate and a high case-fatality rate in infants below the age of vaccination. Two-dose measles vaccination schedules have therefore been reconsidered. In 1993 a WHO study suggested further examination of early two-dose schedules for areas with high transmission rates in young infants, this strategy also being supported by mathematical models. WHO already recommends a two-dose measles vaccine schedule at 6 and 9 months of age for infants in refugee camps, infants admitted to hospital and for infants in disaster situations. However, few data are available to support this strategy and there has been no study of the protective efficacy of a two-dose schedule compared with the usual strategy. We report results from a two-dose standard titre measles vaccine trial currently carried out in Guinea-Bissau where we found good protection among infants, good compliance and increased vaccination coverage.

Methods

Study population

The study was conducted in Bissau, the capital of Guinea-Bissau, in four semi-urban to urban areas, Bandim I, Bandim II, Belem and Mindarà in which there has been an ongoing demographic surveillance of vaccinations, infections, pregnancies, births and deaths since 1978, 1984, 1984, and 1994, respectively. Information is collected every 3 months when a field-worker visits the house. Annually, about 1900 pregnancies, births or new children enter the registration system before the age of 6 months from the four areas.

Study design

The two-dose study was implemented in March 1995 and is planned to include a total of 7700 children. The present study reports from the initial cohort of children born from 1 September 1994 to 31 January 1996. The children were randomized continuously by a computer programme to receive either one dose of IPV at 6 months and one dose of measles vaccine at 9 months, or two doses of measles vaccine at 6 and 9 months. The study was not blinded, as the vaccines administered were noted on the vaccination card. Children born between 1 September 1994 and 15 February 1995 received standard-dose Edmonston-Zagreb (EZ) measles vaccine (Institute of Immunology, Zagreb, Croatia) which was used in Bissau at the time. The remaining children received standard-dose Schwarz (SW) measles vaccine (Rouvax, Pasteur-Merieux, France).

A team of specially trained fieldworkers were allocated to the measles team, and were convocating the infants for the first vaccination at 6 months of age. If the children did not participate they were called again once a week for 8 weeks. At 9 months, the children were again called in the same way for the second vaccination. At each visit, the fieldworker registered whether the child participated, and if the child did not the reason why. The vaccinations took place in the afternoons at the two local health centres in Bandim and Belem. Three Guinean doctors and one nurse were responsible for providing the vaccines. When called for vaccination, the mothers were told that the children would be randomized into two groups, that they would receive either an inactivated polio or a measles vaccine at 6 months, and that everybody would receive a measles vaccine at 9 months. Informed, unwritten consent was obtained. The study was approved by the Ministry of Public
The case definition of measles was made in accordance with WHO recommendations. A generalized maculopapular rash of three or more days duration, and a history of fever of 38°C or more, and at least one of the following: cough, coryza and conjunctivitis. Additionally desquamation was noted, a sign which has been found to be a very reliable indicator of measles infection.

Measles cases reported in the acute phase were visited at home by one of the project physicians. The physician was blind to the immunization group of the child at the time of clinical examination. Cases diagnosed by a project physician or hospitalized with measles have been considered definite cases. Cases reported only by the mother or guardian have been considered less definite. Measles cases occurring before August 1997 were included in the analysis.

Participation rate
When calculating the participation rates, the children who were unable to participate because they had moved, died or were unknown at the address were excluded from the analysis. Children not having received a measles vaccine at 12 months of age were considered unvaccinated.

Statistical analysis
The relative efficacy of the two vaccine strategies was estimated as one minus the rate ratio (RR) of the attack rates in the two-dose and the one-dose group. The exact P-values and 95% confidence intervals (CI) were calculated using the conditional likelihood method as described by Clayton and Hills. Cases occurring within 21 days of vaccination have been considered to have occurred before the vaccine could have had an effect.

Results
Relative efficacy of a one-dose versus a two-dose strategy
Virtually all measles cases were reported in 1995 at the beginning of the trial. Twenty-two children had measles before entry into the study (Table 1). Between 6 and 9 months we compared the efficacy of one dose versus no measles vaccine. Since all definite cases were in the no vaccine group, the relative efficacy was 100% (95% CI: –6% to 100%; two-tailed P = 0.063). If maternally reported cases were included, the relative efficacy for the recipients of measles vaccine was 86% (95% CI: –8% to 97%; two-tailed P = 0.071). After 9 months of age there were only two measles cases making it impossible to compare the one- and two-dose groups. Comparing the protective efficacy of a two-dose versus a one-dose strategy from 6 months of age and onwards, the relative efficacy in the present study was 100% (95% CI: 35%–100%; two-tailed P = 0.016) for the definite cases and 90% (95% CI: 25%–97%; two-tailed P = 0.022) if maternal reports were included. All cases in the present study occurred in the first part of the study where measles immunized children had received standard EZ vaccine.

Participation at 6 months of age
Of 2181 children eligible for participation at 6 months of age, 1869 (86%) participated and 312 (14%) did not. The most common explanations for non-participation were travelling (244/312, 78%), absence from the home during daytime (35/312, 11%) and moving within the study area (19/312, 6%). Seven (2%) refused to participate, and only two mothers and one grandmother specifically expressed that they did not want the child vaccinated against measles before 9 months of age (Table 2). Of the children who participated, 73% did so the first time they were called.

At 9 months, 239 of the non-participants at 6 months were still living in the study area and 121 participated (51%); 26 (11%) had been vaccinated elsewhere. The remaining 92 children were not registered as having been vaccinated, mostly because they were travelling. Mothers often travel, with their breastfeeding children, for the cashew harvest, funeral parties or trading activities.

Participation at 9 months of age
At 9 months of age, 2035 children were eligible for vaccination, of whom 1775 (87%) participated and received measles vaccine before one year of age. Of the remaining 260 children, 11% (29/260) did not participate because they had already had a

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Diagnosis</th>
<th>Mother</th>
<th>PYR</th>
<th>Group</th>
<th>Diagnosis</th>
<th>Mother</th>
<th>PYR</th>
<th>Total period</th>
</tr>
</thead>
<tbody>
<tr>
<td>No vaccine</td>
<td>Definite</td>
<td>5</td>
<td>2</td>
<td>One dose</td>
<td>Definite</td>
<td>2</td>
<td>0</td>
<td>Total measles cases</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td>2</td>
<td></td>
<td>299</td>
<td>Mother</td>
<td>0</td>
<td>1</td>
<td>Total PYR</td>
</tr>
<tr>
<td>One dose</td>
<td>PYR</td>
<td>1</td>
<td></td>
<td>308</td>
<td>PYR</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Two doses</td>
<td></td>
<td>0</td>
<td></td>
<td>1057</td>
<td></td>
<td>0</td>
<td>1</td>
<td>1365</td>
</tr>
</tbody>
</table>

NB: PYR = person years at risk.
22 children had measles before entry into study.
Definite diagnosis is used for measles cases seen by a physician in the acute phase of infection.
measles vaccine. Otherwise the pattern for non-participation at 6 months was repeated (Table 2).

Of the children vaccinated at 9 months, 68% participated the first time they were called. Of 260 non-participants, 139 (53%) had participated at 6 months.

Of the 1962 children who had not moved or died before the age of 12 months, 110 (6%) did not participate either at 6 or 9 months of age (Table 3). Among these 1962 children still living in the study area at 12 months of age, the coverage for measles vaccine was 87.5% (842/962) for the children randomized to one measles vaccine and 93.3% (933/1000) for those randomized to two doses, i.e. a 46% reduction in the risk of not being vaccinated (RR = 0.54; CI: 0.40–0.71).

Return rate

Of the 1869 vaccinated with either inactivated polio or measles vaccine at 6 months of age, 1782 were eligible for vaccination at 9 months of age as they had not moved or died. Of these, 1647 got a measles vaccination between 9 and 11 months of age, and 135 did not get vaccinated. Excluding the 9 children who moved or died before one year of age, the return rate was 93% (1647/1773).

Impact on vaccination coverage of one- and two-dose schedules

The vaccination coverage for attending the first time the child was called for measles vaccination was 79.9% (799/1000) for children randomized to two doses of measles vaccine against 59.5% (572/962) in the group randomized to only one measles vaccine, i.e. a 50% reduction in the risk of not being vaccinated (RR = 0.50; CI: 0.43–0.57).

Discussion

Attempts to implement two-dose measles vaccination schedules in Africa have failed because few returned for the second dose of vaccine. The reason for this is not clear as it is uncertain how much effort was put into informing the population. It has been argued that two-dose schedules were confusing for the mothers,\(^4\) that people were reluctant to accept two doses of measles vaccine, and that adding a second dose did not increase coverage because the same individuals missed both occasions. From our experience, these explanations may not be correct.

We implemented an early two-dose measles vaccination trial by administration of two doses of measles vaccine at 6 and 9 months of age in Bissau, Guinea-Bissau. Given the small number of measles cases which occurred during the trial, it is not possible to give a precise estimate of the relative efficacy of the two schedules though it seems clear that a two-dose schedule at 6 and 9 months of age is better than a one-dose at 9 months schedule in terms of preventing measles among infants. The special attention devoted to and the intensive follow-up of the cohort created an artificially high coverage as there was a marked rise in measles vaccine coverage from 68% in the two-year cohort born before the implementation of the study to 89% in the cohort born between September 1994 and January 1996. The participation rates within the study at both 6 and 9 months were around 86%, and the return rate at 9 months was 93%. These figures probably represent a maximum estimate of what can be accomplished by implementing a second dose of measles vaccine in the Expanded

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### Table 2

<table>
<thead>
<tr>
<th>Participation at 6 months</th>
<th>Interval between 6 and 9 months</th>
<th>Participation at 9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Eligible</td>
<td>2181 (100.0)</td>
<td>2076</td>
</tr>
<tr>
<td>Died</td>
<td>22</td>
<td>18(^b)</td>
</tr>
<tr>
<td>Moved</td>
<td>46</td>
<td>23(^b)</td>
</tr>
<tr>
<td>Excluded(^a)</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Participated</td>
<td>1869 (85.7)</td>
<td>1775 (87.2)</td>
</tr>
<tr>
<td>Travelling</td>
<td>244 (11.2)</td>
<td>194 (9.5)</td>
</tr>
<tr>
<td>Absent from home during daytime</td>
<td>35 (1.6)</td>
<td>17 (0.8)</td>
</tr>
<tr>
<td>Moved inside study area</td>
<td>19 (0.9)</td>
<td>8 (0.4)</td>
</tr>
<tr>
<td>Refused to participate</td>
<td>7 (0.3)</td>
<td>7 (0.3)</td>
</tr>
<tr>
<td>Measles vaccinated elsewhere</td>
<td>3 (0.1)</td>
<td>29 (1.4)</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>3 (0.1)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>1 (0.05)</td>
<td>3 (0.2)</td>
</tr>
</tbody>
</table>

\(^a\) Excluded = Unknown, not called, refused, already vaccinated.

\(^b\) Between 9 and 12 months of age.

### Table 3

<table>
<thead>
<tr>
<th>6 months of age</th>
<th>9 months of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Travelling</td>
<td>89 (81)</td>
</tr>
<tr>
<td>Absence from home during daytime</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Refused to participate</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Measles vaccinated elsewhere</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hospitalized or ill</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Moved inside study area</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Total</td>
<td>110 (100)</td>
</tr>
</tbody>
</table>
Programme on Immunization (EPI). However, the impact of a one-dose versus a two-dose measles vaccination programme on the vaccination coverage was clear. If only the children who participated the first time they were called for a measles vaccination were included in the calculation of coverage, there was a 20% higher measles immunization coverage in the two-dose than in the one-dose group, or a 50% reduction in the risk of not being vaccinated by belonging to the two-dose group.

It is also clear that the same children do not necessarily participate on both occasions, and that about half of the children not participating the first time will participate on the other occasion. Travelling was the most common reason for not participating; very few refused to participate, and no general resistance against a two-dose schedule was encountered. In the present study mothers were individually informed, a situation which cannot be extrapolated to a routine situation. If people are carefully informed about a two-dose schedule through public information and contact with health services we believe that participation rates may be high both at 6 and 9 months of age, just as it has been possible to obtain high immunization coverage for all three polio and diphtheria-pertussis-tetanus vaccinations in many African countries. An early two-dose schedule could be a feasible way of increasing vaccination coverage and preventing early measles cases in Africa.

In order not to increase cost by adding a new vaccination contact in the implementation of a two-dose policy, rescheduling the third diphtheria-pertussis-tetanus and polio vaccines to 6 months of age should be considered. Such a rescheduling would contribute to maintaining immunization contacts throughout the first 9 months of life thereby possibly improving the coverage for measles vaccine. The implications of a similar change in vaccination schedule would have to be assessed. While delaying the third dose of the diphtheria-pertussis-tetanus vaccine could increase the risk of early pertussis infection, it could also improve the immune response thus contributing to improved herd immunity and protection of the infants under 6 months of age. Further studies would be needed to establish the optimal way of reorganizing the vaccination programme, and to assure that this would not lead to an increase in the risk of whooping cough infection which seems unlikely though, if the programme was associated with an improved coverage.

Further studies are needed to examine the antibody levels after two-dose measles vaccination to assure that there is no blunting of responses and to investigate the long-term maintenance of immunity against infection and clinical disease after early one- and two-dose schedules.

The goals set by WHO for measles control in the next decade of 90% coverage and 95% reduction in mortality might be attainable by incorporating a two-dose measles vaccine schedule into the EPI. This has to be seen in relation to the success of ‘catch-up’ vaccination campaigns in Latin America where all children aged 1–14 years of age receive a measles vaccination regardless of previous vaccination status or measles disease history. This strategy has yet to be evaluated in Africa but at least two things may decrease the success of similar vaccination campaigns in Africa. If the administration of the first vaccine is postponed to one year of age this would dramatically increase the measles incidence in children below the age of vaccination. Secondly, there would be major costs related to transport, equipment, salaries and vaccines associated with organizing national immunization days. Many African countries would not have the necessary additional resources. Our results from the study in Guinea-Bissau indicate that a routine two-dose policy is superior to a one-dose policy in terms of clinical protection against measles; and if these results can be confirmed in the longer term then we believe that for the African region the best way of fulfilling the goals for measles control set by the WHO may be an early two-dose strategy.

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