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The effect of early measles vaccination on morbidity and growth: A randomised trial from Guinea-Bissau

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Abstract

Background: Measles vaccine (MV) has beneficial non-specific effects protecting against non-measles infections in some situations. Within a trial of the effect of MV on mortality, we assessed effects of early MV on the secondary outcomes consultations and growth, overall, and by sex and exposure to campaigns with oral polio vaccine (OPV).

Materials and methods: Children were randomly assigned to MV at 4.5+9 months or MV at 9 months as recommended. At enrolment and 9 months children had their mid-upper-arm-circumference (MUAC) and weight measured. Consultations (out/inpatient) were registered at monthly home visits. Weight-for-age and MUAC-for-age Z-scores were obtained using the WHO growth reference and compared by group in linear regression models. Consultation rates between enrolment and 9 months were compared in Cox proportional hazards models, providing consultation Hazard Ratios (HRs) for early MV versus no early MV. We tested whether the effect of early MV was modified by OPV campaigns by splitting observation time at exposure to OPV campaigns.

Results: Among 3548 children enrolled between 2012 and 2015, early MV had no effect on MUAC-for-age (mean difference comparing early MV vs. no MV -0.01, 95% CI -0.06-0.04), weight-for-age (mean difference -0.03, 95% CI -0.07-0.02) or rates of consultations (HR=1.03, 95% CI 0.92-1.16). The rate of consultations for children enrolled was lower after exposure to OPV campaigns (HR=0.81, 95% CI 0.71-0.92). The effect of MV differed before exposure to OPV campaigns (HR=1.12, 95% CI 0.98-1.29) and after OPV campaigns (HR=0.83, 95% CI 0.67-1.03) (test for interaction: p=0.03). Associations did not differ by sex.

Conclusion: Early MV had no overall effect on consultation rates and growth between enrolment and 9 months of age. However, early MV tended to have beneficial effects for children
subsequently exposed to OPV campaigns. As beneficial effects were observed in subgroups, the results should be interpreted with caution.

Clinical trials registration: NCT01644721.

KEYWORDS:
Measles vaccine; Morbidity; Growth; Non-specific (heterologous) effects of vaccines; Childhood vaccination
Introduction

In low-income countries, where the risk of infection with measles among children remains high, WHO recommends measles vaccine (MV) at 9 months of age and a second dose later in life(1). Under special circumstances, such as infants known to be HIV-infected or exposed, an extra dose is recommended at 6 months(1). This policy is based on the assumption that the only effect of measles vaccination is to protect against measles infection. However, a measles vaccination policy based merely on the ability of MV to protect against measles may be insufficient: There is increasing evidence that in addition to disease-specific effects, routine vaccines have non-specific effects (NSEs)(2), which alter the susceptibility to non-targeted infectious diseases(3). The live MV may have beneficial NSEs, being associated with improved overall survival, which cannot be explained merely by prevention of measles(3).

The core of the vaccination programme in low-income countries is based on administration of BCG with oral polio vaccine (OPV) at birth, 3 doses of a diphtheria-tetanus-pertussis(DTP)-containing vaccine, OPV at 6, 10 and 14 weeks and MV at 9 months(4).

In 2003-2009, a randomised trial in Guinea-Bissau showed that children who received an additional MV at 4.5 months of age had 30% (95% CI 6-48%) lower all-cause mortality between 4.5 and 36 months of age compared with children who received only the recommended MV at 9 months(5). The observed effect could not be explained merely by prevention of measles infections, which was very rare during the study period(5). Early administration of MV also reduced the risk of hospital admissions(6, 7). The beneficial effect of MV was strongest for hospital admissions related to respiratory infections (reduction of 63%, 95% CI 11-84%)(6).

To further explore the NSEs of MV, we conducted an early-MV trial in rural Guinea-Bissau between 2012 and 2015, investigating whether an early 2-dose MV strategy; providing MV at 4-6 months in
addition to at 9 months of age would reduce mortality compared with the recommended MV at 9 months (8). Mortality rates were lower than expected and 37% lower than in the previous trial (5).

There was no effect of early MV on mortality (HR=1.05, 95% CI 0.75-1.46). In low-income countries with declining child mortality it becomes increasingly important to assess NSEs of vaccines on child health using other indicators to complement mortality assessment. Early MV might affect outcomes that are less severe and more frequent than death. In the present study, we analysed the effect on the secondary outcomes growth and morbidity in the time window before the control group was measles vaccinated, thus comparing children receiving early MV with children not yet vaccinated.

**Methods**

**Setting and study population**

The trial was conducted in villages followed through the Health and Demographic Surveillance System (HDSS) of the Bandim Health Project (BHP) in rural Guinea-Bissau. The HDSS follows women and children below the age of 5 years through home visits in 182 randomly selected village clusters throughout the country. Women are registered at 13-15 years of age or when they migrate into the area. The trial was conducted in Biombo, Oio and Cacheu health regions. Study villages were visited monthly by a team of BHP field assistants to register new pregnancies and to follow up on registered pregnancies and children below 12 months of age. Children being 12 months or older were visited every four months until the age of 5 years. When a pregnancy or a new child was registered, socioeconomic status was assessed. At all visits, we collected information about pregnancies, births, migrations, hospital admissions, consultations and deaths. Furthermore, information on participation in campaigns implemented by the government health staff was collected. Vaccination status was assessed by inspection of vaccination cards. To ensure that children had completed three doses of pentavalent vaccine (Penta: DTP, Haemophilus Influenzae
type B, Hepatitis B) before enrolment, the mobile teams were accompanied by a nurse, who offered missing routine vaccines according to the national vaccination programme for all children.

**Trial procedures**

The objective of the main trial (8) was to examine the effect of an additional dose of MV on child mortality, and detailed information on study procedures are provided elsewhere (8).

**Enrolment, Informed consent and Randomisation**

Briefly, healthy measles-unvaccinated children aged 4-6 months living in the study villages and who had received the 3rd dose of Penta at least 4 weeks earlier were eligible for the study (Supplementary Figure 1). Potentially eligible children and their mothers were invited to the health post, where the nurse confirmed eligibility by inspecting the child’s vaccination card and invited the child to take part in the trial. The nurse explained that the national MV policy is to vaccinate at 9 months, but children may contract measles infection before 9 months, and we aimed to test whether early MV may be beneficial for the child. The same information was provided in writing.

Following informed consent, the child was examined by the nurse, weighed on an electronic scale (Seca 385) and had mid upper-arm circumference (MUAC) measured using an insertion tape (TALC). Ill children were treated or referred for treatment. Ill children and children with a MUAC<110 mm were not enrolled but could potentially be enrolled at a later visit. Provided fulfilment of the enrolment criteria and informed consent, the children were randomised (1:1) to receive early MV or no early MV in blocks stratified by sex. If randomised to early MV, the child received a standard titre Edmonston-Zagreb vaccine (Serum Institute of India; 0.5 ml, administered subcutaneously). No placebo was given.

**Follow-up: Information on consultations and growth**

At household visits after enrolment mothers were interviewed about the child’s health and
whether the child had been taken for out- or in-patient consultations at health centres or hospitals since the last visit. If a consultation or hospital admission was registered, information on time and place was obtained.

At health facilities, children are registered by name, sex, date of birth, name of mother, residence and diagnosis. A specially trained BHP assistant assessed paper records at the health facilities to obtain further information including diagnosis and treatment.

At the first visit by BHP following the child’s 9-month birthday, the child was weighed, the MUAC measured and all children received the 9-months MV, a standard titre Edmonston-Zagreb vaccine.

Mothers often travel to visit relatives or take part in the harvest of cashew nuts. Therefore, some children would not be home when the field team came to visit. We kept visiting the children during the monthly village visits to offer the routine MV until one year after end of the trial but censored follow-up time at the end of the trial.

**Potential interactions**

Previous studies have demonstrated that the NSEs are stronger for girls than boys (5, 6, 9) and may be stronger in the dry than in the rainy season (6). We therefore assessed whether the effect of early MV varied by sex and season at enrolment.

As part of the efforts to eradicate polio, OPV is given in the routine vaccination programme and as part of national campaigns providing OPV to all children below the age of five years regardless of vaccination status. The age of first dose of OPV (OPV-0) and OPV campaigns may have modified the effect of early MV in the previous trial (10). We therefore analysed whether national campaigns with OPV and age of OPV-0 modified the association between early administration of MV and consultations and growth. For the OPV-0 age, we relied on the information from the vaccination
For campaign OPV, we considered all children eligible for campaigns as exposed from the date of the campaign.

**Statistical analyses**

**Baseline characteristics**

We assessed whether the measured baseline characteristics were comparable in the early MV and no early MV group using Chi-square test for categorical variables and Wilcoxon ranksum test for continuous variables.

**Outcomes**

Our analyses assessed the effect of early MV on morbidity measured by consultations at health facilities regardless of whether the contact led the child to be admitted or not. Furthermore, we evaluated the effect of early MV on growth measured by weight-for-age and MUAC-for-age at 9 months of age.

We compared the rates of consultations in a Cox proportional hazards model with time since enrolment as underlying timescale, overall and by sex. Children entered the analyses at enrolment and were followed to death, migration, registered receipt of 9-month MV, eligibility for MV campaign, end of study or 18 months of age, whichever came first. The proportional hazards assumption was graphically assessed and was tested using Schoenfeld residuals.

A child could have more than one consultation. Children did not contribute with observation time at the day of consultation or during hospital admissions; in the latter case observation time resumed at discharge. Following a consultation, the risk of another event was assumed to be the same as for the first event. We assessed the effect of early MV on two related morbidity outcomes: reported and identified consultations (further details below).
Reported consultations

In the analyses of reported consultations, we included all events reported by the guardian of the child. Children only contributed with observation time if information on consultations was obtained; observation time was interval censored if the child was absent or travelling and no one could provide information, but resumed when relevant information was obtained. In sensitivity analyses, we censored the first 14 days after enrolment to eliminate potential adverse events related to measles vaccination, and we analysed reported consultations with age rather than time since enrolment as underlying timescale.

Identified and cause specific consultations

In secondary analyses we assessed the effect of MV on identified consultations, which were defined as consultations identified in the paper records at the health centres. We counted all identified consultations regardless of whether they were stated by the mother or guardian and assessed the effect overall and for specific causes. Diagnoses registered by the health centre staff were classified as respiratory infections, gastro-intestinal infections, malaria, skin infections, other and missing. Children contributed with time at risk from enrolment to the end of follow up; observation time was censored during hospital admissions.

Growth

We derived the Z-scores for weight-for-age and MUAC-for-age using the 2006 WHO growth reference(11). We compared Z-scores of children, who were randomised to early MV with Z-scores of children randomised to no early MV in linear regression models adjusted for baseline Z-scores. The trial size was determined by the main outcome. For the secondary outcomes, we had 80% power to demonstrate a difference in consultation rates if the real difference was 14% or larger (we anticipated that 10% would seek consultation during a month; cumulative incidence 43% during a
median 124 days of follow up). For MUAC and weight-for-age we had 80% power to show
differences in z-scores of 0.12 (assuming measurements obtained for 90% and standard deviations
of 1.2). All statistical analyses were conducted using Stata 12.

Ethical considerations

The trial was approved by the Ethical Committee in Guinea-Bissau and the Danish Central Ethics
Committee gave its consultative approval. A data safety and monitoring board received trial data
every 3 months to assess whether there were danger signals.

Results

Participants

Between 13th of July 2012 and 4th of December 2015 we assessed 6170 children for eligibility and
enrolled 3750 children of whom 3548 were eligible for the present analyses (Figure 1).

There were no major differences in demographics, socioeconomics or other measured health-
related background factors and no difference in age at enrolment between children randomised to
the early MV group and to the no early MV group (Table 1). Furthermore, the number of deaths
during follow up did not differ by group (Figure 1).

Outcomes

Reported consultations

Between enrolment and 9 months of age, 1262 consultations including 51 hospital admissions (23:
early MV; 28: no early MV) were reported, corresponding to a consultation rate of 1.19
consultations per person year. Early MV did not affect the rate of reported consultations (HR=1.03,
95% CI 0.91-1.15) (Table 2, Figure 2). The effect of early MV did not differ by sex, the HR being 1.03
(95% CI 0.88-1.21) for boys and 1.02 (95% CI 0.86-1.21) for girls (Table 2).
The sensitivity analyses gave similar results: Early MV did not affect consultation rates when age was the underlying timescale (HR=1.03, 95% CI 0.91-1.15) or when the first 14 days were censored (HR=1.01, 95% CI 0.89-1.14) (data not shown).

The effect of early MV on reported consultations did not differ significantly when stratified by season at enrolment; HR=1.11 (95% CI 0.94-1.32) in the dry season and HR=0.96 (95% CI 0.82-1.12) in the rainy season (p=0.20 for test of interaction between season and early MV).

**Identified consultations**

Of the 1262 reported consultations, 863 including 49 hospital admissions (19: early MV; 30: no early MV) were identified in the paper records. The proportion of reported consultations identified did not differ between the groups (441 (69%): early MV; 422 (68%): no early MV). 135 additional consultations were identified though they were not reported resulting in a total of 998 identified consultations (Supplementary Figure 2). Early MV did not affect the rate of identified consultations (HR=1.04, 95% CI 0.90-1.19) (Table 2). Upon review of the diagnoses, we found no cases of measles infection, and the effect of early MV did not vary by disease group (Table 3).

While there was no indications of an effect of early MV on consultations, there tended to be an effect on more severe illness leading to admissions: HR=0.83 (95% CI 0.47-1.46) for reported and HR=0.64 (95% CI 0.35-1.16) for identified admissions (Supplementary Table 1).

**Growth**

Anthropometrics at 9 months of age were assessed for 2998 children prior to reception of 9 month MV (85% of total sample). Between enrolment and 9 months MV, MUAC-for-age Z-score decreased from 0.04 to -0.22 and weight-for-age Z-score decreased from -0.59 to -0.91. Early MV had no effect on either of the growth measures, the difference being -0.01 (95% CI -0.06-0.04) for MUAC-for-age and -0.03 (95% CI -0.07-0.02) for weight-for-age Z-score at 9 months of age (Figure 3, Table 2).
Supplementary Table 2). The percentage of underweight children did not differ between the groups, and for none of the outcomes did the effect vary by sex (Supplementary Table 2).

**Interactions with OPV**

Prior to enrolment and during the follow-up period the study population was exposed to numerous national OPV campaigns (Supplementary Figure 3). Over 80% of children eligible for an OPV campaign had their campaign participation confirmed, and participation in OPV campaigns did not differ by vaccine group (data not shown).

**OPV-0 and OPV campaigns before enrolment**

The effect of early MV on reported consultations did not vary between children exposed to OPV campaigns prior to enrolment and children not exposed to OPV campaign prior to enrolment (Supplementary Table 3). Furthermore, we found no indication that a benefit of early MV was strongest for children receiving OPV-0 early (Supplementary Table 4).

**OPV campaign after enrolment**

After enrolment, the rate of reported consultations was lower after exposure to OPV campaigns compared with the period prior to OPV campaign exposure (HR=0.81, 95% CI 0.70-0.92). Adjusting for season made the difference stronger (HR=0.75, 95% CI 0.65-0.86).

Having been exposed to OPV campaigns before enrolment may have boosted the effect: the HRs being 0.89 (95% CI 0.75-1.05) for children exposed to campaigns for the first time, and 0.65 (95% CI 0.51-0.81) for children also eligible for OPV campaigns prior to enrolment (p=0.02). However, season may have explained part of the difference: HR=0.79 (95% CI 0.66-0.93) and HR=0.64 (95% CI 0.51-0.83) when adjusting for season (p=0.14).
The effect of MV on reported consultations differed before and after exposure to OPV campaigns after enrolment (p=0.03): Before exposure to OPV campaigns children in the early MV group tended to have had more reported consultations compared with measles-unvaccinated children (HR=1.12, 95% CI 0.97-1.28). In contrast, after the exposure to OPV campaigns, early MV tended to protect against consultations (HR= 0.84, 95% CI 0.68-1.04) (Supplementary Table 5). The effect was similar regardless of whether children were OPV-campaign exposed before enrolment or not (Table 4). The same trend was observed for boys and girls, but may have been stronger for girls than for boys. (Supplementary Table 5). Adjusting for season at enrolment or observation did not influence how exposure to OPV campaigns modified the effect of early MV on rates of reported consultations.

Early MV also tended to protect against identified consultations (Supplementary Table 6) and reported hospital admissions (Supplementary Table 7) after exposure to OPV campaigns after enrolment.

**Discussion**

**Main observations**

In the present trial we found no effect of early MV on morbidity and growth. The findings did not support our hypotheses that exposure to early MV would result in higher weight-for-age and MUAC-for-age and lower number of reported consultations. The results were in accordance with the main study findings on child mortality(8). Stratifying by disease group did not modify the results. Neither sex nor season of enrolment affected the association between early MV and rate of reported consultations.

**Strengths and limitations**

The major strengths include the randomised study design and the large number of participants.
Information about consultations was obtained by experienced field workers, and nurses were well trained in performing anthropometric measurements according to best practice. Both field workers and nurses were closely supervised during enrolment and follow-up.

The guardians of participants in the trial were not blinded with regard to allocation group as no placebo vaccine was used. This could potentially influence the results if the mothers’ knowledge about their children’s vaccination status affected their behaviour. Knowledge about vaccine group might not only affect the mothers’ behaviour but might also influence how well they remember whether their child has been taken for consultation. Thus, the lack of blinding could potentially result in recall bias. To reduce the risk of recall bias we obtained information about consultations through monthly visits. Others have found that even with recall periods of 2 weeks, recall rates are lower after the first week (12) and our captured rates therefore presumably underestimate the real rates. However, the proportion of reported consultations identified did not differ between the early MV group and no early MV group, therefore a differential recall bias by group seems unlikely. We also found similar results in self-reported and facility-identified data, which supports the validity of the self-reported data.

**Consistency and contradictions with other studies**

A previous study investigating the effect of early MV on anthropometrics found that early MV was associated with larger MUAC at 24 months of age after both groups had (also) received the 9 months MV, especially for girls (13). The effect was not detectable at 9 months of age. The results from the present study are consistent with results from the previous trial at 9 months of age. Based on the present data we cannot rule out that there may have been better growth in the early MV group after 9 months. However, since we observed no benefit of early MV for other health outcomes, it may also be likely that the effect is not the same in the present trial.
We have previously found that early MV reduced the risk of hospital admissions (6) and the same tendency was observed for health facility contacts resulting in hospital admissions in the present study, but not for milder illness leading to outpatient consultations. In contrast to prior studies, we did not find any indication that an effect of MV was stronger for respiratory infections (6). Nor did we detect an impact on fever and gastro-intestinal symptoms as have recently been observed (14).

The present cohort was followed in parallel with a cohort of children in Burkina Faso. We saw no effect on mortality in either of the sites (8) and nor was there an overall effect on severe morbidity leading to admission in the Burkinabe trial (15). As in Guinea-Bissau, OPV-campaigns were frequent in Burkina Faso during the trial, and campaign OPV tended to have beneficial effects: In Burkina Faso the risk of admission/death was 36% (95% CI 6-56%) lower after a campaign when follow-up was continued beyond the 9 months vaccination (15). In Guinea-Bissau we observed a 19% (95% CI 8-29%) lower rate of seeking health care after OPV campaigns when following children up to 9 months. However, while the effect of early MV in Burkina Faso tended to reduce the risk of admissions and mortality until an OPV campaign (HR=0.83, 95% CI 0.55–1.29) (12), we observed a tendency towards a benefit of MV after a campaign and not before. We have not assessed the effect of early MV on health system contacts after the routine 9 months MV and cannot conclude on the extent to which that explains the contrast.

**Interpretation**

Our sensitivity analysis did not indicate that a potential protective effect of MV was masked by adverse events, since censoring the first 14 days of observation time after enrolment did not alter the conclusions.

Hence, the present data does not support that early MV had an effect on the child morbidity. This lack of an effect could have several different explanations. Our results, considered in isolation,
could indicate that MV had no NSE; but, in the light of the entire evidence on the area, it seems more likely that the explanation should be sought in changes in context in the present trial.

As we have discussed elsewhere(8), several factors differ between the present trial and prior studies:

First, OPV campaigns were more frequent in the present trial, and we speculate that the frequent OPV campaigns may have affected the comparison for mortality. However, the interaction between OPV campaigns and early MV in the present study do not support that OPV after enrolment has neutralised an effect of early MV on child morbidity. The mechanisms whereby OPV and MV exert potential NSEs and how such mechanisms may interact, are still not well understood(16).

Second, since the previous trial(5) was conducted, the routine vaccination programme has changed. It could be speculated that the use of Penta rather than DTP could have an impact, by reducing infections with pathogens that could otherwise have been prevented by the NSE of an additional early MV. Our data to assess the effect of pneumococcal vaccines (PCV) is limited since PCV was only available during the last 6 months of enrolments.

Third, a better underlying health status may imply that the causes of infections were less frequent in the present cohort. The main trial(8) had mortality lower than expected indicating that the children are healthier now than earlier or that a selected group, which may have less to gain from a beneficial NSE, enter the trial. In the present trial the weight-for-age and MUAC-for-age Z-scores did not differ significantly from the WHO growth reference supporting that indication. It can be speculated that the beneficial effect of MV was not detectable because the children have better health since the previous trials.
Finally, it could also be speculated that the outcomes presented here were not suitable for detecting a possible effect of early MV. If the manifestation of symptoms is affected by early MV and/or OPV campaigns, frequencies of health care seeking behaviour may not function as a valid proxy for changes in health status.

**Conclusion**

The results of the present study suggest that early MV had no overall effect on consultations and growth between enrolment and 9 months of age. However, MV tended to be associated with beneficial effects when children received a subsequent dose of campaign OPV. As beneficial effects were observed in subgroups, the results should be interpreted with caution. More research is warranted to understand NSEs, interactions between childhood vaccines and appropriate outcomes for assessing NSEs.

**Acknowledgements**

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We are indebted to the Data Safety and Ethics Monitoring Board, which included Professor Kim Mulholland, Dr Rana Hajjeh, and Dr Jukka Jokinen who oversaw the trial and provided advice on implementation. We thank field teams and the personnel who implemented and supervised data collection, entry, and cleaning (Amabelia Rodrigues, Marie Pedersen, Stine Byberg, Line Storgaard, Bibi Uhre Nielsen, Katarina Funch and Jesper Sloth Hansen) and all the study participants and their families.
Conflicts of interest

None
References

Figure Captions:

Figure 1. Flowchart of participants’ recruitment in the study

Figure 2. Nelson-Aalen cumulative incidence of reported consultations according to vaccination group

Figure 3. Difference in MUAC-for-age and weight-for-age Z-scores between early two-dose MV group and control group at 9 months of age adjusted for baseline Z-scores, overall and by sex

Supplementary Figure Captions:

Supplementary Figure 1. Study design of the early MV trial

Supplementary Figure 2. Data sources in the early MV trial

Supplementary Figure 3. National campaigns during the early MV trial
Table 1. Background factors for early MV group and control group

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<td></td>
<td></td>
<td>0.23³</td>
</tr>
<tr>
<td>None</td>
<td>775 (47)</td>
<td>785 (48)</td>
<td></td>
</tr>
<tr>
<td>Primary (1-4 years)</td>
<td>441 (27)</td>
<td>474 (29)</td>
<td></td>
</tr>
<tr>
<td>Secondary (5+ years)</td>
<td>423 (26)</td>
<td>386 (23)</td>
<td></td>
</tr>
<tr>
<td>Maternal age, years</td>
<td>25 (21, 30)</td>
<td>26 (21, 31)</td>
<td>0.01⁴</td>
</tr>
<tr>
<td>Maternal MUAC, mm</td>
<td>266 (250, 286)</td>
<td>266 (250, 286)</td>
<td>0.64⁴</td>
</tr>
<tr>
<td>Mosquito net</td>
<td>1594 (96)</td>
<td>1597 (97)</td>
<td>0.12³</td>
</tr>
<tr>
<td>All year</td>
<td>1468 (99)</td>
<td>1475 (100)</td>
<td>0.43³</td>
</tr>
<tr>
<td>Pigs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the compound</td>
<td>1184 (81)</td>
<td>1165 (80)</td>
<td>0.69³</td>
</tr>
<tr>
<td>In the house</td>
<td>1040 (71)</td>
<td>1028 (71)</td>
<td>0.86³</td>
</tr>
<tr>
<td>Crowding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. sleeping in the same room</td>
<td>4 (3, 5)</td>
<td>4 (3, 5)</td>
<td>0.13⁴</td>
</tr>
<tr>
<td>No. sleeping in the same bed</td>
<td>3 (2, 3)</td>
<td>3 (2, 3)</td>
<td>0.75⁴</td>
</tr>
<tr>
<td>Symptoms at enrolment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>180 (10)</td>
<td>210 (12)</td>
<td>0.13³</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>148 (8)</td>
<td>144 (8)</td>
<td>0.78³</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36 (2)</td>
<td>41 (2)</td>
<td>0.58³</td>
</tr>
<tr>
<td>Coughing</td>
<td>317 (18)</td>
<td>346 (20)</td>
<td>0.23³</td>
</tr>
<tr>
<td>Oedema</td>
<td>1 (0)</td>
<td>3 (0)</td>
<td>0.32³</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of roof</td>
<td></td>
<td></td>
<td>0.07³</td>
</tr>
<tr>
<td>Straw</td>
<td>637 (36)</td>
<td>590 (34)</td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>1107 (63)</td>
<td>1146 (65)</td>
<td></td>
</tr>
<tr>
<td>Roof tile</td>
<td>13 (1)</td>
<td>23 (1)</td>
<td></td>
</tr>
<tr>
<td>Toilet facilities</td>
<td></td>
<td></td>
<td>0.36³</td>
</tr>
<tr>
<td>None</td>
<td>611 (35)</td>
<td>581 (33)</td>
<td></td>
</tr>
<tr>
<td>Latrine</td>
<td>1140 (65)</td>
<td>1166 (67)</td>
<td></td>
</tr>
<tr>
<td>Inside the house</td>
<td>3 (0)</td>
<td>6 (0)</td>
<td></td>
</tr>
<tr>
<td>Electricity /generator</td>
<td>265 (15)</td>
<td>283 (16)</td>
<td>0.41³</td>
</tr>
<tr>
<td>Radio</td>
<td>1379 (79)</td>
<td>1382 (80)</td>
<td>0.72³</td>
</tr>
<tr>
<td>Cell phone</td>
<td>905 (53)</td>
<td>896 (52)</td>
<td>0.58³</td>
</tr>
<tr>
<td>Eligible to OPV campaign before enrolment</td>
<td>952 (54)</td>
<td>918 (52)</td>
<td>0.20³</td>
</tr>
<tr>
<td>Recorded to have received PCV before enrolment</td>
<td>173 (10)</td>
<td>187 (11)</td>
<td>0.46³</td>
</tr>
</tbody>
</table>

¹median (25% percentile, 75% percentile)
²mean (sd)
³Chi-square test (categorical variables)
⁴Wilcoxon ranksum test (continuous variables)
PCV: pneumococcal vaccine introduced in June 2015.
Table 2. Rates of reported and identified consultations (including hospital admissions) between enrolment and 9 months of age, and consultation hazard ratios for early MV group, compared with controls, overall and by sex.

<table>
<thead>
<tr>
<th></th>
<th>Early MV</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consultation rate (Consultations/Person-years)</td>
<td>n</td>
<td>Consultation rate (Consultations/Person-years)</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>1.21 (641/530)</td>
<td>1516(^1)</td>
<td>1.17 (621/531)</td>
</tr>
<tr>
<td></td>
<td>Boys</td>
<td>1.29 (338/262)</td>
<td>762</td>
<td>1.23 (332/270)</td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>1.13 (303/268)</td>
<td>754</td>
<td>1.11 (289/260)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>0.80 (507/630)</td>
<td>1770</td>
<td>0.76 (491/642)</td>
</tr>
<tr>
<td></td>
<td>Boys</td>
<td>0.86 (269/313)</td>
<td>895</td>
<td>0.85 (276/324)</td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>0.75 (238/317)</td>
<td>875</td>
<td>0.68 (215/318)</td>
</tr>
</tbody>
</table>

Reported consultations: P-value for interaction between vaccine group and sex = 0.92
Identified consultations: P-value for interaction between vaccine group and sex = 0.36
n, number of children included in analysis; HR, hazard ratios; CI, confidence interval.
\(^1\)Numbers deviates from figure 1 as 537 children (early MV: 254, control: 283) did not have information about reported consultations.
\(^2\)HR estimated in a Cox proportional hazards model with time since enrolment as underlying timescale. CI adjusted for randomization of same-sex-twins to the same group.
### Table 3. Rates of identified consultations between enrolment and 9 months of age, and consultation hazard ratios for early MV group, compared with controls, by disease group

<table>
<thead>
<tr>
<th></th>
<th>Early MV Consultation rate (Consultations/Person-years)</th>
<th>No early MV Consultation rate (Consultations/Person-years)</th>
<th>HR (95% CI)(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>All cause</td>
<td>0.80 (507/630)</td>
<td>0.76 (491/642)</td>
<td>1.04 (0.90 - 1.19)</td>
</tr>
<tr>
<td>Respiratory Infection/Cold</td>
<td>0.44 (277/630)</td>
<td>0.42 (270/642)</td>
<td>1.03 (0.86 - 1.24)</td>
</tr>
<tr>
<td>Gastrointestinal Infection</td>
<td>0.17 (108/630)</td>
<td>0.17 (106/642)</td>
<td>1.02 (0.76 - 1.37)</td>
</tr>
<tr>
<td>Malaria</td>
<td>0.08 (48/630)</td>
<td>0.07 (43/642)</td>
<td>1.13 (0.72 - 1.77)</td>
</tr>
<tr>
<td>Other</td>
<td>0.08 (48/630)</td>
<td>0.07 (47/642)</td>
<td>1.02 (0.66 - 1.59)</td>
</tr>
<tr>
<td>Missing</td>
<td>0.07 (45/630)</td>
<td>0.09 (58/642)</td>
<td>0.78 (0.49 - 1.22)</td>
</tr>
</tbody>
</table>

n, number of children included in analysis; HR, hazard ratios; CI, confidence interval. \(^1\)HR estimated in a Cox proportional hazards model with time since enrolment as underlying timescale. CI adjusted for randomization of same-sex-twins to the same group.
Table 4. Rates of consultations between enrolment and 9 months of age, and consultation hazard ratios of recipients of early MV compared with controls in relation to the administration of campaign OPV before enrolment and if the child had been eligible to an OPV campaign after enrolment.

<table>
<thead>
<tr>
<th></th>
<th>No campaign OPV before enrolment</th>
<th>Campaign OPV before enrolment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consultation rates (n)</td>
<td>Consultation rates (n)</td>
</tr>
<tr>
<td></td>
<td>(consultations/person-years) (n)</td>
<td>(consultations/person-years) (n)</td>
</tr>
<tr>
<td>Early MV</td>
<td>1.24 (314/253)</td>
<td>1.18 (327/277)</td>
</tr>
<tr>
<td>No early MV</td>
<td>1.02 (327/267)</td>
<td>1.12 (294/264)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.01 (0.86-1.18)</td>
<td>1.05 (0.89-1.24)</td>
</tr>
<tr>
<td>All children¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not received or not yet received campaign OPV after enrolment</td>
<td>1.37 (199/145)</td>
<td>1.32 (274/207)</td>
</tr>
<tr>
<td></td>
<td>1.21 (187/155)</td>
<td>1.20 (237/198)</td>
</tr>
<tr>
<td></td>
<td>(700)</td>
<td>(816)</td>
</tr>
<tr>
<td></td>
<td>(722)</td>
<td>(773)</td>
</tr>
<tr>
<td>HR (95% CI)²</td>
<td>1.14 (0.93-1.40)</td>
<td>1.10 (0.92-1.32)</td>
</tr>
<tr>
<td>Received campaign OPV after enrolment</td>
<td>1.06 (115/108)</td>
<td>0.76 (53/69)</td>
</tr>
<tr>
<td></td>
<td>1.25 (140/112)</td>
<td>0.87 (57/66)</td>
</tr>
<tr>
<td></td>
<td>(530)</td>
<td>(303)</td>
</tr>
<tr>
<td></td>
<td>(535)</td>
<td>(296)</td>
</tr>
<tr>
<td>HR (95% CI)²</td>
<td>0.84 (0.65-1.08)</td>
<td>0.86 (0.57-1.29)</td>
</tr>
</tbody>
</table>

n, number of children included in analysis; MV, measles vaccine; OPV, oral polio vaccine; HR, hazard ratio.

¹Numbers deviates from figure 1 as 537 (early MV: 254, control: 283) children do not have information about consultations.

²HR estimated in a Cox proportional hazards model with time since enrolment as underlying timescale. CI adjusted for randomization of same-sex-twins to the same group.
Figure 1. Flowchart of participants’ recruitment in the study

Enrolment

Assessed for eligibility
n=6170

Excluded (n=2420)
- Moved prior to visit: n=89
- Died prior to visit: n= 51
- Absent or travelling at all visits: n=1366
- Missing penta3: n=513
- Interval penta3<28 days: n=102
- Too old when first seen after penta3: n=133
- Vaccination card not seen: n=66
- No guardian to give consent: n=10
- Mother declined: n=62
- MUAC less than 110 mm: n= 8
- Ill: n=13
- Already vaccinated elsewhere: n=7

Randomised
n=3750

Children in villages with no monthly morbidity follow-up: n=161

Allocation (n=3589)

Allocated to early MV (n=1786)
Received early MV: n=1786

Allocated to No early MV (n=1803)
Received no early MV: n=1803

Follow-up

Completed follow up: n= 1484
- Censored end of study: n= 52
- Censored at time of MV campaign: n= 5
- Censored on registration of routine MV elsewhere: n=177
- Censored at 18 months due to no routine 9 months MV: n= 27
- Migrated: n=29
- Died: n= 12

Completed follow up: n= 1519
- Censored end of study: n= 48
- Censored at time of MV campaign: n= 5
- Censored on registration of routine MV elsewhere: n=148
- Censored at 18 months due to no routine 9 months MV: n= 36
- Migrated: n=34
- Died: n= 13

Analysis (n=3548)

Analysed: n=1770
- Excluded from analysis: n=16
- Interval between penta3 and enrolment<4weeks: n=5
- Outside age range: n=10
- MUAC<110mm: n=1

Analysed: n=1778
- Excluded from analysis: n=25
- Interval between penta3 and enrolment<4weeks: n=8
- Outside age range: n=11
- MUAC<110mm: n=4
- Fever: n=2
Nelson-Aalen cumulative incidence of consultations

Days since enrolment

Mean number of consultations per child

- - - - Early MV
- - - - No early MV
Figure 3. Difference in MUAC-for-age and weight-for-age Z-scores between early two-dose MV group and control group at 9 months of age adjusted for baseline Z-scores, overall and by sex
BCG, Bacillus Calmette-Guerin Vaccine; OPV, Oral Polio Vaccine; Penta, pentavalent DTP-HepatitisB-H.Influenzae type B vaccine; PCV-13, 13-valent Pneumococcal Conjugate Vaccine; MV, Measles Vaccine; YF, Yellow Fever Vaccine

\(^1\) introduced June 2015
Consultations
1211
Hospital admissions
51
All reported
1262

Identification of reported events

Consultations
814
Hospital admissions
49

Identification of not reported events

Consultations
135
All identified
998

Identified events
Enrolment took place between July 13th 2012 and December 4th 2015.
OPV, Oral Polio Vaccine; VAS, Vitamin A Supplement; MV, Measles Vaccine