A two-centre randomised trial of an additional early dose of measles vaccine: Effects on mortality and measles antibody levels

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summary: In a randomised trial of an extra dose of early measles vaccine in Burkina Faso and Guinea-Bissau, we found no effect on mortality. Children had low antibody levels at enrolment and responded well to early vaccination.

Running title: Effects of early measles vaccination

Abstract

Background: Besides protecting against measles, measles vaccine (MV) may have beneficial non-specific effects. We tested the effect of an additional early MV on mortality and measles antibody levels.

Methods: Children aged 4-7 months in two rural health and demographic surveillance sites in Burkina Faso and Guinea-Bissau were randomised 1:1 to an extra early standard dose of MV (Edmonston-Zagreb strain) or no extra MV 4 weeks after the third diphtheria-tetanus-pertussis-hepatitis B-Haemophilus-influenzae-type-b vaccine. All children received routine MV at 9 months. We assessed mortality through home visits and compared mortality from enrolment to 3 years of age in Cox proportional hazards models, censoring for subsequent non-trial MV. Subgroups of participants had blood sampled at enrolment, before the 9 months MV and in the second year of life to assess measles antibody level.

Results: Among 8309 children enrolled July 18, 2012-December 3, 2015, we registered 145 deaths (mortality rate: 16/1000 person-years). The mortality was lower than anticipated and did not differ by randomisation group (hazard ratio=1.05 (95%CI: 0.75-1.46)).

At enrolment, 4% (16/447) of children in Burkina Faso and 21% (90/422) in Guinea-Bissau had protective measles antibody levels. By 9 months of age, no measles-unvaccinated/unexposed child had protective levels, while 92% (306/333) of early MV recipients had. At final follow-up, 98% (186/189) in the early MV group and 97% (196/202) in the control group had protective levels.

Conclusion: Early MV did not reduce all-cause mortality. Most children were susceptible to measles infection at 4-7 months and responded with high antibody levels to early MV.

Keywords: Measles vaccination, heterologous(non-specific) effects of vaccines, child mortality, measles antibody levels.

Introduction

WHO recommends the first dose of measles vaccine (MV) at 9 months of age in areas with measles transmission[1]. The decision to vaccinate at 9 months of age was made in the late 1970s and was a compromise. It was reasoned that vaccinating earlier would lead to poor seroconversion rates and high rates of subsequent "vaccine failures", while vaccinating later would lead to many children catching measles infection early in life. However, data about different ages of measles vaccination and their impact on child survival were not collected[2].

In the 1970s, most mothers had experienced measles infection. Mothers with a history of natural measles infection transmit higher levels of maternal antibodies to their children[3]. Today, mothers are more likely to have received MV in childhood[4, 5]. They therefore transmit less measles antibodies to their children who become susceptible to measles infection at 3-4 months of age[4, 6].

In addition to protecting against measles, observational studies[7-9] and randomised trials[10, 11] indicate that MV may have beneficial non-specific effects (NSEs), lowering all-cause mortality due to prevention of non-measles infections. Such beneficial NSE have also been shown for other live vaccines such as BCG[12-14] and oral polio vaccine (OPV)[15].

In a previous trial from Guinea-Bissau, providing an early standard dose of Edmonston-Zagreb MV versus no early MV at 4.5 months of age was associated with a Hazard Ratio (HR) of 0.67 (95% confidence interval: 0.38-1.19) between enrolment and 9 months vaccination. All children received MV at 9 months of age, but the early MV group also had a survival advantage from 9-36 months of age (HR=0.71 (0.50-1.01)). Observational studies from the introduction of MV in Guinea-Bissau[16] and MV campaigns[17, 18] also indicate an additional benefit of receiving several doses of MV.

We undertook the present trial to test the hypothesis that an extra early dose of MV reduces all-cause mortality.

Methods

Setting, study design and enrolment of participants

This individually randomised, open-label, two-centre trial assessed the effect of an early dose of MV on mortality between enrolment after 4 months and 36 months of age. The trial was conducted by the Centre de Recherche en Santé de Nouna in Burkina Faso and by the Bandim Health Project in Guinea-Bissau. Both research centres run Health and Demographic Surveillance Systems (HDSSs).

The routine vaccination programme includes 3 doses of pentavalent vaccine (Penta: diphtheria-tetanus-pertussis-hepatitis B-*h. influenzae* type B) at 4 weeks intervals starting from 6 weeks of age in Guinea-Bissau and 2 months of age in Burkina Faso. At 9 months of age, children receive MV and yellow fever vaccine. During the trial Burkina Faso changed to measles and rubella vaccine at 9 months and started providing a second dose at 15 months.

Enrolment was initiated in July 2012 in Bandim HDSS and in May 2013 in Nouna HDSS. Potentially eligible children were visited at home. Children aged 121-215 days were eligible for enrolment 4 weeks after the third dose of Penta provided that they were registered as HDSS residents. After informed consent, children were randomised 1:1 to early Edmonston-Zagreb MV at a standard dose (Supplementary Material) or no early MV in blocks stratified by sex and enrolment team. Following randomisation the child received either a standard dose of MV or no vaccine according to group. Since we were interested in testing the NSEs of MV, we did not use a placebo vaccine that could also have NSEs[19] (Supplementary Material).

Assessment of outcomes

All children were followed through the HDSS routines and in Burkina Faso also through the health facilities. At the first visit after 9 months of age, the child was invited back to the vaccination post to receive the routine MV. The primary outcome was all-cause mortality between randomisation and 36 months of age or “end of study”. Since the purpose of the trial was to examine the effect of one

versus two doses of MV, it was pre-specified to censor children who received non-study MVs. In October 2014, Burkina Faso introduced a second dose of MV at 15 months of age (which was provided also to children up to 18 months). This shortened the follow-up period considerably in Burkina Faso. MV campaigns targeting all children aged 9-59 months occurred in December 2012 and December 2015 in Guinea-Bissau and in November 2014 in Burkina Faso, further shortening the follow-up time. “End of study” depended on the timeline for funding and was December 4, 2015 in Guinea-Bissau when the MV campaign occurred and January 31, 2016 in Burkina Faso.

For all registered deaths, a standard verbal autopsy[20] was conducted by a specially trained field assistant and the probable cause of death assigned by physicians (Supplementary Material).

As a secondary outcome, we assessed levels of measles antibody. In a subgroup of children, we collected blood samples at enrolment, at 9 months (after one vs no MV); a third and final blood sample was obtained at 15 months in Burkina Faso and at 24 months in Guinea-Bissau (after two vs one MV). Blood samples from the mothers were collected at enrolment.

A subgroup of children were visited 14 days after enrolment to register adverse events (Supplementary Material).

Statistical analyses

The sample size was based on a significance level of 5% and 80% power and a hypothesised reduction of 32% in mortality between 4 and 36 months of age. We assumed an average follow-up of 1.4 years. With an expected mortality rate of 30/1000 person years in Guinea-Bissau and 25/1000 in Burkina Faso, we arrived at minimum samples of 3750 in Guinea-Bissau and 4050 in Burkina Faso (Supplementary Material). The analysis plan was reviewed and approved by the DSEMB prior to data lock.

Mortality was compared in Cox proportional hazards models with time since enrolment as underlying timescale and stratified by site and sex. The primary analysis was based on the per-

protocol population. In the per-protocol analysis, follow-up was censored at 3 years of age, migration, at the end of study, or deviations from the planned vaccination schedule (18 months if the scheduled 9 months MV had not been received by then, registration of reception of non-trial MV, eligibility to MV campaigns or routine second dose of MV).

Secondary analyses assessed the effect of the early MV on mortality in two intervals: before the 9 months vaccination and between 9 months vaccination and end of study (Supplementary material). In a secondary intention-to-treat analysis, follow-up was censored at 3 years of age, migration or end of study. Deaths due to accidents were censored in a sensitivity analysis.

Antibody concentrations were measured by Multiplex Immuno-Assay[21] and described by geometric mean concentration and the log-transformed concentrations compared by group using Student's t-test. As in prior publications[5, 22, 23], we compared the proportion of samples with concentrations of protective measles antibody levels using the internationally accepted cut-off of >=125 mIU/ml.

The proportions of children reporting adverse events at the home visit 14 days post-enrolment were compared by calculating relative risks for the intervention relative to the control group stratified by site.

The trial was registered at ClinicalTrials.gov, NCT01644721

Results

Between July 18, 2012 and December 3, 2015, when the planned sample size was reached in Guinea-Bissau, we enrolled a total of 8309 children, 4559 in Burkina Faso (12% more than the originally planned sample of 4050 to compensate for censoring) and 3750 in Guinea-Bissau. Among these children, 4153 were randomised to the intervention group and received early measles vaccination and 4156 to the control group (Figure 1). A total of 104 children were excluded due to protocol

violations (Figure 1) retaining 8205 children in the analyses. Only 6% of children were followed until completing 3 years of age in the per-protocol analysis (Figure 1).

The randomisation resulted in balanced groups with regard to baseline demographic and health characteristics (Table 1). Eighty percent of children had been exposed to OPV campaigns before enrolment (Table 1, Supplementary Table 1).

Until the end of study, we registered 145 deaths in the per-protocol analysis. There was no difference in survival between the two randomised groups; the early MV group had a mortality rate (MR) of 16.8/1000 PYRS and the control group 15.9/1000 PYRS, the HR being 1.05 (0.75-1.46). There was no indication of a site- or sex-differential effect (Figure 2, Table 2).

Splitting the observation time at the 9 months MV, the mortality did not differ by group assignment between enrolment and 9 months (comparing measles vaccinated versus unvaccinated children) HR=1.10 (0.66-1.83) or between 9 months and end of study (2 doses of MV vs 1 dose) HR=1.01 (0.66-1.56) (Supplementary Table 2). Due to restrictions on opening the 10-dose yellow fever vaccine vials and national stock outs, 42% of children in Guinea-Bissau received no yellow fever vaccine on the date of 9 months MV, but were offered the vaccine at a subsequent visit if they had not been vaccinated through the national programme. We found no indication that the effect of early MV varied by whether or not yellow fever vaccine was received with the 9 month MV (Supplementary Table 3).

The intention-to-treat analysis, extending the follow-up beyond the non-trial MVs, included 243 deaths, 129 in the early MV group (MR 18.4/1000 PYRS) and 114 in the control group (MR 16.4/1000 PYRS). The HR was 1.12 (0.87-1.44) (Table 2).

Half of the deaths occurred at home, and the proportion of deaths in hospital did not differ by group (Supplementary Table 4). Deaths were mainly classified as caused by infectious diseases (Supplementary Material). Two deaths in the PP analysis were classified as due to accidents (1 early

MV, 1 control) (Supplementary Table 4). Censoring these deaths, the HR remained unchanged. In the intention-to-treat analysis, when four further deaths due to accidents were censored from the early MV arm, the HR was 1.09 (0.84-1.40) (Supplementary Table 5).

We found no indication of acute adverse events among the 1543 children visited 14 days after enrolment (Table 3, Supplementary Material).

Antibody levels in children were low at enrolment, only 21% in Guinea-Bissau and 4% of children in Burkina Faso had protective antibody levels (Table 4). At 9 months of age, all but 4% of children in the control group (who had presumably been measles vaccinated/exposed (Supplementary Material)) had lost protective maternal antibody levels.

Vaccinated children responded well to early MV and >=90% had protective antibody levels at 9 months of age. In the final sample at 15/24 months, 97-100% were protected (Table 4, Figure 3). Previous studies of two-dose MV strategies have suggested that early MV is associated with lower final antibody levels[23]. A similar tendency was seen in Guinea-Bissau. However, in Burkina Faso where the maternal antibody level was particularly low (Supplementary Material), an early two-dose strategy was associated with a significantly higher final measles antibody level (GMR=1.30 (1.02-1.66)) than among the children, who had followed the current recommendation of one dose at 9 months of age (Table 4).

Discussion

We found no effect of early MV on all-cause mortality in the present trial. The vast majority of children were susceptible to measles infection at 4 to 6 months and practically all measles unvaccinated children were susceptible by 9 months of age. An early 2-dose vaccination schedule gave 97-100% of the children protective antibodies.

Though the study was large, the power was lower than expected due to censoring of follow-up for children who received MV outside of the trial. This shortened the mean follow-up time in Burkina

Faso considerably. Furthermore, in spite of censoring reducing the follow-up time selectively more among the oldest children, the mortality rate during the trial was 16/1000 person years and thus much lower than the expected rate in both Guinea-Bissau (30/1000) and Burkina Faso (25/1000). The mortality has fallen markedly in both sites over the past years[24, 25]. Though this is certainly a celebratory finding, it meant that we had only half the deaths we anticipated in the study. However, there is no indication that had we had the planned power, we might have found a difference in child mortality. By nesting the trial in the HDSS sites we were able to follow the enrolled children and the comparison between the two groups is not affected by a loss to follow-up.

Participants were not blind to group allocation and we used no placebo vaccine. However, with mortality as the outcome, the risk of a differential reporting by group allocation seems unlikely. It could be speculated, that mothers who thought that their children were healthier because they had been allocated to the intervention group, could have a different threshold for seeking health care. We found no indication that this was the case: the number of deaths occurring in health facilities was similar in the two groups.

We assigned causes of death based on verbal autopsies and available health facility data. The diagnostic tools are limited in both settings and the classifications uncertain. Nevertheless, we consider the verbal autopsy data sufficiently accurate to be able to censor deaths due to accidents.

We tested a previous finding that early MV has the potential to lower non-measles mortality, but found no effect. Infectious disease is the main cause of death in the studied age group and the decline in mortality is mainly due to fewer deaths from infectious diseases[26]. Hence, the much lower mortality level may have meant that the remaining causes of death were not influenced by a beneficial NSE of MV.

Other interventions may also have neutralised differences between the two randomised groups. Due to previous findings that receiving diphtheria-tetanus-pertussis vaccine (DTP) after high-titre MV was

associated with increased female mortality[27] and that receiving neonatal vitamin A supplementation (NVAS) removed the beneficial effect of early MV[10], we enrolled per protocol only children who had completed all three doses of DTP-containing vaccine and had not received NVAS in our two dose trial of standard titre MV. Moreover, when we planned the trial, we were not aware of any interaction with OPV. Recently, we reanalysed data from the previous positive early MV trial and found that campaign OPV provided before trial enrolment reduced mortality, especially among children in the control group, and there was no benefit of early MV in this group[28]. Furthermore, campaign OPV before enrolment was associated with a significant reduction in the load of pneumococcus in the control group compared with the early MV group[29]. OPV campaigns had become more frequent during the present trial; 80% of our trial children were exposed to OPV campaigns prior to enrolment whereas only 21% had been exposed in the previous trial[28]. This is another possible explanation as to why early MV had no detectable effect on child survival in the present trial.

It could also be speculated that the use of Penta rather than DTP and the introduction of pneumococcal and rota virus vaccines in the routine vaccination programme could have had an impact, by reducing infections with pathogens that could otherwise have been prevented non-specifically by early MV. Yellow fever vaccines were also not part of the routine vaccination programme in the prior trial. Prior studies suggest that addition of yellow fever vaccine does not alter the effect of the 9 months MV[30, 31] and we found no indication that this explains why there was no effect in the present trial. However, data are scarce.

In rural Guinea-Bissau, the proportion of mothers with protective measles antibodies was comparable to the level found in the prior trial in urban Guinea-Bissau[23], but the median concentration was lower. The proportion of infants with protective antibodies at the time of enrolment (21%) in Guinea-Bissau was also similar to the prior trial, but the proportion in Burkina Faso (4%) was much lower. None of the measles-unvaccinated/unexposed children had protective

measles antibodies at 9 months of age. Consistent with the very low proportion of children with protective antibody levels at 4 months of age in Burkina Faso, their mothers had also much lower antibody levels than the mothers of Guinean children. Concerns about early waning of measles antibodies levels have been raised previously[3, 5, 32]; the present data indicate that this may happen much earlier than 9 months of age, leaving many infants susceptible to measles infection.

In the previous trial, the effect of early MV was particularly pronounced among children who had maternal measles antibodies at the time of vaccination[33]. The lack of an effect in the present trial is unlikely to be due merely to the lower levels of maternal antibodies in the present trial, since maternal antibodies were still present in Guinea-Bissau.

While the present trial does not confirm that an early measles vaccination strategy would lower mortality (with likely explanations given above), it supports that early measles vaccination may be important for improved measles control. In contrast to the assumed negative effect on long-term measles immunity[34], we did not find any indication that vaccinating earlier with a two-dose strategy hampered long-term immunity. Instead, with the low level of pre-vaccination antibodies observed in Burkina Faso and the higher attained final antibody level in the early MV group, vaccinating earlier may improve measles control. We also found no indication that there are any severe adverse reactions connected with early vaccination. Since early vaccination with Edmonston-Zagreb MV is both safe and effective in controlling measles infection, it should be considered in future vaccination strategies.

In conclusion, early MV did not reduce all-cause mortality in this two-centre trial. This could possibly be explained by interference from the NSEs of the frequent OPV campaigns [28, 35]. If that is the case, with the current phase out of OPV campaigns[36, 37] and with the worldwide cessation of OPV, it would still be worthwhile to examine whether early MV has beneficial NSEs in addition to its specific protective effects against measles infection.

Nearly all enrolled children in both Burkina Faso and Guinea-Bissau were susceptible to measles infection well before the currently recommended age for MV. Providing the first dose of MV at 9 months may therefore not be ideal to control measles infection, and a two-dose MV strategy with an early MV followed by MV at 9 months would provide better protection against measles infection.

NOTES

Contributors: ABF, EN, ASi, CM, AR, HB, HCW, OM, CSB, PA designed the trial. ABF, EN, ASi, CM, AR, AZ, MK, SB, SMT, JT, BC, FK obtained the data. ABF, ASc, HB, PA conducted or supervised the analysis. ABF, EN, ASc, HB, HCW, OM, CSB, PA interpreted the data. ABF, EN, ASc, HCW, FK, OM, CSB, PA were the core writing team for the manuscript.

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Conflicts of interests: The authors have declared that no competing interests exist.

Ethical approval: The trial protocol was approved by the relevant ethical committees in Guinea-Bissau (Comité Nacional de Ética na Saúde), Burkina Faso (Le Comité d'Ethique pour la Recherche en Santé, Comité technique d'autorisation d'essais cliniques and le Comité Institutionnel d'Éthique de

Nouna), Germany (The Ethical Committee of the Medical School at University of Heidelberg) and Denmark (The Danish Central Ethical Committee (consultative approval)). Due to changes in national vaccination policies during the course of the study, protocol modifications with respect to timing of blood sample collection and sample size were submitted and approved by the ethical committees. The data safety and ethics monitoring board approved the suggested changes before submission.

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Table 1: Baseline characteristics according to group allocation

	Early MV	**Control**
Number	4106	4099
Male (n(%))	2056 (50%)	2048 (50%)
Age/days (median, IQR)	170 (158-188)	170 (157-187)
Enrolled in the rainy season (n(%)) [1]	2485 (61%)	2455 (60%)
Site		
Burkina Faso (n(%))	2258 (55%)	2238 (55%)
Guinea-Bissau (n(%))	1848 (45%)	1861 (45%)
Markers of child health		
Mid-upper-arm circumference (median (IQR))	138 (130-146)	138 (130-146)
Admitted to hospital prior to enrolment (n(%))	43 (1%)	38 (1%)
Socio-economic status		
Number of persons sleeping in the bed of the child (median (IQR))	3 (2-3)	3 (2-3)
Prior OPV campaign		
Eligible for campaign OPV prior to enrolment (n(%))	3290 (80%)	3247 (79%)

Footnote to Table 1: 1: Rainy season defined as in prior studies: Guinea-Bissau: June-November, Burkina Faso: June-October

Table 2: Mortality by group allocation in the early MV trial in Burkina Faso and Guinea-Bissau.

	Mortality Rate / 1000 PYRS (Deaths/Person years)		Hazard Ratio (95%CI)
	Early MV	**Control**	
Per-protocol analysis[1]			
All	16.8 (74 / 4398)	15.9 (71 / 4453)	1.05 (0.75-1.46)
Boys	16.3 (36 / 2214)	16.1 (36 / 2238)	1.01 (0.63-1.62)
Girls	17.4 (38 / 2184)	15.8 (35 / 2215)	1.09 (0.69-1.72)
Intention-to-treat analysis[2]			
All	18.4 (129 / 6999)	16.4 (114 / 6960)	1.12 (0.87-1.44)
Boys	19.1 (67 / 3505)	17.2 (60 / 3491)	1.11 (0.78-1.58)
Girls	17.7 (62 / 3493)	15.6 (54 / 3469)	1.13 (0.79-1.63)

Footnote to Table 2: 1: Follow-up time: Early MV: mean: 1.07 years; median 0.87 years (Inter-quartile range (IQR): 0.61-1.37); Control: mean: 1.09 years, median: 0.87 years (IQR: 0.61-1.37); 2: Follow-up time: Early MV: mean: 1.70 years; median: 1.79 years (IQR: 1.29-2.32); Control: mean: 1.70 years; median: 1.81 years (IQR: 1.29-2.33)

Table 3: Reported adverse events within the first 14 days after enrolment in the early MV trial in Guinea-Bissau and Burkina Faso.

	Early MV (n (%))	**Control (n (%))**	**Relative risk (95%CI)**
Guinea-Bissau			
Number visited	278	284	
Number with information	217 (78)	228 (80)	
Any symptom since enrolment	71 (33)	82 (36)	0.91 (0.70-1.18)
Symptoms reported			
-Fever	62 (29)	63 (28)	1.03 (0.77-1.39)
-Convulsions	0 (0)	0 (0)	NA
-Other[1]	71 (33)	82 (36)	0.91 (0.70-1.18)
Sought health centres	20 (9)	21 (9)	1.00 (0.56-1.79)
Burkina Faso			
Number visited	480	501	
Number with information	473 (99)	498 (99)	
Any symptom since enrolment	98 (21)	94 (19)	1.10 (0.85-1.41)
Symptoms reported			
-Fever	70 (15)	74 (15)	1.00 (0.74-1.35)
-Convulsions	0 (0)	0 (0)	NA
-Other[2]	68 (14)	59 (12)	1.21 (0.88-1.68)
Sought health centres	47 (10)	54 (11)	0.92 (0.63-1.33)

Footnote to Table 3: 1: Respiratory symptoms: 99 (early MV: 42/ Control: 57); Gastro-intestinal symptoms: 50 (25/25), Other: 11 (8/3) (overlapping symptoms); 2: Respiratory symptoms: 75 (early MV: 40/ Control: 35); Gastro-intestinal symptoms: 50 (20/30), Other: 24 (13/11) (overlapping symptoms)

Table 4: Measles antibody: Proportion protected[1] and levels of antibodies by randomisation group and age at sampling. Stratified by site

	Protective Ab level[1], % (n/N)		Test of no diff.	GMC[2] mIU/mL (95%CI)		GMR[3] (95% CI)
	Early MV	Control		Early MV	Control	
Guinea-Bissau						
Child						
Enrolment	21 (41/196)	22 (49/226)	0.85	57 (49-66)	59 (52-68)	0.97 (0.79-1.18)
9 months	90 (128/142)	3 (5/176)	<0.001	401 (342-471)	11 (9-13)	36.5 (29.1-45.7)
24 months	97 (96/99)	97 (102/105)	0.94	600 (512-705)	699 (598-816)	0.86 (0.69-1.07)
Mother						
Enrolment	95 (184/194)	95 (207/218)	0.96	685 (586-801)	853 (727-999)	0.80 (0.64-1.00)
Burkina Faso						
Child						
Enrolment	3 (7/226)	4 (9/221)	0.62	19 (17-21)	18 (16-21))	1.06 (0.88-1.26)
9 months	93 (178/191)	5 (9/187)	<0.0001	457 (392-533)	10 (8-12)	46.2 (36.5-58.6)
15 months	100 (90/90)	97 (94/97)	0.25	800 (681-940)	614 (513-735)	1.30 (1.02-1.66)
Mother						
Enrolment	93 (211/226)	93 (201/216)	0.90	634 (550-732)	596 (504-706)	1.06 (0.85-1.32)

Footnote to Table 4: 1: Protective Antibody level: >=125 mIU/mL; 2: Geometric mean concentration; 3: Geometric mean ratio

Figure Legends

Figure 1: Flowchart of children in the early measles vaccination trial in Burkina Faso and Guinea-Bissau

Footnote to Figure 1: 1: Not meeting inclusion criteria (n=1328): Migrated (108) or died (54) before 28 days after Penta3; No penta3 before too old (516); Interval<28 days since Penta3 (102); Too old when seen (500); MUAC<110 (34); Ill (12); Malformation (2); 2: Other reasons (n=1717): Absent/travelling (1385); Vaccination card not seen (64); No guardian present (10); Already received MV elsewhere (7); Residential status not confirmed (251).

Figure 2: Kaplan Meier survival graphs for children in the early measles vaccination trial in Burkina Faso and Guinea-Bissau.

Footnote to Figure 2: Based on per-protocol population.

Figure 3: Measles antibody levels at enrolment, 9 months and 15 / 24 months for children in the early measles vaccination trial in Burkina Faso and Guinea-Bissau.

Footnote to Figure 3: Median concentration by group indicated by thick red line. Protective level: >=125 mIU/mL.

Figure 1.

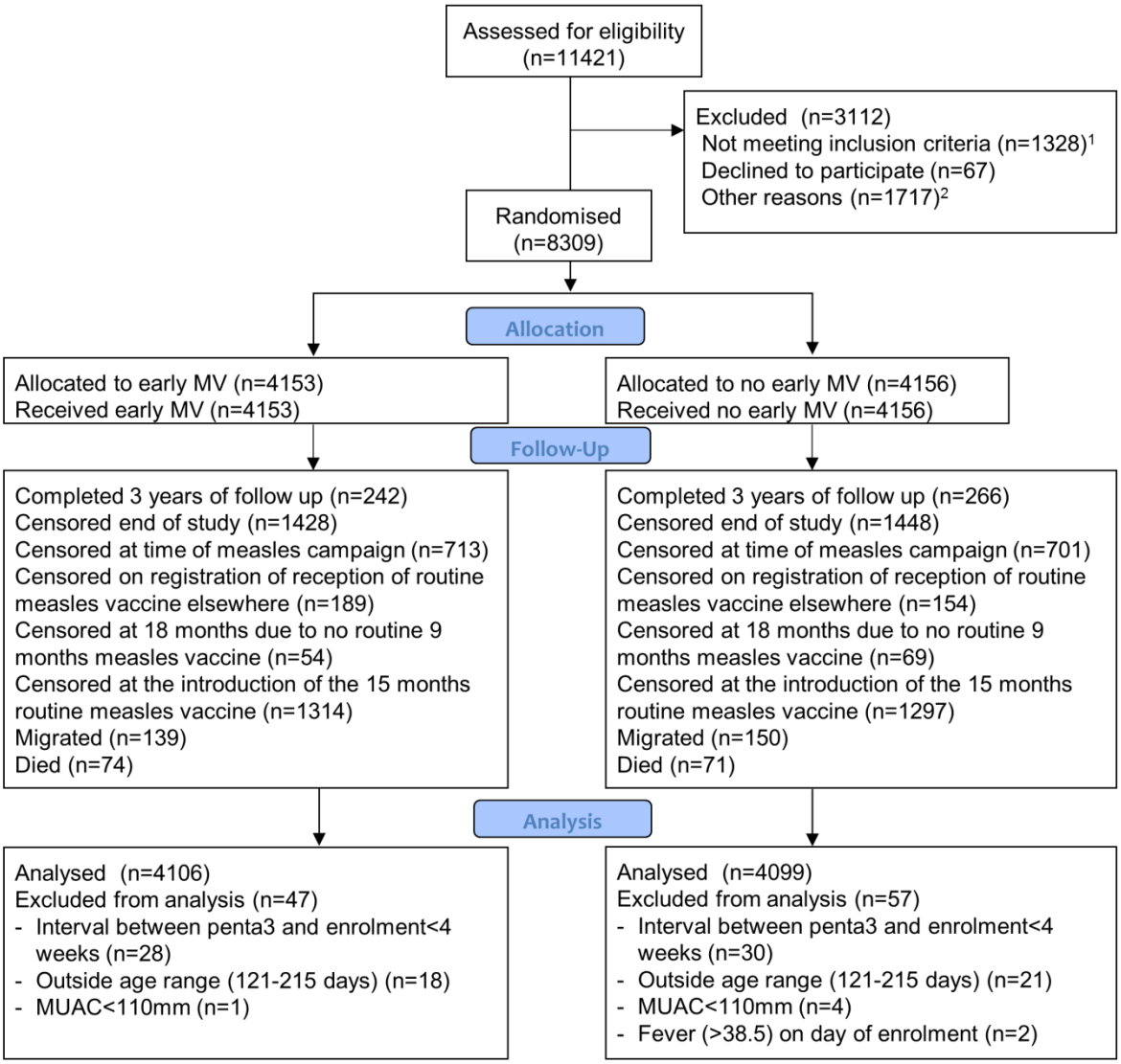

Figure 2.

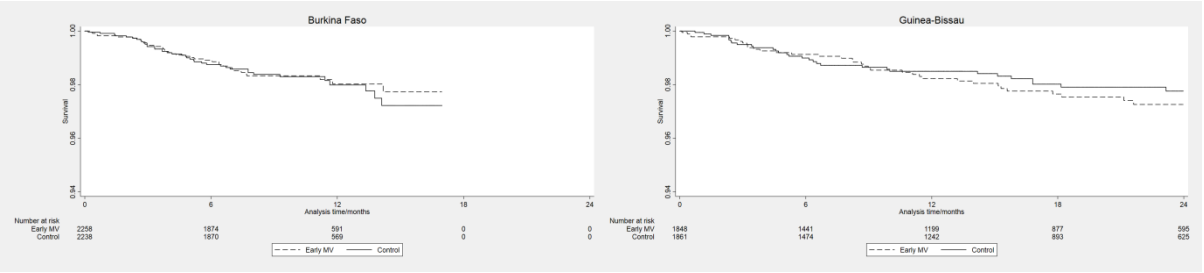

Figure 3.