Campaign with a measles vaccine -

overall effect on mortality and morbidity in children aged 9-59 months from Guinea-Bissau

PhD thesis by Anshu Varma

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Title

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overall effect on mortality and morbidity in children aged 9-59 months from Guinea-Bissau

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2. Varma A, Aaby P, Thysen SM, Jensen AKG, Fisker AB. Reduction in Short-term Outpatient Consultations After a Campaign With Measles Vaccine in Children Aged 9–59 Months: Substudy Within a Cluster-Randomized Trial. *Journal of the Pediatric Infectious Diseases Society* ***2020;*** *XX(XX):1–9 (in print)*

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PREFACE

Next time someone asks me: 'So, what was it like to be a PhD student?' I will probably say:

- At first, the PhD felt: Pure - how can it be any different in the green fields of Guinea-Bissau
- During, the PhD felt: heavy - like the rain drops of a proper Guinean monsoon
- At last, the PhD felt: Developing - at the speed of the best West African dance beats

I feel incredibly privileged that the Bandim Health Project gave me a unique opportunity to join their fascinating, wild, and inspiring project going out of its million ways to make a difference for the world's children by persistently pursuing the 'non-specific-effects of vaccines'. Today, this PhD thesis is here on paper only due to the blood, sweat and tears of countless people before and during my time at the Bandim Health Project, and not to say the very least, due to the many heartfelt mothers and their children. To each and every one of you, please accept my warmest gratitude with this personally written poem in the local language of Guinea-Bissau, Portuguese-Creole:

*Jintis de Projecto de Saúde Bandim na Guinea-**Bissau***
*Na nha corson bo tene un **kau***

*Qualquer **algin***
*Bu sibi abo i **kin***

*Tarbadjo pa saúde de mininos i muito **importante***
*Ora ku no ta pega djuntu la dianti no pudi **jande***

*Obrigado pa sinang kusa de saude de **crianca***
*Obrigado pa mostrang manera bonito de **vida***

*Purdang, si alguns tempo nka fasi **bon***
*Tempa sensa, pega nha **mon***

*Es bo pudi **fia***
*Nunca npudi diskisi kuma bo ta pega kade **dia***

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Ane. Always there with a solution to a problem. I am so grateful for your willingness to have walked next to me on every step of my PhD journey with immense dedication. Our journey has had a tremendous impact on me personally and professionally. Also, thank you for your lovely terrace mint (or what is left of it?!). One day, I will repay you with some homemade 'pudine ki chutney' (classic Indian mint sauce). *Claudino e Equipa Movel*. Nunca npudi diskisi kuma bo pega ba tarbadjo. Sempre ku forca e corson. Bo mostrang ba responsibilidade e communidade unico. Bo na fika na nha corson pa eternal. Pa abos tudu, nespera so bon saude. *Peter*. It was an honor to work with you. Thank you for making me look at things differently. Although, our results were not quite as we had expected, I hope they will contribute to the bigger 'non-specific-effects' picture, once we understand the interaction between the measles vaccine and the oral polio vaccine. *Aksel*. You explained statistics to me in a clear, simple, and patient manner. Thank you for helping me and taking the time when needed. You made me just a tad less furious about the complicated field of statistics, not an easy job, if you ask me. *Christine*. Thank you for vividly sharing your 'why are we doing this' at any given occasion, in oral or writing, all the way through. This contributed to my motivation. I appreciate the opportunities you offered to disseminate our research to non-Bandimers.

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SUMMARY IN ENGLISH

In the last decades, worldwide, numerous measles vaccine campaigns have been implemented to control and eventually eradicate measles. During the same decades, mortality in children aged under-five has decreased tremendously. Meanwhile, accumulating evidence suggests that the measles vaccine protects against other infections than measles, also termed, beneficial non-specific-effects. Thus, measles vaccine campaigns may have efficiently contributed to decreasing the under-five child mortality beyond our common understanding. However, no randomized trial has assessed the beneficial non-specific-effects of a measles vaccine campaign. The trial, RECAMP-MV, presented in this PhD thesis, assessed the overall effect of a measles vaccine campaign among children aged 9–59 months on mortality and morbidity, in a setting with limited measles. The overall effect would capture any potential specific effect and non-specific-effect, and even adverse events, thereby providing a complete risk-benefit profile of a measles vaccine campaign. RECAMP-MV used the data collection platform of the Bandim Health Project in rural Guinea-Bissau, West Africa. In a cluster-randomized trial, 222 village-clusters were randomly assigned to receive a measles vaccine campaign (intervention) or to not receive a measles vaccine campaign (control). This PhD thesis compiles three articles based on RECAMP-MV: Article 1 presented the methodology, rationalities behind choices made, and analysis plans, to facilitate future assessments of measles vaccine campaigns. Article 2 assessed the overall effect of a measles vaccine campaign on outpatient consultation. We observed that the measles vaccine campaign tended to reduce outpatient consultations by 16% (relative risk, 0.84; 95% confidence interval, 0.65-1.11) within 1-2 months from enrolment in a sub-group of 8,319 children (4,437 intervention/3,882 control). This estimate was robust to restrictions on the definition of outpatient consultations. Article 3 assessed the overall effect of a measles vaccine campaign on mortality or hospital admission in a composite outcome. Contrary to our hypothesis, we observed that the measles vaccine campaign did not reduce the composite outcome by 30% (hazard ratio, 1.12; 95% confidence interval, 0.88-1.41) during a median follow-up period of 22 months among 18,411 children (9,636 intervention /8,775 control). This estimate was similar in intention-to-treat analyses. Thus, in the short-term, the measles vaccine campaign was safe an even tended to reduce outpatient consultations. However, in the long-term, the measles vaccine campaign did not reduce mortality or hospital admission. An explanation for this may be its interaction with oral polio vaccine campaigns, as we observed that the measles vaccine campaign increased mortality or hospital admission after oral polio vaccine campaigns but not before after oral polio vaccine campaigns, especially in girls.

SUMMARY IN DANISH

I de seneste årtier er der blandt børn blevet implementeret adskillige kampagner med en mæslingevaccine for at kontrollere og på sigt udrydde mæslinger på verdensplan. I de seneste årtier er børnedødeligheden faldet drastisk på verdensplan. I de seneste årtier er der mere og mere forskning, der tyder på, at mæslingevaccinen beskytter børn mod andre infektioner end mæslinger, også kaldet positive uspecifikke effekter. Mæslingevaccine kampagner kan have været en effektiv måde at holde børnedødeligheden lav på, hvilket ligger udover vores nuværende forståelse af vaccinens virke. Mæslingevaccine kampagners positive uspecifikke effekter er dog ikke blevet evalueret i forsøg. I nærværende ph.d.-afhandling blev forsøget, RECAMP-MV, præsenteret. Vi evaluerede den samlede effekt af en mæslingevaccine kampagne blandt børn fra 9–59 måneder på dødelighed og sygelighed, i en kontekst med begrænset mæslinger. Ved at måle den samlede effekt kunne vi opfange både specifikke og uspecifikke effekter, men også eventuelle bivirkninger, og dermed danne en hel risks-benefits profil på en mæslingevaccine kampagne. RECAMP-MV gjorde brug af dataindsamlingsplatformen på Bandim Health Project i det landlige Guinea-Bissau, Vestafrika. 222 landsbyklynger blev tilfældigt fordelt til at modtage en mæslingevaccine kampagne (intervention) eller til ikke at modtage en mæslingevaccine kampagne (kontrol). Ph.d.-afhandlingen sammenfatter tre RECAMP-MV artikler: Artikel 1 præsenterede protokollen ved at beskrive metode, rationale og analyseplan for at facilitere potentielle fremtidige evalueringer af mæslingevaccine kampagner. Artikel 2 evaluerede den samlede effekt af en mæslingevaccine kampagne på sundhedskonsultationer. Mæslingevaccine kampagnen tenderede til at reducere sundhedskonsultationer med 16% (relativ risiko, 0.84; 95% konfidensinterval, 0.65-1.11) indenfor 1-2 måneder efter forsøgsstart blandt en undergruppe af 8,319 børn (4,437 intervention/3,882 kontrol). Resultatet var robust over for restriktioner i definitionen af sundhedskonsultationer. Artikel 3 evaluerede den samlede effekt af en mæslingevaccine kampagne på dødelighed eller indlæggelse (i et kombineret mål) over en median opfølgningsperiode på 22 måneder. I modsætning til vores hypotese reducerede mæslingevaccine kampagnen ikke det kombinerede mål med 30% (hazard ratio, 1.12; 95% konfidensinterval, 0.88-1.41) blandt 18,411 (9,636 intervention/8,775 kontrol). Resultatet var uændret i intention-to-treat analyser. Med andre ord, på kort sigt var mæslingevaccine kampagnen sikker og tenderede endda til at reducere sundhedskonsultationer, men på lang sigt reducerede mæslingevaccine kampagnen ikke dødelighed eller indlæggelse. En forklaring kan være dens interaktion med oral polio vaccine kampagner, idet vi observerede, at mæslingevaccine kampagnen øgede dødelighed eller indlæggelse efter oral polio vaccine kampagner men ikke før oral polio vaccine kampagner, særligt blandt piger.

ABBREVIATIONS

AEFI	Adverse events following immunization
BHP	Bandim Health Project
CI	Confidence interval
DTP	Diphtheria-tetanus-pertussis
HDSS	Health and demographic surveillance system
HR	Hazard ratio
MV	Measles vaccine
NSE	Non-specific-effects
OPV	Oral polio vaccine
PENTA	Diphtheria-tetanus-pertussis, hepatitis type b, haemophilus influenza type b
PYRS	Person-years
RR	Relative risk
WHO	World Health Organization

1. INTRODUCTION

Worldwide, mortality in children aged <5 years has decreased from 12.6 to 5.4 million deaths during 1990-2017. Despite this tremendous improvement, the under-five mortality is still high and therefore considered an urgent matter. Preventable infectious diseases remain a major cause of death among children under-five, which reflects limited access to basic health interventions, like child routine vaccination programs [1].

Campaigns with vaccines to large child populations over a short period of time have become an important way to support routine vaccination programs [2]. The measles vaccine (MV) is one such vaccine, which has been administered to children under-five in millions of doses through national MV campaigns to eradicate measles since 2000 [3]. This way MV has prevented millions of measles deaths [4]. However, MV may have effects beyond this specific effect against measles.

Since the early 1980's, evidence has grown to suggest that MV also has non-specific-effects (NSE); MV may prevent child mortality due to infections unrelated to measles and thereby have, beneficial NSE [5, 6]. The World Health Organization (WHO) recently commissioned a systematic review and concluded that "*There was consistent evidence of a beneficial effect of measles vaccine* (…)" on child mortality [5] but warranted more trials [7]. To our knowledge, although no randomized trial has assessed the NSE of a national MV campaign among children under-five, observational studies have made this assessment [8, 9]. One study compared the overall effect on mortality one year before and after eligibility to an MV campaign, in addition to a routine vaccination program, among 8,000 children; a 20% (4%-34%) lower mortality was observed, even after censoring measles deaths [8]. Another study compared the overall effect on mortality according to participant status in an MV campaign, in addition to a routine vaccination program, one year after the campaign, among 6,639 children; a 72% (23%–90%) lower mortality was observed, measles caused no deaths [9].

Thus, over the last decades, three concurrent changes have occurred concerning children under-five: (1) Overall mortality has decreased tremendously [1] and the decrease has accelerated in many countries since 2000 [10]. (2) Since 2000, MV campaigns have been widely implemented [4]. (3) Evidence suggests that MV may have substantial beneficial NSE on mortality [5], also if distributed in national campaigns [8, 9]. In other words, MV campaigns may have had an impact on child survival, which lies beyond the common understanding of how MV works and is implemented [11]. We find this important to understand before measles is eliminated and ultimately eradicated.

To date, smallpox is the only disease that has been eradicated [12]. Given that the phaseout strategy for the smallpox vaccine [12] is applied on MV upon future measles eradication [13], MV

campaigns may be phased out and ultimately MV may be removed from routine vaccination programs. However, this may lead to an eradication paradox [14] as it has been suggested for smallpox [15-17]: If MV has beneficial NSE, child mortality may increase even though measles is eradicated because children may be deprived from MV's beneficial NSE.

2. AIM

The aim of the trial, RECAMP-MV, presented in this PhD thesis, was to understand the impact of removing MV campaigns once measles is eradicated. Observing beneficial NSE of MV campaigns in settings without measles could indicate that child health can be improved even after measles eradication and thus, what children under-five may be missing out on, if MV campaigns are phased out upon potential future measles eradication.

2.1 Objective

RECAMP-MV evaluated the overall effect of an MV campaign among children aged 9–59 months on mortality and morbidity, in a setting with limited measles. The overall effect would capture any potential specific effect and NSE, and even adverse events, thereby providing a complete risk-benefit profile of an MV campaign.

In a cluster-randomized trial, village-clusters were randomly assigned to either receive an MV campaign (intervention group) or to not receive an MV campaign (control group). This PhD thesis compiled the following three articles based on RECAMP-MV:

Protocol article: The first article presented the trial methodology, rationalities behind choices made, and analysis plans, which could facilitate future assessments of MV campaigns in not only considering MV's specific effect but also NSE, and thereby MV campaigns' overall effect on child health. Referral in the thesis will be as the Protocol article.

Short-term article: The second article reported on an MV campaign's overall effect on outpatient consultations within 1-2 months after enrolment, in a sub- group of enrolled children. This allowed an assessment of an MV campaign's short-term overall health effect. Referral in the thesis will be as the Short-term article.

Long-term article: The third article reported on an MV campaign's overall effect on mortality or hospital admission in a composite outcome, during an average follow-up period of 18 months. This allowed an assessment of an MV campaign's long-term overall health effect. The hypothesis was a reduction in the composite outcome by 30%. Referral in the thesis will be as the Long-term article.

3. BACKGROUND

This chapter presents a description of measles, its management, epidemiology, and elimination status. Subsequently, a description of MV is presented, from the perspective of its specific effect and NSE.

3.1 Measles

3.1.1 Measles virus

Measles is an acute infection brought about by a measles virus. Presumably, the measles virus evolved where cattle and humans lived closely in the Middle Eastern region but became a disease of humans about 5,000-10,000 years ago [18]. Measles is considered highly contagious as it has a basic reproduction number of 12-18, though, the lower and higher points of the interval may vary [19]. Measles spreads through respiratory droplets, usually over short distances but sometimes through suspension in the air for about 2 hours. Once acquired, measles has an incubation period of about two weeks and first presents by fever with one or more of cough, coryza or conjunctivitis, though, small white spots in the mouth may appear. Three-four days after disease onset, a rash starts from the head and moves down towards arms and legs. Complications have commonly been characterized as pneumonia, diarrhea, and keratoconjunctivitis but rarely the serious acute disseminated encephalomyelitis, measles inclusion body encephalitis, and subacute sclerosing panencephalitis [20].

Photo: Child with measles

3.1.2 Measles management

Measles can be challenging to diagnose. The rash can be absent or altered in immunocompromised or undernourished children. Furthermore, a longer incubation period, milder early symptoms, and a less visible rash can be experienced by children who already have antibodies from maternal immunity or immunoglobulin drugs. Moreover, measles can be confused with other rash causing viruses like, rubella. The most commonly used laboratory method to confirm measles is by detecting measles specific immunoglobulin M antibodies in a blood test; these are detected in most people 1-3 days after a rash onset. Measles has no specific treatment, only supportive care to prevent and manage complications. In the case of uncomplicated measles, recovery is usually within one week from rash onset. To date, vaccinating against measles is considered the most effective way to prevent it [20].

3.1.3 Measles epidemiology before MV

Before MV was introduced, measles was a leading cause of child mortality, globally [20]. In most high-income countries, the largest proportion of measles cases was in school children, though, measles transmission was also an issue in pre-school children, if they lived in densely populated areas. In the United States, about every 2 to 3 years, major measles epidemics would occur. About 500,000 measles cases were reported annually with complications in more than half of these cases and an estimated 500 deaths would be associated with the measles cases. Data indicates that children aged 0-4 years (37%) and 5-9 years (53%) made up the measles cases. By the age of 15 years most measles cases would usually have occurred. Children aged <1 year and adults had the highest risk of death. However, in many low-income countries, measles cases generally occurred in much younger children and serious complications of measles cases were more frequently observed [21]. Malnutrition was proposed as a major determinant, though, crowding may have played a bigger role than expected [22-24].

3.1.4 Measles epidemiology after MV

After MV was introduced, substantial progress happened. From 2000-2018, the global number of measles cases (853,479 to 353,236), measles incidence (145 to 49 cases per 1 million population), and measles deaths (535,600 to 142,300) more than halved. By 2018, about 23 million measles deaths were averted. Nevertheless, the African region seemingly still carries the largest burden [25]. In low-income countries, the case-fatality rate is between 3-6% and in high-income countries between 0.01-0.1% [26]. Though, measles remains a disease of young children, shifts are observed towards wider

age distributions, where incomplete disease control allows unvaccinated children to remain unexposed to measles into adulthood [20]. Nevertheless, although measles is no longer a leading cause of child deaths, it remains within the 10 leading causes of deaths in children aged 1-59 months, globally [27].

3.1.5 Measles elimination

All the WHO regions have the goal of measles elimination by 2020: Absence of measles in a defined geographical area for ≥12 months in the presence of an effective surveillance system (typically ≥95% coverage of two MV doses among children in every district of a country). From 2000-2018, the MV coverage has increased. Globally, the coverage of a 1st MV dose increased from 72%-86% and the coverage of a 2nd MV dose increased from 18%-69%. By 2018, the European region and Western Pacific region were close to a ≥95% coverage level for two MV doses, while the African region was the furthest away (74% coverage of a 1st MV dose and 26% coverage of a 2nd MV dose). Furthermore, by 2018, 42% of the countries with measles elimination goals were verified as having eliminated measles, though, no country in the African region has eliminated measles [25]. As the end of 2020 is approaching, a new goal for measles elimination and potential measles eradication [28] is awaited.

3.2 MV's specific effect

3.2.1 History

MV originated from the United States, where Thomas Peebles and John Enders isolated and cultivated the measles virus in 1954. MV, a live vaccine containing weakened measles virus, was licensed in 1963 from the Edmonston strain and has been used till date, worldwide. From 1989-1992, the WHO recommended the use of a high-titer MV for infants aged 6 months from low-income countries with a high measles incidence in children aged <9 months but this was discontinued [20]; a higher female mortality was observed among the recipients which nevertheless turned out to be related to the vaccination sequence with the non-live vaccine diphtheria-tetanus-pertussis (DTP) rather than the live high-titer MV itself [29]. In 1969, MV was also offered in combination with vaccines for mumps and rubella (MMR) to minimize injections, reduce missed vaccination opportunities, and increase cost effectiveness [21].

3.2.2 Administration

The specific goal of MV is to offer protection against measles [21]. Heat and light exposure can quickly inactivate the measles virus and thus cooled storage and protection from light is recommended before usage. MV may be stored between -70°C and -20°C to maintain its long-term potency but in general MV can be refrigerated at 2°C and 8°C. The MV comes in a freeze-dried powder form in a vial which must be diluted with sterile water cooled down to between 2°C-8°C. Then MV is administered with a 0.5 ml dose through subcutaneous injection, preferably, in the anterolateral thigh or upper arm, depending on age. The reconstituted MV loses 50% of its potency in 1 hour at 20°C-25°C and nearly all potency in 1 hour at 37°C. Reconstituted MV should be used within 6 hours to avoid contamination and loss of effect from temperature deviation and light exposure [26]. In 2020, the price for a 10-dose MV vial, which is most commonly used in low-income countries, was between $0,2370-$0,3180 [30] and MV is generally considered a cost-effective health intervention [31]. Nevertheless, to respond to some of the challenges of storing, preparing, handling, and administering MV, other alternatives are being studied. For example, MV administered with a microneedle patch applied to the skin where a dry vaccine formulation quickly dissolves in the skin, MV administered with dry or liquid vaccine formulation using different aerosol delivery devices, and MV administered as a DNA vaccine potentially immunogenic in the presence of maternal antibodies [21]. Moreover, children may acquire immunity passively through maternal measles antibodies if the mother has had measles or has been measles vaccinated. [21].

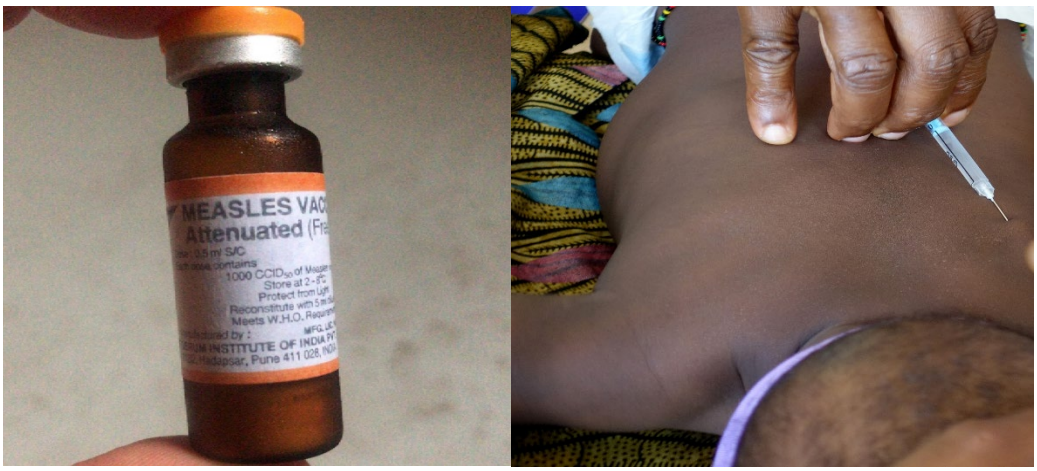

Photo: Administration of measles vaccine

3.2.3 MV delivered through routine vaccination programs

The WHO recommends that in countries with high measles incidence and measles mortality during the first year of life, a 1st MV dose should be administered at 9 months of age, and in countries where transmission is low and measles therefore occurs later in life, a 1st MV dose can be delayed until the age of 12-15 months. Nevertheless, MV is licensed to be administered from the age of 6 months to children likely to be susceptible, but this should be considered as a supplementary dose and not as a part of a routine vaccination program. A 2nd MV dose is needed to reach children who do not become immune after their 1st MV dose, which is approximately 15%, and the timing can be anything between 4 weeks after the 1st MV dose, in the second year of life, or at school entry. In general, countries with a history of stable MV coverage and low measles incidence may offer both MV doses at older ages through routine vaccination programs [26].

3.2.4 MV delivered through campaigns

The WHO recommends that in countries with weak health infrastructures, regular MV campaigns at community levels can be an effective way to protect children without access to routine vaccination program. Furthermore, MV campaigns may also respond to apparent immunity gaps caused by MV shortage or social disruption. In case national MV campaigns are not feasible or cost-effective, subnational MV campaigns may be implemented to prevent the number of susceptible children from accumulating [26]. Generally, the introduction of an MV campaign is through a nationwide catch-up campaign focusing on children aged 9 months-14 years, with the aim of eliminating general population susceptibility. Subsequently, periodic follow-up campaigns every 2-4 years focus on children born since the previous follow-up campaign with the aim of eliminating recent birth cohort susceptibility among children aged 9-59 months [25]. Availability of human resources determines the duration of MV campaigns but usually it should take place within a brief period (4-7 days to one month) and it should be administered irrespective of prior MV exposure [32], to ensure that herd immunity builds up rapidly [26]. Cessation of MV campaigns are only recommended once a national coverage of two MV doses is >90-95% coverage for at least 3 consecutive years [4]. The extent to which MV is offered through campaigns combined with mumps and/or rubella varies across the WHO regions, with the African and Eastern Mediterranean regions relying mostly on MV campaigns [3].

3.2.5 Protection

According to the WHO, the 1st MV dose has an effectiveness of 84% if administered at 9-11 months of age and 92% if administered at >12 months of age [26]. The majority of data suggests, that a single MV dose administered properly protects within a few days to weeks [33] and continues for life in most measles vaccinated [26]. Table 1 presents a brief overview of protection indicators reflecting the discussion on bringing forward the age of the 1st MV dose in countries with high measles transmission and high measles mortality in infants [34, 35] and its potential impact on a 2nd MV dose [36, 37]. Based on these protection indicators, it has been suggested to bring forward the age of the 1st MV dose [35] and that the protection of repeated MV doses is independent from the age at which the 1st MV dose is administered [37].

Table 1: Protection of MV with the 1st MV dose adminstered before or after age 9 months. Protection of subsequent MV doses with the 1st MV dose administered before or after age 9 months [35, 37]

	1st MV[a]		**Repeated MV[a]**	
	<9 mo	≥9 mo	1st MV <9 mo	1st MV ≥9 mo
Vaccine effectiveness[b]	58	83	95%	N/A
Seroconversion[c]	50	85	98	98
Geometric mean titer[d]	248	539	N/A	N/A
T-cell activation	72[e]	65[e]	11.4[f]	10.9[f]

Abbreviation: MV=measles vaccine; MO=months; N/A=not available. [a]In some cases combined with vaccines of mumps and rubella. [b]Proportion of vaccinated children in which measles was prevented if exposed (%). [c]Proportion of children who develop antibodies against measles (%). [d]Concentration level of antibodies against measles (mIU/mL). [e]Proportion of children with T-cell activation in recognizing measles (%). [f]Mean counts in antigen wells/mean counts in control wells.

3.2.6 MV's adverse events and precautions

Generally, adverse events after the 1st MV dose, are mild and usually occur within two weeks after vaccination (table 2).

Table 2: Adverse events following a 1st MV dose [21, 26, 38]

Description	**Timing after MV**	**Duration**	**Risk**
Mild			
Injection pain	<24 hours	2-3 days	N/A
Fever (>39C°)	7th-12th day	1-2 days	common
Rash	7th-10th day	2 days	common
Severe			
Febrile seizure	6th-14th day	N/A	common
Anaphylaxis	Minutes to hours	N/A	rare
Encephalomyelitis	8th-9th day	N/A	rare
Thrombocytopenia	N/A	N/A	rare

Except from the severe adverse event, anaphylactic shock, mild adverse events are less likely to occur after a 2nd MV dose [26], as most children have already gained immunity from their 1st MV dose, and thus a 2nd MV dose allows less replication of the live virus [21]. The few studies that have assessed adverse events after MV campaigns reported that adverse events were rare [39-43], though, most studies had no control group [39-41, 43]. These studies commonly assessed adverse events within one month from the campaign [39-41, 43] but some studies also assessed the adverse events within 6 weeks [42], two months [40], and one year [39] from vaccination. Mostly, adverse events following co-administration of MV with mumps, rubella, and/or varicella vaccines are mild and transient, but febrile seizures seem to be more commonly observed with MMR and varicella combined than MMR and varicella separately, though, not with a 2nd MMR and varicella dose [26]. In terms of precautions, the WHO recommends, that children are not administered with MV if they have moderate to severe concurrent infections, a severely suppressed immune system, or a history of anaphylactic reactions or severe allergic reactions to vaccine components [26].

3.3 MV's NSE

3.3.1 History

In the early 1980's, an observational study in Zaire (now the Democratic Republic of Congo) assessed the MV's effect on reducing measles related mortality [44] but the study revealed something unexpected; children aged 7-21 months who had received MV had a larger reduction in mortality

compared with children in the same group who had not received MV, which seemed unlikely to be explained by the prevention of measles deaths [45]. These observations were pursued in urban Guinea-Bissau among approximately 600 children aged 6-35 months who had been exposed to the introduction of a general MV program in 1980 after a severe measles outbreak in 1979. From 1979-1981, mortality dropped by nearly 50%, a drop that could not be explained by prevention of measles only [46]. Since, numerous studies have been conducted to reproduce these results (figure 1), which has led to several emerging patterns.

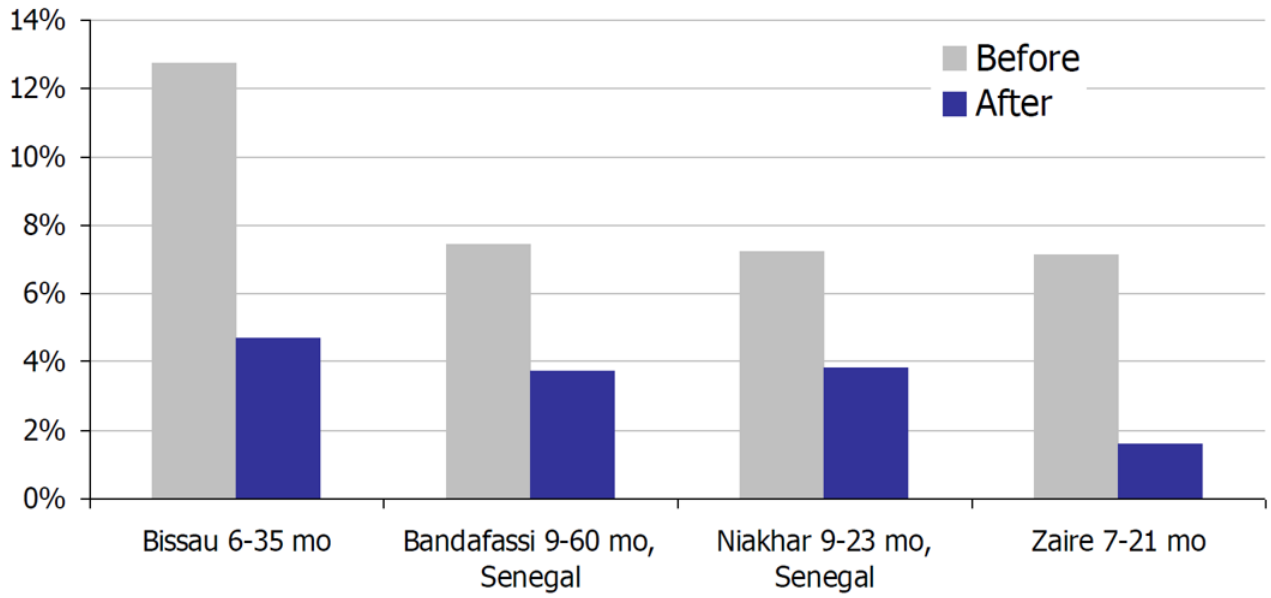

Figure 1: Reductions in child mortality before and after the introduction of MV into routine vaccination programs in Guinea-Bissau [46], Senegal [47, 48], and Zaire [45]. At the time, measles typically explained about 15% of the under-five child deaths in low-income countries [49]. Thus, for example, the 60% reduction observed in Guinea-Bissau (from approximately 13% to approximately 5%) after the introduction of MV suggested that child mortality dropped by nearly 50% due to causes unrelated to measles.

3.3.2 Emerging patterns

Beneficial NSE of MV have been observed at different ages, with pronounced effects is certain sub-groups, and dependent on other vaccines. In terms of age, beneficial NSE of MV may be observed after MV administration at different ages: a routine MV dose administered at 9 months of age [50], an early MV dose administered at 4.5 months of age before routine MV [51, 52] or at 4.5 months of age in addition to routine MV [53, 54], and a 2nd MV dose administered at 18 months of age [55] or

between 9-59 months of age in national MV campaigns [8, 9]. In terms of certain sub-groups, beneficial NSE of MV may be most beneficial if administered: in girls [8, 9, 53, 56], in the presence of measles antibodies acquired through prior MV [8, 9, 53, 57] or the mother [58], in the dry season [56, 59] where respiratory infections are most common [56, 60], in children who did not receive vitamin A at birth [61] or who received vitamin A after MV where MV was the most recent vaccination [62]. In terms of other vaccines, beneficial NSE of MV may vary dependent on sequence and co-administration. Live oral polio vaccine (OPV), has also been suggested to have beneficial NSE [6, 63] and in children who received OPV at birth but not OPV in campaigns, early MV seemed to have a more pronounced beneficial NSE [64]. Non-live, DTP, may have detrimental NSE by increasing mortality, despite protecting against its three specific diseases [65, 66] and MV's beneficial NSE may be inhibited if administered with DTP [67-70] or before DTP [29, 67, 69-71]. The abovementioned patterns have been guiding the research on MV's NSE.

3.3.3 Broader context

Most research on MV's NSE has been conducted in low- or middle-income countries [5]. However, in more recent years, MV's NSE has also been assessed in high-income settings [60, 72-74], where MV may have beneficial NSE on hospital admissions due to any infectious cause [75]. Typically, MMR as the most recent vaccine has been compared to DTP as the most recent vaccine among children in their second year of life [75]. The WHO commissioned systematic review's conclusion on MV's NSE was that MV reduced overall mortality by 26% (49% to -7%) based on four clinical trials and by 49% (58% to 37%) based on 18 observational studies [5] and that further trials were warranted [7]. A short summary is presented of the results reported from trials conducted on MV's NSE not included in the WHO commisioned systematic review, either because the trials were conducted after the review or because the trials reported on outcomes other than mortality (table 3).

Table 3: Results reported from trials assessing MV's NSE not included in the WHO commisioned systematic review [51, 52, 54-57, 61, 76-80]

Publication		Randomisation	Intervention		Control	Outcome			Sample (intervention/control)	Age at enrolment	Follow-up	ES (95% CI)
Author (year)	Enrolment		Type	Strain		Mortality	Morbidity	Other				Overall
Agergaard 2011, Guinea-Bissau (urban)	2005-2008	Individual	MV+ DTP +OPV (missing MV but at least 2xDTP)	Zagreb (standard)	MV +OPV	N/A	Visit at health center or hospital	Growth (z-score)	All: 568 (287/281) AE: 332 (161/171) MUAC: 276 (137/139)	9-48 MO	12 MO	Visit at health center: 1.16 (0.85-1.57) Weight: 0.03 (−0.19;0.26) MUAC: −0.01 (−0.23;0.22) Height: −0.05 (−0.33;0.24). No measles cases.
Martins 2014, Guinea-Bissau (urban)	2003-2007	Individual	Early MV	Zagreb (standard)	9 MO (routine), Zagreb/Schwarz (standard)	Published elsewhere	Hospital admission	N/A	6,417 (2,129/4,288)	4.5 MO	36 MO	0.70 (0.52–0.95). Measles censored: 0.78 (0.58–1.07)
Aaby 2014, Guinea-Bissau (urban)	1993-1997; 2003-2007	Individual	Early MV + detected maternal measles antibody	Zagreb (standard)	9 MO (routine), Zagreb/Schwarz (standard)	Death +/- maternal measles antibodies	Published elsewhere	Published elsewhere	1993-1997: 300 (150/150) 2003-2007: 1,398 (450/948)	4.5 MO	59 MO	Early MV + antibodies: 0.22 (0.07-.64) Early MV + second dose at 9 MO: 0.24 (0.08-0.73). No measles cases
Rasmussen 2016, Guinea-Bissau (urban)	2003-2007	Individual	Early MV	Zagreb (standard)	9 MO (routine), Zagreb/Schwarz (standard)	Published elsewhere	Publised elsewhere	Growth (MUAC cm, weight and height z-score)	4,266 (1,478/2,788)	4.5 MO	24 MO	MUAC: 0.08 (0.02-0.14) Weight: 0.01(−0.04-0.06) Height: 0.01(−0.05-0.07)
Do 2017, Guinea-Bissau (urban)	2011-2013	Individual, sex-specific randomization	Early MV	Zagreb (standard)	No early MV	Published elsewhere	Publised elsewhere	Symptoms, visit at health center, and medicine	1,592 (1,048/544)	4.5 MO	9 MO	Diarrhea: 0.89 (0.82–0.97) Vomiting: 0.86 (0.75–0.98) Fever: 0.93 (0.87–1.00) Visit at health center: 1.00 (0.90–1.11) Medicine: 0.96 (.89–1.04). No measles cases
Brønd 2018, Guinea-Bissau (urban)	2003-2007	Individual	Early MV +/- NVAS	Zagreb (standard)	Zagreb/Schwarz (standard) at 9 MO (routine) +/- NVAS	Published elsewhere	Hospital admission	N/A	5,626 (1,960/3,666)	4.5 MO	18 MO	2 dose - NVAS: 0.66 (0.47–0.93) 2 dose + NVAS: 1.16 (0.82–1.63) (p=.02 for interaction). Measles censored: 2 dose - NVAS: 0.67 (0.48–0.94) 2 dose + NVAS: 1.15 (0.82–1.63)
Fisker 2018, Guinea-Bissau and Burkina Faso (rural)	2012-2015 and 2013-2015	Individual	Early MV	Zagreb (standard)	9 MO (routine)	Death	N/A	N/A	8,205 (4,106/4,099)	4.5 MO	36 MO	1.05 (0.75–1.46). No measles cases.
Schoeps 2018, Burkina Faso (rural)	2013-2015	Individual	Early MV	Zagreb (standard)	9 MO (routine)	Death or	Hospital admission	N/A	4,496 (2,258/2,238)	4.5 MO	36 MO	1.00 (0.83–1.20). No measles cases.
Steiniche 2020, Guinea-Bissau (rural)	2012-2015	Individual	Early MV	Zagreb (standard)	No early MV	Published elsewhere	Visit at health center or hospital	Growth (z-score)	3011 (1516/1495)	4.5 MO	1 YRS	Visit at health center: 1.03 (0.91–1.15) MUAC: -0.01 (-0.06 - 0.04) Weight: -0.03 (-0.07 - 0.02). No measles cases.
Nielsen 2020, Guinea-Bissau (urban). NCT: 01486355	2011-2015	Individual	Early MV	Zagreb (standard)	9 MO (routine)	Death	N/A	N/A	6,598 (4,397/2,201)	4.5 MO	60 MO	1.38 (0.92-2.06). No measles cases.
Byberg 2020, Guinea-Bissau (rural). NCT: 01306006	2011-2015	Cluster (stratified by low/high pre-trial mortality)	MV for all (in MV unvaccinated children aged 9-35 MO regardless of number of children present	Zagreb (standard)	MV restrictive (in MV unvaccinated children aged 9-11 if >6 children present)	Death	Hospital admission	N/A	4,767 (2,428/2,339)	9 MO	59 MO	Death: 1.06 (0.78-1.44) Hospital admission: 0.95 (0.67-1.36)
Berendsen 2020, Guinea-Bissau (urban)	2016-2019	Individual, sex-specific randomization	MV booster (recevied MV1 and 3xpenta but not MV2)	Zagreb (standard)	Nothing	Death or	Hospital admission	Separated outcomes	3,164 (1,566/1,598)	17.5-24 MO	48 MO	Combined: 0.63 (0.31-1.28) Death: 0.50 (0.05-5.44) Hospital admission: 0.62 (0.30-1.28). No measles cases.

Abbreviation: AE=adverse events; CI=confidence interval; ES=estimate (relative risk (RR), hazard ratio (HR), mortality rate ratio); MO=months; MUAC=mid-upper-arm circumference; MV=measles vaccine; N/A=not available; NCT=national clinical trial number; NVAS=neonatal vitamin A supplement; OPV=oral polio vaccine.

As described in section 3.3.3, the WHO commissioned systematic review concluded that MV may reduce overall mortality by 26% (49% to -7%) based on four clinical trials [5]. Nevertheless, to suggest a more current overall effect of MV on child mortality, we generated a pooled estimate based on the trials included in the WHO commisioned systematic review [53, 81-83] and the trials conducted since the review which reported mortality estimates, as shown in table 3 [54, 55, 79, 80]. This yielded a reduction in overall mortality by only 5% (24% to -18%) (figure 2).

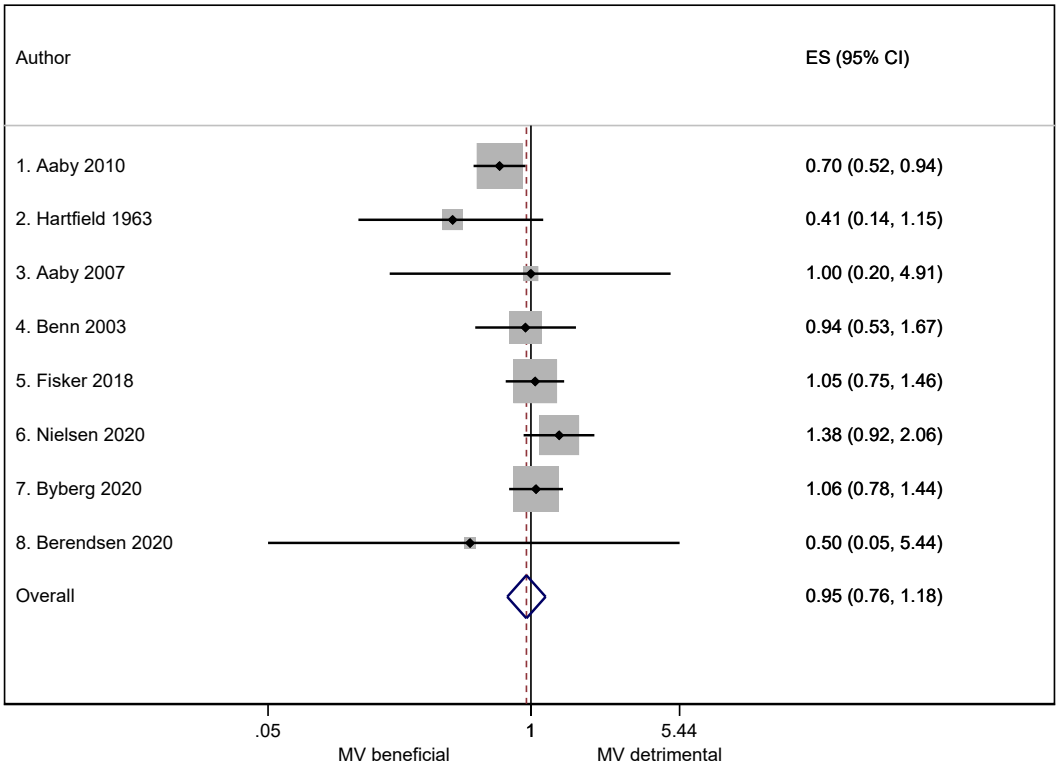

Figure 2: Meta estimate derived from a random effects meta-analysis. Studies with ID 1-4 are based on overall mortality estimates from trials included in the WHO commisioned systematic review [53, 81-83]. Studies with ID 5-8 are based on overall mortality estimates from trials conducted since the WHO commisioned review [54, 55, 79, 80].

4. METHODOLOGICAL FRAMEWORK

This chapter presents a summary of the Protocol article (appendix 4). Parts only briefly covered in the Protocol article, due to space limitations, are expanded here. Within each section, the common components of the Short-term article and the Long-term article are first addressed and then they are followed by descriptions of any article specific components.

4.1 Setting

The Bandim Health Project's (BHP) health and demographic surveillance system (HDSS) monitors mothers and their children living in rural Guinea-Bissau on the West African coast. Information on child health and vaccination status is systematically gathered by three field teams consisting of trained assistants and nurses in nine health regions covering 222 village-clusters. The data is collected every six months and then transported back to the capital, Bissau, where the data is entered, cleaned, and stored, by data management assistants [84].

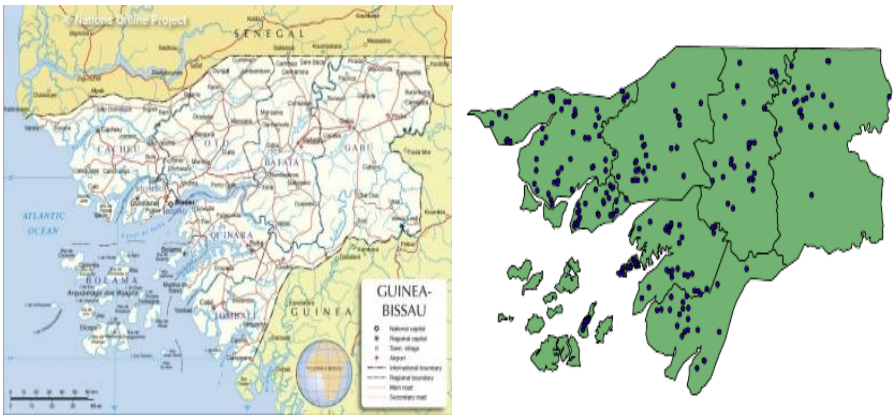

Photo: Left: Map of Guinea-Bissau. Right: Village-clusters in rural Guinea-Bissau's nine health regions: Oio, Biombo, Gabu, Cacheu/Sao Domingos, Bafata, Quinara, Tombali, Bubaque, and Bolama

The village-clusters were defined over time. In 1990, the BHP's rural HDSS was established. Given a rural population of approximately 830,000 at the time and the underlying assumption that 23% of the rural female population was of reproductive age (15-45 years), approximately 5% of the rural female population was sampled (10000 women) across five of the most populous health regions in 20 village-clusters from each health region. Hundred women were registered in each village-cluster. The village-clusters were selected based on a method applied by the Expanded Program on

Immunization to monitor national vaccination coverage in Guinea-Bissau. Within each region, the chance of a village being selected was proportional to the village population. In a selected village, all women within a geographically defined are were selected. If a village had less than 100 fertile women, the neighboring village(s) with the shortest distance was included. Oral consent was retrieved from each woman. By 2006, 182 village-clusters had been selected from all nine health regions. In 2015, the surveillance was intensified in one of the regions by adding an additional 40 clusters and in 2017 these 40 village-clusters were added to the 182 village-clusters as a consequence of the sample size needed for RECAMP-MV. Thus, an open cohort is followed by continuously registering when a girl reaches approximately 15 years of age or when a woman of fertile age moves into a village-cluster. A woman >49 years who moves into a village-cluster is not registered. All children under-five living in the selected village-clusters are followed, also children who may not have been born in the house of a village-cluster but have grown up there. Today, more than 25,000 fertile women and 23,000 under-five children are monitored in the original 182 village clusters [84]. Figure 3 shows how child mortality has been decreasing since the 1990's in rural Guinea-Bissau.

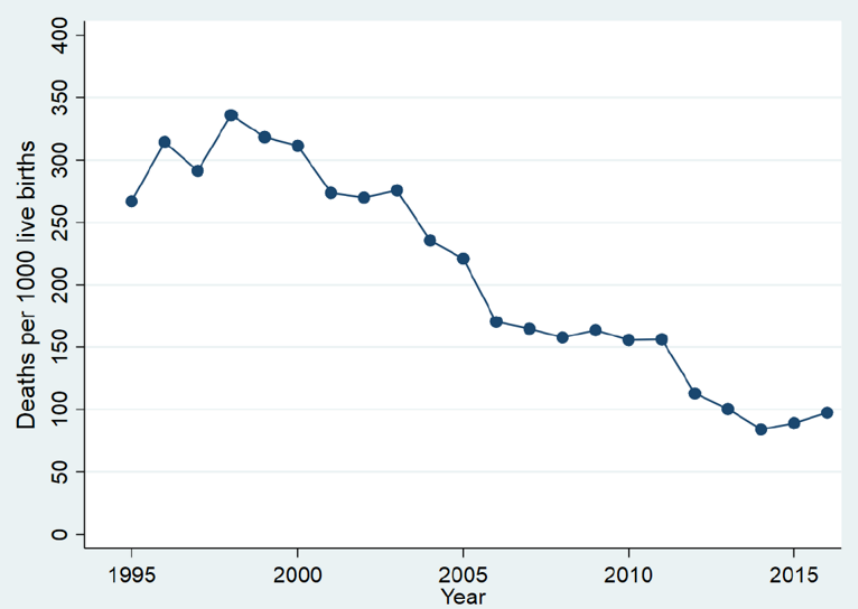

Figure 3: Under-five mortality in rural Guinea-Bissau from 1990-2017

The three field teams who are responsible for collecting data in rural Guinea-Bissau, have usually worked for BHP's rural HDSS for several years, and thereby have a strong knowhow, are attentive to accuracy in obtaining information, and closely relate to mothers and children. The common way of working is as follows. Before a field team arrives to a pre-assigned village in a health

region, the field assistants divide households between them and plan their visit routes. When field assistants enter a village, they acknowledge the presence of any villagers, and thereby create awareness on the field teams' presence from BHP who have come to monitor children and their vaccination status. Thus, information on the presence of the field teams is easily shared between villagers.

Photo: Field assistant conducting interview with mother in household

Upon arrival to a registered household, respective mothers and children are asked for. Although, the presence of the mother is key to valid information, in her absence, guardians (members of the family) or neighboring villagers can usually provide essential information in terms of death or hospital admission, due to shared living. This is what ensures that the field teams can always retrieve information on children and that correct identification of children is strong, as the same field assistants are used to visiting the same villages, over many years. In case of new child registrations, it inherently takes time to build up the same knowhow, but significant errors are prevented by the close supervisor monitoring of child information retrieved by new field team members.

4.2 Trial design

We applied a cluster-randomized design and randomized the 222 village-clusters to either an intervention group, where children were exposed to an MV campaign, or to a control group, where children were not exposed to an MV campaign. We choose a cluster-randomized design for the following reasons. Firstly, the inherent nature of an MV campaign is to take place at a group level as it aims to reach as many as possible in a defined population within a short period of time, regardless

of prior exposure to MV. Secondly, the set-up of a cluster randomized design ensured feasibility in reaching a sizeable sample size compared to previous randomized trials on MV's NSE. Thirdly, most trials have assessed early MV's potential NSE, and thereby in young age-groups, but with an MV campaign mimicking national MV campaigns in Guinea-Bissau, we were able to assess the overall effect in a broader age-group of children.

4.3 Participants

Children living with registered families in the 222 randomized village-clusters were eligible to enter RECAMP-MV, if aged 9-59 months, the usual target group in previous national MV campaigns (table 4). Children were excluded, if they had a/an:

1. overt illness, to indicate moderate or severe concurrent illness
2. axil temperature >39°C, to indicate moderate or severe concurrent illness
3. mid-upper-arm-circumference<110 mm, to indicate severe suppression of the immune system
4. history of allergic reaction after prior vaccination, to indicate risk of allergic reaction
5. enrolment in an ongoing BHP trial offering OPV to children aged 0-8 months

Criteria 1-4 ensured enrolment of children with a suitable health condition for receiving MV and criteria 5 ensured avoidance of data interpretative issues due to potential interactions with other ongoing health interventions.

4.4 Intervention context and administration

In the routine vaccination program of Guinea-Bissau, the 1st MV dose is scheduled at 9 months of age (figure 4). The 2nd MV dose is not a part of the routine vaccination program but has been administered independently from the routine vaccination program through nationally implemented MV campaigns, every third year (table 4). In Guinea-Bissau, there is restriction on the use of routine MV, as it is required that at least 6 children in the target age group 9-12 months are present before a 10-dose vial is opened [80].

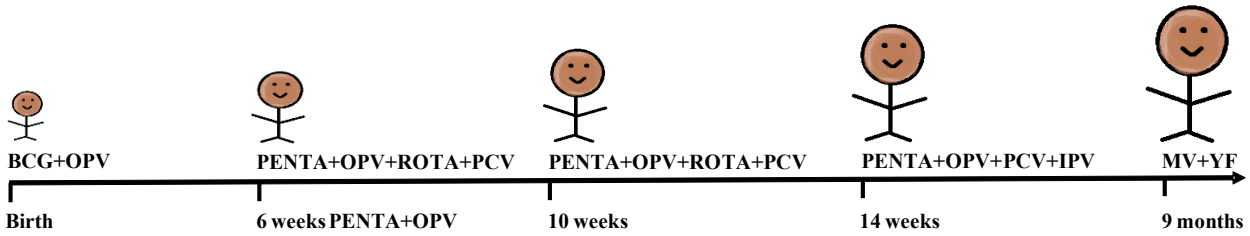

Figure 4: Routine vaccination program in Guinea-Bissau. **Abbreviation:** BCG=Bacille Calmette Guerin vaccine (introduced: 1985). OPV=Oral polio vaccine (introduced: 1985). MV=measles vaccine (introduced: 1985). DTP=diphtheria, tetanus and pertussis (introduced: 1985-2008). PENTA= diphtheria, tetanus, pertussis, hepatitis type b, and haemophilus influenza type b vaccine (introduced: 2008). YF=yellow fever vaccine (introduced: 2008). PCV=pneumococcal conjugate vaccination (introduced: 2015). PCV=pneumococcal conjugate vaccination (introduced: 2015). ROTA=rotavirus vaccine (introduced: 2016). IPV=inactivated polio vaccine (introduced: 2016) [85].

Despite the lack of a 2nd MV dose and some coverage and incidence fluctuations, Guinea-Bissau has maintained a low measles risk profile for the last decade. The last measles outbreak was in 2004 and before 2004 the coverage of a 1st MV dose fluctuated between 35%-68%, whereas for the last decade the coverage has been 80% on average. In 2006 the first national MV campaign was implemented as a part of the measles elimination strategy [3, 85] (table 4).

Table 4: Measles cases [85], MV coverage [85], and MV campaigns [3] in Guinea-Bissau according to the WHO's country data

Year	Cases[a]	1st dose[b]	National MV campaigns				
			Age	Days	Co-administrations	Target	Reached
2004	3,526	80					
2005	0	80					
2006	0	60	6mo-14yr	15	Vit A (6-59mo)+meb (12-59mo)[c]	646,977	91%
2007	1	80					
2008	12	64					
2009	0	79	9-59mo	5	Vit A (6-59mo)+meb (12-59mo)[c]	206,517	100%
2010	26	78					
2011	0	78					
2012	0	90	9-59mo	5	Vit A (6-59mo)+meb (12-59mo)	247,786	89%
2013	0	89					
2014	1	81					
2015	153	90	9-59mo	5	Vit A (6-59mo)+meb (12-59mo)	261,487	86%
2016	0	71					
2017	11	66					
2018	28	79					
2019	60	79	9-59mo	7	Vit A (6-59mo)+meb (12-59mo)	287,545	83%

Abbreviation: MEB=mebendazole MO=months; MV=measles vaccine; VIT A=vitamin A; YR=years. [a]absolute numbers. [b](doses administered/target population)*100. [c]Information derived from local knowledge on campaign administration in Guinea-Bissau.

In RECAMP-MV, field nurses administered a 0.5 ml dose of the WHO prequalified live MV of the Edmonston-Zagreb strain from Serum Institute of India to children in the intervention group, regardless of their prior MV status. Each 10-dose vial was reconstituted with cooled sterile water provided by the manufacturer, using a sterile 5 ml syringe, giving a gentle shake. Field nurses wiped the children's skin with water-soaked cotton on the injection site and administered the dose with a deep subcutaneous injection into the left subscapular region. Field nurses noted the time of vial opening to ensure discarding it within six hours. The cold chain was documented. The group assignment was not registered in the children's vaccination cards to avoid the risk of differential treatment by the health care system. The main MV stock was kept in Denmark in Statens Serum Institut's monitored freezers with an average -20°C. On regular flights smaller vaccine stocks were transported to Guinea-Bissau in thermo boxes with frozen cooling elements. In Guinea-Bissau, the

MV stock was kept in -30 freezers and for the field, MV was transported in the WHO safety approved thermo boxes with frozen cooling elements.

4.5 Randomization

In the randomization of village-clusters, we wanted to ensure a balance in health care access, as this inherently has an impact on child survival. Thus, to minimize the risk of random variation driven by any potential imbalance in health care access, we stratified the cluster-randomization on health region and pre-trial vaccination coverage. Health region would reflect the physical distance to health care services but also potential behavior towards health care services, as certain ethnic groups live in certain health regions. Pre-trial vaccination coverage would reflect received health care.

Based on data from BHP's rural HDSS, for each health region, we extracted information on children who had received a visit approximately one year prior to the initiation of RECAMP-MV. For each child aged 12-23 months, we assessed vaccinations obtained by 12 months of age [86], that had been verified with a seen vaccination card. BCG, 3rd OPV dose, 3rd PENTA dose, and MV were the assessed vaccinations, as they are considered the core routine vaccines in Guinea-Bissau. We constructed a binary variable for each vaccination reflecting whether or not a child had received it before 12 months of age. This fed into a binary variable reflecting whether or not the individual child had been fully vaccinated before 12 months of age. We then calculated the vaccination coverage as the mean of the binary variable at the village-cluster level. Within each region, we identified the median vaccination coverage, which we used as a threshold to define low and high pre-trial vaccination coverage. Within each pre-trial vaccination coverage level, we assigned half of the village-clusters to the intervention group and the other half to the control group for each health region. A person who was not involved in RECAMP-MV defined a seed number and ran a prepared program generating a randomization list for each health region.

4.6 Blinding

No one in RECAMP-MV was blinded towards the cluster-randomization. If the mothers/guardians were blinded, they could have thought that their child was already protected through the trial, which could have prevented them from reaching out to the routine vaccination program. If the field teams were blinded, a placebo would be necessary. The ethical aspect of causing unnecessary pain with saltwater injection in thousands of children is debatable and another vaccine could also have NSE

[87]. Furthermore, as the field teams relied on the cluster-randomization lists to plan logistics and ensure resources before remote field visits, blinding was not feasible.

4.7 Enrolment

Enrolment took place from November 2016 to January 2019. Prior to enrolment, we visited a representative from the health authorities of each health region and:

- explained RECAMP-MV: why, what, when, how and who
- requested collaboration on storing MV in health center fridges
- requested collaboration on waste management of vials
- requested collaboration on alarming us in case of adverse events
- informed about a debriefing upon trial completion

We conducted several rounds of enrolment. As described in the Protocol article, the written informed consent and enrolment both took place in Portuguese Creole, managed by the field teams: (1) the field assistants conducted household visits to invite mothers/guardians of eligible present children to the health post (Appendix 1). (2) at health posts the field nurses/field assistants carefully explained RECAMP-MV and from interested mothers/guardians retrieved signatures or fingerprints if illiterate (Appendix 2). (3) the field nurses performed health check-ups by conducting structured enrolment interviews with mothers/guardians and administered MV to children assigned to the intervention group (Appendix 3).

Photo: Field nurse at the health post

4.8 Follow-up and outcome

All enrolled children were followed through BHP's rural HDSS regular household visits. We took advantage of the same routines and questionnaires as the rural HDSS during follow-up. RECAMP-MV applied the following outcomes:

- Primary outcome: non-accidental mortality or non-accidental hospital admission (overnight stay at health facility), in a composite outcome, onwards referred to as mortality or hospital admission (Long-term article).
- Secondary outcomes: non-accidental mortality (Long-term article), non-accidental repeated hospital admission (Long-term article), cause-specific primary outcome (Long-term article), and outpatient consultation (Short-term article).

For the Short-term article, we conducted an extra follow-up visit in a subgroup of enrolled children within 1-2 months from enrolment in the health regions Oio, Biombo, Gabu, Cacheu/Sao Domingos, Bafata, and Bolama. We revisited children enrolled in RECAMP-MV from January 2017 to September 2018. The outcome, outpatient consultation, was defined as the mother/guardian reporting a first contact with a health facility within 1-2 months after enrolment where the child received medical attention unrelated to an accident and did not stay overnight. Due to delays, some revisits took place >2 months after enrolment. Onwards, we refer to the outcome as outpatient consultation. See the supplementary methods in the Short-term article on how we retrieved information on outpatient consultation.

Photo: Health facility in Guinea-Bissau where outpatient consultations can take place

For the Long-term article, we conducted several follow-up visits to all enrolled children. If a field assistant registered the death of a child, a specially trained field assistant conducted a verbal autopsy at a subsequent visit [88]. Death causes were classified by a physician. See the supplementary methods in the Long-term article for information on how we retrieved information on death and hospital admission. The follow-up took place from January 2017 to May 2019 where an MV campaign was nationally implemented by the Ministry of Health in Guinea-Bissau. Thus, we would be able to disentangle the observed effect in RECAMP-MV from that of the national MV campaign.

Photo: Hospital in Guinea-Bissau

4.9 Pilot phase

During the enrolment pilot phase in the health region, Biombo, from November 2016 to March 2017, we learned that to accommodate demanding logistics, we needed to implement some changes, thus, we, e.g.:

- conducted enrolments in villages with many eligible children over 1-3 days instead of one day
- trained extra field assistants to conduct informed consents
- ensured permission to provide one consent information letter to a mother of several children
- trained field assistants to ask mothers/guardians in the households about any medicine consumption of eligible children; mothers/guardians typically forgot or did not know at the health post what type of medicine their child had taken on the day of enrolment, if any, and thus, requesting them to bring the medicine to the health post ensured that the field nurse could make a better qualified health evaluation of children

4.10 Sample size

As described in the Protocol article, we wanted to verify the total enrolments needed to ensure a better allocation of resources. Thus, for the Long-term article, we re-evaluated the planned sample size of 14,500 children together with a data safety and management board. The revised sample size was based on data from the first complete enrolment and follow-up round in all health regions and as such, only the revised sample size calculations are presented here (table 5). In the Short-term article, logistics determined the sample size of the sub-group. Figure 5 illustrates the design of RECAMP-MV.

Table 5: Sample size based on estimates derived from the first enrolment and follow-up round.

Number of clusters	222
Alpha	0.05
Between cluster variation coefficient	0.25
Number of eligible children to be enrolled	18,000
Observed non-accidental deaths or hospital admission rates	15/1,000 pyrs[a]
Harmonic mean of total projected accumulated observation time per cluster	84 pyrs
Expected reduction	30%
Power	*80%*

Abbreviation: PYRS=person-years. [a]Assuming that the observed composite outcome rate (15/1,000 pyrs) was an average of the rates in the intervention village-clusters and the control village-clusters, and that the real difference between the village-clusters was 30%, we assumed the rates to be 12/1,000 pyrs in the intervention village-clusters and 17/1,000 pyrs in the control village-clusters, when we re-evaluated the sample size.

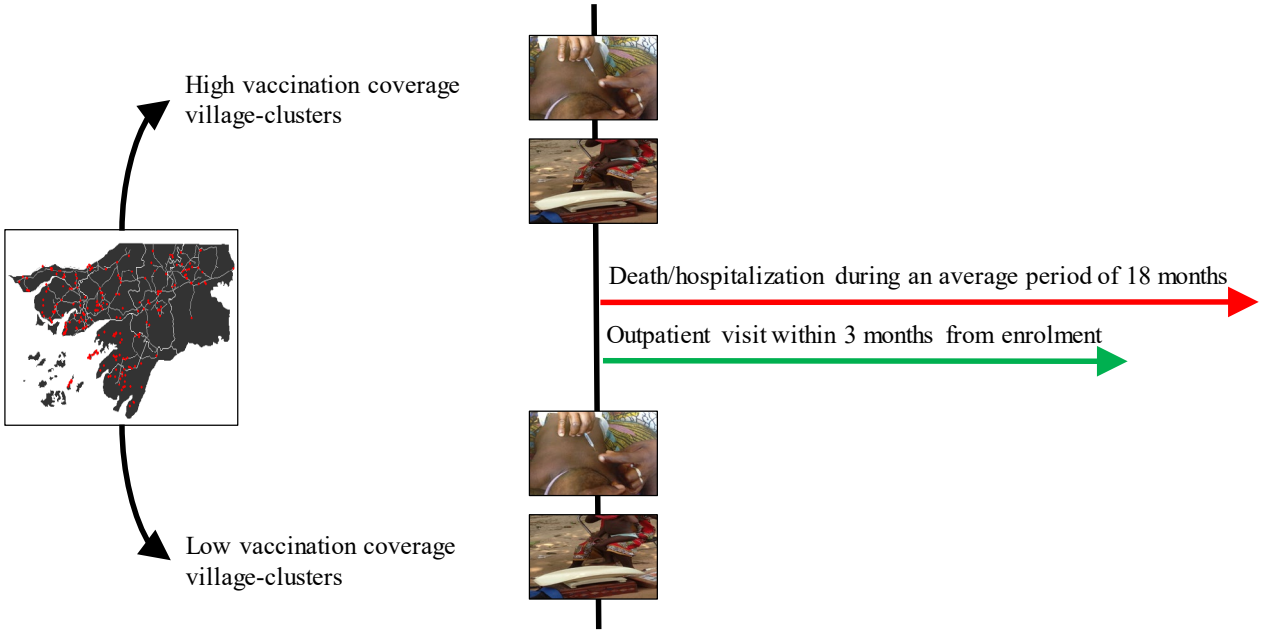

Figure 5: RECAMP-MV trial design.

4.11 Statistical analyses

In STATA 16, we performed planned analyses based on a data analysis plan reviewed by the data safety and monitoring board (Protocol article). We also performed exploratory analyses, described with details in the Short-term article and the Long-term article and each of their supplementary methods. We based the main result in the Short-term article and the Long-term article on per-protocol analyses, as these would establish the biological plausibility of MV's potential beneficial NSE by yielding overall effects under controlled circumstances in the community with ideal vaccine uptake circumstances. However, where possible, we complemented the per-protocol analyses with intention-to-treat analyses, as described in the sections of the statistical analyses for the Short-term article and the Long-term article below. We analyzed all outcomes based on individual level data to gain power and applied a 95% CI. We adjusted for the stratification variables (health region and pre-trial vaccination coverage) already described in section 4.5, and for sex. We accounted for intra-cluster correlation via robust standard errors. We did not use imputation for missing values because we did not expect a large proportion of missing data, given the rural HDSS' experience with gathering the same data through decades. As we were assessing an MV campaign's overall effect via several different analyses that each, to some extent, reflected the same underlying phenomenon of interest,

child health, we did not correct for multiple testing, which we nevertheless needed to take into account when interpreting results, especially for subgroup analyses.

For the short-term article, we had planned the per-protocol analysis of an MV campaign's overall effect on outpatient consultations. The remaining analyses were exploratory per-protocol analyses. We did not complement the per-protocol analyses with intention-to-treat analyses, as we did not have information on outpatient consultations for all children in the sub-group of enrolled children. We applied log-binomial models yielding relative risks (RR), which are generally easy to communicate and interpret for a wider audience.

For the long-term article, we had planned the per-protocol analysis of an MV campaign's overall effect on mortality or hospital admission in a composite outcome. We hypothesized at least a 30% reduction based on estimates from previous studies [5]. Available data on the composite outcome for the majority of the randomly assigned children, allowed us to complement the per-protocol analysis with intention-to-treat analyses (classic and expanded) (see the Protocol article for more details), as these estimates would reflect overall effects under everyday circumstances in the community, where national MV campaigns target children under more flexible conditions. Except from the intention-to-treat analyses, the remaining planned and exploratory analyses, were all per-protocol. The primary outcome and secondary outcomes were analyzed with time to event analyses to include the available information on children who did not experience the composite outcome during RECAMP-MV. We applied Cox proportional hazards models yielding HR. A key advantage of this model was that we could adjust for age via the underlying time scale instead of including age as an explanatory variable in the modelling. This enabled us to adjust for age without imposing parametric assumptions which is desirable because mortality differs over age. Children entered the analysis on their enrolment day, and their follow-up was censored due to one of the following reasons: death due to accident, hospital admission due to accident was ignored but the follow-up time during the hospital admission was censored, migration, or eligibility for the national MV campaign on May 3rd, 2019. We used log-log plots and global tests based on Schoenfeld residuals to assess the model assumption of proportional hazards (constant HR over age).

4.12 Ethics

We retrieved ethical approval from Guinea-Bissau (Comité Nacional de Ética na Saúde, CNES/2016/020) and consultative approval from Denmark (Den Nationale Videnskabsetiske Komité, 1606756). We retrieved written informed consents from mothers/guardians. To the extent

possible, on a monthly base, we were in touch with an adverse event following immunization responsible (AEFI) for each health region to retrieve information on measles outbreaks and any adverse events. We had informed mothers/guardians of children in the control group, that upon completion their children would be offered MV. This was the plan unless a nationally implemented MV campaign would take place, as expected every third year.

Photo: Poster of the national MV campaign in Guinea-Bissau on May 3rd, 2019, marking the end of RECAMP-MV.

5. RESULTS

This chapter briefly presents the main results reported in the Short-term article (appendix 5) and reported in the Long-term article (appendix 6). In general, unless illustrated in figures here, referrals to tables and figures are made to each respective article in the appendices.

5.1 Short-term article

The size of the sub-group of enrolled children was 8,319 (4,437 intervention/3,882 control) coming from 167 clusters (86 intervention/81 control). We conducted revisits with a median of 31 days from enrolment to revisit (31 intervention/32 control) (Short-term article - table 1). We had complete information on 92% of the revisited children (93% intervention/91% control) (Short-term article - figure 1). We found no differences in baseline characteristics (Short-term article - table 1 and supplementary table 1). None of the children were exposed to OPV campaigns during the revisit (Short-term article - table 1). We observed 652 (322 intervention/330 control) outpatient consultations which were not due to accidents or measles (Short-term article - table 2).

Figure 6 shows, that the MV campaign tended to reduce outpatient consultations, especially if caused by respiratory symptoms. Among children who had their vaccination cards seen at enrolment, the reduction tended to be larger in children who prior to enrolment had PENTA (+/- co-administered MV) as the most recent vaccination than in children who prior to enrolment had routine MV (+/- co-scheduled yellow fever vaccine) as the most recent vaccination (figure 6). The overall reduction in outpatient consultations was robust to several restrictions on the outcome definition (Short-term article - table 2) and there were no sex-differential effects (Short-term article - table 3).

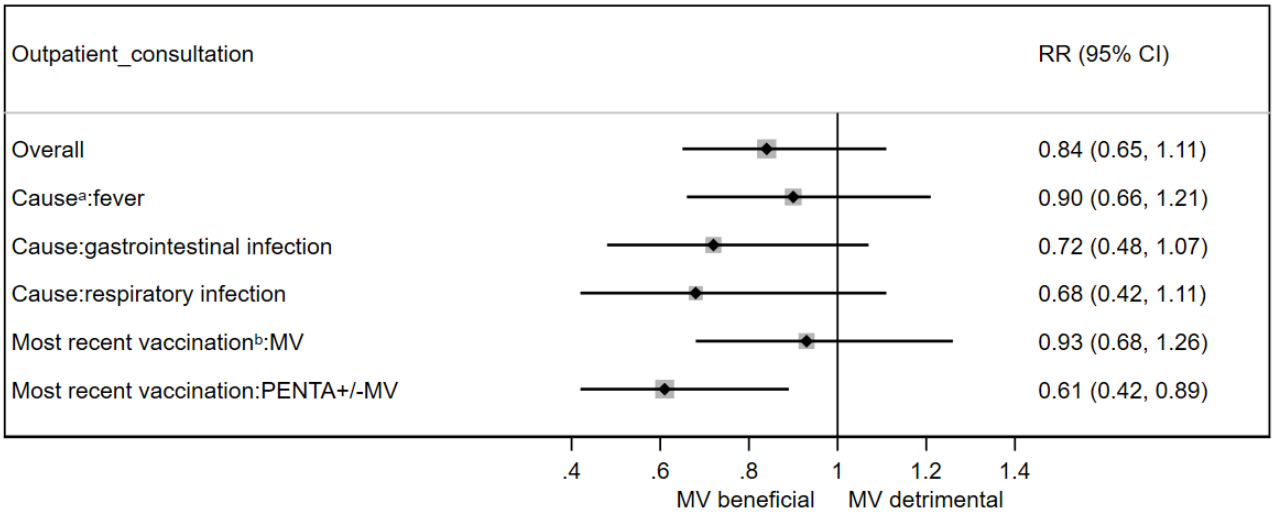

Figure 6: Forest plot of the main results reported in the Short-term article. [a]One outpatient consultation could count in more than one symptom group if a child had multiple symptoms that belonged to different cause categories (Short-term article - supplementary methods). [b]P-value=0.04 for interaction between MV campaign*most recent vaccination. Routine MV could have been co-scheduled with a yellow fever vaccine. **Abbreviation:** CI=confidence interval; MV=measles vaccine; PENTA=diphtheria, tetanus, pertussis, hepatitis b, and haemophilus influenza b; RR=relative risk.

5.2 Long-term article

We enrolled 18,411 children (9,636 intervention/8,775 control) over a two-year period (Long-term article - figure 1). We followed the children for a median of 22 months (22 intervention/22 control) between enrolment and the national MV campaign on May 3rd, 2019 (Long-term article - table 1). Ninety-three percent of the children had their last visit after the national MV campaign (93% intervention/92% control) (Long-term article - figure 1). We found no differences in baseline characteristics (Long-term article - table 1 and supplementary table 1). We observed 379 deaths or hospital admissions (208 intervention/171 control) under 29,405 pyrs at risk (15,423 intervention/13,982 control) (Long-term article - table 2). None were due to measles, 12 deaths were due to accidents which were censored, and the admission period of 6 hospital admissions due to accidents was censored (Long-term article - supplementary table 2).

Figure 7 and figure 8, show, that the MV campaign did not reduce mortality or hospital admission in a composite outcome (figure 7 and figure 8). We observed the same in the intention-to-treat analyses (Long-term article - table 4) and there were no sex-differential effects (Long-term article - table 3). As the MV campaign's overall effect was HR 1.12 (CI 0.88-1.41) (figure 8), we set out to identify potential clustering of deaths or hospital admissions. In the intervention group 38% (31/82) of the deaths and in the control group 46% (30/65) of the deaths, occurred in children enrolled on the same date. In the intervention group 69% (118/170) of the hospital admissions, and in the control group 78% (104/134) of the hospital admissions, occurred in children enrolled on the same date. Thus, we found no indication that the MV campaign may have led to clusters of deaths or hospital admissions.

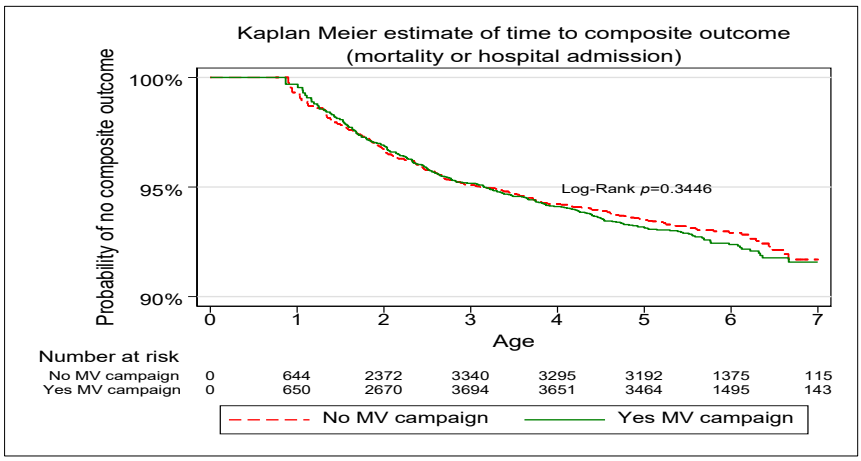

Figure 7: Kaplan Meier plot. **Abbreviation:** MV=measles vaccine.

During follow-up, 75% of the enrolled children were exposed to OPV campaigns (74% intervention/76% control) (Long-term article - table 1). Figure 8 shows, that the MV campaign tended to increase mortality or hospital admission after eligibility for OPV campaigns but not before eligibility for OPV campaigns, an effect which was sex-differential, in that girls tended to have a lower risk before eligibility for OPV campaigns but a higher risk after (figure 8).

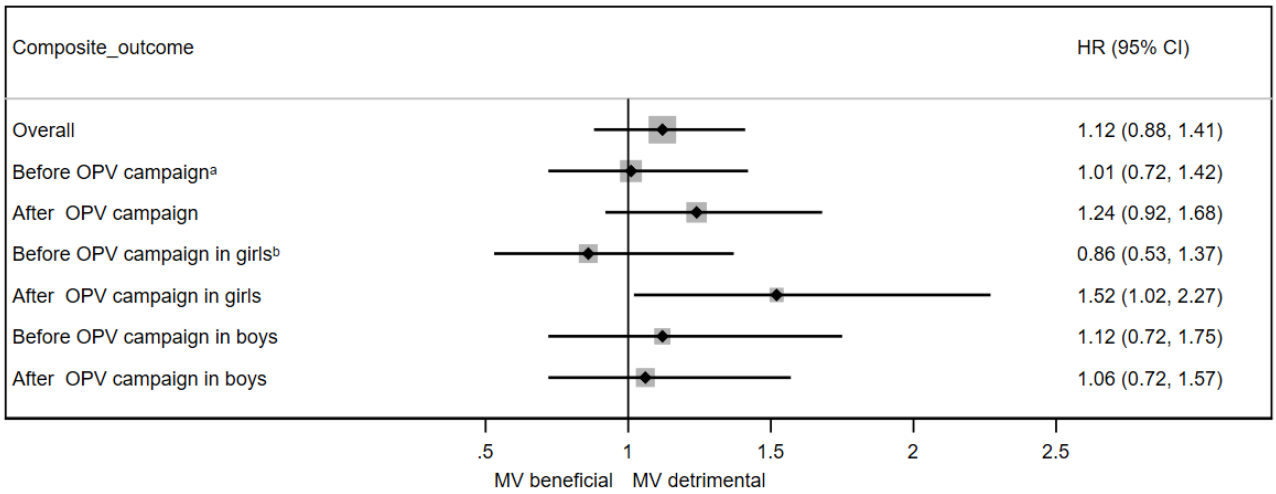

Figure 8: Forest plot of the main results reported in the Long-term article based on the composite outcome. [a]P-value=0.35 for interaction between MV campaign*OPV campaign. [b]P-value=0.11 for interaction between MV campaign*OPV campaign*sex, and p-value=0.06 for interaction between MV campaign*OPV campaign*girls. **Abbreviation:** CI=confidence interval; HR=hazard ratio; MV=measles vaccine; OPV=oral polio vaccine.

Figure 9 and figure 10 show, that when we separated the composite outcome, we observed similar overall effects and differential effects before and after eligibility for OPV campaigns, also by sex, to some extent for mortality (figure 9) but mostly pronounced for hospital admission (figure 10).

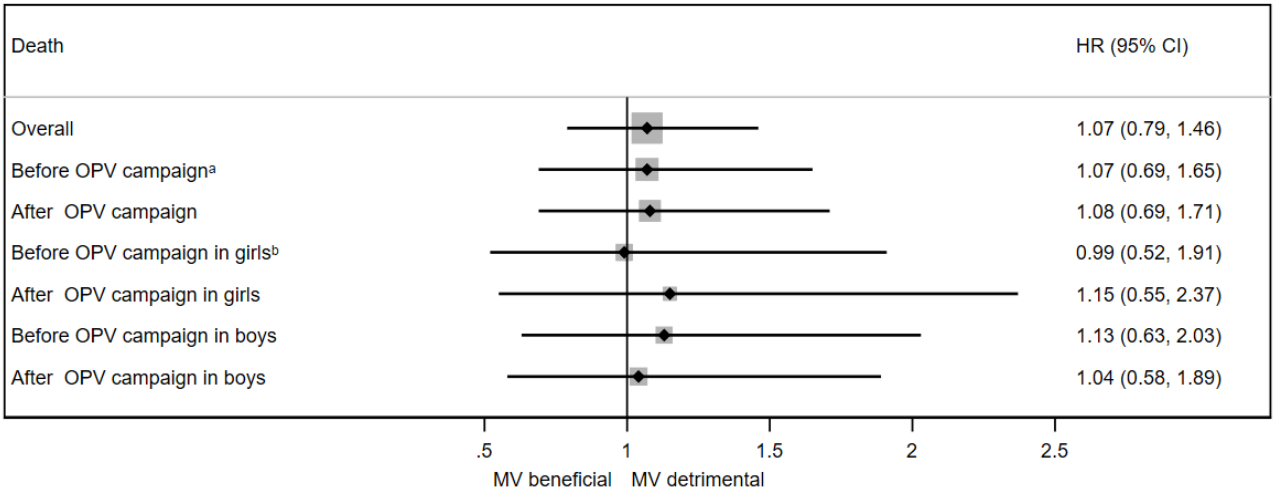

Figure 9: Forest plot of the main results reported in the Long-term article based on death. [a]P-value=0.97 for interaction between MV campaign*OPV campaign. [b]P-value=0.72 for interaction between MV campaign*OPV campaign*sex, and p-value=0.78 for interaction between MV campaign*OPV campaign*girls. **Abbreviation:** CI=confidence interval; HR=hazard ratio; MV=measles vaccine; OPV=oral polio vaccine.

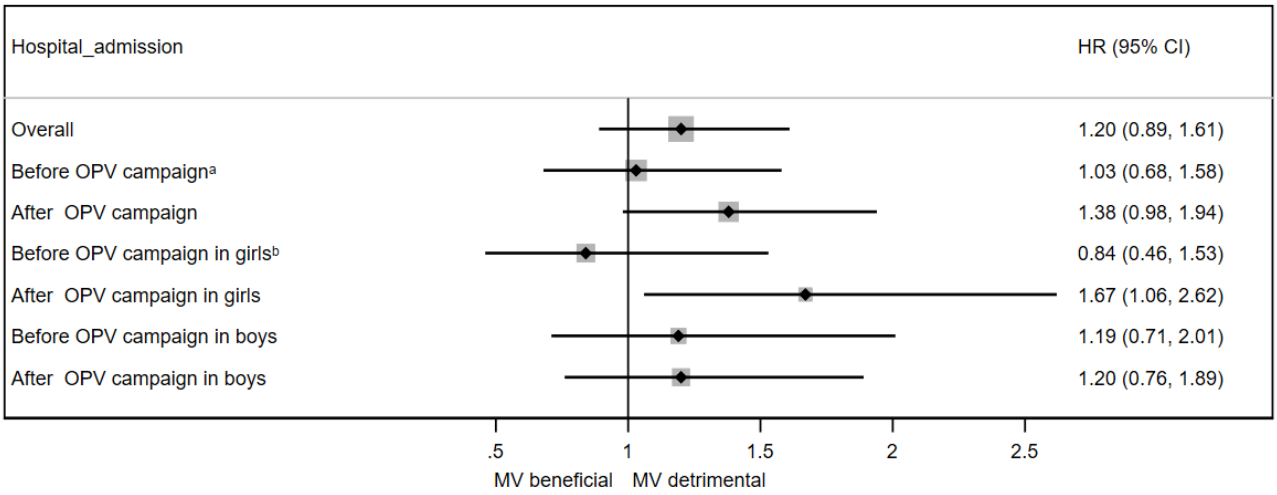

Figure 10: Forest plot of the main results reported in the Long-term article based on hospital admission. [a]P-value=0.26 for interaction between MV campaign*OPV campaign. [b]P-value=0.16 for interaction between MV campaign*OPV campaign*sex, and p-value=0.05 for interaction between MV campaign*OPV campaign*girls. **Abbreviation:** CI=confidence interval; HR=hazard ratio; MV=measles vaccine; OPV=oral polio vaccine.

Given the observation, that the MV campaign tended to increase mortality or hospital admission after OPV campaign eligibility but tended to reduce mortality or hospital admission before OPV campaign eligibility, we conducted a meta-analysis and meta-regression based on RECAMP-MV and trials which reported the estimate of MV's overall effect on death and the proportion of children who had been exposed to OPV campaigns prior to enrolment [79, 80]. In the meta-analysis, the pooled estimate indicated an increase in the overall mortality after MV exposure (figure 11).

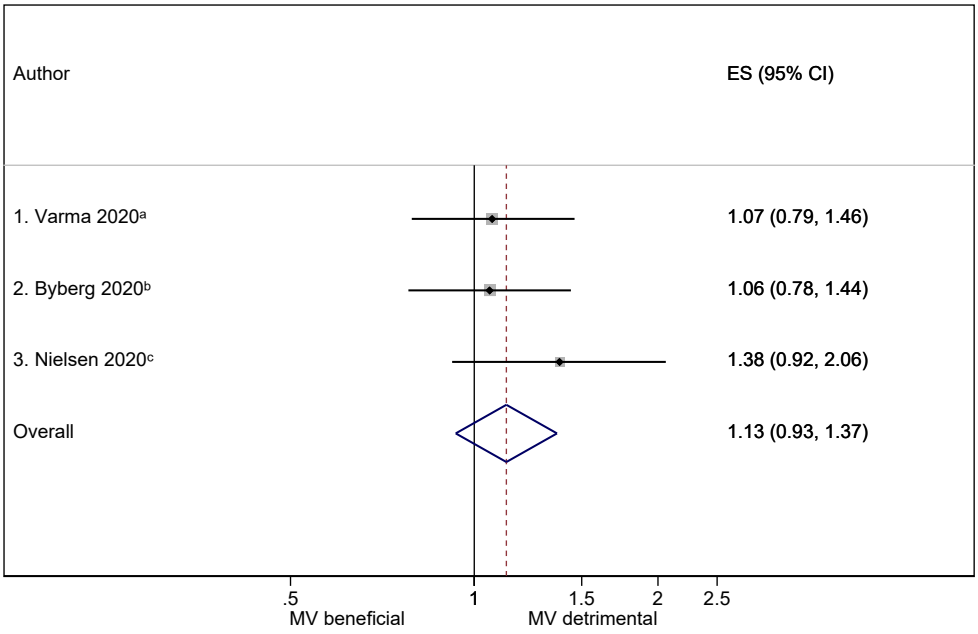

Figure 11: Meta estimate derived from a random effects meta-analysis based on the overall mortality estimates from RECAMP-MV (figure 9) and other trials [79, 80] reporting an overall effect of MV on mortality and reporting the proportion of children exposed to OPV campaigns. When we adjusted for the proportion of children eligible for OPV campaigns before enrolment in the meta-regression ([a]85%, [b]99%, [c]37%), the pooled estimate indicated a reduction in overall mortality (HR 0.64, CI 0.00-117.4). **Abbreviation:** CI=confidence interval; HR=hazard ratio; MV=measles vaccine; OPV=oral polio vaccine.

6. DISCUSSION

This chapter highlights the main results, followed by a discussion of weaknesses, consistency with other studies, and interpretation. Within each section, the common components of the Short-term article and the Long-term article are first addressed and then they are followed by discussions of any article specific components.

6.1 Main results

In the short-term, the MV campaign tended to reduce outpatient consultations, especially if caused by respiratory infections, and among children who prior to enrolment had PENTA (+/- co-administered MV) as the most recent vaccination compared to routine MV (+/- co-scheduled yellow fever vaccine) (section 5.1). In the long-term, the MV campaign did not reduce mortality or hospital admission in a composite outcome. Instead, we observed an increase in mortality or hospital admission after OPV campaign eligibility, which seemed to be driven by a differential effect in girls; the MV campaign tended to increase mortality or hospital admission after OPV campaign eligibility but tended to reduce mortality or hospital admission before OPV campaign eligibility. We observed the same, especially for hospital admission, when we separated the composite outcome (section 5.2).

6.2 Strengths and weaknesses

RECAMP-MV has several strengths which lie within the trial's sample size, cluster-randomization stratified by health region and pre-trial vaccination coverage, and BHP's rural HDSS platform allowing high data quality and follow-up. Nevertheless, we must consider some weaknesses.

Firstly, RECAMP-MV was an unblinded trial. Thus, we cannot rule out differential self-selection to enrolment or differential health care seeking behavior. In terms of self-selection, in both the intervention group and the control group, the proportion of eligible children who had mothers refusing/being busy and thus declining participation was less than 1% and enrolled children in the intervention group did not have a higher risk of their guardians being consent givers instead of their mothers. If mothers/guardians had based their participation decision on information shared by participating villagers, we could have observed a difference in participation and consent givers, but this was not the case. Moreover, the balance we observed in baseline characteristics did not suggest any serious self-selection. In terms of health care seeking behavior, mothers/guardians of children in the intervention group may have changed their threshold for seeking health care potentially caused by a false sense of security or concern from observing their children receive or not receive MV. For

example, in the Short-term article, we observed, that among ill children, the MV campaign tended to reduce outpatient consultations (Short-term article - supplementary table 4) but we cannot know whether this was because mothers/guardians ascribed their symptoms to adverse events or other causes. In either case, it also remains unknown to us, whether mothers/guardians of these children believed that their symptoms were not severe enough to seek outpatient consultation and/or whether their symptoms in fact were less severe. Nevertheless, we would expect more outpatient consultations among children in the intervention group due to fever within two weeks from enrolment, but we did not observe this (Short-term article - table 2 and supplementary table 2), and thus, the observed potential beneficial NSE of a 16% reduction, may give a fair indication of the potential magnitude of risk reduction by an MV campaign in the short-term. As for the Long-term article, in the blinding analyses (Long-term article - supplementary results and supplementary table 16), we observed that the MV campaign did not reduce the risk of dying in health facilities which could have been the case had mothers/guardians gotten a false sense of security, and thereby not contacted the health care system in case of serious illness among their children. Overall, we believe that the impact of non-blinding is limited by the following reasons: Reporting on a death occurrence is unlikely prone to subjectivity. Standard questionnaires were used to retrieve information on outpatient consultation and hospital admission which did not carry information on group assignment. Health care staff deciding whether a child should be admitted/consulted or not remained unknown to group assignment as we did not register group assignment on any child health records.

Secondly, the dates of the outcomes and their causes were based on parental reports. In terms of date, we cannot rule out imprecision. However, as we always asked about an outpatient consultation, hospital admission, and death, since the last field visit, it enabled us to place either of these outcomes before or after enrolment. Moreover, in the Long-term article, due to the regular length of visit intervals of approximately six months, we were also able to place hospital admission and death within approximately six-month intervals. In terms of cause, we also cannot rule out imprecision. The most feasible cause distinction was between outcomes due to accidents or not. As we expect accidental outcomes to be easier to recall than symptoms, we consider the parentally reported accident information, as valid. Had we relied solely on identifying specific diseases, which may be more difficult to recall, the imprecision concern would be genuine. For example, measles may have been confused with another infection, which could have led mothers/guardians to either over- or under report measles related outpatient consultations, deaths, or hospital admissions. Previously, BHP's rural HDSS mothers/guardians have reported suspected measles during periods where results

from blood tests in their respective health regions were negative for measles antibodies but positive for rubella antibodies. Thus, overreporting can occur but as mothers/guardians did not report any outpatient consultation, hospital admission, or death, due to measles, a concern for RECAMP-MV was potential underreporting, though we think the risk is limited: even if mothers/guardians did not recognize their children having measles, we could expect that the approached health care staff would have recognized measles and initiated testing and tracing, given measles' high contagiousness, making it unlikely for mothers/guardians not to recall, when asked. Furthermore, many mothers/guardians have co-living elderly persons who have experienced previous measles outbreaks, and therefore would be able to recognize measles, in case mothers/guardians would not.

Thirdly, there is a risk of chance results. Although we did not adjust for multiple testing, the numerous exploratory analyses still need to be interpreted with caution. This combined with some effect modifier analyses only conducted in sub-groups or across many strata needs to be considered, as it increases the risk of chance results. An example of an effect modifier analysis in a sub-group was the most recent vaccination PENTA (+/- co-administered MV) vs routine MV (+/- co-scheduled yellow fever vaccine) among children with seen vaccination card at enrolment, as observed in the Short-term article. An example of an analysis across many strata was the effect modifier analysis on ethnicity groups, as observed in the Long-term article (Long-term article - supplementary table 12).

Fourthly, in the Short-term article, we only revisited enrolled children once after their enrolment within the revisit period, and thus we may have missed some potential reports of outpatient consultations caused by mothers'/guardians' lack of recall. Furthermore, the sample size was determined by the logistics of the trial.

Fifthly, in the Long-term article, although the cluster-randomization was stratified by health region and pre-trial vaccination coverage, the pre-trial mortality rate in the two preceding years of RECAMP-MV (10.1 per 1,000 pyrs) was higher than the one observed in RECAMP-MV children (4.9 per 1,000 pyrs). When we examined the pre-trial mortality rate in the village-clusters belonging to RECAMP-MV's intervention group and control group, it was higher in the intervention group (intervention 11·1 per 1,000 pyrs/control 8.9 per 1,000 pyrs). This may have reduced the chance of observing beneficial effects of the MV campaign, if the underlying level and pattern of mortality was fundamentally different for children belonging to the village-clusters of the intervention group. However, adjusting for pre-trial mortality did not affect the conclusions and the pre-trial mortality rate did not predict the mortality rate observed during RECAMP-MV (Long-term article - supplementary table 15).

6.3 Comparison with other studies

In the Short-term article, we observed that the MV campaign tended to reduce outpatient consultations and as we discussed in the Short-term article, we found one study supporting this. In a retrospective cohort study from the United Kingdom, adverse events of an MMR campaign among 2,170 children aged 11-15 years, were assessed. Within six weeks from the campaign, participants had less outpatient department visits (4/1,077 vs 14/1,075: RR, 0.29; 95% CI, 0.10-0.87) and cough symptoms (RR, 0.83; 95% CI, 0.70-0.99) than non-participants [42]. However, children were older and not randomized to campaign participation. Two randomized trials from Guinea-Bissau assessed outpatient consultations among children who received MV at 4.5 months of age or no early MV, and who were followed until 9 months of age [51, 52]. Despite younger age groups and individual instead of cluster-randomization, their outcome was also outpatient consultation and their follow-up method was comparable. Both trials showed that early MV was safe, but not that it also reduces outpatient consultation. One of the two trials reported outpatient consultation by cause but results did not indicate a differential effect across respiratory infection, gastrointestinal infection and malaria infection [52]. The retrospective cohort study did not assess the most recent vaccination prior to study participation [42], but the two trials had taken PENTA into account by enrolling children who had received PENTA prior to enrolment; given that no differential effect was observed between early MV vs no early MV [51, 52], we did not find support for our observation on PENTA as a potential effect modifier.

Although, the MV campaign tended to reduce outpatient consultation in the short-term, as discussed in the Long-term article, we did not observe such potential beneficial NSE of the MV campaign in the long-term, on mortality or hospital admission in a composite outcome. Two recent observational studies found that national MV campaigns in addition to the routine vaccination program reduced mortality among children aged 6-59 months [8, 9], inconsistent with the main result in the Long-term article. However, the MV campaigns were co-administered with other health interventions and took place in periods with less frequent OPV campaigns [8, 9]. Since the WHO commisioned systematic review [5], four randomized trials have assessed MV's effect on mortality and/or hospital admission, as described in section 3.3.3 [54, 55, 79, 80]. Although, MV campaigns were not the focus and the age-groups differed, the outcome in all trials was mortality and/or hospital admission and their follow-up method was comparable. In two of the four trials, children were randomized to early MV at 4.5 months of age vs no early MV [54, 79]. In a third trial, village-clusters were randomized to increased MV access regardless of age vs usual practice with a restricted MV

policy [80]. Consistent with the main results in the Long-term article, none of these three trials found an overall beneficial effect of MV on mortality or hospital admission [54, 79, 80]. However, in the fourth trial, children aged 18 months were randomized to a 2nd MV dose vs no 2nd MV dose and a reduction of 37% (28% to 69%) in mortality or hospital admission (as a composite outcome) was reported when children were censored at eligibility for OPV campaigns [55]. Despite sparse events, a combined analysis of three trials focusing on early MV [53, 54, 79] showed that MV tended to increase mortality after eligibility for OPV campaigns but tended to reduce mortality before eligibility for OPV campaigns, especially in girls [89], in line with the main result in the Long-term article.

6.4 Interpretation

As stated in the objective, assessing the overall effect of an MV campaign on mortality and morbidity, would capture any potential specific effect and NSE, and even adverse events, thereby providing a complete risk-benefit profile of an MV campaign (section 2.1).

In terms of the MV campaign's specific effect, ascribing any of the results of RECAMP-MV to the MV campaign's prevention of measles seems unlikely. Even though, during the trial, measles increased from 0 cases in 2016 to 60 cases in 2019 [85], no outpatient consultation, hospital admission, or death was reported by mothers/guardians, as caused by measles. Moreover, neither during our regular presence in the field nor during our regular contact with the Ministry of Health, were we informed about a measles outbreak.

In terms of the MV campaign's beneficial NSE, the Short-term article showed that the MV campaign tended to reduce outpatient consultations within 1-2 months from enrolment. Knowledge on a mechanism behind such potential beneficial NSE of MV remains limited [90], but two immunological theories are prevailing [6]: heterologous immunity, where T-cells facilitate cross-protection towards other pathogens [91], and trained immunity, where epigenetic reprogramming partly facilitates immunological memory in the innate immune system [92]. The Short-term article furthermore showed that the reduction in outpatient consultations may be due to respiratory symptoms. A proposed explanation is that there may be some cross reactivity between MV's measles virus component and acquired viruses like respiratory syncytial, parainfluenza, and influenza [93]. Moreover, the Short-term article showed that the reduction in outpatient consultations was potentially modified by the most recent vaccination prior to enrolment. Children with PENTA (+/- co-administered MV) as the most recent vaccination tended to have a more pronounced reduction in outpatient consultations than children with routine MV (+/- co-scheduled yellow fever vaccine) as

the most recent vaccination. Given previous observations of interactions between PENTA and MV [67, 68], children with PENTA, suggested to have detrimental NSE, may have been worse off and therefore may have had more to gain from the MV campaign, compared to children with routine MV as the most recent vaccination. However, we cannot disentangle whether we observed the strongest benefits for children with PENTA (+/- co-administered MV) as the most recent vaccination, due to PENTA itself or due to its co-administration with routine MV.

In terms of the MV campaign's beneficial NSE, the Long-term article showed that the MV campaign did not reduce mortality or hospital admission in a composite outcome, as we had hypothesized. As discussed in the Long-term article, we made three observations related to OPV campaigns potentially explaining why we did not observe a reduction, especially, in the light of prior studies suggesting potential interference of OPV campaigns on the beneficial NSE of MV [80, 89]. Firstly, as already presented, the MV campaign tended to increase mortality or hospital admission after OPV campaign eligibility but not before, a differential effect seemingly driven by girls. Secondly, this pattern was the same for any vitamin A campaign (+/- co-administered OPV) but not for vitamin A campaign without OPV co-administration (Long-term article - table 3). Thirdly, the majority of RECAMP-MV children were eligible for OPV campaigns both before enrolment (85%) and during follow-up (75%) (Long-term article - table 1). However, as furthermore discussed in the Long-term article, we explored two other potential explanations, though we did not find support for them: (1) New vaccines in the routine vaccination program (against streptococcus pneumoniae, rotavirus, and yellow fever) could have made a difference, as beneficial NSE of MV have mostly been observed in children without exposure to these vaccines. However, we did not observe a reduction in mortality or hospital admission among children without these vaccinations, on the contrary (Long-term article - supplementary results and supplementary table 11). (2) The length of the follow-up period could have made a difference, as an MV campaign's beneficial NSE have previously been observed within a six-month follow-up period [8], but we did not observe a marked change in the overall effect before or after six months, especially when censoring at OPV campaign eligibility (Long-term article - supplementary table 13).

In terms of the MV campaign's expected adverse events, although, the Short-term article showed that fever, a common mild adverse event, was the most frequently reported cause of outpatient consultations, we did not find that it was more common in the intervention group (Short-term article - supplementary table 2). As the majority of children had received their 1st MV dose before they were enrolled in RECAMP-MV (83%) (Short-term article - table 1), we may consider that the MV

campaign was mainly administered as a 2nd MV dose, which is assumed to have fewer adverse events than the 1st MV dose [38]. In the Long-term article, with the main result indicating a 12% increase in mortality or hospital admission and a CI ranging from a 12% decrease to a 41% increase, we cannot make any firm conclusion on the overall effect in the long-term.

Albeit we did observe reductions, these were much lower than what we would expect. The MV campaign tended to reduce outpatient consultations by 16% in the Short-term article, but this reduction was much lower than what has previously been observed for other morbidity outcomes, like hospital admission. Moreover, the MV campaign tended to reduce mortality or hospital admission in girls before OPV campaign eligibility by 14% in the Long-term article, much lower than the 30% we had hypothesized for the composite outcome. Given that we observed that the pre-trial mortality was higher than the mortality observed in RECAMP-MV, this may indicate a lower incidence of severe and/or fatal infections among the enrolled children. RECAMP-MV, as other more recent trials [54, 79, 80], may not be observing beneficial NSE of MV, due to a potential change in the current disease pattern, in the disease pattern specific to the RECAMP-MV children, and/or in the receptiveness to beneficial NSE. Furthermore, there may be disease pattern differences behind outpatient consultations, hospital admissions, and deaths, as individual health outcomes.

Moreover, we speculate about the overall contrast that we observed, as the MV campaign tended to reduce outpatient consultations in the short-term, but not mortality or hospital admission in the long-term, despite the children originating from the same RECAMP-MV cohort. Considering the potential interference of OPV campaigns, we may have observed beneficial NSE of the MV campaign in the short-term and not long-term due to differences in OPV campaign exposure. The sub-group of children in the Short-term article was unexposed to OPV campaigns during the revisit period (Short-term article - table 1) compared to the children in the Long-term article where the majority of the children were exposed to OPV campaigns during the follow-up period (Long-term article - table 1).

In the background chapter of this PhD thesis, a meta-analysis was presented that suggested a current pooled estimate of MV's potential overall effect on child mortality based on trials included in the WHO commisioned systematic review and trials conducted since the review (section 3.3.3). This yielded a reduction of 5% (24% to -18%) (figure 2) which is much lower than a reduction of 26% (49% to -7%) suggested by the systematic review commisioned by the WHO [5]. Given the observations in RECAMP-MV with potential interference from OPV campaigns, we therefore conducted a meta-regression (figure 11) only based on the trials which also reported the proportion of children who had been exposed to OPV campaigns [79, 80]. When we adjusted for the proportion

of children eligible for OPV campaigns before enrolment, the pooled estimate indicated a 36% reduction in overall mortality (0% to -117.4%). Though a wide CI, it nevertheless suggests that the role of OPV campaigns needs to be considered to obtain a true estimate of MV's potential beneficial NSE in the present situation.

7. CONCLUSION

This PhD thesis presented the main results of RECAMP-MV. RECAMP-MV evaluated the overall effect of an MV campaign among children aged 9–59 months on mortality and morbidity, in rural Guinea-Bissau, a setting with limited measles (Protocol article). The results of RECAMP-MV's Short-term article and Long-term article were derived from a cluster-randomized trial, where 222 village-clusters were randomly assigned to receive an MV campaign (intervention group) or not to receive an MV campaign (control group). The short-term article showed that the MV campaign tended to reduce outpatient consultations within 1-2 months from enrolment, suggesting that an MV campaign is safe and may have beneficial NSE in the short-term, potentially caused by respiratory symptoms, and potentially among children with PENTA as their most recent vaccination compared to children with routine MV as their most recent vaccination. The long-term article showed that the MV campaign did not reduce mortality or hospital admission in a composite outcome, contrary to the hypothesis of a 30% reduction. However, during follow-up OPV campaigns were implemented, and we found that, the MV campaign tended to increase mortality or hospital admission after OPV campaign eligibility but tended to decrease mortality or hospital admission before OPV campaign eligibility, especially in girls. Considering the potential interference of OPV campaigns, we may have observed beneficial NSE of the MV campaign in the short-term and not long-term because the sub-group of children in the Short-term article were largely unexposed to OPV campaigns, contrary to the children in the Long-term article.

Photo by Nicolas Le Goff: One of the many field assistants ready to head into the rural fields of Guinea-Bissau to collect child health data

8. PERSPECTIVES

Most studies have assessed MV's beneficial NSE on mortality, but with the decreasing child mortality it is becoming increasingly relevant to consider less severe outcomes. In addition to outpatient consultation and hospital admission, medicine consumption may be a potential outcome to consider. As described in section 4.9, we trained field assistants in reminding mothers/guardians to bring any medicine their children may have consumed on the enrolment day to the field nurse at the health post to ensure a better qualified assessment of children's health status before enrolment. Though, we did not have the opportunity to apply medicine consumption as an outcome in RECAMP-MV, it may be possible to integrate it as a future outcome upon which field assistants retrieve information regularly. Potential recall issues may be circumvented with documentation on any related medical accessory (e.g. packaging, bottle, prescription). Over time, perhaps in collaboration with pharmacies, commonly consumed medicines could feed into a photo archive which field assistants could share with mothers/guardians while retrieving information on medicine consumption during household visits.

As mentioned in section 3.2.2, there are ongoing vaccine developments of MV. The microneedle patch may become able to respond to some of the practical circumstances that prevented blinding in RECAMP-MV, as it would be easier to disguise the intervention, remove unnecessary pain in control children, and make trial implementation less burdensome logistically. Although it would not respond to the ethical aspect of giving placebo which could make mothers/guardians not seek needed routine vaccines because they think they are covered through a trial, in this aspect, microneedle patches could perhaps make a difference for trials enrolling children who have completed their routine vaccination program.

An ongoing cluster-randomized trial, RECAMP-OPV, is assessing the beneficial NSE of an OPV campaign on mortality or hospital admission among children aged 0-8 months in rural Guinea-Bissau (NCT: 03460002). Although a younger age-group, after some follow-up years, it may be possible to assess the interaction between the OPV campaign preceding both routine MV and MV campaigns. With the nearing polio eradication and initiation of replacing OPV with a non-live polio vaccine [94], a phaseout of OPV campaigns may likely precede a phaseout of MV campaigns, which could offer a natural opportunity to study the NSE of MV campaigns in the absence of OPV campaigns. Nevertheless, the observed potential interaction between an MV campaign and an OPV campaign in RECAMP-MV calls for an understanding before a repurposed use of MV campaigns is considered for implementation, once measles is eliminated and eventually eradicated.

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10. APPENDICES

Appendix 1

The explanation given by field assistants to mothers of eligible children in households (in English and Portuguese-Creole)

Appendix 2

The information letter and informed consent administered by field nurses (in English and Portuguese-Creole)

Appendix 3

The enrolment form administered by field nurses for enrolled children (in English and Portuguese-Creole)

Appendix 4

The Protocol article

Publication and following supplementary material: analysis plan

Appendix 5

The Short-term article

Proof version and following supplementary material: methods and tables

Appendix 6

The Long-term article

Draft and supplementary methods, supplementary results, figures, supplementary figures, tables, supplementary tables

Appendix 1

Explanation given by field assistants to mothers of eligible children in households

1. **Past years**: Ministry of health campaigns with measles and oral polio vaccines

2. **Now**: Cases of illness with polio and measles rare

3. **Future:** Campaigns may stop

4. **Before campaigns stop:** PSB examine if good for children's health to stop or continue

5. **To do so:**

    5a. 2 groups
    5b. group 1 → vaccination
    5c. group 2 → no vaccination
    5d. today all children weight and health examination
    5e. end of study all children vaccination

6. **Volunteer participation:** If you want to hear more, go to the post with this form

1. Anos passados: Campanhas do Ministério da Saúde com vacinas contra o sarampo e pólio

2. Agora: Casos de doença com sarampo e polio são raros

3. Futuro: Campanhas podem parar

4. Antes da parar as campanhas: PSB examinar qual é melhor para saúde → parar ou continuar

5. Para fazer isso:

5a. 2 tipo tabanca
5b. tabanca 1 → vacinação
5c. tabanca 2 → sem vacinação
5d. hoje: todas as crianças → pesar e exame de saúde
5e. fim de estudo: todas as crianças → vacinação

6. Participação voluntária: Se você quiser ouvir mais, vá para o post com este formulário

Appendix 2

Information letter and informed consent administered by field nurses

PSB number __ __ __ __ __ __ __ __

Over the past years, the Ministry of Health in Guinea-Bissau has provided the measles and polio vaccine in campaigns. The Bandim Health Project has been working with vaccines in Guinea-Bissau for more than 35 years.

Data collected by the Bandim Health Project show, that the measles and polio vaccine reduces general child mortality. With only little measles and polio infection in Guinea-Bissau, the campaigns with measles and polio vaccine may stop soon. Recent studies show, that campaigns with measles and polio vaccine may reduce general mortality and morbidity among children.

The Bandim Health Project therefore wants to study whether the campaigns with measles and polio vaccine are still beneficial for children in an environment with limited measles and polio infection by implementing an extra campaign in half of the villages followed by the Bandim Health Project. We invite your child to participate in our study. If you want your child to take part, you should come for weighing at the Bandim Health Project nurse post. In intervention villages, after weighing, your child will be offered a measles or polio vaccine. In control villages, your child will be weighed and offered a measles vaccine by study end in late 2018. Participation in the study is voluntary and you can withdraw your consent to participate at any time.

A Bandim Health Project nurse will examine your child's health on the day of enrolment. Whether you choose to withdraw your consent or your child is excluded because it is ill, your child will be treated the same way at future village visits. Your child will have access to free consultations when the Bandim Health Project visits the village. If necessary, essential medicines will be available without cost. Children can have minor adverse reactions to measles vaccine such as pain and tenderness at injection site, fever, or a rash. Children may have minor adverse reactions to the polio vaccine such as self-limiting diarrhea. Severe adverse reactions are rare but can be explained to you upon your request.

All personal information collected in this study is strictly confidential. The results of the study will be published, but the identity of all participants will be hidden. The study is expected to be completed by the end of 2019. You can ask for the results if you are interested. The Bandim Health Project will keep data archived. The ethics committees in Guinea-Bissau and Denmark have approved the study and in the unlikely event, appropriate insurance is in place.

If you have questions to the study at any point please contact the study team through the project supervisor Claudino Correia, 966284608/955435117. He will facilitate the contact to the study responsible Amabelia Rodrigues (a.rodrigues@bandim.org), Ane Bærent Fisker (a.fisker@bandim.org) and Anshu Varma (avar@ssi.dk).Thank you very much for your attention. Do you have any questions?

PSB number __ __ __ __ __ __ __ __

Either the information letter was explained to me or I read it myself. I understand that:

- my child will either be offered a measles or polio vaccine at the weighing session today or a measles vaccine by the study end, depending on the group that my village belongs to.
- my child should still receive all vaccines in the childhood immunization program, as current policy regardless of which group my child belongs to.
- my child will have access to free consultations when the Bandim Health Project visits the village. If necessary, essential medicines will be available without cost.
- my child may experience minor adverse reactions and that the risk of severe adverse reactions is rare.
- my child's participation is based on my full consent. I can withdraw my consent at any time without further explanation. If I remove my child from the study or if my child will be excluded because it is ill, it will not compromise any relation to the Bandim Health Project.

I was given the opportunity to ask any questions about the study and my participation. The questions were answered satisfactorily. My participation is voluntary and based on my sovereign decision.

Name of parent/guardian _____

Signature or fingerprint _____

Dd__ __ / mm__ __ / 20 __ __

I have witnessed the accurate explanation of the information letter to the participant, and he/she has had the opportunity to ask questions about the study and his/her participation. I confirm that the participant has consented.

Name of witness _____

Signature of witness _____

Dd__ __ / mm__ __ / 20 __ __

I _____ (name), nurse of the Bandim Health Project, declare that I have explained the study and its implications to the parent/guardian. He/she understood the explanation, and gave his/her consent to participate.

Signature of Bandim Health Project nurse _____

Dd__ __ / mm__ __ / 20 __ __

Nos últimos anos, o Ministério da Saúde da Guiné-Bissau tem proporcionado a vacina contra o sarampo e polio em campanhas. O Projecto de Saúde Bandim tem vindo a trabalhar com as vacinas na Guiné-Bissau há mais de 35 anos.

Os dados recolhidos pelo programa Projecto de Saúde Bandim, que a vacina contra o sarampo e polio reduz a mortalidade geral da criança. Com apenas pouco infecção sarampo e polio na Guiné-Bissau, as campanhas com a vacina contra sarampo e polio pode parar em breve. Estudos recentes mostram, que as campanhas com a vacina contra o sarampo e polio pode reduzir a mortalidade geral e morbidade entre as crianças.

Por conseguinte, o Projecto de Saúde Bandim quer estudar se as campanhas com a vacina contra sarampo e polio ainda são benéficos para as crianças em um ambiente com infecção sarampo e polio limitados através da implementação de uma campanha extra na metade das aldeias seguido pelo Projeto Saúde Bandim. Convidamos a sua criança a participar em nosso estudo. Se você quer que seu filho participe, você deve vir para a enfermeira no posto do Projecto de Saúde Bandim para pesagem. Nas aldeias de intervenção, após a pesagem, seu filho vai ser oferecido uma vacina contra o sarampo ou polio. Nas aldeias de controle, seu filho vai ser pesado e ofereceu uma vacina do sarampo ao fim do estudo no final de 2018. A participação no estudo é voluntária e você pode retirar seu consentimento de participacao a qualquer momento.

Uma enfermeira do Projeto Saúde Bandim examinará saúde do seu filho no dia da inscrição. Se você optar por retirar o seu consentimento ou o seu filho é excluído porque ele está doente, seu filho vai ser tratado da mesma maneira no futuro visitas a aldeia. Seu filho terá acesso a consultas gratuitas quando o Projecto de Saúde Bandim visitar a aldeia. Se necessário, medicamentos essenciais estarão disponíveis sem custo. A criança pode ter reações adversas menores a vacina contra o sarampo, tais como dor e sensibilidade no local da injeção, febre, ou uma erupção cutânea. As crianças podem ter reações adversas menores à vacina contra a poliomielite, como diarréia auto-limitada. Reacções adversas graves são raros, mas pode ser explicado a você a seu pedido.

Todas as informações pessoais coletadas neste estudo é estritamente confidencial. Os resultados do estudo serão publicados, mas a identidade de todos os participantes serão ocultados. O estudo está prevista para ser concluída até o final de 2019. Você pode pedir os resultados se você estiver interessado. O Projecto de Saúde Bandim irá manter os dados arquivados. Os comitês de ética em Guiné-Bissau e na Dinamarca aprovaram o estudo e, no caso improvável, seguro adequado está no lugar. Se você tem perguntas para o estudo em qualquer ponto entre em contato com a equipe de estudo através do supervisor do projeto Claudino Correia, 966284608/955435117. Ele irá facilitar o contato com o responsável doestudo Amabelia Rodrigues (a.rodrigues@bandim.org), Ane Bærent Fisker (a.fisker@bandim.org) e Anshu Varma (avar@ssi.dk). Muito obrigado pela sua atenção. Você tem alguma pergunta?

RE-CAMP FOLHA DE INFORMAÇÃO Version_110618
PA MAE / RESPONSAVEL

Número de PSB __ __ __ __ __ __ __ __

Data: dd__ __ /mm__ __ /201 __

Ou a carta de informação foi-me explicado ou eu li-o eu mesmo. Eu entendi aquilo:

• meu filho será oferecida uma vacina contra o sarampo ou polio na sessão de pesagem hoje ou uma vacina do sarampo até o final do estudo, dependendo do grupo que minha aldeia pertence.

• meu filho ainda deve receber todas as vacinas no programa de vacinação infantil, como a política atual, independentemente de que grupo o meu filho pertence.

• meu filho terá acesso a consultas gratuitas quando o Projecto de Saúde Bandim visita a aldeia. Se necessário, medicamentos essenciais estarão disponíveis sem custo.

• meu filho pode sofrer de reacções adversas menores e que o risco de reacções adversas graves são raras.

• participação do meu filho é baseada no meu pleno consentimento. Eu posso retirar o meu consentimento a qualquer momento, sem s explicações se eu retirar meu filho a partir do estudo ou se o meu filho vai ser excluído porque ele está doente, não irá comprometer qualquer relação com o Projeto Saúde Bandim.

Foi-me dada a oportunidade de fazer qualquer pergunta sobre o estudo e a minha participação. As perguntas foram respondidas de forma satisfatória. Minha participação é voluntária e com base na minha decisão soberana.

Nome: _____

Mãe: S |__| N |__|, se nao, tipo de relacionamento:_____

Assinatura ou impressão:_____

****

Eu testemunhei a explicação ao participante, e ele / ela teve a oportunidade de fazer perguntas sobre o estudo e seu / sua participação. Confirmo que o participante tenha consentido.

Nome do testemunho: _____

Assinatura da testemunha: _____

****

Eu, CIC |__|*, ADC* |__|*, OAG* |__|*, MRG* |__|*, JDM* |__|, ALO |__|, DPG |__|, ECG |__|, ALI |__|, DAF |__| *funcionário do Projecto de Saúde Bandim, declarar que expliquei o estudo e suas implicações para o mae/responsável. Ele/ela entendeu a explicação, e deu a sua/seu consentimento para participar.*

Assinatura da Projeto Saúde Bandim funtionario: _____

Appendix 3

Enrolment form administered by field nurses for enrolled children

RECAMP enrolment

Estudo: RECAMP number _____

Regidc PSB number: __ __ __ __ __ __ __ __

Background (pre-printed)

REG. Region N°: __ __

Tab. Village N°: __ __

AM. Cluster N°: __ __

MUL. N°: __ __ __

MOR. Household: N°: __ __

telenumero. Mobile number: __ __ __ __ __ __ __ __ __

GEM. Twin: Y|___| N|___|

nomecri. Child's name: _____ noc. N°: __ __ __ __

SEX. Child's sex: M|___| F|___|

DNASC. Child's birth date (check the child's vaccination card): dd__ __ / mm__ __ / 201__

BCGinc. Is the child enrolled in the BCG rural study and < 2 months old? Y|___| N|___|, if yes exclude the child

Visit 1:

B1date1. Date: dd__ __ /mm__ __ /201 __

B1stat1. Status: |___|

B1incl1. Included: Y|___| N|___|

B1assi1. Assistant: N°__ __

Visit 2:

B2date2. Date: dd__ __ /mm__ __ /201 __

B2stat2. Status: |___|

B2incl2. Included: Y|___| N|___|

B2assi2. Assistant: N°__ __

Visit 3:

B3date3. Date: dd__ __ /mm__ __ /201 __

B3stat3. Status: |___|

B3incl3. Included: Y|___| N|___|

B3assi3. Assistant: N°__ __

Status:
P (present) if P then 1=Sent to post, 2=No escort, 3=Refused
A (away shortly)
V (travelling)
M (moved)
F (dead)

B4refu. If the mother refused to go to the post, what is the reason? _____

RE-CAMP enrolment

PSB number __ __ __ __ __ __ __ __

Health examination

C1nurs. Name of nurse: _____

C2acut. Does the child have a severe acute illness? Y|___| N|___| U|___| If yes:

C2acutnam. Which disease? _____

C2treat. Has the child received treatment? Y|___| N|___| U|___|

C2treatnam. If yes, what treatment _____

C2refe. Referred by the BHP nurse: Y|___| N|___| C2refewhy. If no, why _____ If yes:

C2refewhe. Where? _____

C2refemed. What medicine is given by the BHP nurse? _____

C3alle. Has the child had any allergic reaction to a previous vaccine? Y|___| N|___| U|___|, if yes or unknown exclude the child.

C4temp. Temperature of the child: __ __, __ °C, if the child has a temperature ≥ 39.0°C or a severe acute illness as defined by the examining nurse exclude the child.

C5muac. MUAC: __ __ __ mm, if the child's MUAC is < 110 mm and the child is older than 6 months exclude the child and recommend the mother/guardian to bring the child to a health center.

C6weig. Weight: __ __ , __ __ kg

C7exam. The child can be vaccinated according to the health examination guidelines: Y|___| N|___|

C7examwhy. If no, why: _____

C8cons. If yes, read aloud the informed consent to the mother/guardian. Do you agree to participate? Y|___| N|___|

C8conswhy. If no, why _____

Administration of intervention and control children

D1date. Date: dd__ __ / mm__ __ / 201__

D2vacc. Does the child already have a vaccination card? Y|___| N|___| U|___|

D2vacctod. If no or unknown, is a new vaccination card given today? Y|___| N|___|

D2vacctodwhy. If no, why _____

Control village	**Intervention village OPV**	**Intervention village MV**
Nenvac: *No vaccine*	*Oral Polio Vaccine*: 0-8 months D3vacctim.Vaccination time: ___: _____	*Measles Vaccine*: 9-59 months D4vacctim. Vaccination time: ___: _____

Fundo

Numero de PSB: __ __ __ __ __ __ __ __

Região N°: __ __

Tabanca N°: __ __

Amostra N°: __ __

Moranca N°: __ __

RECAMP etikkette

Número de RECAMP
__ __ __ __ __

Nome de criança: _____ N°: __ __ __ __

Nascimento de criança: dd__ __ / mm__ __ /201 __

Sexo de criança: M|___| F|___|

Gêmeo: S |__| N |__|

Número de RECAMP adicionado em Lista Crianca
I__I

Nome de mulher: _____ N°: __ __ __

Telemóvel N°: __ __ __ __ __ __ __ __ __

Visita 1:

Data: dd__ __ /mm__ __ /201 __

Estado: |__|, ver caixa estado no fim da página, se P (presente) mandado |__|, ver caixa mandado no fim da página

Assistente: N°__ __

Visita 2:

Data: dd__ __ /mm__ __ /201 __

Estado: |__|, ver caixa estado no fim da página, se P (presente) mandado |__|, ver caixa mandado no fim da página

Assistente: N°__ __

Visita 3:

Data: dd__ __ /mm__ __ /201 __

Estado: |__|, ver caixa estado no fim da página, se P (presente) mandado |__|, ver caixa mandado no fim da página

Assistente: N°__ __

Estado:
P (presente)
A (ausente)
V (viajando)
M (modou), onde: _____ data: dd__ __ /mm__ __ /201 __
F (faleceu), data: dd__ __ /mm__ __ /201 __
G (ainda gravida)
NM (nada morto)
AB (aborto)

Mandado:
1: enviado para posto
2: não se vêem, mas virá mais tarde
3: sem escolta
4: recusou, qual é a razão? _____ você quer que seu filho seja incluído em nossa próxima visita? S |__| N |__| NS |__|
5: em BCG rural e idade < 2 meses
8: > 5 anos

Se estado a criança estiver presente:

A criança já tem cartão de vacina/registo de vacina: S|__| N|__|, se sim, verifique datas com lista crianca: S|__| N|__|

Forneça à criança um cartão de vacinação hoje: S |__| N |__|

Forneça à criança um cartão de RECAMP hoje: S |__| N |__|

SE A CRIANCA TOMOU MEDIC. HOJE INFORME A MAE PARA LEVAR MEDIC. PARA O POSTO

RECAMP ficha inclusão Version 12_06_2018

LEIA EM VOZ ALTA O CONSENTIMENTO INFORMADO PARA MAE/RESPONSAVEL

PSB enfermeira: CIC |__|, ADC |__|, OAG |__|, LLA |__|, IFC |__|, DAF |__|

Data: dd__ __ /mm__ __ /201 __

Exame de saúde

Peso: __ __ **,** __ __ __ kg, Com roupas (incluindo fralda/dodote) |__| Sem roupas |__|

Braco: __ __ __ mm

Temperatura da criança: __ __, __ ◦C

Entrevista

A criança recebeu tratamento hoje? S |__| N |__| NS |__|, se sim, qual o tratamento?: _____

A crianca ja tomou alguma vacina anterior? S |__| N |__| NS |__|

A criança experimentou alguma reação após uma vacina anterior? S |__| N |__| NS |__|, se sim, qual reacção? _____ se não sabe, você ouviu falar de alguma reação após uma vacina anterior? S |__| N |__|

Avaliacao

A criança tem uma doença aguda grave hoje: S |__| N |__| NS |__|, se sim, que doença: _____

Referido pela enfermeira da PSB: S |__| N |__|, se sim, onde: _____ se não, e se doence grave, motivo de nao mandar: _____

A medicina é administrada pela enfermeira PSB hoje: S |__| N |__|, se sim, qual medicina: _____

LEIA AS DIRETRIZES PARA AVALIAR SE A CRIANCA CUMPRE ALGUM DOS CRITERIOS DE EXCLUSAO

A criança pode ser vacinada de acordo com as diretrizes do exame de saúde: S |__| N |__|, se não, motivo: _____

Administração de crianças de intervenção e controle

Você concorda em deixar seu filho participar deste estudo? S |__| N |__|, se não, porque? _____

Tabanca de Controle

Nenhuma vacina: 0-8 mes |__|

Tabanca de Controle

Nenhuma vacina: 9-59 mes |__|

Tabanca de intervenção VPO

Vacina o oral poliomielite: 0-8 meses |__|

Hora de vacinação: __ __: __ __

Codigo enfermeira: |_____|

Tabanca de intervenção Sarampo

Vacina o sarampo: 9-59 meses |__|

Hora de vacinação: __ __: __ __

Codigo enfermeira: |_____|

OBS: _____

Appendix 4

The Protocol article

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BMC Public Health

STUDY PROTOCOL Open Access

Research protocol of two concurrent cluster-randomized trials: Real-life Effect of a CAMPaign with Measles Vaccination (RECAMP-MV) and Real-life Effect of a CAMPaign with Oral Polio Vaccination (RECAMP-OPV) on mortality and morbidity among children in rural Guinea-Bissau

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Abstract

Background: Measles and oral polio vaccinations may reduce child mortality to an extent that cannot be explained by prevention of measles and polio infections; these vaccines seem to have beneficial non-specific effects. In the last decades, billions of children worldwide have received measles vaccine (MV) and oral polio vaccine (OPV) through campaigns. Meanwhile the under-five child mortality has declined. Past MV and OPV campaigns may have contributed to this decline, even in the absence of measles and polio infections. However, cessation of these campaigns, once their targeted infections are eradicated, may reverse the decline in the under-five child mortality. No randomized trial has assessed the real-life effect of either campaign on child mortality and morbidity. We present the research protocol of two concurrent trials: RECAMP-MV and RECAMP-OPV.

Methods: Both trials are cluster-randomized trials among children registered in Bandim Health Project's rural health and demographic surveillance system throughout Guinea-Bissau. RECAMP-MV is conducted among children aged 9–59 months and RECAMP-OPV is conducted among children aged 0–8 months. We randomized 222 geographical clusters to intervention or control clusters. In intervention clusters, children are offered MV or OPV (according to age at enrolment) and a health check-up. In control clusters, children are offered only a health check-up. Enrolments began in November 2016 (RECAMP-MV) and March 2017 (RECAMP-OPV). We plan 18,000 enrolments for RECAMP-MV with an average follow-up period of 18 months and 10,000 enrolments for RECAMP-OPV with an average follow-up period of 10 months. Data collection is ongoing. The primary outcome in both trials is non-accidental death or non-accidental first non-fatal hospitalization with overnight stay (composite outcome). Secondary outcomes are: non-accidental death, repeated non-fatal hospitalizations with overnight stay, cause-specific primary outcome, outpatient visit, and illness. We obtained ethical approval from Guinea-Bissau and consultative approval from Denmark.

(Continued on next page)

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(Continued from previous page)
Discussion: Cluster randomization and minimum risk of loss to follow-up are strengths, and no placebo a limitation. Our trials challenge the understanding that MV and OPV only prevent measles and polio, and that once both infections are eradicated, campaigns with MV and OPV can be phased out without negative implications on child health and survival.

Trial registration: NCT03460002.

Background

The common public health understanding is that vaccines protect against their target infections and do little else. However, an increasing body of evidence challenges this understanding. Studies from low-income countries suggest that the live measles vaccine (MV) and the live oral polio vaccine (OPV) reduce the under-five child mortality to an extent that cannot be explained by prevention of measles or polio infections; both vaccines seem to have what is termed beneficial non-specific effects (NSEs) [1]. In a systematic review commissioned by the World Health Organization's (WHO) Strategic Advisory Group of Experts on Immunizations (SAGE) it was concluded in 2014 that, "There was consistent evidence of a beneficial effect of measles vaccine (…)" on child mortality. This conclusion was based on four randomized trials and 18 observational studies [2] but SAGE called for more research [3]. Though the effect of OPV was not included in the review, OPV also seems to have beneficial NSEs: In two trials, where infants were randomised to OPV or no OPV at birth, OPV was associated with a 32% lower infant mortality in both trials [4, 5]. Observational studies also indicate that children receiving OPV with a non-live vaccine have better survival than children receiving the non-live vaccine only [6, 7]. We respond to SAGE's call for more research by assessing the NSEs of an MV campaign and an OPV campaign.

In the last decades, billions of children have received MV and OPV through campaigns implemented worldwide with the goal to ultimately eradicate measles and polio infections [8, 9]. The campaigns aim at reaching all children in a broad age-group regardless of pre-campaign vaccination status, also children who are not reached through routine vaccination program services. The campaigns can increase population immunity against the viruses rapidly, thereby interrupting virus transmission, which leads to herd protection [10, 11]. The under-five child mortality has declined on a global scale [12] in the same period as campaigns with MV and OPV have been conducted. Thus, we suggest that past MV and OPV campaigns may have efficiently contributed to reduce the under-five child mortality given their presumed beneficial NSEs, even in the absence of measles and polio infections. Cessation of MV and OPV campaigns after eradication of their targeted infections may therefore reverse the declining trend in the under-five child mortality.

No randomized trial has assessed the real-life effect of an MV campaign or an OPV campaign on child mortality. Two observational studies were published after WHO's SAGE review, and both support that MV campaigns among children reduced the under-five mortality. In a before/after study among 8000 children, mortality in the year following an MV campaign was 20% (4–34%) lower compared with the year prior to the campaign, even after censoring measles deaths (17% (0–31%)) [13]. Another study compared mortality in MV campaign participants (5633) with non-participants (1006) in the year following the campaign, and mortality was found to be 72% (23–90%) lower among participants; no deaths were measles related [14]. In both studies, children who were also measles vaccinated through routine vaccination program services seemed to additionally benefit from the MV campaign [13, 14]. Similarly, OPV campaigns may reduce child mortality considerably. Among children followed in seven trials of vaccines or vitamin A supplements, an OPV campaign was associated with a 19% (5–32%) lower mortality rate [15]. Comparisons of mortality after OPV campaigns with mortality before the campaigns in other cohorts also indicated lower mortality for children exposed to OPV campaigns [16, 17], and adjusted for age, receiving OPV in a campaign was associated with a 91% (20–99%) lower mortality than not receiving OPV in a campaign [18].

In two concurrent cluster-randomized controlled trials, we want to assess the separate effect of an MV campaign and an OPV campaign on child health and survival in the absence of measles and polio infections. We present the research protocol of each trial: Real-life Effect of a CAMPaign with a Measles Vaccination (RECAMP-MV) and Real-life Effect of a CAMPaign with an Oral Polio Vaccination (RECAMP-OPV). We initiated enrolments into RECAMP-MV in November 2016 and will conduct follow-up until eligibility for a national measles vaccination campaign (trial completion is expected by late 2019). We initiated enrolments into RECAMP-OPV in March 2017 and will conduct follow-up until eligibility for any national vaccination campaign or a maximum of 12 months (trial completion is

expected by late 2020). A data safety and monitoring board consisting of a statistician, a pediatrician, and an epidemiologist is providing input to ensure an optimal data collection process.

Objectives

Primary objectives

RECAMP-MV: To assess the real-life effect of an MV campaign among children aged 9–59 months on non-accidental mortality or non-accidental morbidity (composite outcome) in rural Guinea-Bissau, where measles infection is limited. We will test whether an MV campaign can reduce the composite outcome by 30% during an average follow-up period of 18 months.

RECAMP-OPV: To assess the real-life effect of an OPV campaign among children aged 0–8 months on non-accidental mortality or non-accidental morbidity (composite outcome) in rural Guinea-Bissau, where no polio circulates. We will test whether an OPV campaign can reduce the composite outcome by 25% during an average follow-up period of 10 months.

Secondary objectives

To better understand the real-life effect of either campaign on child health and survival we will also assess the effect of each campaign on other health measures and under different scenarios as specified in the statistical analysis section.

Methods/design

Setting

Guinea-Bissau's Ministry of Health has implemented national MV campaigns among children aged 9–59 months every third year since 2006 [19], and OPV campaigns more frequently [15]. Despite some fluctuations in reported measles infection cases [20] and MV coverage [21], Guinea-Bissau has a low risk profile of measles (Table 1) and the last recorded case of indigenous wild poliovirus in Guinea-Bissau was in 1999 [22].

Bandim Health Project (BHP) follows women of fertile age and children under-five in Guinea-Bissau's rural population through a health and demographic surveillance system (HDSS). This enables assessment of child mortality and morbidity. In Guinea-Bissau's nine rural health regions (Oio, Biombo, Gabu, Cacheu, Bafata, Quinara, Tombali, Bubaque, and Bolama), 222 randomly selected geographical clusters with more than 22,000 children under-five are being monitored. The selection process of the geographical clusters has been described elsewhere [23]. Field teams conduct regular visits to all villages in all clusters. At household visits field assistants register pregnancies, and children's vaccination status, mortality, morbidity, nutritional status, campaigns with other health interventions, migration, and whereabouts if absent [23]. This is the implementation platform of RECAMP-MV and RECAMP-OPV.

Design and randomization

The 222 village clusters were randomized to intervention or control clusters stratified by region and access to health services. We defined health service access as vaccination coverage by 12 months of age assessed among children aged 12–23 months [24], using BHP HDSS data from 2015 to 2016. This pre-trial vaccination coverage was based on Bacillus Calmette Guerin (BCG) vaccine, three doses of OPV, three doses of Pentavalent (diphtheria, tetanus, pertussis, hepatitis B, haemophilus influenza type B), and MV. We defined low and high pre-trial vaccination coverage using the median as a cut-off point. Within each of the two coverage strata per region, we assigned one half of the clusters to receive intervention and health check-up, and the other half to receive only health check-up, based on an externally generated random number.

Study population

Children living in BHP's rural HDSS are eligible to enter RECAMP-MV if 9–59 months of age and RECAMP-OPV if 0–8 months of age. A child is excluded if it: 1) is considered overtly ill by the enrolling nurse or 2) has an axillary temperature > 39 °C or 3) is aged > 6 months and has a mid-upper-arm-circumference < 110 mm or 4) has experienced an allergic reaction after a prior vaccination or 5) is followed in another ongoing BHP trial in rural Guinea-Bissau (i.e. children from RECAMP-OPV will not be enrolled into RECAMP-MV once they turn 9 months old, and children who are < 2 months old and enrolled in a randomized trial giving BCG and OPV at a home visit shortly after birth [25] will not be enrolled into RECAMP-OPV). Criteria 1–4 ensure that we avoid enrolment of severely acutely ill or immunocompromised children, and these criteria are based on WHO

Table 1 Measles infection cases, vaccination coverage and vaccination campaigns in Guinea-Bissau according to WHO's country data [20, 21]

Year	2008	2009*	2010	2011	2012*	2013	2014	2015*	2016	2017
Measles infection cases (number)	12	0	26	0	0	0	1	153	0	11
1st routine measles dose (proportion)	64%	79%	78%	78%	90%	89%	81%	90%	71%	66%

*Guinea-Bissau's Ministry of Health implemented a national measles vaccination campaign
Abbreviation: WHO=World Health Organization

recommendations [10, 11], which we have translated into local practice. Criteria 5 is set to avoid data interpretative issues.

Intervention

RECAMP-MV: We offer one dose of a WHO prequalified monovalent live attenuated measles vaccine (Edmonston-Zagreb strain from Serum Institute of India) to children aged 9–59 months in intervention clusters.

RECAMP-OPV: We offer one dose of a WHO prequalified standard bivalent OPV to children aged 0–8 months in intervention clusters. To mimic the way most OPV campaigns are implemented, we initiated the RECAMP-OPV trial with two visits one month apart where logistically feasible. At the second visit, a second dose of OPV is offered to children in intervention clusters, while children in both control and intervention clusters are health examined and weighed.

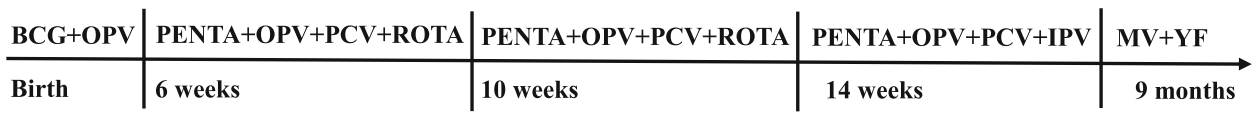
The cold chain for both vaccines is documented. We provide the MV and OPV campaign vaccinations independently from Guinea-Bissau's routine child vaccination program [26] (Fig. 1).

Blinding

It is common practice in Guinea-Bissau that when a mother/guardian visits the health system with a sick child, the mother/guardian brings the child's vaccination card; it could be speculated that health system personnel give low treatment priority to children with high vaccination coverage and vice versa. Thus, to avoid the risk of differential treatment decision by health system personnel, we do not register cluster assignment on the children's vaccination cards.

Sample size considerations

RECAMP-MV: Children are followed from enrolment and until eligibility for a national MV campaign. We aim to have minimum 80% power to detect at least a 30% reduction in non-accidental mortality or non-accidental morbidity (composite outcome) given that this is the true reduction during an average follow-up period of 18 months. The planned sample size was originally based on 182 clusters and a composite outcome rate of 20/1000 person-years among children aged 9–59 months in BHP's rural HDSS. Based on Hayes and Moulton's power formula for a cluster-randomized trial [27], our initial power calculations indicated 86% power to detect at least a 30% reduction if we enrolled 14,500 children (with a between cluster variation coefficient of 0.25 and a harmonic mean (reciprocal of the arithmetic means of the reciprocals) of total projected accumulated observation time per cluster of 107 person-years at risk). After discussions with our data safety and monitoring board we decided to re-evaluate the power calculations for both trials when more information on outcome rates and distribution of enrolments between the clusters was gained, to verify total enrolments needed. This re-evaluation was based on data from the first complete round of enrolment and follow-up visit. As Table 2 shows for RECAMP-MV, we observed a lower composite outcome rate and harmonic mean of total projected accumulated observation time per cluster, than expected. Our data safety and monitoring board supported our decision to enlarge the number of clusters from 182 to 222. This increased the planned enrolments from 14,500 to 18,000 children which gives us 80% power to detect a 30% reduction in the composite outcome (with an assumed control cluster outcome rate of 17/1000 person-years at risk and a harmonic mean of total projected



BCG: Bacillus calmette guerin vaccination
OPV: Oral polio vaccination
PENTA: Hepatitis B + Haemophilus type B + Diptheria-Tetanus-Pertussis vaccinations
PCV: Pneumococcal conjugate vaccination
ROTA: Rotavirus vaccination
IPV: Inactivated polio vaccination
MV: Measles vaccination
YF: Yellow fever vaccination

Fig. 1 Guinea-Bissau's routine child vaccination program

Table 2 Sample size estimates derived from the first complete round of enrolment and follow-up visit of RECAMP-MV and RECAMP-OPV

RECAMP	MV	OPV
Number of clusters	222	
Alpha	0.05	
Between cluster variation coefficient	0.25	
Number of eligible children to be enrolled	18,000	10,000
Observed non-accidental deaths/non-accidental hospitalizations rates	15/1000 pyrs*	48/1000 pyrs**
Harmonic mean of total projected accumulated observation time per cluster	84 pyrs	40 pyrs
Expected reduction	30%	25%
Power	*80%*	*80%*

*Assuming that our observed composite outcome rate (15/1000 pyrs) is an average of the rates in our control and intervention clusters, and that the real difference between the clusters is 30%, we assumed the rates to be 17/1000 pyrs in control clusters and 12/1000 pyrs in intervention clusters when re-evaluating our power calculations

**Assuming that our observed composite outcome rate (48/1000 pyrs) is an average of the rates in our control and intervention clusters, and that the real difference between the clusters is 25%, we assumed the rates to be 55/1000 pyrs in control clusters and 41/1000 pyrs in intervention clusters when re-evaluating our power calculations

Abbreviation: Pyrs = person-years at risk

accumulated observation time per cluster of 84 person-years at risk).

RECAMP-OPV: Children are followed from enrolment and until eligibility for any national vaccination campaign or for a maximum of 12 months. We aim to have minimum 80% power to detect at least a 25% reduction in non-accidental mortality or non-accidental morbidity (composite outcome) given that this is the true reduction during an average follow-up period of 10 months. The planned sample size was originally based on 182 clusters and a composite outcome rate of 70/1000 person-years among children aged 0–8 months in BHP's rural HDSS. Based on Hayes and Moulton's power formula for a cluster-randomized trial [27], our initial power calculations indicated 80% power to detect at least a 25% reduction if we enrolled 6500 children (with a between cluster variation coefficient of 0.25 and a harmonic mean (reciprocal of the arithmetic means of the reciprocals) of total projected accumulated observation time per cluster of 40 person-years at risk). After the re-evaluation we observed a lower composite outcome rate than expected. We enlarged the number of clusters from 182 to 222 and increased the planned number of enrolments from 6500 to 10,000 children which gives us 80% power to detect a 25% reduction in the composite outcome (with an assumed control cluster outcome rate of 55/1000 person-years at risk and a harmonic mean of total projected accumulated observation time per cluster of 40 person-years at risk).

Table 2 summarizes the final sample size calculation estimates for both trials.

Enrolment and follow-up procedures

A pilot phase was initiated in Biombo from November 2016 to March 2017. We trained three field teams, each consisting of at least four field assistants and one enrolling nurse. The consent process, structured interviews during enrolment, and structured interviews during follow-up take place in Portuguese Creole managed by the field teams (interview questions are written in Portuguese and based on BHP's rural HDSS questionnaires used in previous studies). If necessary, a villager is called to act as a translator.

For RECAMP-MV, we plan 2–3 enrolment rounds to visit children who were not home at a previous enrolment visit, or who later move into BHP's rural HDSS area. For RECAMP-OPV more enrolment rounds are needed. The written consent process is two phased: 1) a field assistant conducts a household visit where he explains to the mother/guardian of an eligible and present child that, "In the past the Ministry of Health has provided many MV and OPV campaigns as the mother/guardian probably remembers. Now there is rarely any measles infection and no polio infection in Guinea-Bissau. Therefore, in the future, the campaigns may stop. BHP wants to know if it is good for children's health to stop or continue MV and OPV campaigns. To know this, we will vaccinate in some but not other villages. When the work is done all children aged >9 months in the villages that do not receive vaccines today will be offered MV. If you are interested your child should be brought to our health post today", the field assistant does not inform the mother/guardian about cluster assignment when referring to the health post. 2) at the health post an enrolling nurse/field assistant carefully explains both trials, usually to several mothers/guardians at a time. If a mother/guardian is illiterate a witness independent from the field team is called. After the explanation, any questions from the mothers/guardians are welcomed. If mothers/guardians want their children to participate they are requested to give their signatures/fingerprints on a consent form and then they receive an information letter written in Portuguese.

After consent, the enrolling nurse performs a health check-up of one child at a time (assessing illness, issues with prior vaccination, and measuring axillary temperature, mid-upper-arm-circumference, and weight). If the enrolling nurse experiences that a child is overtly ill, the child's mother/guardian is given health advice, and if necessary

offered health facility transport, irrespective of cluster assignment. Overtly ill children are offered enrolment at a subsequent visit, if recovered.

If a child is assessed healthy in intervention clusters, the child aged 9–59 months is administered a 0.5 ml reconstituted MV from a 10-dose vial by deep subcutaneous injection into the left subscapular region (leftover doses are discarded six hours after reconstitution), and the child aged 0–8 months is administered two oral drops of OPV from a multi-dose vial (leftover doses are discarded after 28 days). If a child is assessed healthy in control clusters, the child is not administered MV or OPV.

All enrolled children are followed through regular household visits by field assistants who collect information on death and hospitalization, among other. The visits are conducted every two months to children < 12 months of age in Oio, Biombo and Cacheu for logistical reasons, and every six months to older children, and in the remaining regions. If a field assistant registers the death of a child, a specially trained field assistant conducts a verbal autopsy at a subsequent visit [28]. An extra follow-up visit is conducted among a subgroup of enrolled children one-two months after enrolment; the mothers/guardians of these children are visited by field assistants to collect information on outpatient visit and maternally reported illness in the elapsed time span. This visit is also utilized to provide a second OPV dose to children aged 0–8 months in intervention clusters. Figure 2 shows the flow from eligibility to follow-up in RECAMP-MV and RECAMP-OPV.

Outcomes

The primary outcome for each trial is defined as a composite outcome to ensure sufficient power. It consists of:

- non-accidental mortality or
- non-accidental morbidity (first non-fatal hospitalization with overnight stay)

The secondary outcomes assess other health measures. They consist of:

- non-accidental mortality
- non-accidental repeated morbidity (at least one non-fatal hospitalization with overnight stay)
- cause-specific primary outcome (malaria, diarrhea, and respiratory infections [29])
- proportion of non-accidental outpatient visits and non-accidental maternally reported illnesses in a sub-group 1–2 months after enrolment in the elapsed time span
- Furthermore in RECAMP-OPV: weight at the extra follow-up visit 1–2 months after enrolment

Adverse reactions

RECAMP-MV: Common mild adverse reactions to MV include injection site reactions (within 24 h), fever (within 7–12 days), or rash (within 7–10 days); all resolve within 1–3 days. Except from febrile seizures, severe adverse reactions are extremely rare (anaphylaxis, thrombocytopenia, and encephalomyelitis) [30]. MV campaigns' safety profile has been evaluated, and severe adverse reactions seem rare [31–35].

RECAMP-OPV: Common mild adverse reactions to OPV include self-limiting diarrhoea [36]. The only severe adverse reaction is vaccine derived polio, which occurs in 2–4 infants in a birth cohort of one million children receiving 4 doses of OPV during the first months of life [11]. The risk of circulating vaccine derived polio has been markedly lowered with the shift from trivalent (type 1–2-3) to bivalent OPV (type 1 and 3) [37], as 94% of the circulating vaccine derived polio was caused by type 2 [38].

To the extent possible, we are in contact with the adverse events following immunization (AEFI) responsible from each region to register any potential adverse reaction caused by our campaigns.

Data management

Data collected by the field teams is transported back to Bissau regularly. Data entry assistants enter the data in DBASE, and they also clean the data based on pre-specified cleaning programs. Data collected during the pilot phase will be included in the analyses to obtain sufficient power. Through crosslinks with other data sources, key variables are verified and data entry errors are captured.

Statistical analyses

Statistical analyses will be performed in STATA by the research group based on data analysis plans which have been reviewed by the data safety and monitoring board (Additional file 1 (RECAMP-MV) and Additional file 2 (RECAMP-OPV)). If further analyses are planned due to new knowledge arising during the trials, potential amendments to the respective data analysis plan will be discussed with the data safety and monitoring board. We will analyse all primary and secondary outcomes based on individual level data as the cluster size varies. We will present confidence intervals of 95%. Absolute numbers of missing values will be presented, when relevant. No missing values will be imputed. No corrections will be made for multiple testing.

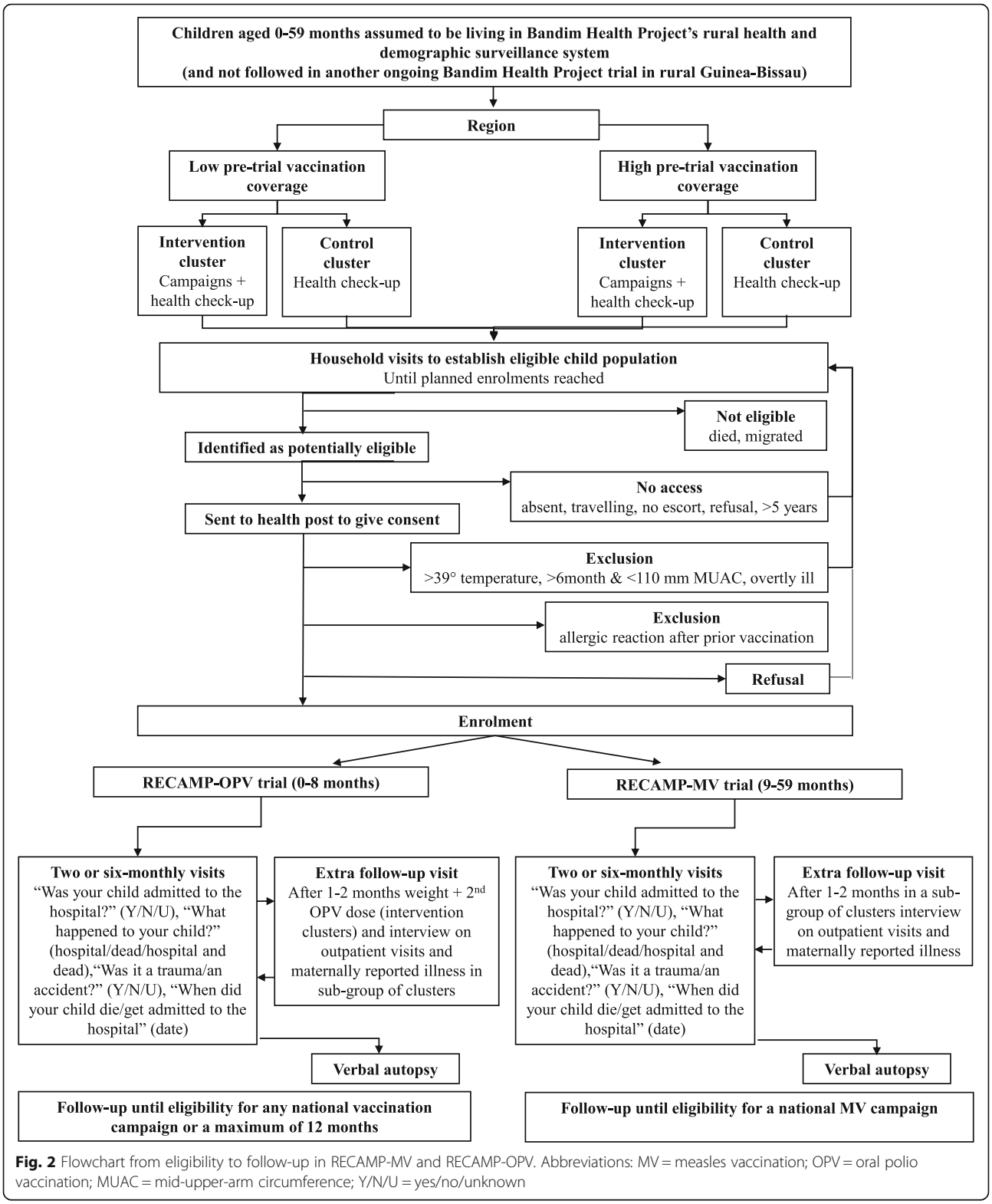


Fig. 2 Flowchart from eligibility to follow-up in RECAMP-MV and RECAMP-OPV. Abbreviations: MV = measles vaccination; OPV = oral polio vaccination; MUAC = mid-upper-arm circumference; Y/N/U = yes/no/unknown

Primary analysis of the primary outcome

The main conclusion in RECAMP-MV and RECAMP-OPV will be based on a per-protocol analysis. The primary outcome will be analyzed in a Cox proportional hazards model, adjusted by region, pre-trial vaccination coverage, and sex, with age as the underlying timescale. We will use cluster-robust standard errors to account for intra-cluster correlation. Children will enter the

analysis on the day of enrolment, and their follow-up will be censored at:

RECAMP-MV: death due to accident, migration or eligibility for a national MV campaign, whichever comes first.
RECAMP-OPV: death due to accident, migration, eligibility for any national vaccination campaign, or a maximum of 12 months of follow-up, whichever comes first.

In both trials, hospital admissions due to accidents are ignored but the follow-up time is censored while the child is admitted.

Secondary outcomes

In per-protocol analyses, we will assess the secondary outcomes: non-accidental mortality, non-accidental repeated morbidity, and cause-specific primary outcome. These secondary outcomes will be analyzed in Cox proportional hazards models as described for the primary outcome. Furthermore, we will analyse outpatient visits and maternally reported illnesses occurring 1–2 months after enrolment in per-protocol analyses using log-binomial regression models adjusted for region, pre-trial vaccination coverage, and sex. In RECAMP-OPV, we will furthermore analyze weight and MUAC 1–2 months after enrolment using multiple regression models adjusted for region, pre-trial vaccination coverage, and sex.

Effect modifier analyses of primary outcome

In per-protocol analyses we will assess potential effect modifiers of the primary outcome (Tables 3 and 4).

Sensitivity analyses of primary outcome

We will assess the robustness of the primary analysis of the primary outcome for each campaign under different scenarios:

- two intention-to-treat analyses: 1) in a classic intention-to-treat analysis children will be included if present in the cluster from the day they were first potentially eligible to enter but did not because they e.g. did not receive the assigned treatment, were excluded due to illness, did not have a mother/guardian to escort them, or had a mother/guardian who refused participation, 2) in an extended intention-to-treat analysis children will be included if living in the cluster from the day they were first potentially eligible to enter (including children from the classic intention-to-treat analysis and children who were absent/travelling) as either campaign may affect other children's health in the community by reducing the general infectious pressure.
- Furthermore, we will assess if different censoring criteria affect the robustness of the results

Ethics and dissemination

Prior to initiating the trials, we obtained ethical approval from Guinea-Bissau's national ethics committee (Comité Nacional de Ética na Saúde: CNES/2016/020) and consultative approval from Denmark's national ethics committee (Den Nationale Videnskabsetiske Komité: 1606756). Then we met with all regional health directorates to inform them about the trials' aim, routines, initiation date, and to request their collaboration. This paper includes amendments resulting from our discussions with the data safety and monitoring board and the sample size enlargements. For these amendments, we obtained ethical approval from Guinea-Bissau's national ethics committee (Comité Nacional de Ética na Saúde: CNES/2018/028) and consultative approval from Denmark's national ethics committee (Den Nationale Videnskabsetiske Komité: 1606756). The trials are registered at www.clinicaltrials.gov.com (identifier NCT03460002). Data is being stored according to a general agreement between the BHP, and the Ministry of Health in Guinea-Bissau, and Statens Serum Institut in Denmark. At the BHP's main office in Guinea-Bissau all questionnaires are physically stored, and databases with enrolment and follow-up information are separately stored at an encrypted server.

Table 3 RECAMP-MV - potential effect modifiers

Effect modifiers	*Rationale*
Prior MV status	Prior MV administration may lead to a larger reduction in non-accidental mortality/non-accidental morbidity than no prior MV administration [13, 14, 39, 40]
Sex	Girls may experience a larger reduction in non-accidental mortality/non-accidental morbidity than boys [40–43]
Season	Enrolment in the dry season may lead to a larger reduction in non-accidental mortality/non-accidental morbidity than enrolment in the rainy season [29, 44]
Campaigns with other health interventions	Vitamin A may amplify a beneficial non-specific effect [45]. Inactivated meningitis A and inactivated polio vaccination [42], and oral polio vaccination [17, 46], may neutralize/invert a between cluster difference. Participation status will be assigned on an ecological level, assuming that children eligible for campaigns with other health interventions receive these interventions on the campaign dates.

Table 4 RECAMP-OPV - potential effect modifiers

Effect modifiers	*Rationale*
Sex	Previous studies have demonstrated that the effect of OPV is stronger in boys than girls [4, 15, 47].
One vs two doses (2nd dose 1 month after enrolment)	Observational studies indicate that additional doses of OPV offer additional benefits [15].
Age at first dose of OPV	A prior study has indicated that the effect of subsequent vaccines may vary with the age at which the gut was primed [16].
Season of enrolment	Some interventions (eg MV and Vitamin A) have stronger effects when given in the dry season [29, 48]. We will investigate whether the effect of OPV varies for children enrolled in the dry season (December–May) versus children enrolled in the rainy season (June–November)
Vitamin A supplements	Vitamin A supplementation may amplify the NSEs of vaccines [49, 50]. We will examine whether the effect of OPV vary before and after being eligible for vitamin A supplementation after enrolment
Prior OPV campaign	Repeated doses of OPV offer additional benefits [15]. If OPV campaigns take place during the study, we will assess whether the effect is similar in children having been exposed/not exposed to prior OPV campaigns.

We will disseminate the results regardless of positive or negative findings. We intend to publish the results in internationally peer-reviewed journals. We will provide the results to WHO, and Guinea-Bissau's Primary Health Program, Institute of Public Health and regional health directorates; the Institute of Public Health will receive a copy of the results. Any significant deviations from this paper will be documented in the reported results.

Discussion

This paper presents the methodology of two concurrent cluster randomized controlled trials named RECAMP-MV and RECAMP-OPV. We will assess the real-life effect of an MV campaign among children aged 9–59 months (RECAMP-MV) and the real-life effect of an OPV campaign among children aged 0–8 months (RECAMP-OPV) on non-accidental mortality or non-accidental morbidity (composite outcome) in rural Guinea-Bissau**,** where measles infection is limited and no polio circulates. Major strengths lie within the cluster randomisation design which allows us to assess each campaign's effect on the general infectious pressure, which would not be possible with individual randomisation. Furthermore, the BHP's rural HDSS ensures a reliable and thoroughly tested data collection and data management infrastructure minimizing the risk of loss to follow-up. In the following, we consider a major limitation, circumstantial challenges, and future perspectives.

The major limitation is insufficient blinding. Only blinding health system personnel can make the campaigns appear to have an effect that does not solely depend on the campaigns. However, blinding the research group, field teams and mothers/guardians would require placebo use. Administering another vaccine may trigger NSEs, which could obscure the assessment of the campaigns' NSEs. Administering saline would be causing many children pain without benefit. However, as death and hospitalization are not subjective, and as their assessment is based on standardized interviews, we expect the risk of differential outcome reporting to be minimized. Though, we do have some speculations about the potential impact of not blinding the mothers/guardians: 1) mothers/guardians in intervention clusters may consider their children as being extra healthy because they have seen their children receive the campaign vaccines. This could make the mothers/guardians less prone to seek help from the health system if their children get ill. Thus, among children whose mothers/guardians state that their children have been ill after enrolment we will assess the proportion of children whose mothers/guardians also state an outpatient visit by cluster assignment. 2) mothers/guardians in intervention clusters could come to know that their children belong to an intervention cluster prior to enrolment because there is no allocation concealment. This could make the mothers/guardians in intervention clusters more motivated to let their children enrol than mothers/guardians in control clusters. Thus, we will assess if there is a difference in the proportion of children whose mothers/guardians choose not to participate for different reasons, by cluster assignment.

We could face some circumstantial challenges. For RECAMP-MV: 1) Guinea-Bissau's low risk profile makes a measles epidemic seem unlikely. It is nevertheless possible. Our regular contact to the AEFI and disease surveillance responsible in the health regions also ensures registration of suspected measles infection cases. However, declared measles infection cases are likely to be misclassifications of other childhood infections as BHP has experienced in previous studies from Guinea-Bissau. Therefore, only reported measles infection cases when regional health directorates confirm circulating measles will be classified as measles. In such instances, field assistants are instructed to pose questions about symptoms, timing, and source of infection based on BHP's

rural HDSS questionnaires used in previous studies. 2) if Guinea-Bissau's Ministry of Health does not announce a national MV campaign during the trial, we will conduct a visit to all children enrolled in control clusters to offer them MV after both trials have ended. For RECAMP-OPV: national OPV campaigns implemented during the trial will shorten the follow-up period, which could reduce the power.

In both trials, it may influence enrolment efficiency that we exclude children from other ongoing BHP trials in rural Guinea-Bissau. However, we expect to have included a sufficient number of clusters to avoid underpowering due to this potential challenge.

If RECAMP-MV and/or RECAMP-OPV demonstrate beneficial NSEs of the expected respective magnitudes in the absence of measles and/or polio infections, it will clearly challenge two understandings. Firstly, MV and/or OPV only prevent measles and/or polio infections. Secondly, once measles and/or polio infections are eradicated MV and/or OPV campaigns can be phased out, saving resources and without any negative implications for child health and survival; phasing out the smallpox vaccine seems to have had an impact on survival in both high [51] and low-income countries [52, 53]. Furthermore, demonstrated beneficial NSEs in RECAMP-OPV will highlight the need to identify alternative ways to keep stimulating the immune system after the discontinuation of OPV in routine vaccination program services.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12889-019-7813-y.

Additional file 1. Analysis plan_RECAMP-MV

Additional file 2. Analysis plan_RECAMP-OPV

Abbreviations

AEFI: Adverse events following immunization; BCG: Bacille-calmette-guerin; BHP: Bandim Health Project; HDSS: Health and demographic surveillance system; MV: Measles vaccination; NSEs: Non-specific effects; OPV: Oral polio vaccination; PYRS: Person-years at risk; RECAMP-MV: Real-life Effect of a CAMPaign with a Measles Vaccine; RECAMP-OPV: Real-life Effect of a CAMPaign with an Oral Polio Vaccine; SAGE: Strategic Advisory Group of Experts on Immunizations; WHO: World Health Organization

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Status of RECAMP-MV and RECAMP-OPV

By the end of 2018, approximately 17,500 children were enrolled into RECAMP-MV and 5400 children were enrolled into RECAMP-OPV. Data collection is ongoing. To date, no publications containing results from either trial have been submitted or published to any journal.

Authors' contributions

Authors are mentioned in alphabetical order. ABF and PAA built the BHP's rural HDSS platform, conceptualized both trials, and drafted the original research protocol. ABF plans and coordinates both trials. ABF, AV and SMT developed and updated enrolment questionnaires and databases. ABF, AV, LMP and SMT developed and updated follow-up questionnaires and databases. ABF, AV, LMP and SMT trained the field teams, supervise the fieldwork, and develop and implement data cleaning programs. ABF, AV, AKGJ, PAA and SMT developed the data analysis plans. ABF and AV drafted the manuscript. All authors approved the final manuscript.

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Availability of data and materials

Upon request to the corresponding authors (only collaboratively).

Ethics approval and consent to participate

Prior to RECAMP-MV and RECAMP-OPV we obtained ethical approval from Guinea-Bissau's national ethics committee (Comité Nacional de Ética na Saúde: CNES/2016/020) and consultative approval from Denmark's national ethics committee (Den Nationale Videnskabsetiske Komité: 1606756). For amendments, we also obtained ethical approval from Guinea-Bissau's national ethics committee (Comité Nacional de Ética na Saúde: CNES/2018/028) and consultative approval from Denmark's national ethics committee (Den Nationale Videnskabsetiske Komité: 1606756). All ethical approvals covered all the study sites in both trials. We obtained a written informed consent to participate from each child's mother/guardian prior to enrolment. Questionnaires and informed consent materials can be shared upon request to the main author.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

The effect of a Measles Vaccination Campaign on morbidity and mortality among children aged 9-59 months in Rural Guinea-Bissau – a Cluster Randomized Controlled Trial

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1. ANALYSES OF BASELINE COMPARABILITY

We will describe baseline characteristics for the MVC-group and the control group. Categorical variables will be presented as frequencies and proportions and continuous variables will be presented as either medians with interquartile ranges or means with standard deviations.

Table 1: Summary of background factors by MVC-group and control group

- Region
- Vaccination coverage
- Age
- Prior MV status
- Sex
- Participation in other health interventions prior to enrolment
- Season
- Weight
- Temperature
- Mid-upper-arm circumference
- Type of acute illness on the day of enrolment
- Medicine intake on the day of enrolment
- Medicine provided by enrolling nurse
- Vaccination card verified
- Socioeconomic factors (maternal education and housing conditions)

2. PRIMARY ANALYSIS OF PRIMARY OUTCOME

Table 2: Primary analysis of primary outcome

Type	per-protocol analysis
Population	children receiving intervention or control assignment as randomly allocated
Censoring	- death due to accident - migration - trial end
Time scale	age
Failure	non-accidental morbidity (first non-fatal hospitalization with overnight stay) OR non-accidental mortality (death)
Stata code	*Analysis* stset outdate, f(combined_outcome=1) origin(date_of_birth) enter(date_of_enrolment) /// exit(censoring_date) stcox group, strata(region vaccination_coverage sex) vce(cl cluster) (If we in general identify evidence for non-proportionality, we will still report the marginal hazard ratios but supplement this measure by hazard ratios for 2-3 properly selected categorical time-periods identified based on the aforementioned proportionality investigations). *Check of proportional hazards assumption* estat phtest, detail stphplot, strata(group) adj(region vaccination_coverage sex) stcox group, strata(region vaccination_coverage sex) vce(cl cluster) tvc(group) texp(_t)[1]

[1]In supplementary investigations, it can in general be considered to replace the term texp(_t) with texp(_t>s) for specific values of s if relevant after assessing the log-log survival curves.

3. PRIMARY ANALYSES OF SECONDARY OUTCOMES

Table 3: Primary analysis of secondary outcome: non-accidental repeated morbidity

Type	per-protocol analysis
Population	children receiving intervention or control assignment as randomly allocated
Censoring	- death due to accident - migration - trial end
Time scale	age
Failure	non-accidental repeated morbidity (at least one non-fatal hospitalization with overnight stay)
Stata code	*Analysis* outdate1=date_of_observation_period_end, indate1=date_of_observation_period_beginning stset outdate1, f(morbidity=1) origin(date_of_birth) enter(date_of_enrolment) /// time0(indate1) exit(censoring_date) id(child_identification_number) stcox group, strata(region vaccination_coverage sex) vce(cl cluster) *Check of proportional hazards assumption* estat phtest, detail stphplot, strata(group) adj(region vaccination_coverage sex) stcox group, strata(region vaccination_coverage sex) vce(cl cluster) tvc(group) texp(_t)

Table 4: Primary analysis of secondary outcome: non-accidental mortality

Type	per-protocol analysis
Population	children receiving intervention or control assignment as randomly allocated
Censoring	- death due to accident - migration - trial end
Time scale	Age
Failure	non-accidental mortality (death)
Stata code	*Analysis* outdate1=date_of_observation_period_end, indate1=date__of_observation_period_beginning stset outdate1, f(mortality=1) origin(date_of_birth) enter(date_of_enrolment) /// time0(indate1) exit(censoring_date) id(child_identification_number) stcox group, strata(region vaccination coverage sex) vce(cl cluster) *Check of proportional hazards assumption* estat phtest, detail stphplot, strata(group) adj(region vaccination_coverage sex) stcox group, strata(region vaccination_coverage sex) vce(cl cluster) tvc(group) texp(_t)

4. EFFECT MODIFIER ANALYSES OF THE PRIMARY OUTCOME

Table 5: Effect modifier analysis of primary outcome

Type	per-protocol analysis
Population	children receiving intervention or control assignment as randomly allocated
Censoring	- death due to accident - migration - trial end
Time scale	age
Failure	non-accidental morbidity (first non-fatal hospitalization with overnight stay) OR non-accidental mortality (death)
Description	We construct a new four-level variable (group EfM) based on the four possible combinations of group and the effect modifier.
Effect modifier (EfM) in three separate models	Prior MV status: yes or no to MV before enrolment Sex: male or female Season: rainy season (June-November) or dry season (December-May) *Individual records will remain as in the primary analysis, and the model allow for interaction with the potential effect modifier.*

Stata code	*Analysis*
	Egen group_EfM=group(group EfM)
	stset outdate, f(combined_outcome=1) origin(date_of_birth) ///
	enter(date_of_enrolment) exit (censoring_date)
	stcox group#EfM EfM, strata(region vaccination_coverage sex) vce(cl cluster)
	contrast group#EfM
	
	Check of proportional hazards assumption
	estat phtest, detail
	stphplot, strata(group EfM) adj(region vaccination_coverage, sex)
	stcox group#EfM EfM, strata(region vaccination_coverage sex) vce(cl cluster) ///
	tvc(group#EfM EfM) texp(_t)

Effect modifier Vitamin A supplement (for other campaigns implemented during enrolment e.g. meningitis A, inactivated polio vaccine, the same	*Vitamin A supplement: to be analysed as a time varying exposure*
	
	Analysis
	Egen group_vitAsup=group(group vitAsup)
	
	stset outdate, f(combined_outcome=1) origin(date_of_birth) ///
	enter(date_of_enrolment) exit (censoring_date) id(child_identification_number)
	stsplit vitAsup, at(0) after(first_vitAsup)
	stcox group#vitAsup vitAsup, strata(region vaccination_coverage sex) ///
	vce(cl cluster)
	contrast group#vitAsup[2]

[2]VAS campaigns are conducted approximately every 6 months and target all children >6 months old. As children receiving VAS after enrolment will be older than children who have not yet received

analysis approach will be applied)	*Check of proportional hazards assumption* estat phtest, detail stphplot, strata(group vitAsup) adj(region vaccination_coverage, sex) stcox group#vitAsup vitAsup, strata(region vaccination_coverage sex) /// vce(cl cluster) tvc(group#vitAsup vitAsup) texp(_t)

VAS, disentangling differential MV effects by age, time since intervention and pre/post VAS is problematic. In an attempt to investigate if it is a time since enrolment-/age-differential effect, rather than a differential effect of campaign MV by VAS, we will furthermore explore the effect in models allowing for 3-way interactions between: MVC-group, pre- vs post-VAS campaign and first 3 months after enrolment vs subsequent. To do so, observation time for each child will be split into 2 further time-bands: the first 3 months after enrolment and subsequent months. We will then test if the effect of MVC-group varies in the resulting 4 groups: A) No VAS, <3 months after enrolment; B) No VAS, >3months after enrolment, C) VAS, <3 months after enrolment; D) VAS, >3months after enrolment.

5. SECONDARY ANALYSES OF SECONDARY OUTCOMES

Table 6: Secondary analyses of secondary outcome: cause specific primary outcome

Type	per-protocol analysis
Population	children receiving intervention or control assignment as randomly allocated
Censoring	- death due to accident - migration - trial end
Time scale	age
Failure	non-accidental morbidity (first non-fatal hospitalization with overnight stay) OR non-accidental mortality (death) due to: malaria, diarrhea, respiratory infection
Stata code	*Analysis* stset outdate, f(combined_outcome=1&cause==X) origin(date_of_birth) /// enter(date_of_enrolment) exit(censoring_date) stcox group, strata(region vaccination_coverage sex) vce(cl cluster) *Check of proportional hazards assumption* estat phtest, detail stphplot, strata(group) adj(region vaccination_coverage sex) stcox group, strata(region vaccination_coverage sex) vce(cl cluster) tvc(group) texp(_t)

Table 7: Secondary analysis of secondary outcome: first non-accidental outpatient visit

Type	per-protocol analysis
Population	children receiving intervention or control assignment as randomly allocated but 1-2 months after assignment visited to inquire about short-term morbidity in the time that as elapsed since assignment
Count	proportion of non-accidental outpatient visits in a sub-group
Stata code	binreg outpatient_visit group b1.reg. b0.vaccination_coverage b1.sex, rr vce(cl cluster)

Table 8: Secondary analysis of secondary outcome: first non-accidental illness

Type	per-protocol analysis
Population	children receiving intervention or control assignment as randomly allocated but 1-2 months after assignment visited to inquire about short-term morbidity in the time that as elapsed since assignment
Count	proportion of non-accidental illness in a sub-group
Stata code	binreg illness group b1.reg. b0.vaccination_coverage b1.sex, rr vce(cl cluster)

6. SENSITIVITY ANALYSES OF PRIMARY OUTCOME

Table 9: Sensitivity analysis of primary outcome censoring for measles cases

Type	per-protocol analysis
Population	children receiving intervention or control assignment as randomly allocated
Censoring	- death due to measles infection - death due to accident - migration - trial end
Time scale	age
Failure	non-accidental morbidity (first non-fatal hospitalization with overnight stay) OR non-accidental mortality (death)
Stata code	*Analysis* stset outdate, f(combined_outcome=1) origin(date_of_birth) enter(date_of_enrolment) /// exit(censoring_date) stcox group, strata(region vaccination_coverage sex) vce(cl cluster) *Check of proportional hazards assumption* estat phtest, detail stphplot, strata(group) adj(region vaccination_coverage sex) stcox group, strata(region vaccination_coverage sex) vce(cl cluster) tvc(group) texp(_t)

Table 10: Sensitivity analysis of primary outcome with intention-to-treat analysis

Type	classic intention-to-treat analysis (ITT-C)
ITT-C population	including all children present in the village from the day they were first potentially eligible to enter the trial but did not because they e.g. did not receive the assigned treatment, were excluded due to illness, had no guardian present, had a guardian who refused participation
Type	extended intention-to-treat analysis (ITT-E)
ITT-E population	including all children living in the village from the day they were first potentially eligible to enter the trial if present and healthy as the intervention may also affect the health of other children in the community by reducing exposure to severe infections (date of entry in analysis=date_of_enrolment_X)
Censoring	- death due to accident - migration - trial end
Time scale	age
Failure	non-accidental morbidity (first non-fatal hospitalization with overnight stay) OR non-accidental mortality (death)
Stata code	*Analysis* stset outdate, f(combined_outcome=1) origin(date_of_birth) enter(date_of_enrolment_X) /// exit(censoring_date) stcox group, strata(region vaccination_coverage sex) vce(cl cluster) *Check of proportional hazards assumption* estat phtest, detail

	stphplot, strata(group) adj(region vaccination_coverage sex) stcox group, strata(region vaccination_coverage sex) vce(cl cluster) tvc(group) texp(_t)

Appendix 5

The Short-term article

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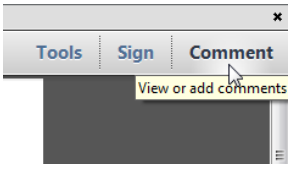

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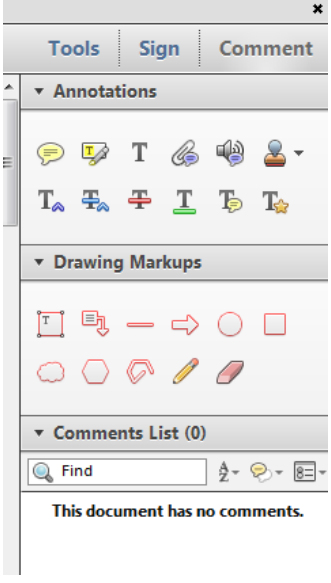

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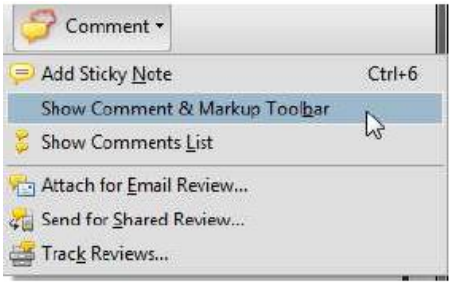

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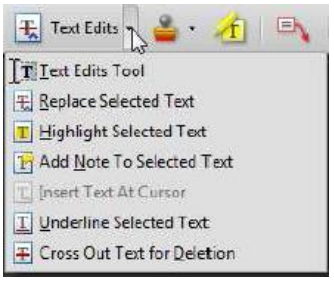

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Journal of the Pediatric Infectious Diseases Society

ORIGINAL ARTICLE

Reduction in Short-term Outpatient Consultations After a Campaign With Measles Vaccine in Children Aged 9–59 Months: Substudy Within a Cluster-Randomized Trial

Anshu Varma,[1,2,3] Peter Aaby,[1,2,3] Sanne Marie Thysen,[1,2,3] Aksel Karl Georg Jensen,[1,3,4] and Ane Bærent Fisker[1,2,3]

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Background. We assessed a measles vaccination campaign's potential short-term adverse events.

Methods. In a cluster-randomized trial assessing a measles vaccination campaign's effect on all-cause mortality and hospital admission among children aged 9–59 months in Guinea-Bissau, children received a measles vaccination (intervention) or a health check-up (control). One month to 2 months later, we visited a subgroup of children to ask mothers/guardians about outpatient consultations since enrollment. In log-binomial models, we estimated the relative risk (RR) of nonaccidental outpatient consultations.

Results. Among 8319 children (4437 intervention/3882 control), 652 nonaccidental outpatient consultations occurred (322 intervention/330 control). The measles vaccination campaign tended to reduce nonaccidental outpatient consultations by 16% (RR, 0.84 [95% confidence interval {CI}, .65–1.11]), especially if caused by respiratory symptoms (RR, 0.68 [95% CI, .42–1.11]). The reduction tended to be larger in children who prior to trial enrollment had a pentavalent vaccination (diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type b) as the most recent vaccination (RR, 0.61 [95% CI, .42–.89]) than in children who prior to trial enrollment had a routine measles vaccination as the most recent vaccination (RR, 0.93 [95% CI, .68–1.26]) (P = .04 for interaction).

Conclusions. In the short term, a measles vaccination campaign seems not to increase nonaccidental outpatient consultations but may reduce them.

Clinical Trials Registration. NCT03460002.

Key words. adverse events; beneficial nonspecific-effects; campaign; children; measles vaccine.

Over the last decades, the world has implemented numerous campaigns with the measles vaccine (MV) to prevent, and ultimately eradicate, measles infection [1].

To our knowledge, few studies have assessed adverse events after MV campaigns [2–6]. Though all studies reported that adverse events were rare, most had no control group [2–4, 6]. The only study using a control group assessed adverse events in school-aged children from a high-income setting [5]. Furthermore, none of the studies considered that MV may have potential beneficial nonspecific effects (NSEs), the ability of MV to protect against other infections than measles, which accumulating evidence is suggesting [7]. Thus, only assessing an MV campaign's adverse events and holding such events against prevention of measles infections may be inadequate to determine an MV campaign's complete risk-benefit.

We conducted a cluster-randomized trial (XXX [RECAMP-MV]) [8] to assess an MV campaign's effect on all-cause mortality and hospital admission among children aged 9–59 months in rural Guinea-Bissau during an average follow-up period of 18 months. Within RECAMP-MV, we conducted the present substudy to assess an MV campaign's potential adverse events and beneficial NSEs in the short term, by measuring the risk of all-cause outpatient consultations within 1–2 months after enrollment.

METHODS

Setting and Population

In rural Guinea-Bissau, the Bandim Health Project runs a health and demographic surveillance system (HDSS) currently monitoring approximately 22 000 children aged 0–59 months in 10 health regions covering 222 geographical village clusters. Field teams of data collection assistants and nurses visit all households every 6 months to interview mothers/guardians about pregnancies and their children's status regarding vaccination,

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mortality, hospital admission, nutrition, participation in campaigns with other health interventions, and migration [9].

Parent Trial Design

Based on the HDSS, we initiated RECAMP-MV [8]. We randomized clusters stratified by health region and preenrollment vaccination coverage to an intervention group or control group. The vaccination coverage estimate was based on the coverage of BCG vaccination, third dose of oral polio vaccine (OPV), third dose of pentavalent vaccine (PENTA; diphtheria, tetanus, pertussis, hepatitis type B, and *Haemophilus influenzae* type b), and measles vaccination by 12 months of age. As in prior studies, we assessed coverage by 12 months of age among children with a seen vaccination card at 12–23 months of age [10]. In November 2016, we initiated enrollment of children aged 9–59 months from all health regions. Nurses offered enrollment to children with written consent from mothers/guardians but excluded children with acute illness, axillary temperature >39°C, mid-upper arm circumference <110 mm, allergic reaction to a prior vaccination, or enrollment in another ongoing Bandim Health Project trial in rural Guinea-Bissau. We offered an MV (standard 0.5-mL dose of the Edmonston-Zagreb strain from Serum Institute of India) to children in the intervention group, irrespective of prior measles vaccination status. The trial was unblinded.

Another Bandim Health Project trial in rural Guinea-Bissau [8] enrolled children aged 0–8 months parallel to RECAMP-MV and had field teams revisit the geographical village clusters in 7 of 10 health regions within 1–2 months after enrollment. We took advantage of these revisits for the present substudy.

Present Substudy Design

We revisited children enrolled in RECAMP-MV from January 2017 to September 2018. We defined the outcome, an outpatient consultation, as the mother/guardian reporting a first contact with a health facility within 1–2 months after enrollment where the child received medical attention unrelated to an accident and did not stay overnight. Due to delays, some revisits took place >2 months after enrollment. Logistics determined the substudy sample size. The interview questions used to retrieve information on the outcome are provided in the Supplementary Methods.

Statistical Analyses

In per-protocol analyses, we assessed an MV campaign's overall effect on outpatient consultations using relative risks (RRs) from log-binomial models with 95% confidence intervals (CIs). We adjusted for health region, preenrollment vaccination coverage, and sex; health region and preenrollment were the stratification variables for the randomization in RECAMP-MV [8], and morbidity patterns commonly differ by sex. Finally, we used a robust standard error accounting for intracluster correlation. We did not adjust for multiple testing. We have provided further details in the RECAMP-MV analysis plan [8]. Additionally, we conducted the following explorative analyses, with the same statistical approach, to assess the overall effect:

- with cause-specific outcomes, based on the most frequently reported symptoms [11];
- with timing-specific outcomes, based on time between enrollment and outcome [2–6, 12];
- with data quality–specific outcomes, based on data collection circumstances;
- by potential effect modifiers, based on background factors associated with magnitude of beneficial NSEs of MV in previous studies: sex [11], prior routine measles vaccination [11], season [11], vitamin A [13] or OPV [14] campaigns, age [15], and having a non-live PENTA vaccination as the most recent vaccination [16, 17]. Furthermore, we explored whether the overall effect was modified by health region and ethnicity, as geographical access and cultural behavior toward healthcare may differ. We conducted Wald tests to compare effects across strata defined by each potential modifier.

Furthermore, in the explorative analyses, we assessed the overall effect with all-cause illness as the outcome, and potential nonblinding issues. In the Supplementary Methods, we have provided details on the exploratory analyses. We conducted all analyses using Stata version 16 software, using a significance level of .05 and conducting 2-sided tests.

Ethical Considerations

The present substudy was part of RECAMP-MV's original protocol and registration (ClinicalTrials.gov identifier NCT03460002) for which we obtained ethical approval in Guinea-Bissau (Comité Nacional de Ética na Saúde, CNES/2016/020) and consultative approval in Denmark (Den Nationale Videnskabsetiske Komité, 1606756). We conducted RECAMP-MV based on the guidelines of the Helsinki Declaration.

RESULTS

During a study period of 21 months, we enrolled 12 183 children to RECAMP-MV who were also potentially eligible for the present substudy. We revisited 8996 children (4750 intervention/4246 control). We obtained information on outpatient consultations for 8319 children (4437 intervention/3882 control) (Figure 1) from 167 clusters (86 intervention/81 control) (Table 1). Thus, we had complete information on 92% of the revisited children (93% intervention/91% control) (Figure 1). We conducted revisits with a median of 31 days from enrollment to revisit (31 intervention/32 control). Ninety-five percent received a revisit within 1–2 months after enrollment (96%

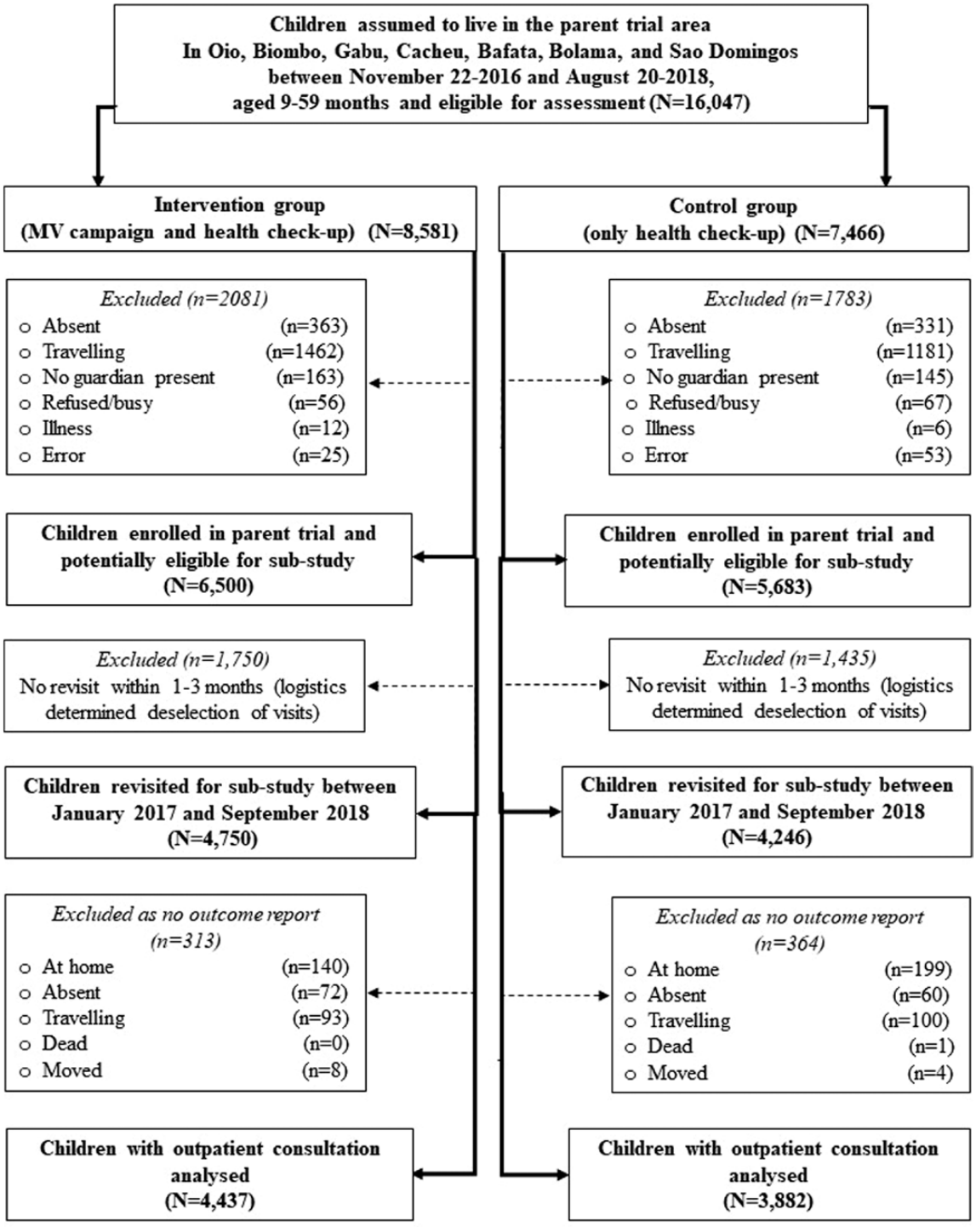

Figure 1. Flowchart of children from eligibility to analysis. Abbreviation: MV, measles vaccine.

intervention/94% control) and the remaining during the third month of follow-up. We found no differences in the baseline characteristics or their missing values (Table 1, Supplementary Table 1).

The total number of first outpatient consultations was 653; 1 (control) was due to an accident, leaving 652 outpatient consultations for the analyses (322 intervention/330 control). The absolute risk of outpatient consultations was 7.9% (7.3% intervention/8.5% control). The MV campaign tended to reduce outpatient consultations by 16% (RR, 0.84 [95% CI, .65–1.11]) and especially if caused by respiratory symptoms (RR, 0.68 [95% CI, .42–1.11]), which was the case for 17% of the outpatient consultations. When

Table 1. Baseline Characteristics of Children per Group Assignment (N = 8319[a])

Characteristic	MV Campaign[b]		No MV Campaign[b]	
No. of children	53.3	(4437)	46.7	(3882)
Sociodemographics				
Male sex	51	(2275)	52	(2007)
Age, mo, median (IQR)	34	(20–46)	33	(21–46)
Health region				
Oio	5	(215)	6	(229)
Biombo	15	(673)	15	(576)
Gabu	20	(909)	18	(685)
Cacheu	1	(48)	1	(25)
Bafata	12	(554)	18	(717)
Bolama	2	(82)	2	(64)
Sao Domingos	13	(564)	12	(460)
Bafata new[c]	31	(1392)	29	(1126)
Ethnicity				
Balanta	10	(431)	10	(399)
Fula	50	(2235)	44	(1700)
Manjaco/Mancanha	4	(176)	2	(78)
Pepel	12	(530)	12	(474)
Mandinga	18	(800)	27	(1047)
Other	5	(233)	4	(157)
Household				
Zinc/metal roof	72	(3207)	71	(2767)
Radio	82	(3630)	84	(3255)
Outdoor toilet	85	(3767)	86	(3328)
Phone (own/house)	53	(2334)	51	(1980)
Mother's age, y, mean (SD)	26	(7.2)	27	(7.1)
Mother went to school	34	(1495)	34	(1332)
Child lives with mother	98	(4328)	98	(3805)
Health status on enrollment day				
Weight, kg, mean (SD)	11.5	(2.6)	11.5	(2.6)
Weight-for-age *z* score, mean (SD)	–1.3	(1.1)	–1.3	(1.1)
MUAC, mm, mean (SD)	146.9	(11.6)	146.5	(11.7)
MUAC-for-age *z* score, mean (SD)	–0.7	(0.9)	–0.7	(0.9)
Temperature, °C, mean (SD)	36.3	(0.5)	36.3	(0.5)
No medicine intake	97	(4297)	98	(3805)
Vaccination status among children with vaccination card seen before enrollment				
Vaccination card seen	75	(3332)	73	(2822)
Already administered routine vaccinations				
BCG	92	(3076)	94	(2647)
PENTA third dose	90	(3006)	91	(2565)
Pneumococcal conjugate third dose[d]	43	(1420)	42	(1198)
Rotavirus second dose[d]	30	(1007)	29	(820)
Yellow fever	74	(2470)	74	(2083)
MV	83	(2749)	82	(2327)
Inactivated polio[d]	15	(505)	15	(411)
Most recent vaccination prior to enrollment[e]				
MV[f]	40	(1792)	40	(1535)
PENTA with MV[g]	6	(274)	7	(275)
PENTA without MV[h]	12	(553)	11	(440)
Eligible for vitamin A campaigns[i]				
Within 1 y prior to enrollment (Jan 2017/Jun 2017)	65	(2876)	61	(2381)
During revisit period (Jan 2017/Jun 2017)	11	(488)	15	(591)
Eligible for OPV campaigns[j]				
Within 1 y prior to enrollment (Nov 2017/Apr 2018)	32	(1400)	29	(1133)
During revisit period (Nov 2017/Apr 2018)	0	(6)	0	(4)

Table 1. Continued

Characteristic	MV Campaign[b]		No MV Campaign[b]	
Timing				
Enrolled during rainy season (Jun-Nov)	63	(2786)	66	(2576)
Follow-up time, d, median (IQR)	31	(29–41)	32	(30–39)
Followed within 1–2 mo	96	(4280)	94	(3637)
Clusters				
Clusters	51	(86)	49	(81)
Children in cluster, median (IQR)	78	(56–106)	64	(50–95)

Abbreviations: IQR, interquartile range; MUAC, mid-upper arm circumference; MV, measles vaccine; OPV, oral polio vaccine; PENTA, diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type b vaccine; SD, standard deviation.

[a]Missing values in each variable are provided in Supplementary Table 1.

[b]Data are presented as percentage (No.) unless otherwise indicated.

[c]We added clusters from another part of Bafata after approval of a protocol amendment concerning a sample size increase in the parent trial.

[d]Year of introduction in routine vaccination program: pneumococcal conjugate (2015), rotavirus (2015), and inactivated polio (2016).

[e]1285 children with other combinations of their most recent vaccination not included.

[f]MV as most recent vaccination; a co-scheduled yellow fever vaccine could have been given, but not BCG, OPV, PENTA, rotavirus, pneumococcal conjugate, or inactivated polio.

[g]PENTA with MV as most recent vaccination; other vaccines co-scheduled with PENTA or MV (OPV, rotavirus, yellow fever, pneumococcal conjugate, inactivated polio) could have been given but not BCG.

[h]PENTA as most recent vaccination; other vaccines co-scheduled with PENTA (OPV, rotavirus, pneumococcal conjugate, inactivated polio) could have been given but not BCG, MV, or yellow fever.

[i]Coadministration with mebendazole, and excluding vitamin A campaigns with vaccines.

[j]Coadministration with vitamin A.

we restricted the outcome definition to outpatient consultations, where mothers/guardians presented written documentation from a health facility, the RR was 0.66 (95% CI, .43–1.03). When we restricted the analysis to information on outpatient consultations reported by the mother, the RR was 0.79 (95% CI, .61–1.05) (Table 2). Of the total outpatient consultations, 49% were fully dated (46% intervention/54% control); the remaining mostly reported month of occurrence. The effects in different timing categories were similar to the pattern observed for the overall effect (Table 2, Supplementary Table 2).

We examined background factors that were potential effect modifiers. The reduction in outpatient consultations tended to differ by the most recent vaccination prior to enrollment. Among children with no prior routine measles vaccination, the reduction tended to be larger (RR, 0.62 [95% CI, .43–.89]) than among children with prior routine measles vaccination (RR, 0.84 [95% CI, .62–1.14]) ($P = .17$ for interaction). Furthermore, children with PENTA (with or without co-scheduled vaccines and with or without coadministered MV) (RR, 0.61 [95% CI, .42–.89]) as their most recent vaccination tended to have larger reductions than children with MV (with or without co-scheduled yellow fever vaccine) as their most recent vaccination (RR, 0.93 [95% CI, .68–1.26]) ($P = .04$ for interaction) (Table 3). Apart from ethnicity (Supplementary Table 3), the remaining potential effect modifiers assessed had less strong tests of interactions (sex, season, vitamin A/OPV campaigns, and age [Table 3] and health region [Supplementary Table 3]).

The total number of children with information on illness was 8296 (4425 intervention/3871 control). A total of 1410 children had an illness episode since enrollment; 6 episodes were due to accidents (4 intervention/2 control), leaving 1404 illnesses for the analyses (727 intervention/677 control). The absolute risk of illness was 16.9% (16.4% intervention/17.5% control). The MV campaign had no marked effect on illness (RR, 0.95 [95% CI, .81–1.12]) (Supplementary Table 2). Among children whose mothers/guardians reported that they had been ill since enrollment, the risk of outpatient consultations tended to be lower in the intervention group than in the control group (RR, 0.88 [95% CI, .77–1.02]) (Supplementary Table 4).

DISCUSSION

After a measles vaccination campaign, we observed no increased risk of short-term adverse events. In contrast, the measles vaccination campaign tended to reduce the risk of nonaccidental outpatient consultations among children aged 9–59 months in rural Guinea-Bissau. This finding was robust to several restrictions on the outcome definition.

Strengths and Weaknesses

The randomized design, large sample size, and high proportion followed up are strengths. No placebo use is a genuine limitation. Thus, we cannot rule out that differential healthcare-seeking behavior may have affected our findings. Mothers/guardians of children in the intervention group could have anticipated more adverse events or better future health. This could have changed their threshold for seeking healthcare; among ill children, we observed that children in the intervention group tended to have a lower risk of outpatient consultations than children in the control group. However, we cannot know whether this difference was due to mothers/guardians of ill children in the intervention group ascribing their symptoms to adverse events or other causes.

Table 2. Effect of Measles Vaccination Campaign on Outpatient Consultations: Overall, Cause Specific, Data Quality Specific, and Timing Specific (Log-Binomial Model)

AQ12 XXX	MV Campaign, % (No.)		No MV Campaign, % (No.)		RR[b]	(95% CI)
No. of consultations (N = 8319[a])	53.3	(4437)	46.7	(3882)		
	Outpatient Consultations Proportion, % (Events per No. of Persons)					
Overall	7.3	(322/4437)	8.5	(330/3882)	0.84	(.65–1.11)
Cause specific[c]						
Fever	5.3	(234/4437)	5.8	(224/3882)	0.90	(.66–1.21)
Gastrointestinal	1.7	(75/4437)	2.3	(91/3882)	0.72	(.48–1.07)
Respiratory	1.1	(49/4437)	1.5	(60/3882)	0.68	(.42–1.11)
Data quality specific						
Medical test performed[d]	3.6	(157/4371)	4.4	(169/3812)	0.80	(.56–1.15)
With written documentation from health facility[e]	1.4	(61/4418)	2.0	(78/3868)	0.66	(.43–1.03)
Report by mother[f]	7.7	(243/3148)	9.7	(244/2522)	0.79	(.61–1.05)
With cause report[g]	7.0	(310/4425)	8.3	(321/3873)	0.84	(.64–1.09)
Timing specific						
Within 0–14 d	0.6	(27/4263)	1.0	(36/3722)	0.62	(.36–1.07)
Within 15–28 d	1.4	(58/4236)	1.6	(58/3686)	0.85	(.54–1.35)
Within >28 d[h]	1.5	(63/4178)	2.1	(76/3628)	0.69	(.38–1.24)

Abbreviations: CI, confidence interval; MV, measles vaccine; RR, relative risk.

[a]Outpatient consultations due to accident (1 control), measles (0), with missing date (22), with unknown day of month (305), occurring prior to enrollment (7).

[b]Adjusted for stratification variables health region and preenrollment vaccination coverage, and sex, and using a robust standard error accounting for intracluster correlation.

[c]Symptoms: fever (70%), gastrointestinal (25%), respiratory (17%), other (4%), malaria (1%), unknown (2%), missing (1%). Gastrointestinal cause covers symptoms such as diarrhea, vomiting, and abdominal pain. Respiratory cause covers symptoms such as cough, cold, breathing difficulties, and chest pain. For example, if a mother/guardian reported a child having vomited and coughed prior to an outpatient consultation, the child was included in both the respiratory and gastrointestinal cause categories for an outpatient consultation.

[d]136 children not included as missing/unknown status on medical test.

[e]33 children not included as missing/unknown status on written documentation from health facility.

[f]2649 children not included as there was no report by mother.

[g]21 children not included as there was no report on symptom.

[h]Among children receiving a revisit after 28 days.

In either case, we also cannot know whether mothers/guardians of ill children in the intervention group believed that their symptoms were not severe enough to seek outpatient consultation and/or whether their symptoms in fact were less severe. Nevertheless, due to expected mild fever following measles vaccination [12], we would expect more outpatient consultations among children in the intervention group; thus, the observed potential beneficial NSEs may not be fully reflected in the 16% risk reduction.

Another limitation is relying on symptoms reported by mothers/guardians to define cause of outpatient consultations. Accidents could have gone unnoticed since we did not ask directly about accident as a cause, but we expect an accident to be easier to recall and more likely to be reported than vague symptoms. Measles infections may have been confused with other infections, which could have led mothers/guardians to either over- or underreport outpatient consultations due to measles infection. We have previously observed in the rural HDSS population that mothers/guardians reported suspected measles cases during periods where serological tests from the same health regions were negative for measles antibodies but positive for rubella antibodies. Thus, we know that overreporting may occur. However, as mothers/guardians in our substudy did not report any outpatient consultation due to measles infection, a concern here is potential underreporting, but we think that the risk is limited; even if mothers/guardians may not have recognized a measles infection, the consulting healthcare staff would likely recognize a measles infection and initiate tracing and testing, making it unlikely for mothers/guardians not to recall when asked. Furthermore, many mothers/guardians have co-living elderly persons who have experienced previous measles outbreaks and therefore would be able to recognize a measles infection, in case mothers/guardians would not.

A third limitation is that some of the effect modifier analyses included only some of the children. For example, we only assessed prior measles vaccination and most recent vaccination among children who had their vaccination card seen at enrollment. A fourth limitation is that we only revisited children once after enrollment, and thus we may have missed some outpatient consultations due to the lack of mothers'/guardians' recall. Finally, there is a risk of chance findings, due to the many tests we conducted in the exploratory analyses, and this alongside the study size being determined by logistics should be taken into account when interpreting our main and exploratory findings.

Consistency With Previous Studies

A retrospective cohort study on adverse events of a measles-mumps-rubella (MMR) campaign in the United Kingdom

Table 3. Potential Effect Modifiers of Measles Vaccination Campaign on the Risk of Outpatient Consultations (Log-Binomial Model)

XXX AQ13

	MV Campaign, % (No.)		No MV Campaign, % (No.)		RR[b]	(95% CI)	*P* Value[c]
No. of consultations (N = 8319[a])	53.3	(4437)	46.7	(3882)			
	Outpatient Consultations Proportion, % (Events per No. of Persons)						
Sex							.85
Male	7.2	(163/2275)	8.4	(169/2007)	0.86	(.64–1.16)	
Female	7.4	(159/2162)	8.6	(161/1875)	0.83	(.61–1.15)	
Prior routine MV among children with seen vaccination card							.17
No	8.8	(49/559)	14.7	(69/469)	0.62	(.43–.89)	
Yes	7.1	(194/2749)	8.3	(193/2327)	0.84	(.62–1.14)	
Most recent vaccination prior to enrollment among children with seen vaccination card[d]							.04
MV[e]	7.6	(137/1792)	8.4	(129/1535)	0.93	(.68–1.26)	
PENTA with or without MV[f]	6.5	(54/827)	10.9	(78/715)	0.61	(.42–.89)	
Season							.45
Dry	7.3	(120/1651)	10	(134/1306)	0.74	(.51–1.09)	
Rainy	7.3	(202/2786)	7.6	(196/2576)	0.91	(.63–1.33)	
Eligible for vitamin A campaigns within 1 y prior to enrollment[g]							.39
No	9.1	(142/1561)	11.9	(178/1501)	0.78	(.51–1.19)	
Yes	6.3	(180/2876)	6.4	(152/2381)	0.98	(.72–1.34)	
Eligible for vitamin A campaigns during revisit period[g]							.38
No	6.1	(242/3949)	7.2	(238/3291)	0.81	(.58–1.13)	
Yes	16.4	(80/488)	15.6	(92/591)	1.04	(.67–1.62)	
Eligible for OPV campaigns within 1 y prior to enrollment[h]							.35
No	8.2	(249/3037)	8.7	(239/2749)	0.92	(.71–1.19)	
Yes	5.2	(73/1400)	8.0	(91/1133)	0.65	(.34–1.28)	
Eligible for OPV campaigns during revisit period[h]							.90
No	7.2	(321/4431)	8.5	(329/3878)	0.84	(.65–1.11)	
Yes	16.7	(1/6)	25.0	(1/4)	0.72	(.06–8.42)	
Age group, mo[i]							.40
8.9 to <20.5	11.6	(130/1117)	13.6	(131/963)	0.86	(.66–1.12)	
20.5 to <33.5	7.6	(83/1085)	10.6	(106/996)	0.72	(.49–1.03)	
33.5 to <46.4	5.3	(60/1127)	5.2	(50/958)	1.02	(.67–1.55)	
46.4–60	4.4	(49/1108)	4.5	(43/965)	0.97	(.55–1.71)	

Abbreviations: CI, confidence interval; MV, measles vaccine; OPV, oral polio vaccine; PENTA, diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type b vaccine; RR, relative risk.

[a]Accident (1 control), measles (0).

[b]Adjusted for stratification variables health region and preenrollment vaccination coverage, and sex, and using a robust standard error accounting for intracluster correlation.

[c]Wald tests to compare effects across strata defined by each potential modifier.

[d]When we conducted the effect modifier analysis with the 3 groups MV, MV with PENTA, and MV without PENTA, the model did not converge, and thus we present the analysis for combination of the 2 PENTA groups. In the PENTA with MV strata, the numbers of outpatient consultations were 9/274 (intervention) and 12/275 (control). In the PENTA without MV strata, the numbers of outpatient consultations were 45/553 (intervention) and 66/440 (control). AQ14

[e]MV as most recent vaccination; a co-scheduled yellow fever vaccine could have been given, but not BCG, OPV, PENTA, rotavirus, pneumococcal conjugate, or inactivated polio.

[f]PENTA with or without MV as most recent vaccination; other vaccines co-scheduled with PENTA or MV (OPV, rotavirus, yellow fever, pneumococcal conjugate, inactivated polio) could have been given but not BCG.

[g]Coadministration with mebendazole, and excluding vitamin A campaigns with vaccines.

[h]Coadministration with vitamin A.

[i]Groups based on interquartile range.

among 2170 children aged 11–15 years showed findings in line with ours. MMR campaign participants were less likely to visit an outpatient department due to any cause (4/1077 vs 14/1075: RR, 0.29 [95% CI, .10–.87]) and had a lower risk of reporting cough symptoms (RR, 0.83 [95% CI, .70–.99]) than nonparticipants, within 6 weeks after the campaign [5]. However, the study population was much older and the study design was not randomized.

Two randomized trials from Guinea-Bissau assessed the risk of all-cause outpatient consultations after early measles vaccination (administered at 4.5 months of age) compared to no early measles vaccination [18, 19]. Although both trials enrolled much younger children and randomized them individually, thus not assessing an MV campaign, their outcome was the same as ours, and their follow-up method comparable. Both trials showed that early MV was safe, but neither trial showed lower risks of all-cause outpatient consultations until the children reached 9 months of age and received their routine measles vaccination. One trial reported outpatient consultations by cause (respiratory, gastrointestinal, and presumed malaria) but, unlike our substudy, results did not indicate a differential effect [19]. Both trials assessed some background factors comparable to our potential effect modifiers, sex and season. In line with our finding, sex differences were small or absent [18, 19], but our observation of a more beneficial effect in the dry season was not supported [19].

Interpretation

Our main finding supports that an MV campaign is safe in the short term, since we found no increased risk of adverse events leading to outpatient consultations within 1–3 months after an MV campaign.

Aside from injection site reactions, the most common adverse events of measles vaccination are mild and usually characterized as fever and/or rash (5%–10%) [12]. Despite fever being the most common cause of outpatient consultations in our substudy, we found no indication that it was more common among children in the intervention group. The majority of children in the intervention group had received routine measles vaccination prior to enrollment (83% among children with a seen vaccination card) and therefore the MV campaign was mainly administered as a second MV dose, which is assumed to have fewer adverse events than a first MV dose [12].

Although confirmed measles infection cases increased during the substudy period from 0 cases in 2016 to 28 cases in 2018 [20], none of the outpatient consultations were reported as due to measles infection. Hence, in the short term, an MV campaign may have beneficial NSEs. Furthermore, these may be more pronounced for outpatient consultations due to respiratory symptoms, in line with a randomized trial assessing the risk of early measles vaccination on hospital admissions [11]; some cross-reactivity between the MV's measles virus component and acquired viruses such as respiratory syncytial virus, parainfluenza virus, and influenza virus may explain this pattern [21]. The reduction in outpatient consultations for children with PENTA (with or without coadministered MV) as the most recent vaccination, which tended to differ from the effect among children with MV (with or without co-scheduled yellow fever vaccine) as the most recent vaccination, suggests that the sequence of a live and non-live vaccine matters. Children with the non-live PENTA as the most recent vaccination could have had the most to gain from a campaign with live MV [16]. Although previous studies have observed that prior measles vaccination increases the magnitude of beneficial NSEs [22], on the contrary, we observed this for no prior measles vaccination. This may be because we cannot fully disentangle the effect of prior routine measles vaccination from the effect of having PENTA as the most recent vaccination.

Our results suggest that in the short term, an MV campaign may not only be safe but also potentially beneficial for children aged 9–59 months in rural Guinea-Bissau. Thus, in a risk-benefit evaluation of an MV campaign, we may need to consider not only estimating the measles infection cases avoided but also assessing the impact on overall health.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. A. B. F., A. K. G. J., A. V., and P. A. conceptualized the substudy. A. B. F. planned and coordinated the substudy. A. B. F., A. V., and S. M. T. developed and updated follow-up questionnaires and databases for the substudy. A. B. F., A. V., and S. M. T. trained field teams, supervised fieldwork, and developed and implemented data cleaning programs for the substudy. A. V. drafted the manuscript with help from A. B. F. All authors approved the final version of the manuscript.

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SUPPLEMENTARY METHODS

Applied interview questions for the outcome outpatient consultation

In Portuguese-Creole, assistants asked, "*Since our last visit*":

1. *Has [the child] been ill?*" (yes/no/unknown), if yes
    a. "*What did [the child] have?*" (open question on symptoms)
2. *"Did you bring [the child] for an outpatient consultation?"* (yes/no/unknown), if yes
    a. *"What day did you bring [the child] for an outpatient consultation?"* (date)
    b. "*Do you have documentation of this date (e.g. prescription)?*" (yes/no/unknown)
    c. "*Did [the child] have a medical test performed?*" (yes/no/unknown)

We used item 2 for the overall effect, item 1a for cause, item 2a-c for data quality indicators, and item 2a for timing.

Cause specific outcomes

To assess the effects of MV by cause, we classified outpatient consultations by symptoms reported (item 1a) (fever, gastrointestinal, and respiratory) [10]. An outpatient consultation could count in more than one symptom group if a child had multiple symptoms that belonged to different cause categories. For the outcome all-cause illness, we used item 1.

Data quality specific outcomes

We assessed data quality by restricting outpatient consultations to be:

- with a medical test taken; ensuring accurate recall by mother/guardian
- confirmed by written documentation from a health facility; ensuring valid occurrence and date
- reported with a cause; ensuring illness as the purpose of a health facility visit

and by restricting the analysis to information reported by the mother; ensuring valid source of report

Timing specific outcomes

We assessed outpatient consultations occurring in the following intervals: 0-14 days, 15-28 days, or >28 days. Mild and common adverse events are expected <14 days from measles vaccination [11] and studies have commonly assessed adverse events up to one month after measles vaccination [2-6]. For each timing category, we assessed effects by cause and data quality indicators.

Blinding

We assessed potential non-blinding issues:

- Among children, whose mothers/guardians reported that they had been ill since enrolment, we assessed the risk of outpatient consultations. Mothers/guardians of children in the intervention group may have anticipated more adverse events or better future health, changing their threshold for seeking health care.
- We assessed the risk of the consent giver being a guardian. Guardians of children in the intervention group may have been more inclined to be escorts in the absence of mothers.
- We assessed the risk of a mother/guardian declining to participate. Mothers/guardians of eligible children in the intervention group may have been less inclined to reject participation.

Supplementary Table 1: Missing/unknown status in baseline variables. Percentage (n).

	MV campaign		No MV campaign	
	%	n	%	n
Missing values				
Sociodemographics				
Ethnicity	1	(32)	1	(27)
Roof	2	(105)	2	(87)
Radio	2	(109)	3	(111)
Toilet	3	(120)	3	(109)
Phone	4	(164)	4	(153)
Age, mother	2	(75)	2	(59)
Mother's school[a]	3	(119)	3	(101)
Lives with mother	0	(1)	0	(1)
Health on enrolment day				
Weight[b]	1	(44)	1	(49)
MUAC[b]	0	(14)	0	(16)
Temperature	1	(25)	0	(5)
Medicine intake	0	(0)	0	(15)
Vaccination status on enrolment day among children with a vaccination card seen				
Vaccination card	3	(133)	3	(102)
BCG	1	(31)	1	(30)
PENTA 3rd	0	(9)	0	(8)
Pneumococcal conjugate vaccine 3rd	0	(4)	0	(3)
Rotavirus 2nd	0	(10)	0	(9)
Yellow fever	1	(24)	1	(25)
MV	1	(24)	1	(26)
Inactivated polio	0	(0)	0	(1)

Abbreviations: MV=measles vaccine; MUAC=mid-upper-arm circumference; BCG=Bacille Calmette Guerin; OPV=oral polio vaccine; PENTA=diphtheria, tetanus, pertussis, hepatitis B, and haemophilus influenza B vaccine.

[a]When error tracked in original variable on mother's school, new variable introduced during trial.
[b]For z-score 1 missing value in control group as not fulfilling flag value requirement for z-score calculation.

Supplementary Table 2: Effect of MV campaign on outpatient consultations: outcome is timing specific and cause specific or timing specific and data quality specific. Effect of MV campaign on outcome illness. Log-binomial model.

N=8319[a]	MV campaign (%, n) 53·3 (4437)		No MV campaign (%, n) 46·7 (3882)			
	Outpatient consultations proportion % (events per number of persons)				RR[b]	(95% CI)
Within 0-14 days						
Cause specific[c]						
Fever	0·4	(17/4263)	0·4	(16/3722)	0·91	(0·43-1·91)
Gastrointestinal	0·2	(8/4263)	0·4	(16/3722)	0·41	(0·18-0·93)
Respiratory	0·1	(3/4263)	0·3	(10/3722)	0·24	(0·07-0·91)
Data quality specific						
Medical test performed	0·4	(18/4263)	0·5	(18/3716)	0·83	(0·42-1·62)
With written documentation from health facility	0·2	(9/4263)	0·3	(12/3722)	0·63	(0·28-1·39)
Report by mother	0·9	(26/3027)	1·2	(28/2408)	0·70	(0·41-1·19)
With cause report	0·6	(26/4262)	1·0	(36/3722)	0·60	(0·34-1·04)
Within 15-28 days						
Cause specific[c]						
Fever	1·1	(47/4236)	1·1	(42/3686)	0·93	(0·55-1·57)
Gastrointestinal	0·3	(11/4236)	0·4	(16/3686)	0·61	(0·26-1·44)
Respiratory	0·2	(8/4236)	0·2	(7/3686)	0·97	(0·35-2·72)
Data quality specific						
Medical test performed	0·9	(38/4229)	0·9	(32/3679)	0·99	(0·57-1·75)
With written documentation from health facility	0·5	(22/4235)	0·8	(29/3686)	0·65	(0·33-1·31)
Report by mother	1·6	(48/3001)	2·0	(47/2380)	0·78	(0·48-1·28)
With cause report	1·4	(58/4236)	1·6	(58/3686)	0·85	(0·54-1·35)

Within >28 days[g]						
Cause specific[c]						
Fever	1·2	(50/4178)	1·5	(56/3628)	0·73	(0·38-1·41)
Gastrointestinal	0·6	(23/4178)	0·5	(18/3628)	1·07	(0·49-2·29)
Respiratory	0·2	(8/4178)	0·4	(15/3628)	0·42	(0·17-1·03)
Data quality specific						
Medical test performed	0·7	(29/4167)	1·1	(40/3608)	0·61	(0·29-1·27)
With written documentation from health facility	0·7	(29/4175)	1·0	(37/3627)	0·65	(0·35-1·19)
Report by mother	1·6	(48/2953)	2·4	(55/2333)	0·69	(0·37-1·28)
With cause report	1·5	(61/4176)	2·1	(75/3627)	0·68	(0·38-1·21)
Illness[d]	16·4	(727/4425)	17·5	(677/3871)	0·95	(0·81-1·12)

Abbreviations: MV=measles vaccine; RR=relative risk; CI=confidence interval.

[a]Accident (1 control), measles (0) and missing due to lack of date (22), unknown day of month (305) or occurring prior to enrolment (7).

[b]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation.

[c]Gastrointestinal cause covers symptoms such as diarrhoea, vomiting, and abdominal pain. Respiratory cause covers symptoms such as cough, cold, breathing difficulties and chest pain. E.g. if a mother/guardian reported a child having vomited and coughed prior to an outpatient consultation, the child was included in both the respiratory and gastrointestinal cause categories for an outpatient consultation.

[d]Accident (4 intervention/2 control), measles (0), and missing illness report (23).

Supplementary Table 3: Potential effect modifiers of MV campaign on the risk of outpatient consultations. Log-binomial model.

N=8319[a]	MV campaign (%, n) 53·3 (4437) Outpatient consultations proportion % (events per number of persons)	No MV campaign (%, n) 46·7 (3882)	RR[b] (95% CI)	p-value[c]
Health region				0·23
Oio	5·6 (12/215)	8·3 (19/229)	0·67 (0·16-2·76)	
Biombo	14·4 (97/673)	15·5 (89/576)	0·93 (0·61-1·44)	
Gabu	2·1 (19/909)	5·0 (34/685)	0·43 (0·22-0·84)	
Cacheu	16·7 (8/48)	28·0 (7/25)	0·59 (0·21-1·67)	
Bafata	6·7 (37/554)	5·2 (37/717)	1·27 (0·71-2·31)	
Bolama	28·0 (23/82)	31·3 (20/64)	0·90 (0·49-1·65)	
Sao Domingos	9·9 (56/564)	7·6 (35/460)	1·30 (0·71-2·38)	
Bafata new[d]	5·0 (70/1392)	7·9 (89/1126)	0·63 (0·32-1·26)	
Ethnicity				0·16
Balanta	6·3 (27/431)	9·5 (38/399)	0·63 (0·34-1·17)	
Fula	4·8 (107/2235)	7·3 (124/1700)	0·65 (0·41-1·04)	
Manjaco/Mancanha	11·9 (21/176)	19·2 (15/78)	0·64 (0·37-1·11)	
Pepel	15·7 (83/530)	17·3 (82/474)	0·92 (0·58-1·46)	
Mandinga	4·3 (34/800)	4·8 (50/1047)	0·90 (0·44-1·82)	
Other	20·2 (47/233)	11·5 (18/157)	1·77 (0·91-3·46)	

Abbreviations: MV=measles vaccine; RR=relative risk; CI=confidence interval.

[a]Accident (1 control), measles (0).

[b]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation.

[c]Wald tests to compare effects across strata defined by each potential modifier.

[d]We added clusters from another part of Bafata after approval of a protocol amendment concerning a sample size increase in the parent trial.

Supplementary Table 4: Potential non-blinding issues. Percentage (n). Log-binomial model.

	MV campaign		No MV campaign			
	%	n	%	n	RR[a]	(95% CI)
Among children, whose mothers/guardians reported illness						
N=1404	52	727	48	677		
Outpatient consultations reported	44	(321/727)	49	(329/677)	0·88	(0·77-1·02)
Among children enrolled						
N=8319	53	4437	47	3882		
Guardian as consent giver	27	(1193/4437)	28	(1087/3882)	0·97	(0·83-1·13)
Among children eligible for assessment						
N=16047	53	8581	47	7466		
Mothers/guardians who refused/were busy	0·7	(56/8581)	0·9	(67/7466)	0·75	(0·48-1·18)

Abbreviations: MV=measles vaccine; RR=relative risk; CI=confidence interval.

[a]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation.

Appendix 6

The Long-term article

Title page

Title

Real-life effect of a measles vaccination campaign on non-accidental mortality/hospital admissions: a cluster-randomised trial among children aged 9-59 months in rural Guinea-Bissau

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Word count

Text limit 3500

Abstract limit 250

Summary

Background Campaigns with measles vaccine (MV) are conducted to control and eventually eradicate measles but may have effects beyond measles prevention. We assessed the real-life-effects of an MV campaign, hypothesising a 30% reduction in overall mortality/hospital admissions.

Methods In a cluster-randomized trial, we enrolled children aged 9-59 months from Guinea-Bissau for MV and health check-up (intervention group) or health check-up (control group). In Cox proportional hazards models with age as underlying timescale, we assessed an MV campaign's effects on non-accidental mortality/hospital admissions, estimating hazard ratios (HR). We followed children until eligibility for a nationally implemented MV campaign.

Findings Among 18411 children (9636 intervention/8775 control), 379 non-accidental deaths/hospital admissions occurred (208 intervention/171 control) during a median follow-up period of 22 months (22 intervention/22 control). The MV campaign did not reduce mortality/hospital admissions (HR 1·12, 95% CI 0·88-1·41). During follow-up, two campaigns with oral polio vaccine (OPV) targeted the enrolled children. The MV campaign tended to increase mortality/hospital admissions after eligibility for OPV campaigns (HR 1·24, 95% CI 0·92-1·68) but not before (HR 1·01, 95% CI 0·72-1·22). This effect was sex-differential: girls tended to have a lower risk before eligibility for OPV campaigns (HR 0·86, 95% CI 0·53-1·37) but a higher risk after (HR 1·52, 95% CI 1·02-2·27) (p=0·11 for interaction between MV campaign, eligibility for OPV campaigns, and sex, and p=0.06 for interaction between MV campaign and eligibility for OPV campaigns, among girls)

Interpretation An MV campaign did not reduce overall mortality/hospital admissions. Concurrent OPV campaigns may have played a role.

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Introduction

In the last decades, the world has implemented numerous campaigns with measles vaccine (MV) to control and eventually eradicate measles infection [1]. During the same decades child mortality has decreased tremendously [2]. Meanwhile, accumulating evidence suggests, that MV protects against other infections than measles, also termed beneficial non-specific-effects (NSE) [3]. An epidemiological review commissioned by the World Health Organization concluded that, "*There was consistent evidence of a beneficial effect of measles vaccine* (…)" on all-cause child mortality [4]. Thus, MV campaigns may have efficiently contributed to the decrease in all-cause child mortality beyond our common understanding.

To our knowledge, only two studies have assessed an MV campaign's real life effect [5, 6]. One study compared all-cause mortality after vs before an MV campaign among 8000 children and observed a 20% (4%-34%) lower mortality [5]. Another study compared all-cause mortality between participants and non-participants of an MV campaign among 6639 children and observed a 72% (23%–90%) lower mortality [6]. While both studies showed substantially lower all-cause mortality among children exposed to MV campaigns, it is difficult to draw a firm conclusion based on their observational designs.

We conducted a cluster-randomised trial (RECAMP-MV: Real-life Effects of a CAMPaign with Measles Vaccine) [7] to assess whether an MV campaign reduces the risk of non-accidental mortality or hospital admissions (in a composite outcome) by 30%, among children aged 9-59 months from rural Guinea-Bissau, a setting with limited measles infection [8, 9].

Methods

Study design and participants

We have reported the design and methods of RECAMP-MV in our published protocol and statistical analysis plan [7]. Briefly, RECAMP-MV was a cluster-randomised trial using the platform of the Bandim Health Project's rural health and demographic surveillance system (HDSS) in Guinea-Bissau [10]. This system monitors roughly 22,000 children aged 0-59 months in 10 health regions covering 222 village clusters.

Every 6 months, field teams of assistants and nurses visit the villages in the rural HDSS. At the visits, field assistants conduct structured interviews with mothers to register any pregnancies and child births/deaths. Furthermore, for children under surveillance, field assistants register their routine vaccinations (supplementary figure 1), participation in other health interventions (supplementary figure 2), and hospital admissions. After any registered deaths/hospital admissions, field assistants conduct short interviews on the cause of deaths/hospital admissions [10]. For deaths, additionally a verbal autopsy is conducted by specially trained field assistants [11]. The surveillance stops when children have reached 5 years of age, migrated or died. In the case of migration or death, the date of the event is collected. This was the data collection platform for RECAMP-MV targeting children aged 9-59 months. Mortality in children aged 9-59 in 2014-16 (2 years prior to starting enrolment) living in the rural HDSS was 10·1 per 1000 person years.

Randomisation and masking

We randomised village clusters stratified by health region and pre-trial vaccination coverage. The coverage of Bacillus Calmette-Guérin (BCG) vaccination, oral polio vaccination (OPV), pentavalent vaccination (diphtheria, tetanus, pertussis, hepatitis type b, haemophilus influenza type b) (PENTA), and measles vaccination, all by 12 months of age, was the base of our estimated pre-trial vaccination

coverage. For each region, we created low and high pre-trial vaccination coverage strata using the median coverage as a cut-off. A researcher, who was not a part of the RECAMP-MV team, assigned half of the clusters within each stratum to the intervention group and the other half to the control group, using computer generated random numbers. RECAMP-MV was an unblinded trial. Mortality two years prior to the trial implementation tended to be higher in the intervention group (11·1/1000 PYRS) than in the control group (8.9/1000 PYRS), p=0.13.

Procedures

We initiated enrolment among children aged 9-59 months in November 2016. At village visits, field nurses made a health-check of all eligible children aged 9-59 months. A child was offered enrolment if it was not: acutely ill, with high fever (axillary temperature>39°C), severely malnourished (mid-upper-arm circumference<110 mm), allergically reactive to prior vaccination, or followed in concurrent Bandim Health Project rural trials. Field nurses administered a standard 0.5 ml MV dose of the Edmonston-Zagreb strain from Serum Institute of India, to children in the intervention group. In January 2019, we completed enrolments.

We followed the enrolled children in both groups through the rural HDSS from January 2017 to May 2019. We extended the surveillance of enrolled children beyond 5 years of age. A national MV campaign implemented by Guinea-Bissau' Ministry of Health on May 3rd, 2019 marked the end of our trial. To ensure information on the enrolled children's deaths/hospital admissions status right before the national MV campaign, we visited them after the national MV campaign and paid the last visits in December 2019.

The study protocol was approved by Guinea-Bissau's national ethics committee (Comité Nacional de Ética na Saúde: CNES/2016/020) and Denmark's national ethics committee provided consultative approval (Den Nationale Videnskabsetiske Komité: 1606756). We enrolled children

whose mothers/guardians had given a written informed consent. We registered RECAMP-MV at Clinicaltrials.gov (NCT03460002).

Outcomes

We defined our primary outcome as non-accidental death or non-accidental hospital admission (first non-fatal hospital admission with overnight stay). In the supplementary methods, we have provided the interview questions used to retrieve information on each component. Onwards, we refer to our primary outcome as 'mortality/hospital admissions', implicitly understood as all-cause but unrelated to accidents and reported by mothers/guardians.

We estimated that enrolling 18,000 children would give us 80% power to detect a 30% reduction in mortality/hospital admissions. This sample size calculation was based on the overall event rate that we observed in the data from our first complete enrolment and follow-up round [7], which we then applied in the power formula for cluster-randomised trials by Hayes and Moulton [12].

Secondary outcomes for all enrolled children were mortality, repeated hospital admission, and cause-specific mortality/hospital admissions (malaria infection, gastrointestinal infection, and respiratory infection). Secondary outcomes for a sub-group of enrolled children were non-accidental outpatient consultation and non-accidental illness, which we used to assess short-term adverse events within 1-3 months from enrolment, an assessment we have reported elsewhere [13].

Statistical analyses

We used Cox proportional hazards models with age as the underlying timescale to compare event rates in the intervention group and control group, based on individual level data. We estimated hazard ratios (HR) with 95% confidence intervals (CI) adjusted for the stratification variables (health region and pre-enrolment vaccination coverage), and sex. We used robust standard errors to account for

intra-cluster correlation. Based on Schoenfeld residuals, we assesed the proportional hazards assumption with a global test and log-log plot.

We based our main conclusion on a per-protocol analysis of the MV campaign's overall effect on mortality/hospital admissions censoring follow-up at death due to accident, migration, or trial end (eligibility for the national MV campaign on May 3rd, 2019). We ignored hospital admissions due to accidents but censored the admission periods.

Unless otherwise specified, we used the same statistical approach to conduct pre-defined analyses of:

- secondary outcomes (mortality, repeated hospital admission, cause-specific mortality/hospital admissions)
- potential effect modifiers based on factors previously shown to be associated with the magnitude of MV's beneficial NSE, using Wald tests to compare effects across the strata of each potential modifier
    - before enrolment (routine MV [14], OPV [15]/vitamin A [16] campaigns)
    - at enrolment (sex [17], season [17])
    - during follow-up (OPV [15]/vitamin A [16] campaigns)
- mortality/hospital admissions with two robustness approaches
    - classic intention-to-treat; including children who were present in the village on the day, they were first potentially eligible to be enrolled
    - extended intention-to-treat; including children regardless of presence as long as they were living in the village on the day, they were first potentially eligible to be enrolled

Unless otherwise specified, we used the same statistical approach to conduct explorative analyses, which we have described in the supplementary methods. For all the statistical analyses, we used STATA 16.

Role of the funding source

The funding agencies of RECAMP-MV had no role in the trial design, data collection, data analysis, data interpretation, or dissemination. The corresponding author had full access to all data in RECAMP-MV and had final responsibility for the decision to submit for publication.

Results

We enrolled 18411 children (9636 intervention/8775 control) over a two-year period (November 2016-January 2019) (figure 1) and found no differences in their baseline characteristics (table 1 and supplementary table 1). We followed the children for a median of 22 months (22 intervention/22 control) between enrolment and the national MV campaign on May 3rd, 2019 (table 1). Ninety-three percent of the children had their last visit after the national MV campaign (93% intervention/92% control) (figure 1). Among the children, who received their last visit before the national MV campaign, the majority had migrated (figure 1). Few were censored 5 days before the national MV campaign (figure 1), as they were not reached on their planned visit after the national MV campaign due to inaccessible village roads.

We censored 12 deaths due to accidents (5 intervention/7 control) and ignored 6 hospital admissions due to accidents (2 intervention/4 control) but censored the admission periods. None of the deaths/hospital admissions were related to measles infection (supplementary table 2). For the analyses, we observed 379 deaths/hospital admissions (208 intervention/171 control) under 29·405 person-years at risk (15·423 intervention/13·982 control), generating an absolute rate of 12·8 deaths/hospital admissions per 1000 person-years at risk (13·5 intervention/12·2 control). The MV campaign did not reduce the risk of mortality/hospital admissions (HR 1·12, 95% CI 0·88-1·41) (table 2). We found no indication that the proportional hazards assumption was violated (details for the model check in appendix 1). We observed similar estimates for mortality (HR 1·07, 95% CI 0·79-1·46) and repeated hospital admissions (HR 1·20, 95% CI 0·89-1·61). Mortality/hospital admissions due to respiratory infections tended to be reduced (HR 0·82, 95% CI 0·42-1·63) but not due to other main causes (table 2). None of the analyses of the pre-defined potential effect modifiers showed strong interaction tests (table 3). When we analysed deaths/hospital admissions with a classic

intention-to-treat approach (HR 1·15, 95% CI 0·92-1·45) and an extended intention-to-treat approach (HR 1·14, 95% CI 0·93-1·41), there was little change in the overall estimate (table 4).

During follow-up, the enrolled children were targeted by four vitamin A campaigns: two co-administered with OPV and two without any co-administered vaccine. After eligibility for OPV campaigns the HR for mortality/hospital admissions was 28% lower than before (HR 0·72, 95% CI 0·55-0·94) adjusted for intervention group, a decline which was stronger in the control group than in the intervention group (supplementary table 3). Hence, the MV campaign tended to increase mortality/hospital admissions after eligibility for OPV campaigns (HR 1·24, 95% CI 0·92-1·68) but not before (HR 1·01, 95% CI 0·72-1·22). Similar differences were observed before/after eligibility for campaigns with vitamin A+/- OPV but less pronounced before/after eligibility for only vitamin A campaigns (table 3). For mortality (supplementary table 4 and 5) and hospital admissions (supplementary table 6 and supplementary table 7) as separate outcomes, we observed similar effects though, the differential effect appeared stronger for hospital admissions.

We explored whether the results from our pre-defined effect modifier analyses varied by sex. We found that the overall effect in boys was similar before/after eligibility for OPV campaigns (HR_{before} 1·12, 95% CI 0·72-1·75) (HR_{after} 1·06, 95% CI 0·72-1·57). However, this was not the case for girls who tended to have a 14% lower risk before eligibility for OPV campaigns (HR 0·86, 95% CI 0·53-1·37) but a 52% higher risk after eligibility for OPV campaigns (HR 1·52, 95% CI 1·02-2·27) (p=0·11 for interaction between MV campaign, eligibility for OPV campaigns, and sex, and p=0.06 for interaction between MV campaign and eligibility for OPV campaigns among girls) (supplementary table 8). The sex-differntial interaction was less pronounced for mortality (supplementary table 9) than for hospital admissions (supplementary table 10). We did not observe strong interactions for the remaining potential pre-defined effect modiers prior MV and season, each by sex (supplementary table 8).

Due to the unexpected overall result, we explored further potential effect modifiers. The routine vaccination programme changed in 2008 and 2015 (Supplementary figure 1), and we assessed whether effects varied by exposure to new routine vaccinations (pneumococcal conjugate, rotavirus, and yellow fever). We observed that the MV campaign did not reduce mortality/hospital admissions among children without these newer vaccines (supplementary results, supplementary table 11). Furthermore, we did not observe benefits among children who as their most recent vaccination had received non-live PENTA (supplementary table 11). Among demographic background factors assessed as potential effect modifiers, except for ethnicity, health region and age group did not show strong tests of interaction with the MV campaign (supplementary table 12). Furthermore, the effect of the MV campaign did not seem to change over time, neither during follow up period (supplementary table 13) nor during calendar time (supplementary table 14, supplementary figure 3, supplementary figure 4). Using time since enrolment as the underlying time axis (supplementary table 14), or adjusting for pre-trial mortality (supplementary table 15) had little effect on the main result .

The MV campaign could have affected the health care seeking behaviour and participation decision of mothers/guardians as the trial was unblinded but we did not observe any strong indications hereof (supplementary results, supplementary table 16).

Discussion

Among 18411 children, an MV campaign did not reduce deaths/hospital admissions by 30% as hypothesised. Instead, we observed that an MV campaign increased deaths/hospital admissions after OPV campaign eligibility. Explorative analyses indicated that this was driven by a differential effect in girls: The MV campaign increased deaths/hospital admissions in girls after OPV campaign eligibility but reduced deaths/hospital admissions in girls before OPV campaign eligibility. This was also observed for death and especially for hospital admissions, as separated outcomes.

The strengths of RECAMP-MV lie within its sample size, cluster-randomisation stratified by health region and pre-trial vaccination coverage, no loss to follow up, and complete observation time on 93% of the enrolled children. However, some potential weaknesses must be considered.

Firstly, although RECAMP-MV was a trial with randomisation stratified by access to health care and region, pre-trial mortality was higher in the intervention group. This may have reduced our chance of observing if the MV campaign was associated with beneficial effects. However, adjusting for quartile of pre-trial mortality did not affect conclusions.

Secondly, RECAMP-MV is an unblinded trial. Thus, we cannot rule out differential self-selection to enrolment. However, in the intervention group, neither did eligible children have a lower risk of mothers refusing/being busy, nor did enrolled children have a higher risk of their guardians being consent givers instead of mothers. Either of these could have been the case, if mothers/guardians based their participation decision on information shared by participating neighbours. Also, the observed balance in baseline characteristics did not suggest serious self-selection. Given the hard nature of our primary outcome, we believe that the impact of non-blinding on outcome reporting is limited. We can however not rule out differential healthcare seeking behaviour. This could have been the case, if mothers/guardians of children in the intervention group had gotten a false sense of security from observing their children receive MV, and thereby increased

the threshold for seeking health care. Nevertheless, we did not observe that children in the intervention group had a lower risk of dying in health facilities.

Thirdly, since information on deaths/hospital admissions was based on parental reports, we cannot rule out imprecision in the date of event. However, as we always asked about an event since the last field visit, it not only enabled us to place the event before or after trial enrolment but also to place it during an approximately 6-month interval. Without such fixed intervals, our observation time could have been significantly shorter or longer than what was reported. With the parental reports, we also cannot rule out differential cause misclassification. However, as the most important distinction was between accidental and non-accidental events, which we asked the mothers/guardians about directly, and there was no difference in the accident proportion between the groups, we consider parentally reported accident information, as valid. Had we relied solely on report of disease, which may be more difficult to recall and perhaps more prone to differential misclassification, the concern would be genuine.

Fourthly, we conducted some effect modifier analyses in sub-groups of children, as we only assessed prior vaccinations and the most recent vaccination prior to enrolment, among children who had their vaccination cards seen at enrolment. Also, some effect modifier analyses were assessed across many strata, such as ethnicity, health region, and different periods of follow-up and calendar time. This combined with our numerous exploratory analyses needs to be considered, as it increases the risk of chance findings.

When comparing with prior studies, two observational studies from Guinea-Bissau assessed an MV campaign's overall effect among children, where the majority had already received MV through a routine vaccination programme. Both found a reduced risk of mortality after MV campaign exposure among children aged 6-59 months [5, 6], which is not consistent with our main result. However, both assessed MV campaigns co-administered with other health interventions and were

conducted in periods with less frequent OPV campaigns [5, 6]. Since the epidemiological review commissioned by the World Health Organization [4], three randomised trials on MVs NSE have been conducted [18-20]. Although these trials did not assess MV campaigns or children in the same age group as RECAMP-MV, they assessed the effect of MV on mortality and/or hospital admissions. The trials took place during 2011-2019 and either randomised children to additional early MV (at 4.5 months of age) before routine MV (at 9 months of age) [18, 19], or randomised village clusters to increased MV access regardless of age [20]. In line with our main result, none of the trials found an overall beneficial effect of MV. Nevertheless, despite sparse events, it is worth mentioning that a combined analysis of early MV trials also showed that receiving early MV reduced mortality only until OPV campaign eligibility (HR 0·56, 95% CI 0·34-0·90), while it tended to increase mortality after OPV campaign eligibility (HR 1·25, 95% CI 0·95-1·66). In children who had also received OPV before being randomised to early MV, the negative effect of MV after eligibility to OPV campaign may have been stronger for girls [21].

We suggest that the main explanation for why we did not observe beneficial NSE of an MV campaign, as we had hypothesised, is that eligibility for OPV campaigns may have interfered with the MV campaign's effect. Three observations support this. Most RECAMP-MV children were eligible for OPV campaigns before enrolment and during follow-up. The MV campaign tended to increase mortality/hospital admissions after and not before OPV campaign eligibility, driven by a sex-differential effect among girls. We observed the same sex-differential pattern for any vitamin A campaign (+/-co-administered OPV) but not for only vitamin A campaign, thus OPV likely explains the difference in the observed estimates. We believe that these observations in the context of prior studies supporting the potential interference of OPV campaigns on the beneficial NSE effect of MV [21], support our explanation.

We explored two other potential explanations but did not find support for these. MV's beneficial NSE have mostly been observed in children without routine vaccinations against streptococcus pneumoniae, rotavirus, and yellow fever but we did not observe that the MV campaign's effect was beneficial for children without these vaccinations. Furthermore, an MV campaign's beneficial NSE has been observed within a six-month follow-up period [5] but we did not observe that the MV campaign's effect changed markedly before/after 6 months, especially when censoring at OPV campaigns.

Nevertheless, even if the MV campaign reduced deaths/hospital admissions in girls before OPV campaign eligibility, the magnitude of this reduction was substantially lower than what we had hypothesised. We observed that the pre-trial mortality was much higher than what we observed among the enrolled children in our trial. Thus, we speculate that more recent trials, including RECAMP-MV, may not be observing as strong beneficial NSE of MV because the current disease pattern or the disease pattern among the children enrolled differs. If a larger share of deaths/admissions are made up by cases, which are not as receptive to beneficial effects as in prior studies, that could contribute to our observation. Also, we do not know to what extent a potential change in disease pattern would apply to hospital admissions, though prior studies indicate some similarities between cause of death and hospital admission [17, 22].

From an adverse events perspective, MV is considered safe [23] but to our knowledge an MV campaign has not been evaluated with a randomised design. Our main finding did not indicate that an MV campaign reduces mortality/hospital admissions. In contrast, our data is consistent with a negative overall effect of an MV campaign. Although this finding may be due to chance, it emphasizes the importance of evaluating the overall effect of an MV campaign to capture its complete risk-benefit, and also, the need to clarify its potential interaction with other health interventions, like OPV campaigns, to gain efficiently from its potential beneficial NSE and also its specific effects.

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The Long-term article - Supplementary methods and results

Supplementary methods

Interview questions from short interview on cause of deaths/hospital admissions

Field assistants posed the following questions to mothers/guardians in Portuguese-Creole:

"*Where is [the child]?*" (present/moved/absent/travelling/dead),

If migrated: *When did [the child] move away?*" (date)

If dead:

"*When did [the child] die?*" (date)

"*Where did [the child] die?*" (home/health facility/hospital/other)

"*Was it an accident?*" (yes/no/unknown)

"*Did [the child] have any of the following symptoms (fever, diarrhoea, paleness, cough/respiratory difficulties, convulsions, or measles)?*" (yes/no/unknown)

"*What was the cause?*" (open question)

Has [the child] been at the hospital?" (yes/no/unknown), if yes

"*When was [the child] admitted?*" (date)

"*How long was [the child] admitted for?*" (open question)

"*What was the cause?*" (open question)

"*Was it an accident?*" (yes/no/unknown)

For deaths, a specially trained field assistant conducted a verbal autopsy [11] interviewing the parents and/or other household members on symptoms and health care seeking behaviour. We used the cause of death classified by a local physician based on the verbal autopsy conducted after the follow-up visit. If no cause was determined in the verbal autopsy, we classified the cause based on information retrieved from the short interview on cause of death conducted on the follow-up visit, as we did for hospital admission.

Pre-defined potential effect modifiers by separate components of the outcome

We explored whether each component of the composite outcome was potentially modified by eligibility to OPV/vitamin A campaigns during follow-up and eligibility to OPV/vitamin A campaigns during follow-up by sex.

Pre-defined potential effect modifiers by sex

We explored whether the overall effect varied by each pre-defined potential effect modifier and sex:

- before enrolment (routine MV, eligibility to OPV/vitamin A campaigns)
- at enrolment (season)
- during follow-up (eligibility to OPV/vitamin A campaigns)

We supplemented Wald tests comparing effects across strata of each potential modifier with Wald tests of the interaction between the MV campaign and the potential effect modifier by sex.

Prior routine vaccination as potential effect modifiers

We explored whether the overall effect varied by prior routine vaccination:

- the most recent vaccination being a non-live PENTA
- newly introduced routine vaccinations (pneumococcal conjugate, rotavirus, and yellow fever) (Supplementary figure 1)

Demographic background factors as potential effect modifiers

We explored whether the overall effect varied by demographic factors:

- health region, as geographical access to health care may differ
- ethnicity, as cultural behavior towards health care may differ
- age group (also with time since enrolment, as the underlying time axis)

Changing effects over time: time bands as potential effect modifiers

- We explored whether the overall effect varied during the follow-up period by splitting the observation period at 14 days, 6 months, and 12 months, all by sex and OPV campaign eligibility.
- We explored whether the overall effect varied by calendar time by splitting the observation time at birth cohort years and 6 monthly seasonal periods, all by sex and eligibility to OPV campaign eligibility.
- We explored whether the overall effect was different if we used time since enrolment as the underlying time axis instead of age.

Imbalance in pre-trial mortality

To assess the potential effect of the imbalance in pre-trial mortality on our main finding, we assessed whether the effect of the MV campaign changed when adjusted for pre-trial mortality. To do so, we divided village clusters into quartiles of pre-trial mortality among children aged 9-59 months in the two years prior to initiating RECAMP-MV, and repeated the main analysis adjusted for pre-trial mortality stratum.

Potential non-blinding issues

We explored the following potential non-blinding issues (with log-binomial models estimating relative risks (RR)):

- death at a health facility among dead children; mothers/guardians of children in the intervention group may have gotten a false sense of security increasing their threshold for seeking health care, and thus causing deaths to less commonly occur at a health facility

- guardian as a consent giver; in the absence of mothers, guardians of children in the intervention group may have been more motivated to be escorts
- participation decline; mothers/guardians of eligible children in the intervention group may have been less inclined to decline participation

Supplementary results

Reception of new vaccines prior to enrolment

We found no indication that the MV campaign's effect was beneficial for children unexposed to the new routine vaccinations (pneumococcal conjugate, rotavirus, and yellow fever). In contrast, the MV campaign's negative effect were more pronounced for children unexposed to the pneumococcal vaccine HR=1·41 (0·95-2·11), the rotavirus vaccine HR=1·24 (0·89-1·72) or the yellow fever vaccine HR=1·88 (1·18-3·01). For the yellow fever vaccine, we observed a strong differential effect (p=0.02 for interaction between the MV campaign and yellow fever vaccine) (supplementary table 11).

Blinding

Very few (<1%) declined trial participation and the rates did not differ significantly between the intervention group and control group (supplementary table 16). Fifty-nine of the 147 deaths occurred in a health facility. Deaths in health facilities may have been more commnon in the intervention group compared to the control group, RR=1·39 (0·92-2·12) (supplementary table 16).

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Figure 1 and Supplementary Figures

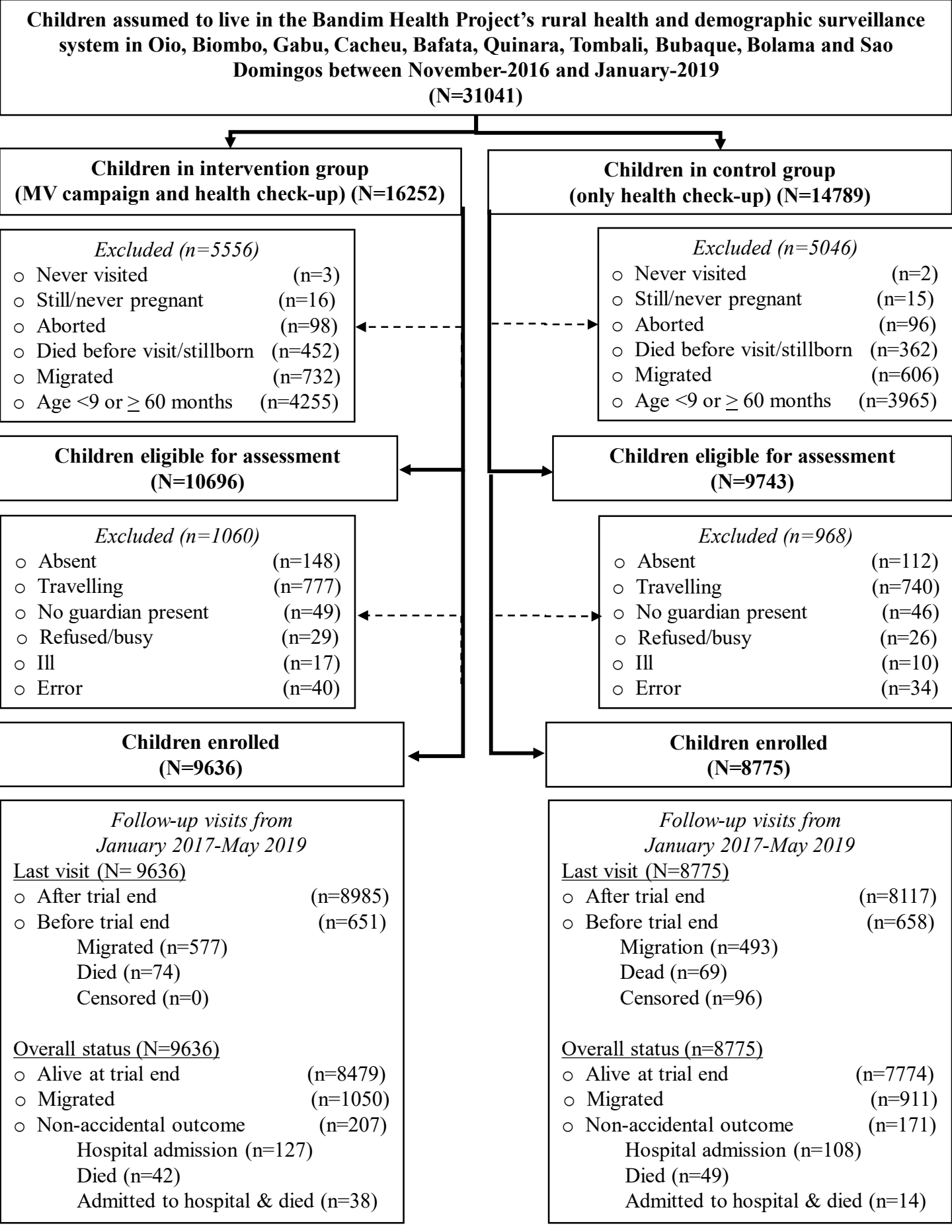
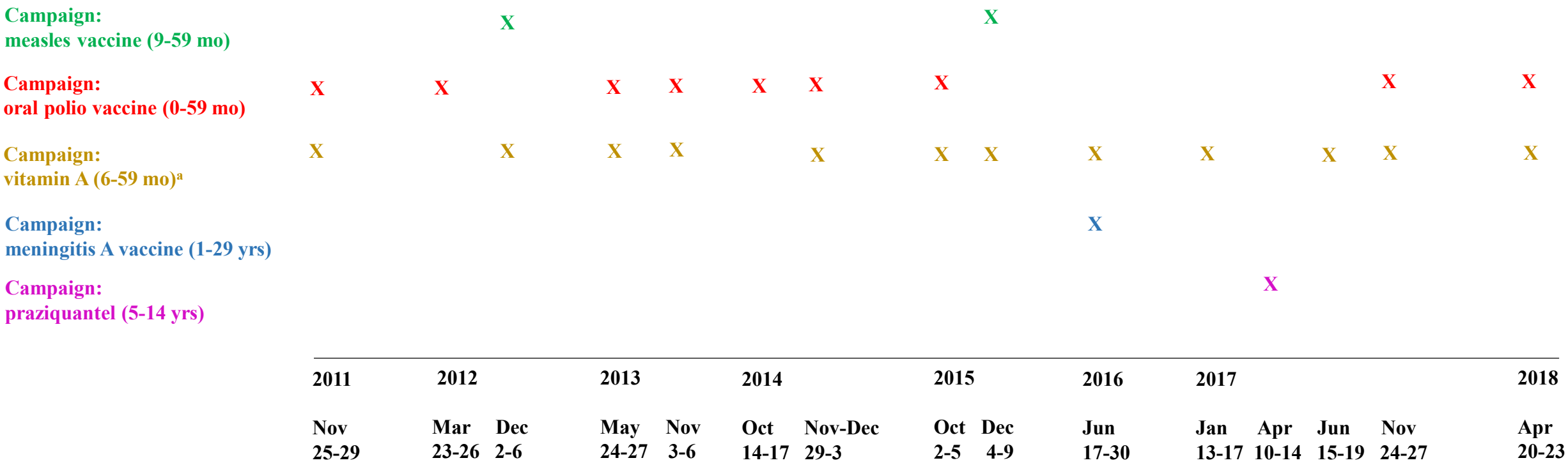


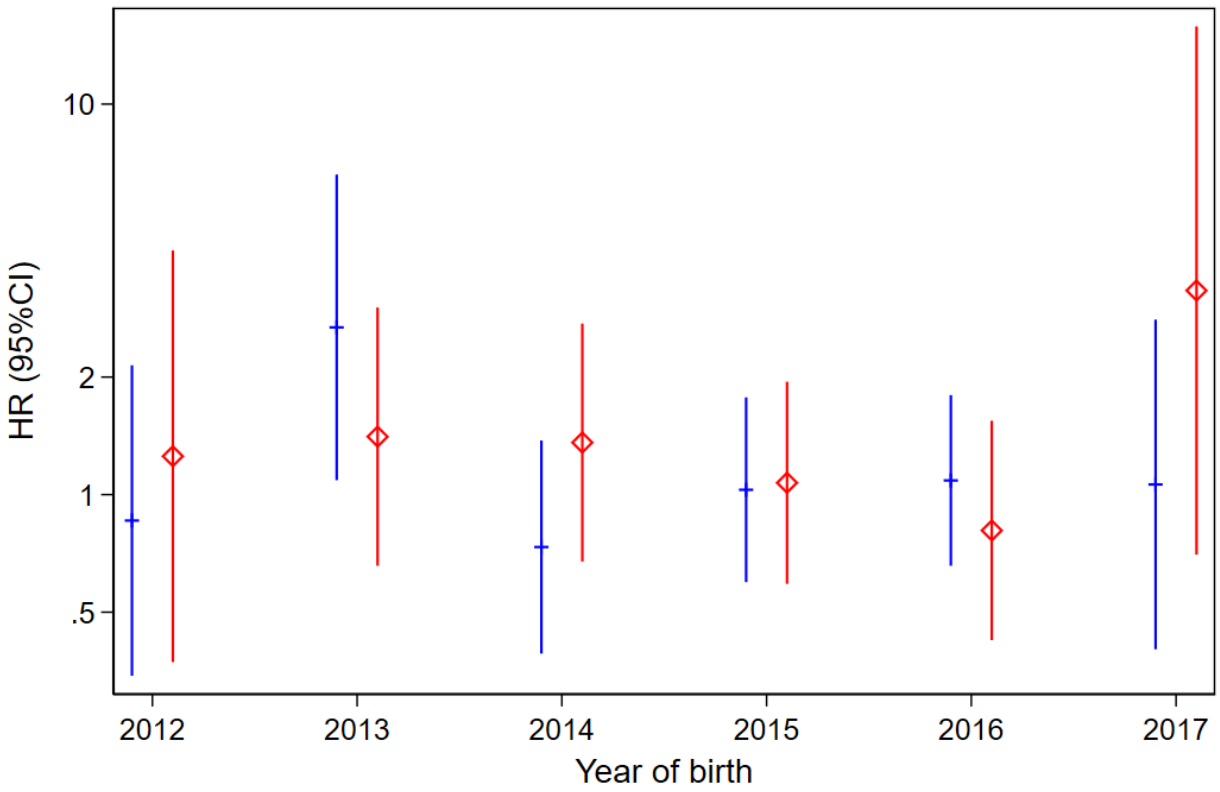
Figure 1: Flow of children from eligibility to analysis. **Abbreviations:** MV=measles vaccine.

Birth:	**BCG (1981)**	+	**OPV (1981)**				
Week 6:	**PENTA[a] (2008)**	+	**OPV (1981)**	+	**PCV (2015)**	+	**ROTA (2015)**
Week 10:	**PENTA[a] (2008)**	+	**OPV (1981)**	+	**PCV (2015)**	+	**ROTA (2015)**
Week 14:	**PENTA[a] (2008)**	+	**OPV (1981)**	+	**PCV (2015)**	+	**IPV (2016)**
9 months:	**MV (1979)**	+	**YF (2008)**				

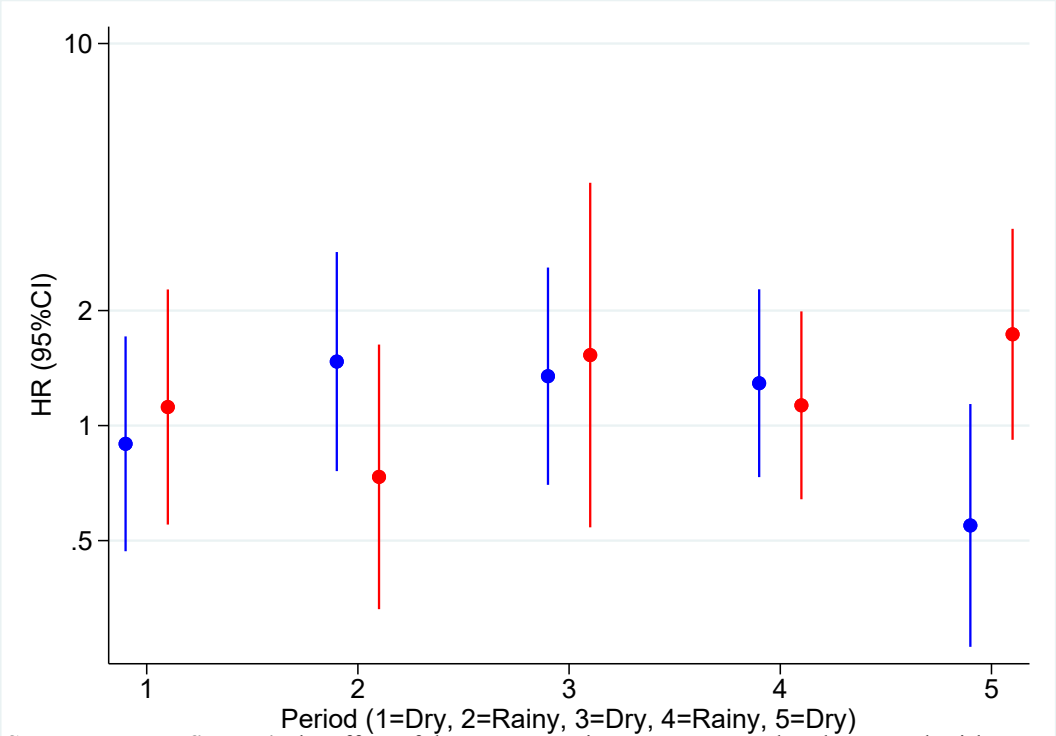
Supplementary figure 1: Routine vaccination program of Guinea-Bissau with age of administration and year of introduction.
Abbreviations: BCG=Bacille Calmette Guerin vaccine; OPV=oral polio vaccine; PENTA=diphtheria, tetanus, pertussis, hepatitis type b, and haemophilus influenza type b vaccine; MV=measles vaccine; PCV=pneumococcal conjugate vaccination; ROTA=rotavirus vaccine; IPV=inactivated polio vaccine; YF=yellow fever vaccine. [a]Diphtheria, tetanus, pertussis was introduced in 1984 to be administered at 6, 10, and 14 weeks and replaced by PENTA in 2008.



Supplementary figure 2: Health campaigns implemented before enrolment and during follow-up in Guinea-Bissau by date. **Abbreviations:** mo=months. yrs=years. [a]Co-administered mebendazole (12-59 mo).



Supplementary figure 3: The effect of the MV campaign in birth cohorts. Blue=boys. Red=girls



Supplementary figure 4: the effect of the MV campaign per season. Blue=boys. Red=girls.

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Tables and Supplementary Tables

N=18411[a]	MV campaign[b]		No MV campaign[b]	
	52·3	(9636)	47·7	(8775)
Socio-demographics				
Male	51	(4908)	51	(4483)
Age, months, median (IQR)	33	(20-46)	33	(21-46)
Health region				
Oio	14	(1381)	16	(1396)
Biombo	11	(1102)	11	(927)
Gabu	11	(1107)	10	(880)
Cacheu	9	(866)	6	(489)
Bafata	9	(823)	13	(1112)
Quinara	8	(765)	9	(774)
Tombali	7	(721)	9	(828)
Bubaque	2	(235)	2	(201)
Bolama	1	(133)	2	(145)
Sao Domingos	9	(857)	8	(723)
Bafata new[c]	17	(1646)	15	(1300)
Ethnicity				
Balanta	24	(2289)	25	(2208)
Fula	31	(2974)	26	(2282)
Manjaco/Mancanha	6	(616)	5	(397)
Pepel	9	(888)	9	(816)
Mandinga	15	(1464)	20	(1758)
Other	14	(1308)	14	(1218)
Household characteristics				
Zinc/metal roof	70	(6698)	66	(5770)
Radio	81	(7821)	82	(7238)
Outdoor toilet	80	(7711)	81	(7108)
Phone (own/house)	53	(5086)	50	(4431)
Mother's age at birth of child, yrs, mean (SD)	27	(7·2)	27	(7·2)
Mother attended school	40	(3878)	41	(3629)
Child lives with mother	97	(9316)	97	(8508)
Health status on enrolment day				
Weight, kg, mean (SD)	11·6	(2·6)	11·7	(2·6)
Weight for age, z-score, mean (SD)	-1·2	(1·1)	-1·2	(1)
MUAC, mm, mean (SD)	147·6	(11·9)	147·3	(11·9)
MUAC for age, z-score, mean (SD)	-0·6	(0·9)	-0·6	(0·9)
No medicine intake	97	(9392)	98	(8583)
Vaccination status among children with vaccination card seen before enrolment				
Vaccination card seen	76	(7277)	74	(6458)
Already administered routine vaccinations				
BCG	93	(6733)	93	(5986)
PENTA 3rd (+OPV)	90	(6557)	90	(5835)
Pneumococcal conjugate 3rd	43	(3094)	42	(2726)
Rotavirus 2nd	29	(2102)	29	(1892)
Yellow fever	73	(5295)	72	(4669)
MV	81	(5872)	80	(5192)
Inactivated polio	14	(1038)	14	(895)
Most recent vaccination prior to enrolment[d]				
MV[e]	40	(3881)	40	(3529)
PENTA+MV[f]	5	(498)	5	(448)
PENTA[g]	13	(1237)	13	(1103)
Eligible for other vaccination campaigns				
Before enrolment[h]				
Any OPV campaign (since 2012)	85	(8228)	85	(7497)
Any vitamin A campaign (since 2012)	98	(9480)	98	(8593)
During follow-up				
Any OPV campaign[i]	74	(7166)	76	(6630)
Any vitamin A campaign[j]	76	(7315)	77	(6759)
Only vitamin A campaign[k]	48	(4672)	45	(3973)
Timing				
Enrolled during rainy season (Jun-Nov)	47	(4548)	51	(4434)
Follow-up time, months, median (IQR)	22	(11-25)	22	(11-25)
Clusters				
Number of clusters visited[l]	50	(111)	50	(110)
Children per cluster, median (IQR)	101	(78-123)	85	(68-133)

MV=measles vaccine; MUAC=mid-upper-arm circumference; IQR=interquartile range; BCG=Bacille Calmette Guerin vaccine; OPV=oral polio vaccine; PENTA=diphtheria, tetanus, pertussis, hepatitis type b, and haemophilus influenza type b vaccine.

[a]Missing values in each variable are provided in Supplementary table 1.
[b]Data is presented with % (n), unless otherwise stated.
[c]We added clusters from another part of Bafata after approval of a protocol amendment on a sample size increase.
[d]2932 children (1,611 intervention/1,321 control) with other combinations of their most recent vaccination were not included.
[e]MV as most recent vaccination; co-scheduled yellow fever could have been given, but not BCG, OPV, PENTA, rotavirus, pneumococcal conjugate and inactivated polio.
[f]PENTA+MV as most recent vaccination; other vaccines co-scheduled with PENTA or MV could have been given (OPV, rotavirus, yellow fever, pneumococcal conjugate, inactivated polio) but not BCG.
[g]PENTA as most recent vaccination; other vaccines co-scheduled with PENTA could have been given (OPV, rotavirus, pneumococcal conjugate, inactivated polio) but not BCG, MV and yellow fever.
[h]OPV campaigns may be co-administered with vitamin A+mebendazole. Vitamin A campaigns are co-administered with mebendazole but +/- co-administered OPV.
[i]Children were under follow up at the time of OPV campaigns in 2017 (November) or 2018 (April). OPV campaigns were co-administered with vitamin A+mebendazole.
[j]Children were under follow up at the time of vitamin A campaigns in 2017 (January, June, November) or 2018 (April). Vitamin A campaigns are co-administered with mebendazole but +/- co-adminstered OPV.
[k]Children were under follow up at the time of vitamin A campaigns in 2017 (January, June). Vitamin A campaigns are co-administered with mebendazole but not OPV.
[l]One cluster in the control group of Bafata msf was not visited due to inaccessibility.

Table 1: **Baseline characteristics of children per group assignment. Percentage (n). Median (interquartile range). Mean (standard deviation).**

Number of children=18411	MV campaign (%, n) 52·3 (9636)		NoMV campaign (%, n) 47·7 (8775)			
	Rate	**(events/1000 PYRS)**	**Rate**	**(events/1000 PYRS)**	**HR[a]**	**(95% CI)**
Mortality/hospital admission[b]	13·5	(208/15423)	12·2	(171/13982)	1·12	(0·88-1·41)
Mortality	5·3	(82/15544)	4·6	(65/14083)	1·07	(0·79-1·46)
Hospital admission (repeated)[c]	10·9	(170/15541)	9·5	(134/14082)	1·20	(0·89-1·61)
Mortality/hospital admission due to malaria infection[d]	4·3	(66/15423)	4·0	(134/14082)	1·09	(0·89-1·61)
Mortality/hospital admission due to gastrointestinal infection[d]	3·9	(60/15423)	3·3	(46/13982)	1·13	(0·77-1·66)
Mortality/hospital admission due to respiratory infection[d]	1·2	(18/15423)	1·3	(18/13982)	0·82	(0·42-1·63)

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; PYRS=person-years at risk

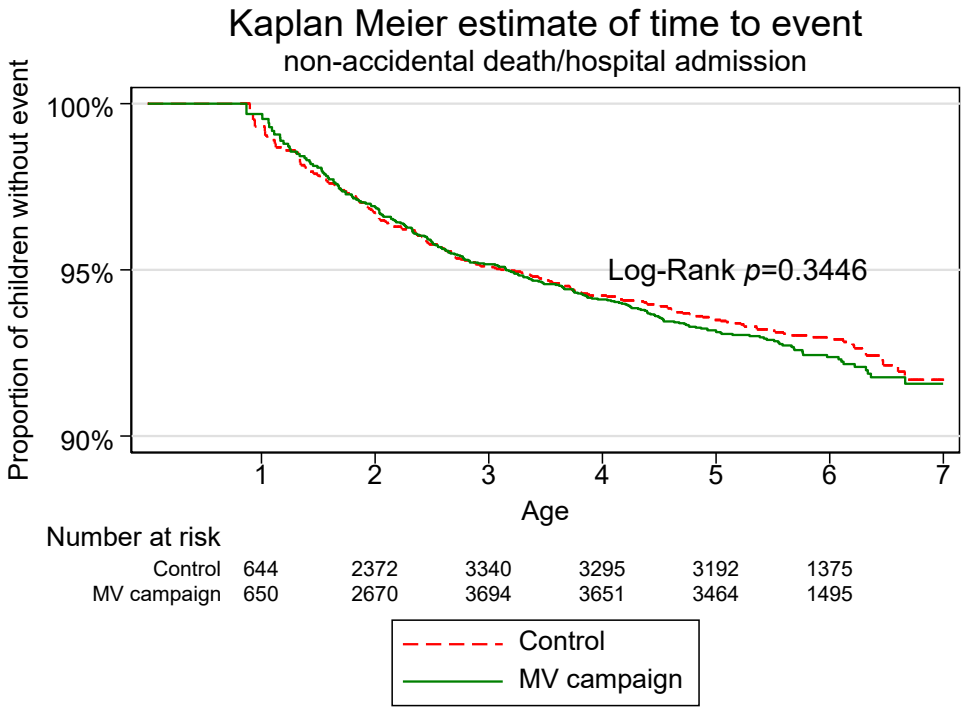
[a]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[b]We censored 12 deaths due to accident (5 intervention/7 control) and the admission period of 6 hospital admissions due to accident (2 intervention/4 control). None of the deaths or hospital admissions were due to measles infection. See Supplementary table 2b for details on causes.

[c]Admitted children re-entered the analysis at discharge from the hospital

[d]Children with deaths/hospital admissions due to other causes then the one in question were censored.

Table 2: **Effect of MV campaign on non-accidental mortality/hospital admission. Per-protocol analyses with Cox proportional hazards model.**



Number of children=18411	MV campaign (%, n) 52·3 (9636) Rate (events/1000 PYRS)		No MV campaign (%, n) 47·7 (8775) Rate (events/1000 PYRS)		HR[a]	(95% CI)	p-value[b]
Sex							0·73
Boys	14·8	(118/7947)	13·6	(99/7255)	1·09	(0·81-1·47)	
Girls	12·0	(90/7476)	10·7	(72/6728)	1·17	(0·85-1·59)	
Season							0·56
Dry	13·0	(126/9685)	11·4	(92/8085)	1·19	(0·85-1·64)	
Rainy	14·3	(82/5738)	13·4	(79/5898)	1·02	(0·72-1·46)	
Prior routine MV among children with seen vaccination card							0·62
No	17·0	(37/2176)	14·0	(26/1863)	1·34	(0·82-2·17)	
Yes	12·9	(124/9625)	10·9	(93/8528)	1·17	(0·87-1·57)	
Eligible for any OPV campaign before enrolment since 2012							0·69
No	21·8	(56/2572)	19·7	(46/2332)	1·20	(0·79-1·79)	
Yes	11·8	(152/12851)	10·7	(125/11650)	1·09	(0·84-1·43)	
Observation time split[c] at any OPV campaign during follow-up[de]							0·35
Before	16·8	(96/5714)	17·5	(88/5041)	1·01	(0·72-1·42)	
After	11·5	(112/9708)	9·3	(83/8941)	1·24	(0·92-1·68)	
Observation time split[c] at any vitamin A campaign during follow-up[f]							0·21
Before	14·7	(51/3479)	16·6	(51/3067)	0·89	(0·59-1·35)	
After	13·1	(157/11944)	11·0	(120/10915)	1·22	(0·93-1·59)	
Observation time split[c] at only vitamin A campaign during follow-up[g]							0·56
Before	14·7	(102/6950)	13·9	(93/6711)	1·04	(0·77-1·42)	
After	12·5	(106/8473)	10·7	(78/7271)	1·20	(0·84-1·73)	

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; OPV=oral polio vaccine; PYRS=person-years at risk

[a]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[b]Wald tests to compare effects across strata defined by each potential modifier.

[c]Children can contribute with observation time both before eligibility for the respective campaign and after, unless they experienced an event or were censored before the respective campaign.

[d]Follow up time split at OPV campaigns in 2017 (Nov) or 2018 (Apr). OPV campaigns were co-administered with vitamin A+mebendazole.

[e]Analysis on eligibility for OPV campaign as the main effect adjusted for the MV campaign and with the MV campaign as a potential effect modifiers is presented in supplementary table 3.

[f]Follow up time split at eligibility for vitamin A campaigns in 2017 (Jan, Jun, Nov) or 2018 (Apr). Vitamin A campaigns are co-administered with mebendazole (to children >12 months) and nationally distributed approximately every 6 months +/- co-adminstered OPV. To disentangle time and vitamin A campaign effects, we furthermore split follow up time at 3 months after enrolment. Test of interaction between MV campaign, eligibility for vitamin A campaign and timeband (<3 or >3 months from enrolment); p=0.95.

[g]Follow-up time split at vitamin A campaigns in 2017 (Jan, Jun). Vitamin A campaigns are co-administered with mebendazole (to children >12 months) and nationally distributed approximately every 6 months +/- co-adminstered OPV. To disentangle time and vitamin A campaign effects, we furthermore split follow up time at 3 months after enrolment.Test of interaction between MV campaign, eligibility for vitamin A campaign and timeband (<3 or >3 months from enrolment); p=0.95

Table 3: **Potential pre-defined effect modifers of MV campaign on the risk of non-accidental mortality/hospital admission. Per-protocol analyses. Cox proportional hazards model.**

	MV campaign (%, n) Rate (events/1000 PYRS)		No MV campaign (%, n) Rate (events/1000 PYRS)		HR[a]	(95% CI)
N=18803	52·3	(9842)	47·7	(8961)		
Classic intention-to-treat[bc]	14·2	(223/15734)	12·5	(179/14316)	1·15	(0·91-1·45)
N=21386	52·4	(11209)	48	(10177)		
Extended intention-to-treat[de]	14·7	(259/17580)	13·0	(208/15969)	1·14	(0·93-1·41)

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; PYRS=person-years at risk

[a]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[b]In addition to children included per-protocol, we included children who were present in the village on the day they were first potentially eligible to be enrolled but were not enrolled as they did not receive the assigned group status by error, were excluded due to illness, had no escort present, or had a mother/guardian who refused participation.

[c]We censored 12 deaths due to accident (5 intervention/7 control) and the admission period of 6 hospital admissions due to accident (2 intervention/4 control). None of the deaths/hospital admissions were due to measles infection.

[d]In addition to children included per-protocol, we included children regardless of their presence as long as they were living in the village on the day they were first potentially eligible to be enrolled (MV may also affect the health of other children in the community by reducing the overall infectious pressure).

[e]We censored 12 deaths due to accident (5 intervention/7 control) and the admission period of 7 hospital admissions due to accident (3 intervention/4 control). None of the deaths/hospital admissions were due to measles infection; 50 children without verbal autopsy after death notification at follow-up visit (32 intervention/18 control), thus, their cause was based on symptoms and history information retreived at follow-up visit; 2 children entered the analysis shortly before 5 years of age but were excluded from the analysis as they did not receive a subsequent visit; One hospital admission was dropped as its duration was not overnight.

Table 4: **Effect of MV campaign on non-accidental mortality/hospital admission. Robustness analyses. Cox proportional hazards model.**

	MV campaign[a]		No MV campaign[a]	
	52·3	(9636)	47·7	(8775)
Socio-demographics				
Ethnicity	1	(97)	1	(96)
Household characteristics				
Zinc/metal roof	1	(139)	2	(136)
Radio	3	(245)	3	(243)
Toilet	2	(197)	2	(205)
Phone	4	(374)	4	(376)
Mother's age at birth of child, yrs, mean (SD)	2	(185)	2	(193)
Mother's school attendence	4	(365)	3	(269)
Child lives with mother	0	(16)	0	(9)
Health status on enrolment day				
Weight, kg	1	(75)	1	(80)
MUAC, mm	0	(30)	0	(30)
Medicine intake	0	(2)	0	(28)
Vaccination status among children with vaccination card seen before enrolment				
Vaccination card seen	0	(14)	0	(10)
Already administered routine vaccinations				
BCG	1	(50)	1	(49)
PENTA 3rd	0	(18)	0	(14)
Pneumococcal conjugate 3rd[d]	0	(9)	0	(6)
Rotavirus 2nd[d]	0	(20)	0	(13)
Yellow fever	1	(37)	1	(39)
MV	1	(38)	1	(40)
Inactivated polio[d]	0	(4)	0	(2)

MV=measles vaccine; MUAC=mid-upper-arm circumference; BCG=Bacille Calmette Guerin vaccine; PENTA=diphtheria, tetanus, pertussis, hepatitis type b, and haemophilus influenza type b vaccine.

Supplementary table 1: **Missing/unknown baseline characteristics of children per group assignment. Percentage (n).**

N=159[a]	Mortality							
	MV campaign		No MV campaign		MV campaign		No MV campaign	
	55	(87)	45	(72)	52	(13)	48	(12)
	Primary cause				Secondary cause			
Malaria infection	29	(25)	22	(16)	8	(1)	0	(0)
Gastrointestinal infection	13	(11)	24	(17)	0	(0)	33	(4)
Respiratory infection	8	(7)	7	(5)	15	(2)	0	(0)
Severe malnutrition	3	(3)	4	(3)	8	(1)	0	(0)
Accident	6	(5)[b]	10	(7)[c]	0	(0)	0	(0)
Other, unspecified	15	(13)	21	(15)	0	(0)	8	(1)
Other, specified	15	(13)[d]	10	(7)[e]	69	(9)[f]	58	(7)[g]
Unknown/missing	11	(10)	3	(2)	N/R	N/R	N/R	N/R

N=310	Hospital admission			
	MV campaign		No MV campaign	
	55	(172)	45	(138)
Malaria infection	23	(40)	30	(42)
Gastrointestinal infection	31	(53)	24	(33)
Respiratory infection	6	(10)	9	(13)
Fever +/- other symptoms[h]	35	(60)	38	(52)
Accident	1	(2)	3	(4)
Other, specified	13	(23)[i]	6	(8)[j]
Unknown/missing	6	(10)	12	(16)

MV=measles vaccine; N/R=not relevant

[a]23 children without verbal autopsy after death notification at follow-up visit (14 intervention/9 control), thus, their cause was based on symptoms and history information retreived at follow-up visit

[b]accidents: drowning (2), tree branch fell on child (1), burn (1), fell down (1)

[c]accidents: wall fell on child (1), choking (1), traffic accident (1), drowning (1), burn (1), injury during play (2)

[d]other, specified: viral hepatitis (1), nutritional anemia (2), chronic liver disease (4), renal failure (2), congenital malformation (2), infection with inflammation and edema (1), infection with inflammation (1)

[e]other, specified: nutritional anemia (2), congenital malformation (2), fever and anemia (1), fever and headache (1), unknown (1)

[f]other, specified: nutritional anemia (7), external cause of death (1), intoxication (1)

[g]other, specified: nutritional anemia (4), renal failure (1), intoxication (2)

[h]fever, convulsion, diarrhea, vomiting, anemia, malaria, coughing, body pain

[i]other, specified: abcsess (4), anemia (4), convulsion (3), weakness (2), tooth ache (1), edema (2), body pain (3), typhoid (1), genital issue (1), yellow fever (2)

[j]other, specified: anemia (1), convulsion (1), edema (2), body pain (3), itch/rash (1)

Supplementary table 2: **Cause of mortality/hospital before the nationally implemented MV campaign in May 2019 per group assignment. Percentage (n).**

	After eligibility for OPV campaign[a] (%, n)		Before eligibility for OPV campaign[a] (%, n)				
	52·3	(9636)	47·7	(8775)			
	Rate (events/1000 PYRS)		**Rate (events/1000 PYRS)**		**HR[b]**	**(95% CI)**	**p-value[c]**
Mortality/hospital admissions adjusted for MV campaign	10·5	(195/18649)	17·1	(184/10756)	0·72	(0·55-0·94)	
MV campaign							0·35
Yes	11·5	(112/9708)	16·8	(96/5714)	0·79	(0·55-1·12)	
No	9·3	(83/8941)	17·5	(88/5041)	0·64	(0·46-0·89)	
MV campaign by sex[d]							0·11
Boys no	10·6	(49/4641)	19·1	(50/2613)	0·75	(0·48-1·17)	
Boys yes	11·7	(59/5023)	20·2	(59/2925)	0·71	(0·47-1·07)	
Girls no	7·9	(34/4300)	15·7	(38/2428)	0·51	(0·33-0·79)	
Girls yes	11·3	(53/4686)	13·3	(37/2790)	0·91	(0·53-1·55)	

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; OPV=oral polio vaccine; PYRS=person-years at risk

[a]Children can contribute with observation time both before eligibility for the respective campaign and after, unless they experienced an event or were censored before the respective campaign. Follow up time split at OPV campaigns in 2017 (Nov) or 2018 (Apr). OPV campaigns were co-administered with vitamin A+mebendazole.

[b]HR comparing rates after vs before the OPV campaigns. Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[c]Wald tests to compare effects across strata defined by each potential modifier.

[d]Wald test of interaction between eligibility for OPV campaign and MV campaign among girls p=0·06.

Supplementary table 3: **Eligibility for OPV campaign analysed as the main effect adjusted for the MV campaign and with the MV campaign as a potential effect modifier. Per-protocol analyses. Cox proportional hazards model.**

	After eligibility for OPV campaign[a] (%, n)		Before eligibility for OPV campaign[a] (%, n)				
	52·3	(9636)	47·7	(8775)			
	Rate(events/1000PYRS)		**Rate (events/1000 PYRS)**		**HR[b]**	**(95% CI)**	**p-value[c]**
Mortality adjusted for MV campaign	3·6	(67/18836)	7·4	(80/10790)	0·77	(0·52-1·15)	
MV campaign							0·97
Yes	3·8	(37/9812)	7·9	(45/5732)	0·78	(0·47-1·29)	
No	3·3	(30/9025)	6·9	(35/5058)	0·77	(0·46-1·28)	
MV campaign by sex[d]							0·72
Boys no	3·8	(18/4693)	7·6	(20/2623)	0·79	(0·44-1·42)	
Boys yes	4·3	(22/5088)	8·9	(26/2936)	0·73	(0·39-1·35)	
Girls no	2·8	(12/4332)	6·2	(15/2435)	0·75	(0·34-1·67)	
Girls yes	3·2	(15/4723)	6·8	(19/2796)	0·86	(0·39-1·91)	

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; OPV=oral polio vaccine; PYRS=person-years at risk

[a]Children can contribute with observation time both before eligibility for the respective campaign and after, unless they experienced an event or were censored before the respective campaign. Follow up time split at OPV campaigns in 2017 (Nov) or 2018 (Apr). OPV campaigns were co-administered with vitamin A+mebendazole.

[b]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[c]Wald tests to compare effects across strata defined by each potential modifier.

[d]Wald test of interaction between eligibility for OPV campaign and MV campaign among girls p=0·78.

Supplementary table 4: **Eligibility for OPV campaign analysed as the main effect on non-accidental mortality adjusted for the MV campaign and with the MV campaign as a potential effect modifier. Per-protocol analyses. Cox proportional hazards model.**

Number of children=18411	MV campaign (%, n)		No MV campaign (%, n)				
	52·3	(9636)	47·7	(8775)			
	Rate (events/1000 PYRS)		Rate (events/1000 PYRS)		HR[a]	(95% CI)	p-value[b]
Eligible for any OPV campaign before enrolment since 2012							0·61
No	11·1	(29/2605)	8·5	(20/2363)	1·21	(0·71-2·04)	
Yes	4·1	(53/12939)	3·8	(45/11720)	1·01	(0·68-1·51)	
Observation time split[c] at any OPV campaign during follow-up[de]							0·97
Before	7·9	(45/5732)	6·9	(35/5058)	1·07	(0·69-1·65)	
After	3·8	(37/9812)	3·3	(30/9025)	1·08	(0·69-1·71)	
Observation time split[c] at any vitamin A campaign during follow-up[f]							0·95
Before	7·5	(26/3484)	6·2	(19/3075)	1·09	(0·61-1·94)	
After	4·6	(56/12059)	4·2	(46/11008)	1·07	(0·74-1·53)	
Observation time split[c] at only vitamin A campaign during follow-up[g]							1·00
Before	6·1	(43/6994)	5·0	(34/6756)	1·07	(0·71-1·61)	
After	4·6	(39/8550)	4·2	(31/7327)	1·07	(0·68-1·69)	

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; OPV=oral polio vaccine; PYRS=person-years at risk

[a]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[b]Wald tests to compare effects across strata defined by each potential modifier.

[c]Children can contribute with observation time both before eligibility for the respective campaign and after, unless they experienced an event or were censored before the respective campaign.

[d]Follow up time split at OPV campaigns in 2017 (Nov) or 2018 (Apr). OPV campaigns were co-administered with vitamin A+mebendazole.

[e]Analysis on eligibility for OPV campaign as the main effect adjusted for the MV campaign and with the MV campaign as a potential effect modifiers is presented in supplementary table 4.

[f]Follow up time split at eligibility for vitamin A campaigns in 2017 (Jan, Jun, Nov) or 2018 (Apr). Vitamin A campaigns are co-administered with mebendazole (to children >12 months) and nationally distributed approximately every 6 months +/- co-adminstered OPV. To disentangle time and vitamin A campaign effects, we furthermore split follow up time at 3 months after enrolment. Test of interaction between MV campaign, eligibility for vitamin A campaign and timeband (<3 or >3 months from enrolment); p=0.86.

[g]Follow-up time split at vitamin A campaigns in 2017 (Jan, Jun). Vitamin A campaigns are co-administered with mebendazole (to children >12 months) and nationally distributed approximately every 6 months +/- co-adminstered OPV. To disentangle time and vitamin A campaign effects, we furthermore split follow up time at 3 months after enrolment.Test of interaction between MV campaign, eligibility for vitamin A campaign and timeband (<3 or >3 months from enrolment); p=0.89

Supplementary table 5: **Potential pre-defined effect modifers of MV campaign on the risk of non-accidental mortality. Per-protocol analyses. Cox proportional hazards model.**

	After eligibility for OPV campaign[a] (%, n)		Before eligibility for OPV campaign[a] (%, n)				
	52·3	(9636)	47·7	(8775)			
	Rate (events/1000 PYRS)		Rate (events/1000 PYRS)		HR[b]	(95% CI)	p-value[c]
Hospital admission adjusted for MVcampaign	8·8	(166/18835)	12·8	(138/10788)	0·70	(0·51-0·94)	
MV campaign							0·26
Yes	10·1	(99/9810)	12·4	(71/5731)	0·79	(0·54-1·15)	
No	7·4	(67/9025)	13·2	(67/5057)	0·59	(0·39-0·89)	
MV campaign by sex[d]							0.16
Boys no	8·7	(41/4693)	14·1	(37/2623)	0·75	(0·44-1·27)	
Boys yes	10·8	(55/5088)	15·0	(44/2935)	0·76	(0·48-1·19)	
Girls no	6·0	(26/4332)	12·3	(30/2435)	0·43	(0·26-0·69)	
Girls yes	9·3	(44/4723)	9·7	(27/2796)	0·84	(0·45-1·57)	

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; OPV=oral polio vaccine; PYRS=person-years at risk

[a]Children can contribute with observation time both before eligibility for the respective campaign and after, unless they experienced an event or were censored before the respective campaign. Follow up time split at OPV campaigns in 2017 (Nov) or 2018 (Apr). OPV campaigns were co-administered with vitamin A+mebendazole.

[b]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[c]Wald tests to compare effects across strata defined by each potential modifier.

[d]Wald test of interaction between eligibility for OPV campaign and MV campaign among girls p=0·05.

Supplementary table 6: **Eligibility for OPV campaign analysed as the main effect on non-accidental repeated hospital admission adjusted for the MV campaign and with the MV campaign as a potential effect modifier. Per-protocol analyses. Cox proportional hazards model.**

Number of children=18411	**MV campaign (%, n)**		**No MV campaign (%, n)**				
	52·3	(9636)	47·7	(8775)			
	Rate (events/1000 PYRS)		**Rate (events/1000 PYRS)**		**HR[a]**	**(95% CI)**	**p-value[b]**
Eligible for any OPV campaign before enrolment since 2012							0·55
No	17·7	(46/2605)	14·8	(35/2363)	1·36	(0·82-2·26)	
Yes	9·6	(124/12937)	8·4	(99/11719)	1·15	(0·83-1·59)	
Observation time split[c] at any OPV campaign during follow-up[de]							0·26
Before	12·4	(71/5731)	13·2	(67/5057)	1·03	(0·68-1·58)	
After	10·1	(99/9810)	7·4	(67/9025)	1·38	(0·98-1·94)	
Observation time split[c] at any vitamin A campaign during follow-up[f]							0·13
Before	10·3	(36/3484)	13·3	(41/3074)	0·85	(0·51-1·45)	
After	11·1	(134/12058)	8·4	(93/11008)	1·35	(0·97-1·88)	
Observation time split[c] at only vitamin A campaign during follow-up[g]							0·39
Before	11·6	(81/6993)	11·4	(77/6756)	1·06	(0·73-1·55)	
After	10·4	(89/8549)	7·8	(57/7326)	1·37	(0·87-2·14)	

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; OPV=oral polio vaccine; PYRS=person-years at risk

[a]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[b]Wald tests to compare effects across strata defined by each potential modifier.

[c]Children can contribute with observation time both before eligibility for the respective campaign and after, unless they experienced an event or were censored before the respective campaign.

[d]Follow up time split at OPV campaigns in 2017 (Nov) or 2018 (Apr). OPV campaigns were co-administered with vitamin A+mebendazole.

[e]Analysis on eligibility for OPV campaign as the main effect adjusted for the MV campaign and with the MV campaign as a potential effect modifier is presented in supplementary table 6.

[f]Follow up time split at eligibility for vitamin A campaigns in 2017 (Jan, Jun, Nov) or 2018 (Apr). Vitamin A campaigns are co-administered with mebendazole (to children >12 months) and nationally distributed approximately every 6 months +/- co-adminstered OPV. To disentangle time and vitamin A campaign effects, we furthermore split follow up time at 3 months after enrolment. Test of interaction between MV campaign, eligibility for vitamin A campaign and timeband (<3 or >3 months from enrolment); p=0.97.

[g]Follow-up time split at vitamin A campaigns in 2017 (Jan, Jun). Vitamin A campaigns are co-administered with mebendazole (to children >12 months) and nationally distributed approximately every 6 months +/- co-adminstered OPV. To disentangle time and vitamin A campaign effects, we furthermore split follow up time at 3 months after enrolment.Test of interaction between MV campaign, eligibility for vitamin A campaign and timeband (<3 or >3 months from enrolment); p=0.81

Supplementary table 7: **Potential pre-defined effect modifiers of MV campaign on the risk of non-accidental repeated hospital admission. Per-protocol analyses. Cox proportional hazards model.**

Number of children=18411	MV campaign (%, n) 52·3 (9636)		NoMV campaign (%, n) 47·7 (8775)				
	Rate (events/1000PYRS)		Rate (events/1000 PYRS)		HR[a]	(95% CI)	p-value[b]
Prior routine MV among children with seen vaccination card by sex[c]							0·34
Boys no	14·4	(16/1114)	16·1	(16/994)	0·99	(0·53-1·84)	
Boys yes	13·9	(70/5031)	11·9	(52/4380)	1·12	(0·78-1·62)	
Girls no	19·8	(21/1062)	11·5	(10/869)	1·87	(0·85-4·11)	
Girls yes	11·8	(54/4595)	9·9	(41/4147)	1·24	(0·84-1·83)	
Season by sex[d]							0·40
Boys dry	15·0	(75/4992)	12·9	(55/4275)	1·22	(0·81-1·85)	
Boys rainy	14·6	(43/2955)	14·8	(44/2979)	0·89	(0·56-1·43)	
Girls dry	10·9	(51/4693)	9·7	(37/3809)	1·13	(0·73-1·76)	
Girls rainy	14·0	(39/2782)	12·0	(35/2918)	1·21	(0·74-1·98)	
Eligible for any OPV campaign since 2012 before enrolment by sex[e]							0·45
Boys no	28·2	(38/1348)	22·9	(28/1224)	1·27	(0·77-2·09)	
Boys yes	12·1	(80/6599)	11·8	(71/6030)	1·01	(0·71-1·43)	
Girls no	14·7	(18/1224)	16·2	(18/1108)	1·07	(0·56-2·05)	
Girls yes	11·5	(72/6252)	9·6	(54/5620)	1·19	(0·84-1·69)	
Observation time split at any OPV campaign during follow-up by sex[f]							0·11
Boys before	20·2	(59/2925)	19·1	(50/2613)	1·12	(0·72-1·75)	
Boys after	11·7	(59/5023)	10·6	(49/4641)	1·06	(0·72-1·57)	
Girls before	13·3	(37/2790)	15·7	(38/2428)	0·86	(0·53-1·37)	
Girls after	11·3	(53/4686)	7·9	(34/4300)	1·52	(1·02-2·27)	
Observation time split at any vitamin A campaign during follow-up by sex[g]							0·36
Boys before	16·9	(30/1778)	17·3	(27/1562)	0·98	(0·56-1·72)	
Boys after	14·3	(88/6169)	12·6	(72/5693)	1·12	(0·79-1·59)	
Girls before	12·3	(21/1701)	15·9	(24/1505)	0·79	(0·44-1·41)	
Girls after	11·9	(69/5775)	9·2	(48/5222)	1·36	(0·95-1·93)	
Observation time split at only vitamin A campaign during follow-up by sex[h]							0·74
Boys before	15·4	(55/3575)	14·2	(48/3369)	1·03	(0·68-1·56)	
Boys after	14·4	(63/4372)	13·1	(51/3885)	1·14	(0·74-1·77)	
Girls before	13·9	(47/3375)	13·5	(45/3342)	1·05	(0·69-1·59)	
Girls after	10·5	(43/4100)	8·0	(27/3386)	1·34	(0·82-2·19)	

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; PYRS=person-years at risk

[a]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[b]Wald tests to compare effects across strata defined by each potential modifier.

[c]Wald test of interaction between MV campaign and prior MV among girls p=0·35

[d]Wald test of interaction between MV campaign and season among girls p=0·85

[e]A similar analysis on vitamin A and sex was not possible as there were strata without any events. Wald test of interaction between MV campaign and OPV campaign before enrolment among girls p=0·76.

[f]Follow up time split at OPV campaigns in 2017 (Nov) or 2018 (Apr). OPV campaigns were co-administered with vitamin A+mebendazole. Wald test of interaction between MV campaign and OPV campaign among girls p=0·06.

[g]Follow up time split at vitamin A campaigns in 2017 (Jan, Jun, Nov) or 2018 (Apr). Vitamin A campaigns are co-administered with mebendazole but +/- co-administered OPV. Wald test of interaction between MV campaign and vitamin A campaign among girls p=0·10.

[h]Follow up time split at vitamin A campaigns in 2017 (Jan, Jun). Vitamin A campaigns are co-administered with mebendazole but not OPV. Wald test of interaction between MV campaign and vitamin A campaign among girls p=0·46.

Supplementary table 8: **Pre-defined potential effect modifiers of MV campaign on the risk of non-accidental mortality/hospital admission by sex. Per-protocol analyses. Cox proportional hazards model.**

Number of children=18411	MV campaign (%, n)		No MV campaign (%, n)				
	52·3	(9636)	47·7	(8775)			
	Rate (events/1000 PYRS)		Rate (events/1000 PYRS)		HR[a]	(95% CI)	p-value[b]
Eligible for any OPV campaign since 2012 before enrolment by sex[c]							0·64
Boys no	13·9	(19/1371)	9·7	(12/1243)	1·31	(0·64-2·67)	
Boys yes	4·4	(29/6653)	4·3	(26/6073)	0·97	(0·56-1·67)	
Girls no	8·1	(10/1234)	7·1	(8/1120)	1·05	(0·43-2·55)	
Girls yes	3·8	(24/6286)	3·4	(19/5647)	1·07	(0·61-1·87)	
Observation time split at any OPV campaign during follow-up by sex[f]							0.72
Boys before	8·9	(26/2936)	7·6	(20/2623)	1·13	(0·63-2·03)	
Boys after	4·3	(22/5088)	3·8	(18/4693)	1·04	(0·58-1·89)	
Girls before	6·8	(19/2796)	6·2	(15/2435)	0·99	(0·52-1·91)	
Girls after	3·2	(15/4723)	2·8	(12/4332)	1·15	(0·55-2·37)	
Observation time split at any vitamin A campaign during follow-up by sex[g]							0·57
Boys before	7·9	(14/1781)	7·7	(12/1566)	0·97	(0·44-2·13)	
Boys after	5·4	(34/6243)	4·5	(26/5750)	1·13	(0·67-1·92)	
Girls before	7·0	(12/1704)	4·6	(7/1509)	1·29	(0·51-3·33)	
Girls after	3·8	(22/5816)	3·8	(20/5258)	0·98	(0·57-1·68)	
Observation time split at only vitamin A campaign during follow-up by sex[h]							0·10
Boys before	5·8	(21/3600)	6·2	(21/3392)	0·85	(0·49-1·46)	
Boys after	6·1	(27/4424)	4·3	(17/3924)	1·37	(0·69-2·71)	
Girls before	6·5	(22/3394)	3·9	(13/3364)	1·42	(0·72-2·81)	
Girls after	2·9	(12/4125)	4·1	(14/3403)	0·72	(0·36-1·46)	

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; BCG=Bacille Calmette Guerin; OPV=oral polio vaccine; PENTA=diphtheria, tetanus, pertussis, hepatitis type b, and haemophilus influenza type b vaccine; PYRS=person-years at risk

[a]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[b]Wald tests to compare effects across strata defined by each potential modifier.

[c]Wald test of interaction between MV campaign and prior MV among girls p=0·53

[d]Wald test of interaction between MV campaign and season among boys p=0·01

[e]A similar analysis on vitamin A and sex was not possible as there were strata without any events. Wald test of interaction between MV campaign and OPV campaign before enrolment among girls p=0·97.

[f]Follow up time split at OPV campaigns in 2017 (Nov) or 2018 (Apr). OPV campaigns were co-administered with vitamin A+mebendazole. Wald test of interaction between MV campaign and OPV campaign among girls p=0·78.

[g]Follow up time split at vitamin A campaigns in 2017 (Jan, Jun, Nov) or 2018 (Apr). Vitamin A campaigns are co-administered with mebendazole but +/- co-administered OPV. Wald test of interaction between MV campaign and vitamin A campaign among girls p=0·60.

[h]Follow up time split at vitamin A campaigns in 2017 (Jan, Jun). Vitamin A campaigns are co-administered with mebendazole but not OPV. Wald test of interaction between MV campaign and vitamin A campaign among girls p=0·17.

Supplementary table 9: **Pre-defined potential effect modifiers of MV campaign on the risk of non-accidental mortality by sex. Per-protocol analyses. Cox proportional hazards model.**

Number of children=18411	MV campaign (%, n)	No MV campaign (%, n)			
	52·3 (9636)	47·7 (8775)			
	Rate (events/1000 PYRS)	**Rate (events/1000 PYRS)**	**HR[a]**	**(95% CI)**	**p-value[b]**
Eligible for any OPV campaign since 2012 before enrolment by sex[c]					0·76
Boys no	23·3 (32/1371)	17·7 (22/1244)	1·40	(0·74-2·65)	
Boys yes	10·1 (67/6652)	9·2 (56/6072)	1·09	(0·73-1·63)	
Girls no	11·3 (14/1234)	11·6 (13/1120)	1·31	(0·63-2·75)	
Girls yes	9·1 (57/6285)	7·6 (43/5647)	1·21	(0·79-1·84)	
Observation time split at any OPV campaign during follow-up by sex[f]					0.16
Boys before	15·0 (44/2935)	14·1 (37/2623)	1·19	(0·71-2·01)	
Boys after	10·8 (55/5088)	8·7 (41/4693)	1·20	(0·76-1·89)	
Girls before	9·7 (27/2796)	12·3 (30/2435)	0·84	(0·46-1·53)	
Girls after	9·3 (44/4723)	6·0 (26/4332)	1·67	(1·06-2·62)	
Observation time split at any vitamin A campaign during follow-up by sex[g]					0·11
Boys before	12·4 (22/1780)	12·1 (19/1565)	1·10	(0·55-2·19)	
Boys after	12·3 (77/6242)	10·3 (59/5750)	1·21	(0·79-1·83)	
Girls before	8·2 (14/1703)	14·6 (22/1509)	0·62	(0·32-1·25)	
Girls after	9·8 (57/5815)	6·5 (34/5258)	1·60	(1·04-2·45)	
Observation time split at only vitamin A campaign during follow-up by sex[h]					0·17
Boys before	12·8 (46/3599)	10·9 (37/3392)	1·16	(0·71-1·93)	
Boys after	12·0 (53/4424)	10·4 (41/3923)	1·20	(0·72-1·99)	
Girls before	10·3 (35/3394)	11·9 (40/3364)	0·94	(0·59-1·49)	
Girls after	8·7 (36/4125)	4·7 (16/3403)	1·84	(0·97-3·48)	

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; BCG=Bacille Calmette Guerin; OPV=oral polio vaccine; PENTA=diphtheria, tetanus, pertussis, hepatitis type b, and haemophilus influenza type b vaccine; PYRS=person-years at risk

[a]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[b]Wald tests to compare effects across strata defined by each potential modifier.

[c]Wald test of interaction between MV campaign and prior MV among girls p=0·99

[d]Wald test of interaction between MV campaign and season among girls p=0·95

[e]A similar analysis on vitamin A and sex was not possible as there were strata without any events. Wald test of interaction between MV campaign and OPV campaign before enrolment among girls p=0·84.

[f]Follow up time split at OPV campaigns in 2017 (Nov) or 2018 (Apr). OPV campaigns were co-administered with vitamin A+mebendazole. Wald test of interaction between MV campaign and OPV campaign among girls p=0·05.

[g]Follow up time split at vitamin A campaigns in 2017 (Jan, Jun, Nov) or 2018 (Apr). Vitamin A campaigns are co-administered with mebendazole but +/- co-administered OPV. Wald test of interaction between MV campaign and vitamin A campaign among girls p=0·02.

[h]Follow up time split at vitamin A campaigns in 2017 (Jan, Jun). Vitamin A campaigns are co-administered with mebendazole but not OPV. Wald test of interaction between MV campaign and vitamin A campaign among girls p=0·09.

Supplementary table 10: **Pre-defined potential effect modifers of MV campaign on the risk of non-accidental repeated hospital admission by sex. Per-protocol analyses. Cox proportional hazards model.**

Number of children=18411	MV campaign (%, n)		No MV campaign (%, n)				
	52·3	(9636)	47·7	(8775)			
	Rate (events/1000 PYRS)		Rate (events/1000 PYRS)		HR[a]	(95% CI)	p-value[b]
Most recent vaccination prior to enrolment among children with seen vaccination card[c]							0·15
MV[d]	14·3	(89/6239)	10·2	(59/5761)	1·39	(0·98-1·96)	
PENTA+MV[e]	9·7	(8/829)	15·1	(11/731)	0·58	(0·25-1·35)	
PENTA[f]	17·0	(33/1942)	13·9	(23/1659)	1·36	(0·81-2·27)	
Any prior pneumococcal conjugate vaccination among children with seen vaccination card							0·32
No	10·6	(62/5868)	7·5	(38/5084)	1·41	(0·95-2·11)	
Yes	16·7	(100/5974)	15·3	(82/5353)	1·11	(0·81-1·53)	
Any prior rotavirus vaccination among children with seen vaccination card							0·77
No	11·1	(96/8684)	9·0	(68/7596)	1·24	(0·89-1·72)	
Yes	20·9	(66/3157)	18·3	(52/2835)	1·15	(0·77-1·73)	
Prior yellow fever vaccination among children with seen vaccination card							0·02
No	17·6	(56/3187)	10·0	(28/2800)	1·88	(1·18-3·01)	
Yes	12·2	(105/8615)	12·0	(91/7594)	1·00	(0·74-1·35)	
Prior yellow fever vaccination among measles vaccinated children with seen vaccination card							0·03
No	17·9	(20/1117)	5·9	(6/1014)	3·14	(1·23-8·03)	
Yes	12·2	(104/8508)	11·6	(87/7510)	1·05	(0·78-1·42)	

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; BCG=Bacille Calmette Guerin; OPV=oral polio vaccine; PENTA=diphtheria, tetanus, pertussis, hepatitis type b, and haemophilus influenza type b vaccine; PYRS=person-years at risk

[a]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[b]Wald tests to compare effects across strata defined by each potential modifier.

[c]Among children having PENTA (+/- co-administered MV), the risk of deaths/hospital admissions was HR=1·09 (95%CI 0·70-1·70) (p=0·37 for interaction).

[d]MV as most recent vaccination; co-scheduled yellow fever could have been given, but not BCG, OPV, PENTA, rotavirus, pneumococcal conjugate and inactivated polio.

[e]PENTA+MV as most recent vaccination; other vaccines co-scheduled with PENTA or MV could have been given (OPV, rotavirus, yellow fever, pneumococcal conjugate, inactivated polio) but not BCG.

[f]PENTA as most recent vaccination; other vaccines co-scheduled with PENTA could have been given (OPV, rotavirus, pneumococcal conjugate, inactivated polio) but not BCG, MV and yellow fever.

Supplementary table 11: **Prior routine vaccination as potential effect modifers of MV campaign on the risk of non-accidental mortality/hospital admission other than the pre-defined potential effect modifiers. Per-protocol analyses. Cox proportional hazards model.**

Number of children=18411	MV campaign (%, n)		No MV campaign (%, n)				
	52·3	(9636)	47·7	(8775)			
	Rate (events/1000 PYRS)		Rate (events/1000 PYRS)		HR[a]	(95% CI)	p-value[b]
Health region							0·16
Oio	7·5	(19/2526)	6·0	(15/2504)	1·19	(0·64-2·19)	
Biombo	11·6	(24/2061)	13·0	(23/1774)	0·93	(0·42-2·04)	
Gabu	12·0	(26/2172)	15·9	(27/1699)	0·80	(0·51-1·27)	
Cacheu	5·7	(9/1574)	8·0	(7/880)	0·77	(0·33-1·78)	
Bafata	16·4	(22/1344)	12·9	(24/1858)	1·10	(0·53-2·31)	
Quinara	14·3	(20/1394)	7·3	(10/1368)	2·03	(0·79-5·19)	
Tombali	18·3	(21/1145)	5·4	(7/1289)	3·88	(1·5-10·05)	
Bubaque	77·1	(27/350)	64·8	(18/278)	1·22	(0·71-2·08)	
Bolama	48·8	(9/184)	44·5	(9/202)	1·44	(0·57-3·66)	
Sao Domingos	9·6	(13/1348)	9·9	(11/1111)	0·96	(0·47-1·93)	
Bafata new[c]	13·6	(18/1324)	19·6	(20/1019)	0·63	(0·32-1·23)	
Ethnicity							0·04
Balanta	10·5	(41/3896)	6·1	(22/3582)	2·18	(1·22-3·91)	
Fula	14·3	(58/4067)	15·2	(48/3151)	0·84	(0·52-1·35)	
Manjaco/Mancanha	8·3	(9/1082)	17·7	(12/676)	0·66	(0·31-1·38)	
Pepel	11·3	(19/1678)	14·9	(23/1545)	0·86	(0·41-1·81)	
Mandinga	12·1	(29/2392)	14·1	(40/2829)	0·81	(0·51-1·31)	
Other	22·1	(48/2175)	12·7	(26/2053)	1·55	(0·92-2·62)	
Age group[d]							0·64
9-20 months	21·5	(79/3683)	19·0	(63/3310)	1·22	(0·86-1·73)	
20-33 months	12·7	(49/3857)	13·4	(48/3569)	0·93	(0·62-1·41)	
33-46 months	10·1	(40/3954)	9·2	(32/3462)	1·04	(0·69-1·57)	
46-60 months	10·2	(40/3929)	7·7	(28/3642)	1·30	(0·74-2·29)	

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; BCG=Bacille Calmette Guerin; OPV=oral polio vaccine; PENTA=diphtheria, tetanus, pertussis, hepatitis type b, and haemophilus influenza type b vaccine; PYRS=person-years at risk

[a]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[b]Wald tests to compare effects across strata defined by each potential modifier.

[c]We added clusters from another part of Bafata after approval of a protocol amendment on a sample size increase.

[d]We found no difference in the estimates when we used time since enrolment as the underlying time axis (data not shown)

Supplementary table 12: **Demographic background factors as potential effect modifers of MV campaign on the risk of non-accidental mortality/hospital admission based on other factors than the pre-defined potential effect modifiers. Per-protocol analyses. Cox proportional hazards model.**

Number of children=18411[a]	MV campaign (%, n) 52·3 (9636)		No MV campaign (%, n) 47·7 (8775)				
	Rate (events/1000 PYRS)		Rate (events/1000 PYRS)		HR[b]	(95% CI)	p-value[c]
Observation time split[d] at 14 days after enrolment							0·66
Before	13·6	(5/369)	8·9	(3/336)	1·52	(0·38-6·18)	
After	13·5	(203/15054)	12·3	(168/13646)	1·11	(0·88-1·41)	
Observation time split[d] at 6 months after enrolment							
Before/after							0·54
Before	18·4	(87/4734)	18·3	(79/4320)	1·03	(0·72-1·49)	
After	11·3	(121/10689)	9·5	(92/9662)	1·19	(0·89-1·59)	
By sex[e]							0·07
Boys before	23·2	(56/2417)	19·9	(44/2211)	1·20	(0·76-1·91)	
Boys after	11·2	(62/5531)	10·9	(55/5044)	1·00	(0·68-1·48)	
Girls before	13·4	(31/2317)	16·60	(35/2109)	0·81	(0·47-1·41)	
Girls after	11·4	(59/5158)	8·01	(37/4619)	1·49	(1·01-2·19)	
Censored by eligibility for OPV campaign							0·94
Before	18·9	(79/4184)	19·2	(73/3796)	1·00	(0·68-1·48)	
After	11·1	(17/1530)	12·0	(15/1245)	0·97	(0·47-2·02)	
By sex and censored by eligibility for OPV campaign[f]							0·86
Boys before	23·0	(49/2135)	21·5	(42/1955)	1·12	(0·71-1·78)	
Boys after	12·7	(10/790)	12·2	(8/658)	1·16	(0·44-3·09)	
Girls before	14·6	(30/2049)	16·8	(31/1841)	0·85	(0·49-1·46)	
Girls after	9·5	(7/740)	11·9	(7/587)	0·76	(0·25-2·31)	
Observation time split[d] at 12 months[g] after enrolment							0·96
Before	15·1	(134/8860)	13·9	(112/8068)	1·11	(0·82-1·52)	
After	11·3	(74/6563)	10·0	(59/5914)	1·13	(0·79-1·61)	
By sex[h]							0·06
Boys before	18·5	(84/4535)	15·5	(64/4141)	1·22	(0·84-1·79)	
Boys after	10·0	(34/3412)	11·2	(35/3114)	0·85	(0·51-1·41)	
Girls before	11·6	(50/4325)	12·2	(48/3927)	0·97	(0·62-1·51)	
Girls after	12·7	(40/3151)	8·6	(24/2800)	1·56	(0·98-2·47)	

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; OPV=oral polio vaccine; PYRS=person-years at risk

[a]We found no difference in the overall effect when applying time from enrolment as the underlying time axis HR=1·10 (95%CI 0·87-1·39)

[b]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[c]Wald tests to compare effects across strata defined by each potential modifier.

[d]Children can contribute with observation time before the respective time interval and after, unless they experienced an event or were censored before the respective time interval.

[e]Wald test of interaction between MV campaign and follow-up time split at 6 months among girls p=0·08.

[f]Wald test of interaction between MV campaign and follow-up time split at 6 months among girls p=0·87.

[g]As we had too few children with observation time after 12 months having censored for OPV campaigns and the national MV campaign, further analyses similar to follow-up time split at 6 months were not possible to conduct.

[h]Wald test of interaction between MV campaign and follow-up time time split at 12 months among girls p=0·15.

Supplementary table 13: **Follow-up period potential effect modifiers of MV campaign on the risk of non-accidental mortality/hospital admission. Per-protocol analyses. Cox proportional hazards model.**

Number of children=18411[a]	MV campaign (%, n)		No MV campaign (%, n)				
	52·3	(9636)	47·7	(8775)			
	Rate (events/1000 PYRS)		**Rate (events/1000 PYRS)**		**HR[b]**	**(95% CI)**	**p-value[c]**
Birth cohort[d]							
By year[e]							0·51
Year 2012	8·8	(17/1929)	9·9	(17/1715)	0·98	(0·44-2·18)	
Year 2013	12·0	(38/3172)	5·8	(17/2952)	1·86	(0·99-3·46)	
Year 2014	8·9	(33/3723)	9·5	(31/3273)	0·95	(0·61-1·49)	
Year 2015	14·5	(53/3644)	13·4	(45/3368)	1·06	(0·71-1·59)	
Year 2016	20·6	(51/2470)	23·0	(52/2259)	0·97	(0·65-1·43)	
Year 2017	33·0	(16/484)	21·7	(9/415)	1·61	(0·76-3·41)	
Observation time split by period of follow-up[df]							
By season[g]							0·84
Dry season 2017	16·1	(45/2795)	16·6	(44/2649)	0·98	(0·58-1·68)	
Rainy season 2017	18·3	(40/2191)	16·3	(29/1774)	1·17	(0·69-1·96)	
Dry season 2018	8·5	(28/3308)	6·0	(18/3002)	1·41	(0·79-2·51)	
Rainy season 2018	17·3	(60/3476)	14·2	(46/3236)	1·21	(0·81-1·81)	
Dry season 2019	9·6	(35/3652)	10·2	(34/3321)	0·96	(0·59-1·56)	

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; OPV=oral polio vaccine; PYRS=person-years at risk

[a]We did not find a difference in the overall effect when applying time from enrolment as the underlying time axis (data not shown)

[b]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[c]Wald tests to compare effects across strata defined by each potential modifier.

[d]Children can contribute with observation time before the respective time interval and after, unless they experienced an event or were censored before the respective time interval.

[e]Data also reported by sex in supplementary figure 3.

[f]Follow-up time split at 1 December and 1 June.

[g]Data also reported by sex in supplementary figure 4.

Supplementary table 14: **Calender period potential effect modifers of MV campaign on the risk of non-accidental mortality/hospital admission. Per-protocol analyses. Cox proportional hazards model.**

Number of children=18411	MV campaign (%, n)		No MV campaign (%, n)			
	52·3	(9636)	47·7	(8775)		
	Rate	**(events/1000 PYRS)**	**Rate**	**(events/1000 PYRS)**	**HR[a]**	**(95% CI)**
Mortality/hospital admission[bc]	13·5	(208/15423)	12·2	(171/13982)	1·11	(0·86-1·43)
Mortality[d]	5·3	(82/15544)	4·6	(65/14083)	1·05	(0·76-1·44)

MV=measles vaccine; HR=hazard ratio; CI=confidence interval; PYRS=person-years at risk

[a]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.

[b]We censored 12 deaths due to accident (5 intervention/7 control) and the admission period of 6 hospital admissions due to accident (2 intervention/4 control). None of the deaths or hospital admissions were due to measles infection . See Supplementary table 2b for details on causes.

[c]Adjusted for pre-trial mortality level. Using the lowest quartile as the reference, the estimates for the higher mortality quartiles was: 2nd: HR=0·99 (95%CI 0·65-1·53); 3rd HR=1·16 (95%CI 0·80-1·68); 4th HR=1·10 (95%CI 0·77-1·56)

[d]Adjusted for pretrial mortality level. Using the lowest quartile as the reference, the estimates for the higher mortality quartiles was: 2nd: HR=1·35 (95%CI 0·75-2·43); 3rd HR=0·84 (95%CI 0·51-1·40); 4th HR=1·22 (95%CI 0·73-2·03)

Mortality in children aged 9-59 in 2014-16 (2 years prior to starting enrolment) living in the rural HDSS was 10·1 per 1000 person years. Mortality two years prior to the trial implementation tended to be higher in the intervention group (11·1/1000 PYRS) than in the control group (8.9/1000 PYRS), HR=1.22 (0.94-1.58)

Supplementary table 15: **Effect of MV campaign on non-accidental mortality/hospital admission or death, adjusted for pre-trial mortality. Per-protocol analyses with Cox proportional hazards model.**

	MV campaign (%, n)		No MV campaign (%, n)		RR[a]	(95% CI)
Among children eligible for assessment, mothers/guardians refusing/busy at any visit[b]	1	(115/10696)	1	(132/9743)	0·81	(0·57-1·16)
Among children enrolled, guardian as consent giver	29	(2763/9636)	30	(2600/8775)	0·97	(0·89-1·06)
Among all deaths, deaths occurring at a health facility[c]	45	(37/82)	34	(22/65)	1·39	(0·92-2·12)

MV=measles vaccine; RR=relative risk; CI=confidence interval.

[a]Adjusted for stratification variables health region and pre-enrolment vaccination coverage, and sex, and using a robust standard error accounting for intra-cluster correlation.

[b]If mothers/guardians refused, field assistants asked for their permission to offer child enrolment at a subsequent visit. If mothers/guardians were busy, field assistants by default offered child enrolment at a subsequent visit.

[c]Death place: home (50%), health center (14%), hospital (26%), other (2%), unknown/missing (8%).

Supplementary table 16: **Potential non-blinding issues. Log-binomial model.**

Appendix 1: Log-minus-log plot