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Impact of H1N1 influenza vaccination on child morbidity in Guinea-Bissau

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SUMMARY

In October 2010, in response to the influenza pandemic, an H1N1 campaign was conducted in Guinea-Bissau. To investigate possible non-specific effects (NSE) of the H1N1 influenza vaccine on general child health, we studied the effect of the H1N1 influenza vaccination campaign participation on childhood consultation rates.

Among 10,290 children living in the suburbs of Bissau, the capital of Guinea-Bissau, and whom we followed through the health demographic surveillance system at the Bandim Health project, we had information on 5980 of the children (60%) who participated in the H1N1 influenza vaccination campaign and 1747 (18%) children who had not participated. No information was obtained for the remaining 22%. After the H1N1 influenza vaccination campaign, the consultation rates declined for both participants and non-participants, consistent with seasonal and age differences in morbidity patterns. The decline may have been smaller for campaign-participants with a hazard ratio (HR) of 0.80 [95% confidence interval [CI] 0.75;0.85] than for non-participants with a HR=0.68 [95%CI: 0.58;0.80], p=0.06 for same decline, indicating that H1N1 influenza vaccines may have effects on the susceptibility to unrelated infections.

ABSTRACT

Background: In addition to vaccines' specific effects, vaccines may have non-specific effects (NSE) altering the susceptibility to unrelated infections. Non-live vaccines have been associated with negative NSEs. In 2010 a campaign with the non-live H1N1-influenza vaccine targeted children 6-59 months in Guinea-Bissau.

Methods: Bandim Health Project runs a health and demographic surveillance system site in Guinea-Bissau. Using a Cox proportional hazards model, we compared all-cause consultation rates after versus before the campaign, stratified by participation status.

Results: Among 10,290 children eligible for the campaign, 60% had participated, 18% had not and for 22% no information was obtained. After the H1N1 campaign the consultation rates tended to decline more for participants (HR=0.80 [95%CI: 0.75; 0.85]) than for non-participants (HR=0.68 [95%CI: 0.58;0.79]), p=0.06 for same effect.

Conclusion: The decline in the vaccinated group may have been smaller than the decline in the non-vaccinated group consistent with H1N1-vaccine increasing susceptibility to unrelated infections.

WORD COUNT: 150

KEYWORDS

Campaigns, Child Morbidity, H1N1, H1N1-vaccine, Non-specific / heterologous effects of vaccines

CONFLICTS OF INTEREST

Nothing to declare.

FUNDING

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INTRODUCTION

In March and April 2009, an H1N1 influenza pandemic emerged from Mexico and the United States of America. On June 11, 2009, the pandemic had spread widely and the WHO declared it to have reached phase 6, the highest level[1]. Vaccine development was promptly initiated[2]. In August 2009, a vaccine was available[1]. It was initially used in high-income countries and later donated to low-income countries. From February to September 2010, WHO delivered 32 million doses of H1N1 vaccine to 34 countries in the WHO African Region[3], the majority of which were distributed after the main period of H1N1 transmission[3]. Due to vaccine shortage, high-risk groups (health care workers, pregnant women and people with chronic diseases) were to be vaccinated first, followed by children in order to reduce community transmission; children themselves were not identified as a high-risk group[4]. In Guinea-Bissau, the donated vaccines were used in a national H1N1 vaccination campaign during October 2010.

The effects of vaccines may go beyond the disease specific protective effect, i.e. the vaccines have non-specific effects (NSEs) altering the susceptibility to other infections[5]. WHO's Strategic Advisory Group of Experts on Immunization (SAGE) recently commissioned a review of potential NSEs of Bacillus Calmette–Guérin (BCG), measles vaccine (MV) and diphtheria-tetanus-pertussis vaccine (DTP). The review concluded that the live BCG and MV were associated with lower mortality than could be explained by preventing tuberculosis and measles, i.e. they appeared to have beneficial NSEs. No such effects were seen for the non-live DTP vaccine[6]. The NSEs of MV was stronger for girls but the review did not find any sex-difference of DTP[6]. We have argued that the absence of a sex-differential effect of the non-live DTP vaccine is caused by inclusion of studies with survival and frailty bias[7]. SAGE recommended further research into NSEs[8]. Until now, it is mainly vaccines in the routine vaccination programme, which have been studied with regard to their NSEs. However, other vaccines may also have NSEs[9]. Safety investigation of H1N1 vaccines have assessed associations between vaccination and rare

syndromes such as narcolepsy[10] and Guillian Barré Syndrome[11], but no study has assessed the effect of H1N1 vaccination on general child health.

We took advantage of the health and demographic surveillance system (HDSS) of Bandim Health Project (BHP) to study the potential NSEs of the H1N1 campaign among children in Guinea-Bissau. Since H1N1 influenza morbidity causes few of the total number of consultations, we used relative changes in all-cause consultation rates before and after the H1N1 campaign among children exposed and unexposed to H1N1 vaccine, to investigate NSE. We tested the hypothesis that children vaccinated with H1N1 vaccine, in spite of being protected against the target H1N1 influenza, would have higher rates of consultations than if they had not been vaccinated.

METHODS

Setting and population

Since 1978, BHP has maintained an HDSS in suburbs of Bissau, the capital of Guinea-Bissau. Six districts with approximately 100,000 inhabitants are under surveillance. We defined the study cohort for the present study as children who were between 6 months and 5 years at the time of the campaign and living in the study area.

All households in the study area are visited monthly to identify newborn children, pregnant women and deaths. Background information, including the mother's education, type of roof, electricity, and toilet facility, is collected at the first visit after birth. All children in the study area are visited every 3 months until they are 3 years old. At these visits, information on routine immunizations and hospital admissions is collected. If the child is present, the mid-upper-arm-circumference (MUAC) is measured. At all visits, the vaccination card is sought inspected.

Influenza surveillance was not conducted in Guinea-Bissau, but data from the neighbouring country, Senegal, indicate H1N1 influenza was circulating in the region in October 2010[12].

Information on H1N1 vaccination

In October 2010, a national H1N1 campaign took place in Guinea-Bissau. Children aged 6 months to 5 years, pregnant women and diabetics were eligible for vaccination with the non-live unadjuvanted Panenza H1N1 vaccine (Sanofi-Pasteur).

The campaign was a "fixed post campaign", where children had to be brought to a vaccination post staffed by health workers. The vaccine was registered on the child's vaccination card or a special campaign card. A BHP field assistant, equipped with a list of all the children registered in the area, was present at all posts and registered which children received the vaccine. The first round of the campaign took place on October 14-16, but as there were still many vaccines left due to low coverage, a second round was conducted from October 22-25.

In the weeks after the campaigns, BHP conducted follow-up visits to children with no information on campaign participation. At home visits, information on participation status was retrieved either from the vaccination card or by interview with the caretaker. Information that a child had not received the vaccine could only be provided by the caretaker; in other words, lack of information about campaign vaccination on the vaccination card was not considered conclusive.

If no one was present to provide information, the household was visited up to three times; if no information could be obtained, the vaccination status was classified as unknown.

Post-campaign follow-up was initiated after the first campaign round, before it was known that a second round would be conducted. Between the two rounds, information that a child had not participated in the campaign was obtained for 368 children. As these children may have received H1N1 vaccines in the second round, they have been excluded from the present study.

Information on outcomes

Information on consultations (all causes) was obtained from three health centres in the study area and from the National Hospital Simão Mendes. In each location, a BHP assistant registers all children seeking consultations, with ID numbers, address, name, birthdate and mother's name.

Statistical analyses

We compared the distribution of background factors between participants, non-participants, and children with no information, and between participants and non-participants only. The categorical variables were tested using a chi-squared test; a Kruskal-Wallis-test was used for age at the time of the campaign (Figure 1).

Main analysis – participants and non-participants before and after the 2010 campaign:

We defined two periods, a "Before H1N1 campaign period" and an "After H1N1 campaign period". The before and after periods were , demarcated by two other vaccination campaigns: an Oral Polio Vaccine (OPV) and vitamin A supplementation (VAS) campaign taking place May 28-June 2, 2010, and an OPV campaign taking place March 23-26, 2011 (Figure 2). Thus, the "Before H1N1 campaign period" started on May 31, 2010 and ended on October 14, 2010 when the H1N1 campaign began. The "After H1N1 campaign period" began on October 14, 2010 and ended March 25, 2011. The surveillance period after the H1N1 campaign was defined individually for each child, as the date that we obtained information on their campaign status (vaccinated, non-vaccinated or no-information).

We compared the post-campaign consultation rate to the pre-campaign in a Cox proportional hazard model with age as underlying time scale. Thus, age was controlled for in all models. We allowed the effect of calendar time to vary with campaign participation status by including an interaction term (campaign status*before/after H1N1 campaign), thus conducting a multiplicative difference-in-differences analysis to assess whether the change over time depended on vaccination status.

A child contributed time at risk from the date of entry until a consultation. Follow-up was censored on date of migration out of the study area, death, at 5 years of age, or end of the study period, whichever came first. The Cox-models allowed for repeated events; the children re-entered the analysis the day after they had a consultation.

The consultation hazards ratio (HR) for "after" versus "before" the H1N1 campaign among participants was compared with the HR among non-participants to investigate interaction between calendar time and participation status. All analyses were performed overall and stratified by sex.

Vitamin-A supplementation: After the H1N1 campaign a VAS campaign took place on December 16-20, 2010. Previous studies have indicated amplification of NSEs by VAS[13-15]. We therefore conducted an ecological analysis of the consultation rates split on December 18, 2010, assuming all children participated in the VAS campaign (Supplementary Material).

Sensitivity analyses and adjustment for potential confounders: Participation in vaccination campaigns has previously been shown to be associated with maternal education, ethnicity and residential district[14, 15]. We therefore assessed whether controlling for these factors and other background factors listed in Table 1 changed the estimated HR. Background factors were classified as in prior studies (Supplementary Material)

If patterns of travelling outside the study area differed for participants and non-participants, that could contribute to a differential detection of consultations. Among children <3 years, who were followed through 3-monthly home visits, we therefore assessed whether adjusting for the proportion of visits which registered a child as travelling affected the estimates.

Vaccination has a known frequent side effect of elevated body temperature within the first days of vaccination. As fever is a common reason for consulting a doctor, we censored the first week after the date of vaccination to investigate if this could be accountable for skewed consultation rates.

Ecological analysis: comparing 2010 with 2009:

In the after-versus-before comparison, adjusting for season is problematic, since the majority of the period before the H1N1 campaign was in the rainy season and the period after the H1N1 campaign was in the dry season. Therefore, we compared the population level consultation rates after the H1N1 campaign in 2010 with those in the same period in 2009 (Supplementary material).

RESULTS

A total of 10,290 children were included in the analysis; 5980 (60%) received the H1N1 vaccine, 1747 (18%) were not vaccinated; for 2195 (22%) no information on vaccination status could be obtained (Figure 1).

The participant and non-participant groups differed significantly on most background parameters, with the non-participating children generally being slightly worse off with regard to their socio-economic status: There was a higher proportion of mothers with no formal education and fewer had an indoor toilet. Furthermore, a majority came from the Muslim ethnic groups (Fula/Mandinga) (Table 1). Censoring due to death (0.2% (12/5980) among participants; 0.2% (4/1749) among non-participants) or migration (2.6% (157/5980) among participants and 3.8% (66/1749) among non-participants) did not differ significantly by participation status.

Main analysis

A total of 2616 consultations were registered for all the children included in the study in the period before the H1N1 campaign; 2036 consultations were registered after the campaign. The rate of consultations declined from 106.3 per 100 person years (PYRS) to 77.7 per 100 PYRS among participants and from 68.0 to 42.8 among non-participants. The consultation rate was lower in the “After H1N1 campaign period” than in the “Before H1N1 campaign period” for both participants (HR=0.80 [95% confidence interval(CI): 0.75;0.85]) and non-participants

(HR=0.68 [95%CI: 0.58;0.79]). Thus, the decline was smaller for participants than non-participants, the interaction between participation status and time gave a p-value of 0.06 (Table 2). Adjusting for season, ethnic group and maternal schooling, the factors which were associated with the largest changes in the HR (8-9% changes when adjusted for one of the factors at a time), only changed the estimates slightly. The adjusted hazard ratio (aHR) was 0.80 [95%CI: 0.75;0.85] for campaign participants and 0.67 [95%CI: 0.58;0.79] for non-participants, p=0.05 for interaction between participation status and time.

As shown by the curve displaying the estimated mean number of consultations (Figure 3), the incidence of registered consultations declined with age. However, this decline with age seemed somewhat offset after the H1N1 campaign among participants; the slope of the curve being steeper for the time period after the campaign, compared with the before period among campaign participants, while this was not the case among non-participants (Figure 3).

Stratified by sex, the differential change in consultation rate after-versus-before the H1N1 campaign was present for both boys and girls (Table 2). Limiting the analysis to children below 3 years of age or adjusting for travel activity did not alter conclusions (data not shown).

Postponing the entry date one week from the time of vaccination or censoring the first week after a consultation, also did not alter the conclusions (data not shown).

Vitamin A supplementation

When the post-H1N1 observation period was subdivided at the time of the Vitamin A campaign, the differential effect by participation status was stronger after the vitamin A campaign (p=0.01) than before (p=0.93) (Supplementary results, Supplementary Table 1).

Ecological analysis

The rates of consultations were higher between October 14, 2010 and March 25, 2011 than during the same the period in 2009 (Supplementary results, Supplementary Table 2).

DISCUSSION

Main findings

We found an overall decline in consultation rates after versus before the H1N1 campaign, this decline tended to be smaller for the participants than for the non-participants.

Strengths and weaknesses

To our knowledge, this is the first study of the NSEs of an H1N1 influenza vaccine on overall child morbidity. Information was carefully collected at the individual level. Through the Bandim HDSS we could identify and follow both the participants and non-participants before and after the campaign. Only children who were alive at the time of the campaign could enter the analysis. However, mortality among the followed children was very low and rates were similar among participants and non-participants. Hence, the loss to follow-up for this reason is unlikely to explain any differential pattern between the participants and non-participants.

The distribution of background factors indicates that the two groups are heterogeneous. This could bias a direct comparison of participants and non-participants. In our study, we compared the relative changes in consultation rates before and after the H1N1-campaign within the different groups (participants and non-participants), thus avoiding the potentially biased direct comparison of participants and non-participants. We compared consultation rates after the H1N1 campaign to the rates among a similar cohort of children followed the previous year. Compared with the prior year, we found a higher rate of consultations after the campaign for both boys and girls in particular among campaign participants.

Consistencies with previous studies

Few studies have assessed the effect of H1N1 influenza vaccines on overall morbidity or mortality. We recently found that age-adjusted mortality after the H1N1 vaccination campaign was higher among children followed within randomised trials of vaccines and vitamin A in Guinea-Bissau[16]. In Kenya, self-reported respiratory symptoms and days off from work was higher among vaccinated hospital staff than among unvaccinated hospital staff[17] and in a small randomised controlled trial in Hong Kong, children receiving the trivalent inactivated influenza vaccine (including the H1N1 strain) had higher rates of non-influenza respiratory infections[18]. In Japan, no increase in mortality after H1N1 vaccination among patients with idiopathic intestinal pneumonia was observed[19]. The H1N1 vaccine may have reduced the risk of admission with influenza/pneumonia during the pandemic in Canada[20].

Overall, the rates of consultations were lower among the campaign non-participants than participants in both the pre- and post-campaign periods. Lower consultation rates among non-campaign participants have previously been observed[21] and likely reflects differences in health seeking behaviour within the two groups.

Interpretations

Influenza surveillance data from Senegal indicate that H1N1 influenza was circulating at the time of the study[12]. If H1N1 influenza was circulating, vaccinated children less susceptible to H1N1 influenza, would be expected to seek fewer consultations for influenza. If H1N1 vaccine had no NSE, this should have caused a larger decline in rates of consultations among the H1N1 vaccinated children. Since this was not the case, we interpret our findings as a suggestion that the non-live H1N1 vaccine, in likening with other non-live vaccines, may increase susceptibility to other infections. This may be the case for DTP[22], Hepatitis B[23] and inactivated polio vaccine[24], for

241 which overall mortality has been higher in spite of protection against the targeted infections. However, in con-
242 trast to what has been seen for other non-live vaccines, we did not find any indication that a potential negative
243 effect of H1N1 was strongest for girls in the present study.

244 The biological mechanism behind the NSEs are unknown. However, an increasing number of studies have located
245 mechanisms in both the innate and adaptive immune system producing heterologous immunity[5, 25, 26]. Inter-
246 estingly, the non-live trivalent seasonal influenza vaccine was recently compared with the live BCG vaccine for
247 its effects on the innate immune system. The data indicated that trivalent influenza vaccine exerts NSEs, which
248 differed from those observed following BCG vaccination; while BCG exerted an overall immunostimulatory effect.
249 Influenza vaccination was associated with decreased production of among others IFN-gamma and IL-1beta upon
250 stimulation with heterologous pathogens, i.e. "innate tolerance", which could be indicative of negative non-spe-
251 cific effects[27]. Further research in this area is still needed to investigate mechanisms behind NSEs of non-live
252 vaccines.

253 ***Implications***

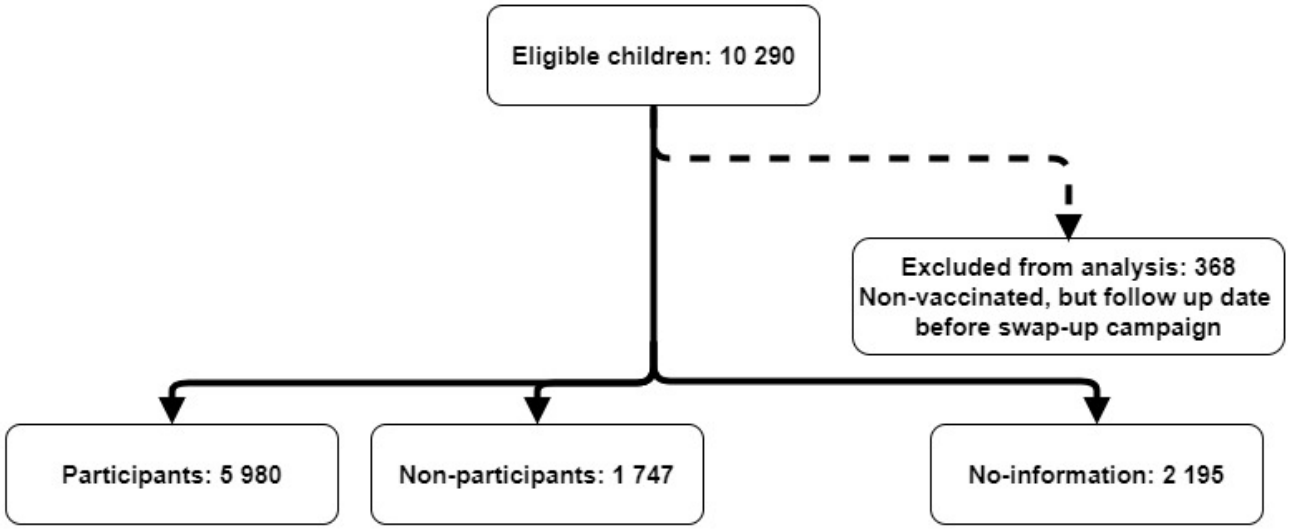
254 NSEs merit further investigations. Vaccines are being distributed with consideration of only their specific targeted
255 effects. Our data do not permit any conclusions on effects in defined high-risk groups. However, in populations
256 experiencing little risk of the targeted infections, the relative importance of the NSEs is large. Administration of
257 influenza vaccines in lower-risk areas and to population groups outside the defined high-risk population groups
258 should therefore be considered carefully and with respect to both targeted and NSEs. Establishing whether the
259 inactivated influenza vaccines have important NSEs requires information on overall health to ensure that a spe-
260 cific protection is not counteracted. For example, in a recent randomised placebo-controlled trial assessing the
261 effect of vaccination in pregnancy, early infant mortality tended to increase in spite of lower rates of influenza
262 in the infants[28].

To investigate the NSEs further, non-live influenza vaccines and the recently developed live seasonal influenza vaccines[29] could be compared head-to-head for their overall effects in randomised trials. It is crucial, that the effect of rolling out new vaccines is carefully assessed. For example, in the recent trials of the RTS,S/AS01 malaria vaccine there was some effect of the vaccine on malaria prevention[30] but in spite of the specific protective effect, vaccination was associated with a significant higher all-cause mortality for girls[9].

CONCLUSION

There was an overall reduction in consultation rates after the H1N1 campaign. However, the H1N1 vaccinated group had a smaller reduction in consultation rates compared with the non-vaccinated group. This could indicate a negative NSE of the H1N1 influenza vaccine and warrants further studies.

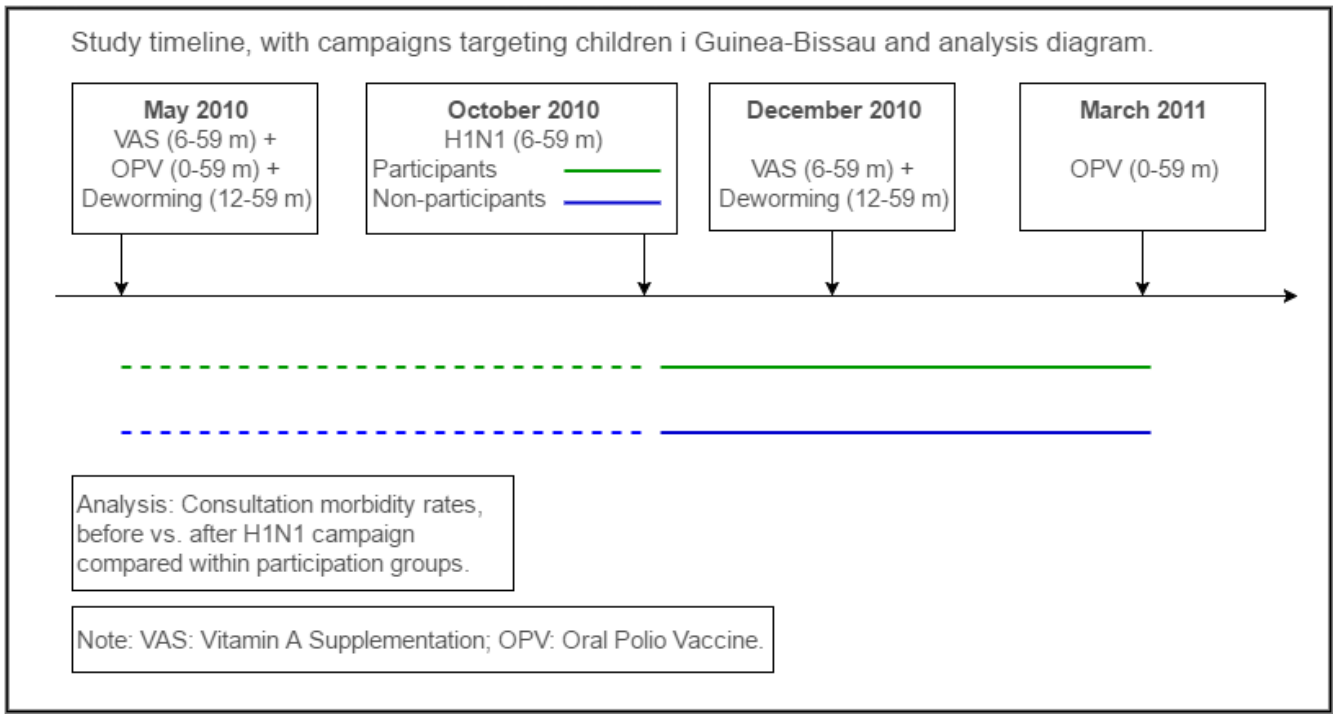
272 **Figure 1: Flowchart of children eligible for study of the effect of H1N1 influenza vaccine on child morbidity in**
273 **Guinea-Bissau.**



274

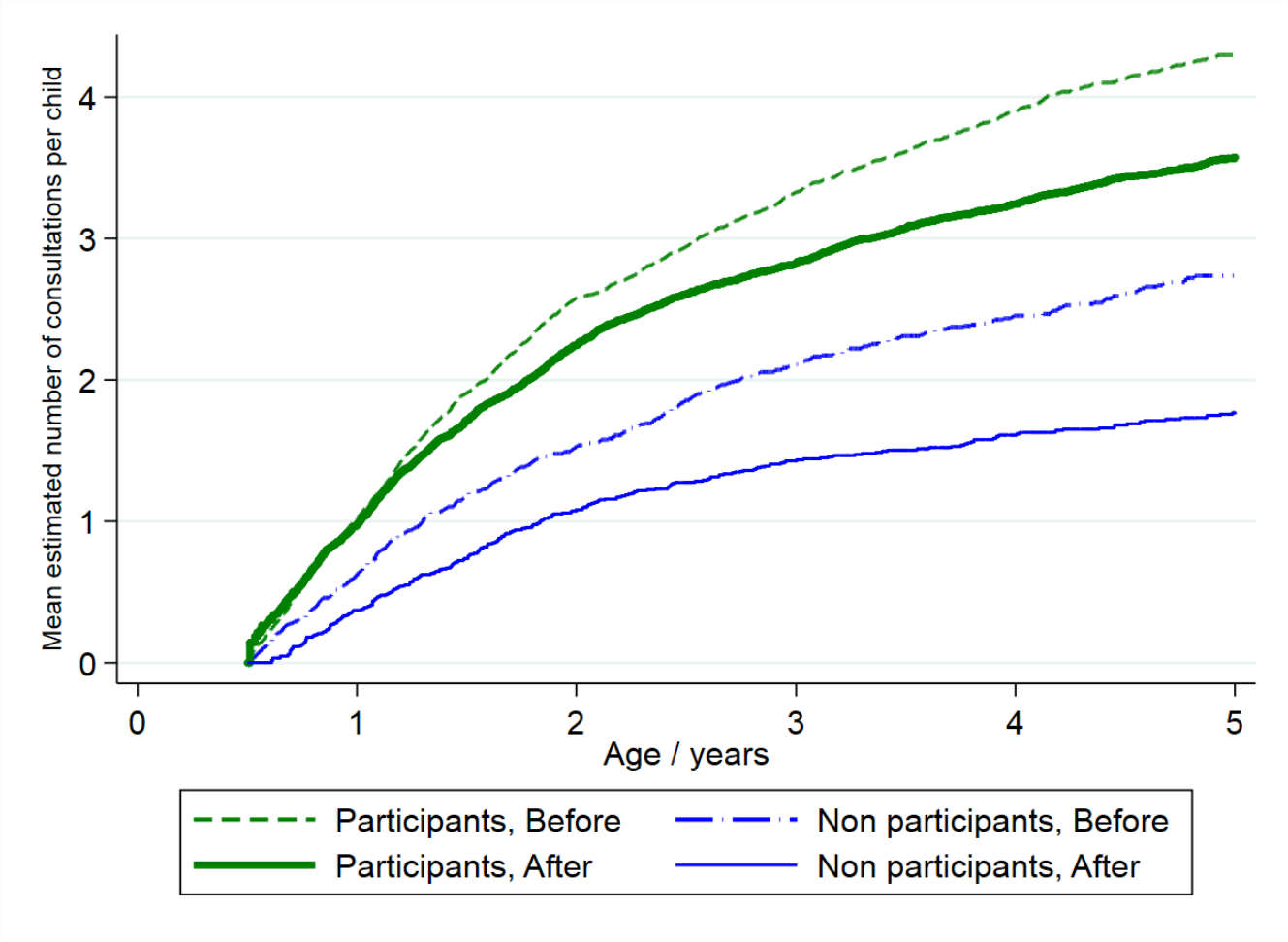
275 **Figure 2: Timeline for study of the effect of H1N1 influenza vaccine on child morbidity in Guinea-Bissau.**

276



277

278 **Figure 3: Cumulative hazard estimates of mean number of consultations per child**



279

280
281 **Table 1: Baseline characteristics among children eligible for the H1N1 vaccination campaign**

	Participants N (%)	Non-participants N (%)	No information N (%)	P for different distribution, all groups	P for different distribution, part. vs. non-part.
Number	5 980 (60)	1 747 (18)	2 195 (22)		
Male	3 036 (51)	881 (50)	1 078 (49)	0.53	0.80
Age*	30.3 [29.9;30.7]	29.9 [29.1;30.6]	30.7 [30.1;31.4]	<0.001	0.27
Most recent routine vaccination at the time of the campaign					
Vaccination card never seen	65 (1)	48 (3)	174 (8)	<0.001	<0.001
Seen card	5 874 (98)	1 692 (97)	1 998 (91)	<0.001	<0.001
BCG[a] ± OPV[b]	73 (1)	73 (4)	123 (6)		
Penta[c]/DTP[d] ± OPV±BCG	1 721 (29)	578 (34)	675 (34)		
OPV	663 (11)	195 (12)	254 (13)		
MV[e]+YF[f]+Penta+OPV+BCG	191 (3)	76 (4)	82 (4)		
YF	199 (3)	40 (2)	30 (2)		
MV+YF+/-OPV	2 982 (51)	689 (41)	778 (39)		
Unvaccinated	151 (3)	96 (6)	253 (13)		
Under 3 years of age	3 718 (62)	1 071 (61)	1 200 (55)	<0.001	<0.001
Most recent routine vaccination at camp among <3years					
BCG ± OPV	65 (2)	64 (6)	103 (9)	<0.001	<0.001
Penta/DTP ± OPV±BCG	1 153 (31)	395 (37)	453 (38)		
OPV	192 (5)	70 (7)	80 (7)		
MV+YF+Penta+OPV+BCG	138 (4)	55 (5)	53 (4)		
YF	75 (2)	14 (1)	7 (1)		
MV+YF+/-OPV	2 068 (56)	449 (42)	474 (40)		
Unvaccinated	27 (1)	24 (2)	30 (3)		
Socioeconomic background factors					
Electricity in the household					
Yes	1 798 (30)	466 (27)	476 (22)	<0.001	0.02
No	4 132 (69)	1 263 (72)	1 692 (77)		
No information	50 (1)	18 (1)	16 (1)		
Toilet					
Inside house	973 (16)	210 (12)	242 (11)	<0.001	<0.001
Outside house	4 954 (83)	1 519 (87)	1 925 (88)		
No information	53 (1)	18 (1)	17 (1)		
Maternal education					
None	1 327 (22)	584 (33)	785 (36)	<0.001	<0.001
1-4 years	840 (14)	237 (14)	311 (14)		

5+ years	3 567 (60)	794 (45)	894 (41)		
No information	246 (4)	132 (8)	194 (9)		
Type of roof					
Straw	167 (3)	58 (3)	67 (3)	0.54	0.29
Hard	5 767 (96)	1 671 (96)	2 102 (96)		
No information	46 (1)	18 (1)	15 (1)		
Ethnic group					
Pepel	1 888 (32)	508 (29)	548 (25)	<0.001	<0.001
Fula/Mandinga	1 255 (21)	615 (35)	788 (36)		
Manjaco/Mancanha	1 217 (20)	239 (14)	315 (14)		
Other	1 572 (26)	370 (21)	516 (24)		
No information	48 (1)	15 (1)	17 (1)		
Area of residence					
Bandim	2 614 (44)	855 (49)	1 059 (48)	<0.001	<0.001
Belem & Mindara	970 (16)	192 (11)	348 (16)		
Cuntum	2 396 (40)	700 (40)	777 (36)		

*Age on Oct. 14, 2010 in months, with upper and lower quartile range.

[a]BCG: Bacillus Calmette-Guérin

[b]OPV: Oral Polio Vaccine

[c]Penta: Diphtheria, pertussis, tetanus, hepatitis B and Haemophilus influenza type B (Hib)

[d]DTP: Diphtheria, Tetanus, and Pertussis

[e]MV: Measles vaccine

[f]YF: Yellow fever Vaccine

290 **Table 2: Consultation rates among children aged 6-59 months before and after the H1N1 vaccination campaign**
291 **in urban Guinea-Bissau.**

292

All	Before[a] H1N1 rate; /100 PYRS (no of cons./ PYRS)	After[b] H1N1 rate; /100 PYRS (no of cons./ PYRS)	Crude HR [CI] (after/before)	P-value for interaction	Adjusted[c] HR [CI] (after/before)	P-value for interaction
Campaign participants	106.3 (2 211/2 081)	77.7 (1 770/2 279)	0.80 [0.75:0.86]	0.06	0.80 [0.75:0.85]	0.05
Non-participants	68.0 (405/596)	42.8 (266/622)	0.68 [0.58:0.79]		0.67 [0.58:0.79]	
Girls						
Campaign participants	104.2 (1 064/1 021)	74.9 (841/1 122)	0.78 [0.71:0.86]	0.24	0.79 [0.72:0.86]	0.19
Non-participants	66.7 (198/297)	41.7 (128/307)	0.68 [0.54:0.85]		0.66 [0.53:0.84]	
Boys						
Campaign participants	108.2 (1 147/1 060)	80.3 (929/1 156)	0.82 [0.75:0.89]	0.13	0.81 [0.74:0.88]	0.13
Non-participants	69.3 (207/299)	43.8 (138/315)	0.68 [0.55:0.85]		0.68 [0.55:0.84]	

293

[a] Before: Refers to the time from the child enters the analysis; whichever comes first of May 31, 2010, the age of 6 months or registration of the child.
[b] After: Refers to the time from the H1N1 vaccination campaign until the child becomes 5 years of age, moves or dies or the March 25, 2011, whichever comes first.
[c] Adjusted for season, ethnic group and mothers schooling.

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