Tropical Medicine and International Health doi:10.1111/tmi.12889

VOLUME 22 NO 7 PP 846–856 JULY 2017

Seasonal variation in child mortality in rural Guinea-Bissau

Bibi Uhre Nielsen[1,2], Stine Byberg[1,2,3], Peter Aaby[1,2], Amabelia Rodrigues[1], Christine Stabell Benn[1,2,3] and Ane Bærent Fisker[1,2,3]

1 *Bandim Health Project, INDEPTH Network, Bissau, Guinea-Bissau*
2 *Research Center for Vitamins and Vaccines, Bandim Health Project, Statens Serum Institut, Copenhagen, Denmark*
3 *OPEN, Institute of Clinical Research, University of Southern Denmark/Odense University Hospital, Odense, Denmark*

Abstract

OBJECTIVES In many African countries, child mortality is higher in the rainy season than in the dry season. We investigated the effect of season on child mortality by time periods, sex and age in rural Guinea-Bissau.

METHODS Bandim health project follows children under-five in a health and demographic surveillance system in rural Guinea-Bissau. We compared the mortality in the rainy season (June to November) between 1990 and 2013 with the mortality in the dry season (December to May) in Cox proportional hazards models providing rainy *vs*. dry season mortality rate ratios (r/d-mrr). Seasonal effects were estimated in strata defined by time periods with different frequency of vaccination campaigns, sex and age (<1 month, 1–11 months, 12–59 months). Verbal autopsies were interpreted using InterVa-4 software.

RESULTS From 1990 to 2013, overall mortality was declined by almost two-thirds among 81 292 children (10 588 deaths). Mortality was 51% (95% ci: 45–58%) higher in the rainy season than in the dry season throughout the study period. The seasonal difference increased significantly with age, the r/d-mrr being 0.94 (0.86–1.03) among neonates, 1.57 (1.46–1.69) in post-neonatal infants and 1.83 (1.72–1.95) in under-five children (*P* for same effect <0.001). According to the InterVa, malaria deaths were the main reason for the seasonal mortality difference, causing 50% of all deaths in the rainy season, but only if the InterVa included season of death, making the argument self-confirmatory.

CONCLUSION The mortality declined throughout the study, yet rainy season continued to be associated with 51% higher overall mortality.

keywords child mortality, seasons, Guinea-Bissau, cause of death, sex, age groups

Introduction

The 4th Millennium Development Goal aimed to reduce under-five child mortality by two-thirds between 1990 and 2015. In 2015, the decline had only reached 53% [1]. Many countries, especially in Africa, still witness very high child mortality levels. Guinea-Bissau in West Africa is one of these countries with the fifth-highest infant mortality in the world [2].

A seasonal pattern in mortality has been observed in neighbouring countries to Guinea-Bissau [3, 4]. In urban Guinea-Bissau from 1991 to 1996, child mortality was 15% (4–28%) higher during the rainy season (June to November) than in the dry season (December to May) [5], possibly due to seasonal fluctuations in the load of infectious pathogens [6–9]. Presumably, the proportion of season-dependent causes of death could differ in rural and urban areas. Thus, the seasonal difference in mortality in rural areas might vary from urban areas.

In recent years, child health interventions such as oral polio vaccine (OPV), vitamin A supplementation (VAS) and measles vaccination campaigns have been provided in Guinea-Bissau. The protective effect of VAS against mortality seems to be stronger when VAS is administered during the dry season [10, 11]; the same pattern has been observed for measles vaccine [12]. The frequency of OPV and/or VAS campaigns has increased over time: there were no regular campaigns prior to February 1998, annual campaigns from February 1998 to October 2005 and biannual campaigns since November 2005. Measles vaccination campaigns have been conducted every 3 years since 2006 [13].

The aims of this observational study were to describe the seasonal variation in under-five child mortality by

time period, sex and age group in rural Guinea-Bissau from 1990 to 2013 and to compare the major causes of death in the rainy season and the dry season.

Methods

Setting

Since 1990, Bandim health project (BHP) has maintained a longitudinal health and demographic surveillance system (HDSS) in the rural areas of Guinea-Bissau. Initially surveillance covered five regions with a total of 100 village clusters, 20 clusters selected in each region using the methodology for the Expanded Programme on Immunization surveys [14]. Each cluster comprised of 100 women of fertile age and their children. In 2006, surveillance was expanded to include 182 clusters in 10 regions. Visits were conducted biannually by mobile teams throughout the study.

Children are under surveillance from the date of registration, preferably before birth, until their fifth birthday if they continue to stay in the study area. Pregnancies, births, deaths and migrations are registered at every visit. All children under surveillance who die or migrate out of the study area have a date of death or date of migration registered. Since 2005, a simple verbal autopsy (VA) interview has been conducted with relatives for every deceased child. Based on closed questions and open narrative, the VA interview is performed by field assistants and collects information on symptoms and events in the period leading up to the death of the child.

Study population

All live-born children followed in the HDSS between 01.01.1990 and 31.12.2013 were included in this study. Children contributed time at risk from the latest of either date of birth or date of registration until their fifth birthday, date of migration, date of death or 31.12.2013, whichever came first. The time at risk was split into rainy season (1st of June–30th of November) and dry season (1st of December–31st of May) to compute the mortality rates (MR) for both seasons.

Statistical analyses

Mortality by season. Mortality rate ratios (MRR) for the rainy season *vs.* the dry season were estimated in Cox regression models using age as underlying timescale. The analyses were stratified by time periods (no regular campaigns (01.01.1990–01.02.1998), annual campaigns (02.02.1998–18.11.2005) and biannual campaigns (19.11.2005–31.12.2013)) (see overview of child health interventions in Table S1). The analyses were additionally stratified by sex and age groups: neonates (0–28 days), post-neonatal infants (1–11 months) and older children (1–4 years).

Estimates are presented crude and adjusted for birth year (categorised into 5-year periods) and sex. All MRRs were estimated in models stratified by village clusters. Estimates are presented for both the 100 original clusters (main text) and for all the clusters (Appendix S1), as 82 clusters were only surveyed from 2006. In additional analyses, the effect of season was estimated in each region. To investigate potential bias, sensitivity analyses were executed by omitting children registered after birth and 27 villages where more than 300 days passed between two successive visits.

Verbal autopsies. VAs were interpreted using the computer program InterVA version 4.RC1 (www.interva.net; Umeå University) to derive causes of death (Appendix S1). As part of the required *a priori* probabilities, the malaria prevalence was set to be high [15], and the HIV prevalence was set to be low [16, 17]. A child was assigned up to three causes of death each with a likelihood score (between 0 and 1) [18] and an indeterminate cause for the residual fraction [19, 20]. Likelihood scores related to a particular cause of death were then added within strata defined by either season or season plus age to determine the proportions within the strata. Additional InterVA analyses were performed by leaving out the season variables in the InterVA analyses to clarify how season of death influenced the cause of death estimations. The malaria transmission pattern in urban Guinea-Bissau has previously been reported to change from an endemic pattern to an epidemic pattern near 2011 [21]. We therefore also conducted InterVA analyses separately for deaths between 2005 and 2010 and for deaths between 2011 and 2013, to investigate whether the proportions of the causes of deaths changed over time. All analyses were performed in STATA version 12 (StataCorp, College Station, TX).

Ethical considerations

The study does not include biologically or physically invasive or potentially dangerous procedures. The collection of data by the mobile teams has been going on for 23 years at the request of the Ministry of Health.

Results

A total of 62 436 live-born children were included from the original clusters; among these children, there were

9670 deaths during 185 697 person-years (pyrs). If we included all clusters, there were 81 292 children and 10 588 deaths during 233 011 pyrs.

Seasonal effects overall and by time period

There was a marked decline in mortality over the three time periods, particularly from the second to the third: the rainy season MR was 97 deaths per 1000 pyrs in the first period (01.01.1990–01.02.1998), then declined to 72 in the second period (02.02.1998–18.11.2005) and to 36 in the third (19.11.2005–31.12.2013). Likewise, in the dry season, the initial MR was 66, then declined to 51 in the second period and to 25 in the third (Table 1).

In the original clusters, the overall MRR for rainy *vs.* dry season remained similar over years; with the adjusted MRRs being 1.54 (95% CI: 1.43–1.66), 1.47 (1.38–1.57) and 1.50 (1.38–1.62) in the three periods ($P = 0.64$ for interaction between season and time period) (Table 1). The overall adjusted MRR for the rainy *vs.* the dry season was 1.51 (1.45–1.58). If the analysis was extended to include all clusters, the absolute mortality was slightly lower, but the relative difference between the rainy and dry season was unchanged (Table S2).

Seasonal effects by sex

The mortality among boys was higher than among girls in both seasons. Comparing the rainy season mortality with dry season mortality for boys showed an adjusted MRR of 1.45 (95% CI: 1.37–1.53), while the effect was stronger for girls adjusted MRR: 1.59 (1.50–1.69) ($P = 0.02$ for interaction between season and sex) (Table 1). The sex-differential effect of season was unchanged if the analysis was extended to include all clusters (Table S2).

The seasonal difference between the two sexes was especially pronounced for older children (1–4 years): the MRR for girls was 1.97 (95% CI: 1.80–2.15); which differed significantly from that in boys (MRR: 1.72 (1.58–1.87)) ($P = 0.03$ for interaction between season and sex after infancy) (Table 2).

Seasonal effects in age groups

The adjusted MRR for the rainy *vs.* the dry season among neonates was 0.94 (95% CI: 0.86–1.03). For both post-neonatal infants and older children (1–4 years), the rainy season was associated with an increase in mortality. Post-neonatal infants had an adjusted MRR of 1.57 (95% CI: 1.46–1.69), while older children had an MRR of 1.83 (95% CI: 1.72–1.95) ($P < 0.001$ for same effect of rainy season in the three age groups) (Table 1). The excess mortality in the rainy season was similar for children aged 1–2 years (1.82 (1.69–1.95)) and children aged 3–4 years (1.86 (1.65–2.11)) (Data not shown).

Robustness of the results

The results were similar when all clusters were included (Table S2 and S3) and not affected by excluding children registered after birth or 27 villages, which could only be visited once per year (data not shown). Although the effect of season differed significantly between regions ($P = 0.005$), the rainy season mortality was higher than the dry season mortality in all regions. The seasonal difference in mortality was strongest in the two eastern regions due to a stronger effect of season among the oldest children (Table S4).

Causes of deaths

Interviews on cause of death were conducted for 85% (3270/3840) of the deaths since 2005. The median time between the date of death and the date of interview was 95 days. 70% (2335/3270) of the deaths occurred at home; only 23% (753/3273) occurred at health facilities. The remaining 6% occurred elsewhere (e.g. on the way to the hospital or on a journey) or location of death was unknown. None of these parameters differed by season of death overall (Table S5) or by region (data not shown).

The verbal autopsies suggested that among the main causes of death, malaria varied the most between seasons. The proportion of malaria deaths was much higher in the rainy season (50%) than in the dry season (19%) (Figure 1). In contrast, the proportions of deaths due to diarrhoea, respiratory infections and the proportion of the indeterminate causes of death were higher in the dry season (Figure 1). Malnutrition was rare (<6%) in all age groups (Figure 2).

According to the InterVA, seasonal differences in cause of death were limited to the post-neonatal period (Figure S2). If the season of death was not provided as an input in the InterVA analyses, the seasonal difference between the causes of death was greatly reduced (Figure 3). In this situation, around 60% of all deceased children aged 1–4 years were estimated to be caused by malaria in both rainy season and dry season. Although the distribution of cause of death did not differ between 2005–2010 and 2011–2013 (Figure S1), the mortality rate for older children (1–4 years) continued to fall between 2005 and 2010 and between 2011 and 2013 (data not shown).

Table 1 Rainy *vs.* dry season mortality by time period, sex and age in the 100 original clusters followed in rural Guinea-Bissau 1990–2013††

	Rainy			Dry			Crude mortality rate ratio (95% CI)†	Test for interaction, *P*-value	Adjusted MRR (95% CI)†‡§	Test for interaction, *P*-value
	n	MR¶ (95% CI)	Deaths/pyrs	*n*	MR¶ (95% CI)	Deaths/pyrs				
Time period										
01 January 1990–01 February 1998	16 159	97 (93–101)	1842/19 016	16 585	66 (62–70)	1210/18 309	1.54 (1.43–1.65)	0.62	1.54 (1.43–1.66)	0.64
02 February 1998–18 November 2005	27 919	72 (70–75)	2483/34 335	27 801	51 (48–53)	1662/32 751	1.47 (1.38–1.56)		1.47 (1.38–1.57)	
19 November 2005–31 December 2013	32 599	36 (34–38)	1449/40 666	32 836	25 (24–27)	1024/40 621	1.48 (1.36–1.60)		1.50 (1.38–1.62)	
Sex§										
Boys	29 820	61 (60–63)	2984/47 443	30 007	45 (44–47)	2098/46 206	1.44 (1.37–1.53)	0.03	1.45 (1.37–1.53)	0.02
Girls	30 343	60 (57–62)	2773/46 560	30 487	39 (37–41)	1772/45 464	1.59 (1.49–1.68)		1.59 (1.50–1.69)	
Age										
0–28 days	21 941	627 (587–670)	880/1403	25 881	658 (620–698)	1096/1666	0.95 (0.87–1.04)	0.001	0.94 (0.86–1.03)	0.001
1–11 months	49 281	96 (92–100)	1987/20 739	49 288	62 (59–66)	1218/19 569	1.56 (1.45–1.68)		1.57 (1.46–1.69)	
1–4 years	51 814	40 (39–42)	2907/71 875	52 055	22 (21–24)	1582/70 446	1.82 (1.71–1.93)		1.83 (1.72–1.95)	

n, Number of children in each stratum. Most children contribute time at risk in both seasons, many in two time periods and in more than one age group.
†Estimated in a Cox model stratified by village cluster. Furthermore adjusted for age, as age was underlying timescale.
‡Furthermore adjusted for birth year (5-year periods) and sex.
§75 children with an unknown sex were excluded in the analyses.
¶Mortality rate per 1000 person-years.
††Overall adjusted MRR: 1.50 (1.44–1.57).

Table 2 Rainy *vs.* dry season mortality; interactions between age groups and sex and age group and time period in the 100 original clusters followed in rural Guinea-Bissau 1990–2013

	Rainy			Dry			Crude mortality rate ratio (95% CI)†	Test for interaction, *P*-value	Adjusted MRR (95%CI)†‡§	Test for interaction, *P*-value
	n	MR¶ (95% CI)	Deaths/pyrs	*n*	MR¶ (95% CI)	Deaths/pyrs				
Age & sex§										
0–28 days										
Boys	10 998	741 (680–808)	517/698	13 059	751 (695–812)	628/836	0.98 (0.87–1.10)	0.53	0.96 (0.85–1.08)	0.68
Girls	10 907	501 (451–556)	352/703	12 784	539 (492–592)	447/829	0.92 (0.80–1.06)		0.92 (0.80–1.06)	
1–11 months										
Boys	24 579	98 (92–104)	1011/10 361	24 616	64 (59–69)	623/9746	1.55 (1.40–1.71)	0.82	1.56 (1.41–1.72)	0.83
Girls	24 671	94 (88–100)	970/10 372	24 648	60 (55–65)	590/9818	1.58 (1.42–1.75)		1.59 (1.43–1.76)	
1–4 years										
Boys	25 499	40 (38–42)	1456/36 385	25 631	24 (22–25)	847/35 624	1.70 (1.56–1.85)	0.03	1.72 (1.58–1.87)	0.03
Girls	26 310	41 (39–43)	1451/35 485	26 418	21 (20–23)	735/34 818	1.95 (1.78–2.13)		1.97 (1.80–2.15)	
0–28 days										
01 January 1990–01 February 1998	7034	779 (702–865)	353/453	8063	746 (675–824)	390/523	1.03 (0.89–1.19)	0.17	1.03 (0.89–1.19)	0.18
02 February 1998–18 November 2005	6968	640 (570–720)	283/442	8103	662 (595–737)	338/510	0.95 (0.81–1.12)		0.95 (0.81–1.11)	
19 November 2005–31 December 2013	8061	481 (424–545)	244/508	9862	582 (525–644)	368/632	0.84 (0.71–0.98)		0.84 (0.71–0.99)	
1–11 months										
01 January 1990–01 February 1998	13 288	134 (125–144)	743/5548	13 562	78 (71–86)	413/5294	1.74 (1.54–1.96)	0.03	1.74 (1.54–1.96)	0.04
02 February 1998–18 November 2005	17 367	119 (111–127)	834/7005	17 207	86 (79–93)	546/6369	1.40 (1.26–1.56)		1.41 (1.26–1.57)	
19 November 2005–31 December 2013	21 071	50 (45–55)	410/8186	21 165	33 (29–37)	259/7906	1.56 (1.33–1.82)		1.58 (1.35–1.84)	
1–4 years										
01 January 1990–01 February 1998	12 183	57 (53–62)	746/13 015	12 597	33 (30–36)	407/12 492	1.59 (1.44–1.75)	0.07	1.77 (1.56–1.99)	0.05
02 February 1998–18 November 2005	23 924	51 (48–54)	1366/26 888	23 748	30 (28–32)	778/25 872	1.72 (1.59–1.87)		1.72 (1.57–1.88)	
19 November 2005–31 December 2013	28 404	25 (23–27)	795/31 972	28 635	12 (11–14)	397/32 082	1.96 (1.80–2.13)		2.06 (1.82–2.32)	

n, Number of children in each stratum. Most children contribute time at risk in both seasons, many in two time periods and in more than one age group.
†Estimated in a Cox model stratified by village cluster. Furthermore adjusted for age, as age was underlying timescale.
‡Furthermore adjusted for birth year (5-year periods) and sex.
§75 children with an unknown sex were excluded in the analyses.
¶Mortality rate per 1000 person-years.

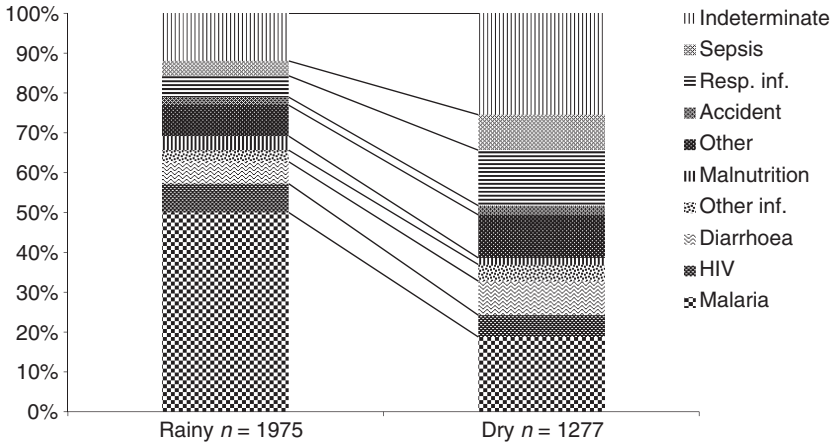

Figure 1 Causes of death by season since 2005 (Classified by InterVA). Information on season of death was included in the InterVA analyses. 18 children with a verbal autopsy consisting of insufficient information were excluded by the program.

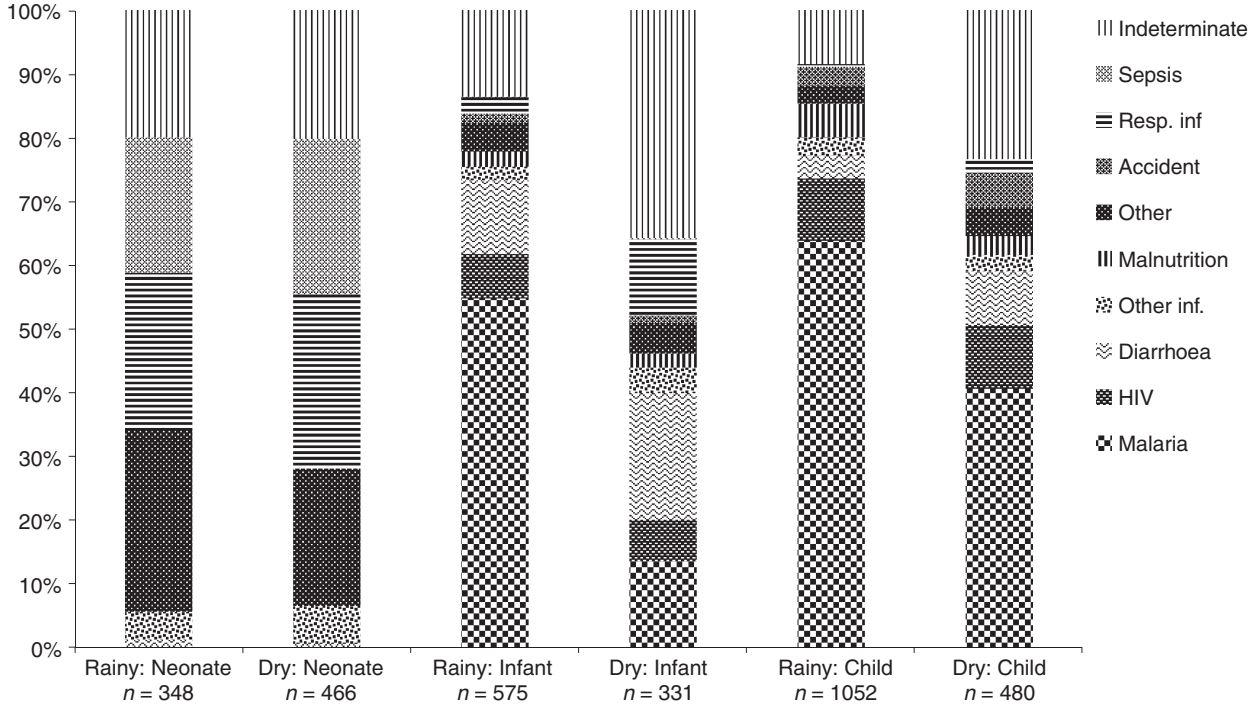

Figure 2 Causes of death by age and season since 2005 (Classified by InterVA). Information on season of death was included in the InterVA analyses. 18 children with a verbal autopsy consisting of insufficient information were excluded by the program.

Discussion

Main findings

During the study period (1990–2013), the mortality rates in the BHP study area of rural Guinea-Bissau declined by almost two-thirds in both seasons. The decline was predominantly seen between the second period (02.02.1998–18.11.2005) and third period (19.11.2005–31.12.2013). The mortality rate was 51% higher in the rainy season than in the dry season throughout. The effect of season was most pronounced in girls and in children aged 1–4 years. 50% of deaths in the rainy season were classified to be due to malaria *vs.* 19% in the dry season, but these figures were

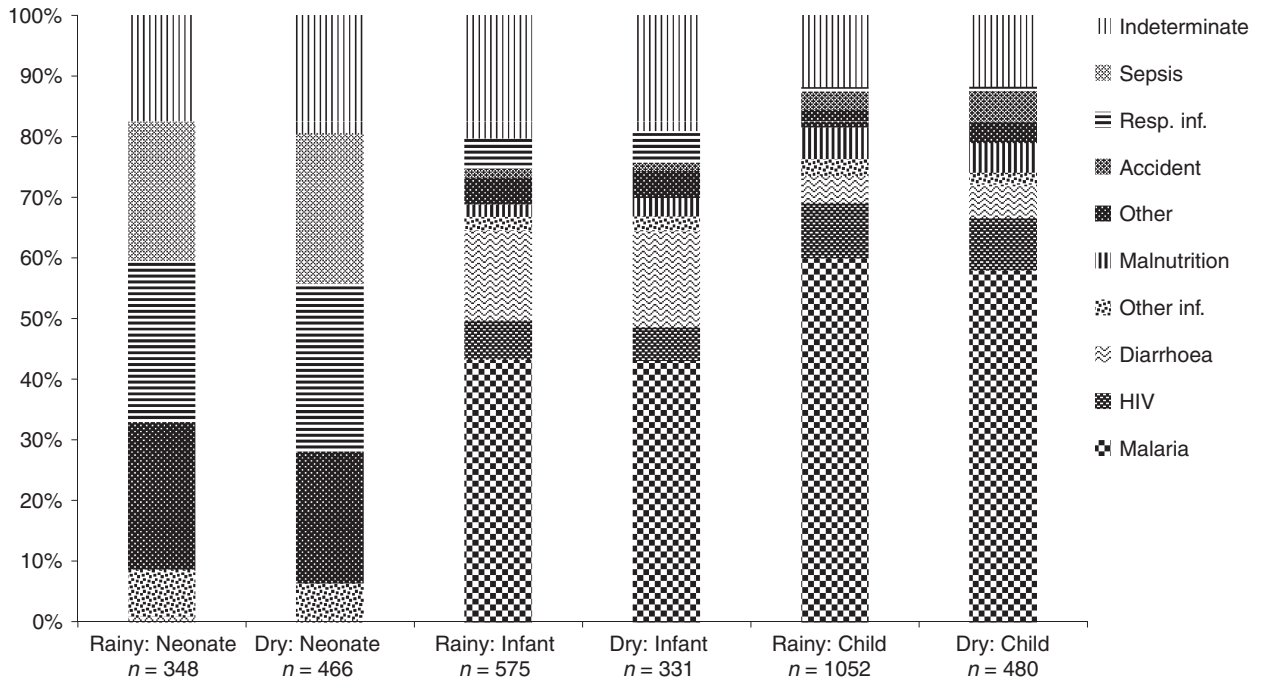

Figure 3 Causes of death by age processed without season since 2005 (Classified by InterVA). Information on season of death was excluded in the InterVA analyses. 18 children with a verbal autopsy consisting of insufficient information were excluded by the program.

highly dependent on the assumptions fed into the InterVA program.

Strengths and weaknesses

Data were collected in randomly selected village clusters all over Guinea-Bissau. The number of children surveyed and included in this study exceeded 80 000 making it one of the largest studies on seasonal mortality. Season as exposure is a fixed determinant as the timing and the amount of precipitation have not changed over the years [21]. The information on a child's vital status is virtually always possible to obtain by asking relatives or neighbours in a village [22]. However, due to the nature of the data collection, there may have been some misclassification of deaths by season.

The information on deaths was based on follow-up of already registered children and pregnancies; therefore, the risk of missing a death was minimised. However, the registration may have been slightly less effective in the rainy season because a few villages experienced flooded roads and were inaccessible. There are indeed slightly fewer person-years in the rainy season than the dry season for the neonatal age group. However, the rates should not be affected by this, and excluding children registered after birth and children registered in villages, which could not be visited during the rainy season, did not change the results.

The verbal autopsies may be subject to recall bias and the *a priori* probabilities for the different causes of death encoded in the InterVA may not be representative of rural Guinea-Bissau. Nevertheless, it has been shown that the *a priori* probabilities could significantly be changed internally in the InterVA program with no consequence for the composition of the causes of death in the population [23]. Thus, the causes of death estimated by the program are deemed reliable, even though the *a priori* probabilities in the program are not identical to the *a priori* probabilities in Guinea-Bissau.

Consistency with previous studies

A systematic review of several studies from Africa demonstrated that rainy season was associated with higher all-cause child mortality. This was observed in the Gambia, Senegal, Ghana, Nigeria, Kenya, Tanzania and Burkina Faso [24].

Seasonal differences of mortality have previously been described by using 50 years of surveillance data from neighbouring rural Gambia [4]. The findings corroborate our study, with higher mortality for post-neonatal infants

(odds: 1.53) and for children aged 1–4 years (odd: 2.59). Furthermore, there was also a trend towards seasonal difference in mortality being more pronounced for girls than for boys [4].

A generally higher mortality in the rainy season was found to be due to higher incidence of malaria, malnutrition, septicaemia, respiratory infections and diarrhoea in the rainy season in other African countries [25, 26]. In the present study, we also identified malaria as the predominant cause of death in the rainy season, but respiratory infections and diarrhoea were mainly causes of death in the dry season. This was similar to a study from Burkina Faso, which also used InterVA [19].

The proportion of deaths due to malaria in our study seemed to be similar to an older study from Burkina Faso, where malaria caused 52% of all the deaths in under-five children in the rainy season and 35% in the dry season [25]. This is surprisingly high as the prevalence of malaria has decreased in recent years throughout Africa [27, 28]. The malaria incidence in urban Guinea-Bissau changed around 2011 from an endemic pattern to an epidemic pattern with peaks in October-November and with almost no cases during the rest of the year for children below 15 years [21]. It seems likely that a similar change in the malaria incidence also occurred concurrently in rural Guinea-Bissau. However, when separate VA analyses were performed for the two periods 2005–2010 and 2011–2013, there was no indication of a similar time-related change in the proportion of deaths due to malaria (Figure S1). Also, the seasonal difference of the malaria proportions disappeared when the season of death was left out from the InterVA input; this indicates that the malaria classification in InterVA is strongly dependent on season of death. Thus the InterVA may have overestimated the proportion of malaria deaths, and our finding of a very high proportion of malaria deaths in the rainy season should be interpreted with great caution.

Interpretation

Fluctuations in pathogen load, malnutrition and contamination of water supplies have been the most frequent explanations for higher mortality in the rainy season [29–31]. In addition to different pathogen loads, season may also affect the immune system indirectly. Prior studies from Guinea-Bissau have found a smaller thymus size [32] and a lower CD4+/CD8+ T-lymphocytes ratio in the rainy season [33]. A study from The Gambia showed higher levels of lymphocytes, monocytes and platelets in the rainy season [34]. These effects may in themselves be disadvantageous in relation to mortality [32].

We found a significantly stronger effect of season for girls than for boys from 1 to 4 years, although girls have a lower mortality in both seasons. It could be speculated that the higher MRR for the rainy *vs*. the dry season among girls (1–4 years) is a product of sex-differential susceptibility to diseases with different seasonal patterns. If boys are more susceptible to death by diseases prevalent in the dry season, that may explain why the difference was less pronounced for boys than for girls. Data suggest that boys are more often admitted with pneumonia, also in areas with no sex-differential treatment [35], which could lend some support to this explanation. However, the causes of the sex-differential seasonal mortality patterns need to be further explored.

There was a tendency towards an increasing adverse effect of rainy season during the study for children 1–4 years. A worldwide study based on vital registration data and verbal autopsies assigned the worldwide decline in mortality mainly to a reduction in pneumonia and diarrhoea and less to a reduction in malaria as the cause of death among post-neonatal children [28]. Assuming that these mortality changes were the same in rural Guinea-Bissau, the reduction in pneumonia and diarrhoea would have been predominant in the dry season and the minor reduction in malaria would have been predominant in the rainy season. Thus, the relative difference between the reductions in the causes of death would have increased the adverse effect of the rainy season among post-neonatal children. The VA reaching back to 2005 cannot substantiate a general decrease in pneumonia and diarrhoea as there was no difference between 2005–2010 and 2011–2013. However, we cannot rule out that such a change may have occurred prior to 2005.

In rural areas, the distance to health centres is often a challenge; lack of money to pay for transportation and flooded roads might complicate the situation further [36–38]. However, the place of death did not differ by season in our study. Nor did place of death vary by season when stratified by region, and does therefore not explain the stronger effect of season in the east of the country.

The decline in mortality over time periods was marked. In prior publications, we have found mortality reducing effects of the OPV (unpublished data), and measles vaccination campaigns [39]. The coverage of the campaigns is estimated to be higher than 80% in the capital (unpublished data). In the rural areas, we would assume similar high coverage, as the campaigns are conducted with outreach to the villages. Based on a prior study [39], we speculate that vaccination campaigns may have been some of the drivers of the fall in mortality. Previous studies have also reported that interventions have marked sex-differential effects; for example, measles vaccination

and measles campaigns have had the strongest beneficial for girls [12, 13, 39], and OPV campaigns have had a stronger beneficial effect for boys [39]. Although sex-differential effects on childhood interventions could contribute to the sex difference in mortality, it is beyond this study to draw any firm conclusions on the contribution hereof.

It is likely that other factors in rural Guinea-Bissau generated the decline in child mortality, such as an increase in malaria preventive measures [21]. Overall, the broad diversity of health interventions in Guinea-Bissau supports that many causes of death have been reduced simultaneously. Economical and educational improvements are also known to reduce child mortality [41, 42]. A global study from 1990 to 2013 has estimated the effect of socioeconomic factors on the under-five child mortality to be a 1.6% mortality reduction per 10% increase in income per person and an 8.5% mortality reduction per year increase in maternal schooling [43]. However, the increase in maternal schooling has been limited in rural Guinea-Bissau. Among women giving birth in 1992–1993, 87% had not attended school, and in 2002–2003, this percentage was still 85% [44]. Nevertheless, there has been little measurable improvement in the health care system, and during the same period, there has been no decline in mortality of women of fertile age [46]; hence, the explanation may be sought among interventions selectively affecting young children.

Implications

In conclusion, rainy season remains an important risk factor for post-neonatal infant and child mortality in Guinea-Bissau. Seasonal variations in infectious diseases may constitute a great part of the explanation.

According to the VAs, a great proportion of the deaths mainly in the rainy season are due to malaria. Although the incidence of malaria may be overestimated, interventions targeting malaria may still be important. Data from urban Guinea-Bissau indicate that long-lasting insecticide-treated bed nets (LLIN) may be the most efficient malaria prophylaxis [21] with a payable cost [45], and distributing LLINs has been a priority also in rural Guinea-Bissau [46]. Furthermore, availability of rapid tests and treatment at local health centres may have the potential to lower mortality.

The VAs indicate that diarrhoea is a common cause of death in rural Guinea-Bissau. Diarrhoea is partly preventable and also treatable in remote areas by using rehydration. Thus, attempts to communicate how to prevent diarrhoea (in the radio [47]) and access to rehydration in rural Guinea-Bissau could be cheap life-saving interventions. Making the interventions available in the health system does however not make any difference if the heath facilities are not sought. Less than a quarter of the deaths occurred in a health facility, and efforts to increase the access to and use of the health system may also be indicated.

While better availability of treatment for ill children may lower mortality in both the rainy season and the dry season, there may also be something to gain by optimising the timing of preventive health interventions and by improving the understanding of how they may affect boys and girls differently. Previous results have indicated that, for example VAS and measles vaccination campaigns may be more efficient if provided during the dry season. More research on seasonal differences in childhood interventions and on their potential sex-differential effects is encouraged.

Acknowledgements

The work was funded by Danielsen Fonden (9683-1100), DANIDA (104.Dan.8-920), European Union FP7 Support for OPTIMUNISE (Health-F3-2011-261375) and the Danish National Research Foundation (DNRF-107).

References

1. UNICEF. Levels & Trends in Child Mortality 2015. (Available from: http://www.childmortality.org/files_v20/download/IGME%20report%202015%20child%20mortality%20final.pdf: 2015). Report no. [17 June 2016]
2. CIA. The World Factbook 2014. (Available from: https://www.cia.gov/library/publications/the-world-factbook/rankorder/2091rank.html) [18 Jul 2016]
3. Delaunay V, Etard JF, Preziosi MP, Marra A, Simondon F. Decline of infant and child mortality rates in rural Senegal over a 37-year period (1963–1999). *Int J Epidemiol* 2001: **30**: 1286–1293; discussion 94–95.
4. Rayco-Solon P, Moore SE, Fulford AJ, Prentice AM. Fifty-year mortality trends in three rural African villages. *Trop Med Int Health* 2004: **9**: 1151–1160.
5. Veirum JE, Biai S, Jakobsen M *et al.* Persisting high hospital and community childhood mortality in an urban setting in Guinea-Bissau. *Acta Paediatr* 2007: **96**: 1526–1530.
6. Fischer TK, Valentiner-Branth P, Steinsland H *et al.* Protective immunity after natural rotavirus infection: a community cohort study of newborn children in Guinea-Bissau, west Africa. *J Infect Dis* 2002: **186**: 593–597.
7. Perch M, Sodemann M, Jakobsen MS *et al.* Seven years' experience with *Cryptosporidium parvum* in Guinea-Bissau, West Africa. *Ann Trop Paediatr* 2001: **21**: 313–318.
8. Jaenson TG, Gomes MJ, Barreto dos Santos RC *et al.* Control of endophagic Anopheles mosquitoes and human

malaria in Guinea Bissau, West Africa by permethrin-treated bed nets. *Trans R Soc Trop Med Hyg* 1994: **88**: 620–624.
9. Dowell SF, Whitney CG, Wright C, Rose CE Jr, Schuchat A. Seasonal patterns of invasive pneumococcal disease. *Emerg Infect Dis* 2003: **9**: 573–579.
10. Benn CS, Diness BR, Roth A *et al.* Effect of 50 000 IU vitamin A given with BCG vaccine on mortality in infants in Guinea-Bissau: randomised placebo controlled trial. *BMJ* 2008: **336**: 1416–1420.
11. Fisker AB, Aaby P, Bale C *et al.* Does the effect of vitamin A supplements depend on vaccination status? An observational study from Guinea-Bissau. *BMJ Open* 2012: **2**: e000448.
12. Aaby P, Martins CL, Garly ML *et al.* Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: randomised controlled trial. *BMJ* 2010: **341**: c6495.
13. Martins CL, Benn CS, Andersen A *et al.* A randomized trial of a standard dose of Edmonston-Zagreb measles vaccine given at 4.5 months of age: effect on total hospital admissions. *J Infect Dis* 2014: **209**: 1731–1738.
14. WHO. Immunization coverage cluster survey - reference manual. Department of Immunization, Vaccines and Biologicals, 2005.
15. WHO. Global health indicators - part II. 2010. Report no.
16. WHO. Global health observatory data repository. World Health Organization, 2015. Report no.
17. Umeå Centre for Global Health. InterVA-4 - User Guide 2016. (Available from: http://www.interva.net/) [01 Jul 2016]
18. Byass P, Fottrell E, Dao LH *et al.* Refining a probabilistic model for interpreting verbal autopsy data. *Scand J Public Health* 2006: **34**: 26–31.
19. Ramroth H, Lorenz E, Rankin JC *et al.* Cause of death distribution with InterVA and physician coding in a rural area of Burkina Faso. *Trop Med Int Health* 2012: **17**: 904–913.
20. Streatfield PK, Khan WA, Bhuiya A *et al.* Cause-specific childhood mortality in Africa and Asia: evidence from INDEPTH health and demographic surveillance system sites. *Glob Health Action* 2014: **7**: 25363.
21. Ursing J, Rombo L, Rodrigues A, Aaby P, Kofoed PE. Malaria transmission in Bissau, Guinea-Bissau between 1995 and 2012: malaria resurgence did not negatively affect mortality. *PLoS One* 2014: **9**: e101167.
22. Aaby P, Jensen H, Gomes J, Fernandes M, Lisse IM. The introduction of diphtheria-tetanus-pertussis vaccine and child mortality in rural Guinea-Bissau: an observational study. *Int J Epidemiol* 2004: **33**: 374–380.
23. Fottrell E, Kahn K, Tollman S, Byass P. Probabilistic methods for verbal autopsy interpretation: interVA robustness in relation to variations in a priori probabilities. *PLoS One* 2011: **6**: e27200.
24. Burkart K, Khan MM, Schneider A *et al.* The effects of season and meteorology on human mortality in tropical climates: a systematic review. *Trans R Soc Trop Med Hyg* 2014: **108**: 393–401.
25. Jaffar S, Leach A, Greenwood AM *et al.* Changes in the pattern of infant and childhood mortality in upper river division, The Gambia, from 1989 to 1993. *Trop Med Int Health* 1997: **2**: 28–37.
26. Hammer GP, Some F, Muller O, Kynast-Wolf G, Kouyate B, Becher H. Pattern of cause-specific childhood mortality in a malaria endemic area of Burkina Faso. *Malar J* 2006: **5**: 47.
27. WHO. World malaria report 2015. 2015.
28. Liu L, Oza S, Hogan D *et al.* Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015: **385**: 430–440.
29. Mutisya M, Orindi B, Emina J, Zulu E, Ye Y. Is mortality among under-five children in Nairobi slums seasonal? *Trop Med Int Health* 2010: **15**: 132–139.
30. Diallo AH, Meda N, Sommerfelt H *et al.* The high burden of infant deaths in rural Burkina Faso: a prospective community-based cohort study. *BMC Public Health* 2012: **12**: 739.
31. Jaffar S, Leach A, Greenwood A, Greenwood B. Season of birth is not associated with delayed childhood mortality in Upper River Division, The Gambia. *Trop Med Int Health* 2000: **5**: 628–632.
32. Aaby P, Marx C, Trautner S *et al.* Thymus size at birth is associated with infant mortality: a community study from Guinea-Bissau. *Acta Paediatr* 2002: **91**: 698–703.
33. Lisse IM, Aaby P, Whittle H, Jensen H, Engelmann M, Christensen LB. T-lymphocyte subsets in West African children: impact of age, sex, and season. *J Pediatr* 1997: **130**: 77–85.
34. Dopico XC, Evangelou M, Ferreira RC *et al.* Widespread seasonal gene expression reveals annual differences in human immunity and physiology. *Nat Commun* 2015: **6**: 7000.
35. Nair H, Simoes E, Rudan I *et al.* Global and regional burden of hospital admissions for severe acute lower. *Lancet* 2013: **381**: 1380–1390.
36. Poel EV, O'Donnell O, Doorslaer EV. What explains the rural-urban gap in infant mortality: household or community characteristics? *Demography* 2009: **46**: 827–850.
37. Blanford JI, Kumar S, Luo W, MacEachren AM. It's a long, long walk: accessibility to hospitals, maternity and integrated health centers in Niger. *Int J Health Geogr* 2012: **11**: 24.
38. Schoeps A, Gabrysch S, Niamba L, Sie A, Becher H. The effect of distance to health-care facilities on childhood mortality in rural Burkina Faso. *Am J Epidemiol* 2011: **173**: 492–498.
39. Fisker AB, Rodrigues A, Martins C *et al.* Reduced all-cause child mortality after general measles vaccination campaign in rural Guinea-Bissau. *Pediatr Infect Dis J* 2015: **34**: 1369–1376.
40. Lund N, Andersen A, Hansen AS *et al.* The effect of oral polio vaccine at birth on infant mortality: a randomized trial. *Clinical Infectious Diseases* 2015: **61**: 1504–1511. (1537-6591 (Electronic)).
41. O'Hare B, Makuta I, Chiwaula L, Bar-Zeev N. Income and child mortality in developing countries: a systematic review and meta-analysis. *J Roy Soc Med* 2013: **106**: 408–414.

42. King R, Mann V, Boone PD. Knowledge and reported practices of men and women on maternal and child health in rural Guinea Bissau: a cross sectional survey. *Bmc Public Health* 2010: **10**: 319.
43. Wang H, Liddell CA, Coates MM *et al.* Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**: 957–979.
44. Byberg S, Østergaard M, Rodrigues A *et al.* Analysis of risk factors for infant mortality in the 1992–3 and 2002–3 birth cohorts in rural Guinea-Bissau. In press (*PLoS ONE*).
45. Mane M, Fisker AB, Ravn H, Aaby P, Rodrigues A. Trends and determinants of mortality in women of reproductive age in rural Guinea-Bissau, West Africa–a cohort study. *BMC Women's Health* 2013: **13**: 48.
46. Goodman CA, Coleman PG, Mills AJ. Cost-effectiveness of malaria control in sub-Saharan Africa. *Lancet* 1999; **354**: 378–385.
47. The Alliance for Malaria Prevention. The Alliance for Malaria Prevention - expanding the ownership and use of mosquito nets. Country profile - Guinea-Bissau. 2015.
48. Einarsdottir J, Passa A, Gunnlaugsson G. Health education and cholera in rural Guinea-bissau. *Int J Infect Dis* 2001: **5**: 133–138.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Methods and results.

Figure S1. Causes of death stratified by periods (2005–2010 and 2011–2013) and by season (classified by InterVA).

Table S1. Vitamin A supplementation (VAS) and vaccine campaigns.

Table S2. Seasonal mortality by sex and age in all of the 182 village clusters followed in rural Guinea-Bissau 1990–2013.

Table S3. Seasonal mortality by sex and age in all of the 182 Village clusters followed in rural Guinea-Bissau 1990–2013.

Table S4. Seasonal mortality by region in the original 100 village clusters followed in rural Guinea-Bissau 1990–2013.

Table S5. Characteristics of verbal autopsies (VA) by season of death.

Corresponding Author **Bibi Uhre Nielsen**, Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, 2300 Copenhagen S, Denmark. Tel.: +45 2842 5419; E-mail: BIUN@ssi.dk