

Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa

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Abstract

Objective To examine the association between routine childhood vaccinations and survival among infants in Guinea-Bissau.

Design Follow up study.

Participants 15 351 women and their children born during 1990 and 1996.

Setting Rural Guinea-Bissau.

Main outcome measures Infant mortality over six months (between age 0-6 months and 7-13 months for BCG; diphtheria, tetanus, and pertussis; and polio vaccines and between 7-13 months and 14-20 months for measles vaccine).

Results Mortality was lower in the group vaccinated with any vaccine compared with those not vaccinated, the mortality ratio being 0.74 (95% confidence interval 0.53 to 1.03). After cluster, age, and other vaccines were adjusted for, BCG was associated with significantly lower mortality ratio (0.55 (0.36 to 0.85)). However, recipients of one dose of diphtheria, tetanus, and pertussis or polio vaccines had higher mortality than children who had received none of these vaccines (1.84 (1.10 to 3.10) for diphtheria, tetanus, and pertussis). Recipients of measles vaccine had a mortality ratio of 0.48 (0.27 to 0.87). When deaths from measles were excluded from the analysis the mortality ratio was 0.51 (0.28 to 0.95). Estimates were unchanged by controls for background factors.

Conclusions These trends are unlikely to be explained exclusively by selection biases since different vaccines were associated with opposite tendencies. Measles and BCG vaccines may have beneficial effects in addition to protection against measles and tuberculosis.

Introduction

Measles vaccine is strongly associated with better childhood survival in developing countries.^{1 2} Since this effect cannot be explained by the specific prevention of measles,^{1 3 4} standard measles vaccine may be associated with a non-specific beneficial activation of the immune system.¹ This effect would be observed only in areas with high mortality.⁵ Similar studies of BCG, polio, and diphtheria, tetanus, and pertussis vaccines have not been carried out in countries with a high mortality.

Worldwide, BCG is the most widely used vaccine and has been recommended for tuberculosis control in developing countries for more than 40 years. The protection provided by BCG is controversial as it has variable efficacy in different settings.^{6 7} Routine vaccinations with diphtheria, tetanus, and pertussis vaccine and polio vaccine provide good protection against the specific diseases. The recommended schedule is based on studies of seroconversion and protection and on assumed feasibility of the schedule.⁸ The effect of these vaccines has been assumed to be proportionate to the impact of the specific infections.

Guinea-Bissau in West Africa is one of the world's poorest countries. It has the sixth highest childhood mortality according to Unicef estimates.⁹ Since the early 1990s we have followed a representative cohort of 10 000 mothers and their children from the rural areas of Guinea-Bissau. Because the survival of recipients of routine vaccines has not been investigated in areas with high mortality, we examined the association between vaccination and survival in rural Guinea-Bissau.

Participants and methods

Cohort study

A longitudinal study of women of fertile age and their prospectively registered offspring was initiated in 1990 in the five most populous regions of Guinea-Bissau. The study was set up to assess mortality, including perinatal, childhood, and maternal mortality,¹⁰ and to monitor the use of health services. In each region, 20 clusters of 100 women were selected by the method recommended by the Expanded Programme on Immunisation for surveys of immunisation coverage. The children were followed to death, migration, or the age of 5 years; there was no loss to follow up because it was always possible to get information on all children from relatives living in the same compound. Data were collected by a mobile team of five to six assistants from the Bandim Health Project.

Vaccination status

The vaccination schedule recommended in Guinea-Bissau is BCG and polio at birth; diphtheria, tetanus, and pertussis and polio at 6, 10, and 14 weeks; and measles at 9 months of age. At each visit, vaccination status was determined by inspection of the immunisation card. Children who had no date on their card or

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who were declared to have received no vaccination were considered unvaccinated. We excluded children whose cards could not be inspected because the mother was absent or the card could not be found. Since we could not advise communities about the team's visit, many mothers were away on the day of the visit. Most mothers in rural Guinea-Bissau keep their children's vaccination cards with their personal belongings locked in a trunk. Hence, if the mother was not present, the vaccination card could not be seen.

Analysis and statistical methods

We estimated the effect of vaccinations by analysing mortality according to the vaccination status assessed at the initial visit. Information on deaths was obtained at the subsequent visit, and therefore children had to be visited twice to be included in the study. Intervals between visits were mostly 5 to 7 months. As children were 0-6 months old when first seen, the impact of BCG, polio, and diphtheria, tetanus, and pertussis vaccines was assessed between the initial visit and the following visit or six months later. Survival over a longer follow up period would be confounded increasingly by the effect of measles vaccine. We calculated estimates separately for recipients of polio and diphtheria, tetanus, and pertussis vaccines, but these were virtually identical as the two vaccines are always administered together. The effect of measles vaccine was examined between the second visit at 7-13 months of age and the subsequent visit or six months later.

We examined differences in the prevalence ratio for background factors for vaccinated and unvaccinated children by using a generalised linear model with binomial variability and a logarithmic link function adjusting for age.^{11 12} To estimate the mortality ratio for vaccinated and unvaccinated children, we used a Cox proportional hazards model,¹³ taking length of follow up into consideration and adjusting by stratification for age, period, season, and cluster.

Results

Study population and vaccination coverage

Between February 1990 and April 1996, we registered 15 351 women of fertile age and 11 460 pregnancies, resulting in 8752 children who were alive at the first visit and whose survival was ascertained at the second visit; 8104 were under 7 months old when first seen. Of the 8752 children, 429 died and 214 moved between the first and second visit, and 752 had no third visit before the end of the study, leaving 7357 children to be followed between the second and third visit. Of the 7357 children, 323 died and 183 moved before the third visit. At the first visit, 5754 (66%) had their vaccination card inspected; 2981 (34%) were absent and 17 (0.2%) had lost their card.

We examined differences in background factors for vaccinated and unvaccinated children, controlling for age and cluster. Vaccinated children had more contact with the health system, their mothers being more likely to have received tetanus vaccination during pregnancy and to have given birth outside the home. Vaccinated children had larger arm circumference and their mothers tended to be younger and have fewer children, to have a latrine in their compound, and not to belong to the Balanta or Pepel ethnic groups (see *BMJ's* website for details).

BCG vaccine

Mortality for the 5274 children aged 0-6 months was lower in the group vaccinated with any vaccine compared with those not vaccinated, the mortality ratio being 0.74 (95% confidence interval 0.53 to 1.03). For children vaccinated with BCG the mortality ratio was 0.72 (0.54 to 0.96) (table 1). The ratio became 0.55 (0.36 to 0.85) after age, diphtheria, tetanus, and pertussis vaccine, and cluster were adjusted for; estimates varied between 0.50 and 0.58 and were significant when background factors were controlled for. If we excluded children who were considered unvaccinated because they had no vaccination card, the mortality ratio for BCG vaccine among children who were seen was 0.33 (0.17 to 0.65).

Table 1 Mortality during six months of follow up according to BCG vaccination status and age at initial visit, Guinea-Bissau, 1990-6

Age (months)	Mortality (%)	
	Vaccinated	Not vaccinated
0-1	3.0 (21/705)	5.2 (55/1058)
2-3	3.1 (37/1187)	4.8 (26/539)
4-6	4.8 (67/1409)	4.3 (16/376)
Total	3.8 (125/3301)	4.9 (97/1973)

The effect of BCG was stronger when the analysis was restricted to infants aged 0 to 2 months, who would not receive measles vaccine during the next six months (mortality ratio 0.43 (0.25 to 0.75)). Since children weighing less than 2500 g are not supposed to receive BCG, unvaccinated children could represent a negatively selected group. After 31 days of age all children would presumably weigh more than 2500 g; we therefore analysed data on children aged 1 to 2 months who were either unvaccinated or vaccinated with BCG after 31 days of life. The protective effect of BCG was high in this subgroup (0.19 (0.04 to 0.95)).

Diphtheria, tetanus, and pertussis and polio vaccines

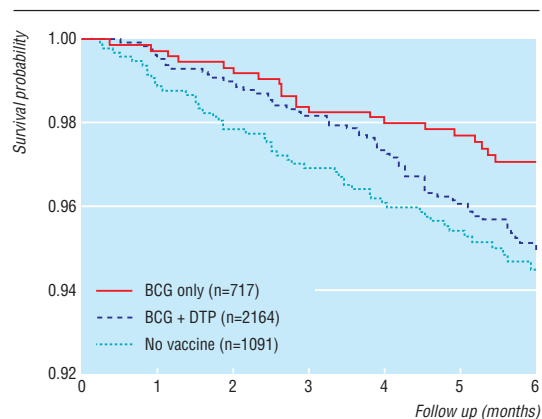
Since diphtheria, tetanus, and pertussis and polio vaccines are administered from 6 weeks of age, the analyses were limited to children aged 1.5-6 months at the initial visit. Of the 5274 children examined at 0-6 months of age, 3972 were aged 1.5-6 months; 1822 had no dose of diphtheria, tetanus, and pertussis vaccine (72 died before the second visit), 1295 had received one dose (62 died), and 855 had had two or

Table 2 Mortality during six months of follow up among children who did and did not receive one dose of diphtheria, tetanus, and pertussis vaccine* according to BCG vaccination status and age at initial visit, Guinea-Bissau, 1990-6

Age (months)	Mortality (%)	
	Vaccinated	Not vaccinated
1.5-3		
No BCG	10.0 (1/10)	4.9 (36/734)
BCG	3.9 (28/709)	2.5 (14/560)
4-6		
No BCG	11.1 (1/9)	4.2 (15/357)
BCG	5.6 (32/567)	4.1 (7/171)
Total	4.8 (62/1295)	4.0 (72/1822)

*Children who had received more than one dose of diphtheria, tetanus, and pertussis vaccine are not included.

more doses (32 died). After age, BCG vaccination, and cluster were adjusted for in a Cox analysis estimating the effect of one and two to three doses separately, one dose of diphtheria, tetanus, and pertussis vaccine was associated with a mortality ratio of 1.84 (1.10 to 3.10) and two to three doses with a ratio of 1.38 (0.73 to 2.61) compared with children who had received no dose of these vaccines (table 2, figure). Mortality was also increased in the analysis combining one to three doses of diphtheria, tetanus, and pertussis (1.72 (1.03 to 2.87)) and diphtheria, tetanus, and pertussis or polio vaccine (1.67 (1.00 to 2.77)). Adjustment for background factors did not affect the estimates, except for adjustment for arm circumference, which increased the effect of one dose of diphtheria, tetanus, and pertussis to 2.50 (1.31 to 4.78). If we excluded children considered unvaccinated because they had no card, the mortality ratio for one to three doses of diphtheria, tetanus, and pertussis vaccine among children whose card was seen was 1.78 (1.05 to 3.02).



Kaplan-Meier survival curves for recipients of BCG, recipients of BCG and at least one dose of diphtheria, tetanus, and pertussis (DTP) or polio vaccine, and non-recipients of all vaccines. Six months' follow up of 3972 children aged 1.5-6 months at initial visit, Guinea-Bissau, 1990-6

Measles vaccine

Children aged 7 to 13 months who had received measles vaccine at the second visit had a mortality ratio of 0.51 (0.30 to 0.85) compared with unvaccinated children (table 3). The ratio was 0.48 (0.27 to 0.87) after age, BCG vaccination, and cluster were adjusted for and varied from 0.45 to 0.56 when background factors were controlled for, all estimates except one being significant. The estimate was unaffected by controls for other vaccinations. If we excluded children considered unvaccinated because they had no card, the mortality ratio for measles vaccine among children whose card was seen was 0.48 (0.27 to 0.87). The reduction in mortality was unrelated to measles deaths; nine of 94 deaths in the unvaccinated and one of 19 deaths in the vaccinated groups were reported to be due to measles (table 3). When deaths from acute measles were excluded, the mortality ratio was 0.51 (0.28 to 0.95) for children vaccinated against measles compared with initially unvaccinated children.

Table 3 Mortality during six months of follow up according to measles vaccination status and age at start of six months, Guinea-Bissau, 1990-6

Age (months)	Mortality (%)	
	Vaccinated	Not vaccinated
7-8	3.3 (3/90)	4.4 (48/1089)
9-11	1.6 (11/701)	3.6 (41/1130)
12-13	2.0 (5/245)	3.2 (5/159)
Total	1.8 (19/1036)	4.0 (94/2378)

Discussion

In Guinea-Bissau, we found that BCG and measles vaccines were associated with better survival and diphtheria, tetanus, and pertussis and polio vaccines with higher mortality compared with unvaccinated children. The estimates are unlikely to be due to registration problems. The initial recruitment for the study was based on a random selection of clusters. The survival analysis had no loss to follow up, and the statistical model compared only vaccinated and unvaccinated children from the same community. We got information on vaccination status for around two thirds of the children, a high proportion given that the communities were not informed beforehand about the day of the visit. Furthermore, there was no indication that those not presenting a vaccination card reacted differently to the vaccines. Vaccines are appreciated by mothers in rural Guinea-Bissau, and there would seem no reason to fake vaccination dates on cards. However, some vaccinated children may have been registered as unvaccinated because a nurse forgot to note the date on the child's card or a guardian reported the child not having a card. Such misclassification would lessen rather than exaggerate the mortality differences presented here.

As this was an observational study the effects we found could be due to behavioural differences between mothers of vaccinated and unvaccinated children. Mothers of vaccinated children apparently had more frequent contact with the health care system. Having "concerned mothers" could possibly explain a beneficial effect associated with BCG and measles vaccines; however, the negative association with diphtheria, tetanus, and pertussis and polio vaccines is difficult to explain. Alternatively, sick children could be brought more often to health centres and therefore receive more vaccines. This seems unlikely as vaccine recipients had larger arm circumferences than unvaccinated children and it would not explain the better survival of children who received BCG and measles vaccines.

Do BCG and measles vaccines have a non-specific beneficial effect?

The reduction in mortality after measles and BCG vaccination is larger than the proportion of deaths attributed to these diseases among infants and young children. Exclusion of deaths from measles did not change the mortality ratio between vaccinated and unvaccinated children. A similar analysis could not be made for BCG since infant tuberculosis is poorly defined. Tuberculosis is estimated to have a much smaller effect on childhood mortality than measles.¹⁴ However, we found that the effect of BCG vaccine was as large as that of measles vaccine. It therefore seems

implausible that the positive effect is merely due to BCG protecting against primary tuberculosis. The effect of BCG was not due to early recipients constituting a group with better survival. Future studies should assess the extent to which the impact of BCG in childhood can be explained by prevention of tuberculosis.

BCG vaccine has been used to stimulate the immune system in certain chronic diseases, including cancer.¹⁵⁻¹⁸ In Guinea-Bissau and the Gambia, early BCG vaccination protected against atopy,¹⁹ and BCG vaccination at birth was associated with the stimulation of a Th1-type immune response.²⁰ The better survival associated with BCG vaccine could therefore reflect a non-specific protection against other infections as suggested for measles vaccine.¹ Children vaccinated against diphtheria, tetanus, pertussis, and polio were more atopic than non-vaccinated children in Bissau.¹⁹ The fact that the adjuvant of diphtheria, tetanus, and pertussis, aluminium hydroxide, is a strong promoter of a Th2-type immune response in mice may be important.²¹

Implications of results

Our results will have to be interpreted with caution. However, unless selection bias is switching back and forth at different ages, it seems difficult to explain both good survival for BCG and measles vaccine recipients and poor survival for recipients of diphtheria, tetanus, and pertussis and polio vaccines. Some of these vaccines are therefore likely to have major non-specific effects on child survival.¹

If BCG vaccine has beneficial effects, these should be considered when testing new, more specific vaccines against tuberculosis in the future. The use of a new vaccine could be associated with higher mortality, as was the case when the high titre measles vaccine was introduced.²² Should diphtheria, pertussis, and tetanus or polio vaccines be found to have negative effects on mortality despite their protection against specific diseases, new vaccine formulations might improve the effect of the vaccination programme.

Our observations emphasise the importance of immunisations in developing countries; vaccinated children had much lower mortality. Changes in the vaccination schedules²³ or type of vaccines used in developing countries could improve coverage and child survival.

Contributors: IK supervised the last year of data collection and wrote the first draft of the paper. HJ supervised data control and carried out the statistical analyses. PA initiated the study, supervised data collection, carried out the first analyses, and wrote the final version of the paper. HJ and PA will act as guarantors.

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Competing interests: None declared.

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What is already known on this topic

Measles vaccine may be associated with a non-specific survival benefit in countries with a high mortality

No attempt has been made to assess the effect of other routine immunisations on mortality in developing countries

What this study adds

BCG and measles vaccines were associated with reductions in mortality in rural Guinea-Bissau

The effect for measles vaccine could not be explained by the prevention of measles infection

Diphtheria, tetanus, and pertussis and polio vaccines were associated with higher infant mortality

Non-specific effects of routine immunisations should be considered when planning immunisation programmes in developing countries

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Commentary: an unexpected finding that needs confirmation or rejection

Paul Fine

The paper from Guinea Bissau in this issue, on routine vaccinations and child survival, may cause concern. An observational study undertaken under difficult circumstances, it reports three surprising trends: lower than expected mortality associated with BCG and with measles vaccines and higher than expected relative mortality associated with diphtheria-tetanus-pertussis (DTP)-polio vaccine, each of them just over the edge of conventional statistical significance.

One should first question whether the results are valid. This is ostensibly a cohort study, following-up infants with different initial vaccination status, but the design and presentation are complicated.

Of paramount importance is the comparability of the groups being compared. Vaccines are not distributed at random anywhere, and this may be particularly so in as disadvantaged a population as that in Guinea Bissau. The assignment of vaccination status in this study is not entirely clear, as written records were not available for a high proportion of infants and we are told of infants "who were declared to have received no vaccination." Table 2 in the long version of this article on the *BMJ*'s website gives a breakdown of variables associated with vaccination status, and, not surprisingly, all vaccines appear to be associated with greater than average use of health services (mothers of vaccinated infants were 1.2 times more likely to have received tetanus vaccines than were mothers of non-vaccinated children). Might this explain the higher survival of recipients of BCG and measles vaccines? The table also shows that mothers of recipients of DTP-polio vaccine were younger than those of recipients of BCG or measles vaccines, though we do not know why. But we do know that high infant mortality is associated with low maternal age¹: is it a coincidence that infants of these young mothers had a relative increase in mortality? The authors have adjusted for "background factors," but exactly which factors were included is not clear, and, given the complexity of these trends, it is unlikely that the groups were fully comparable as a result.

The numerical results are anomalous. In all the tables we see evidence of decreasing mortality with increasing age at start of follow up among the unvaccinated infants, as expected; but in both the BCG and DTP tables we see *increasing* mortality with age among infants who were vaccinated. This is contrary to expectation, and is not discussed. Such trends may reflect small numbers, but so may the overall associations of mortality with vaccination status, as the significance of each depends on a single or very few events. It is strange that the effect of DTP is associated with one dose but is not significant for two or three doses—which is not what we expect of a causal influence. The results thus fall short on three of the classic attributes of causality: gradient, strength, and coherence.

Beyond the issue of validity, the paper is potentially misleading in its description of the apparent influence of DTP-polio vaccine. Given that DTP was tightly

linked to prior BCG vaccination (only 19 infants received DTP without prior BCG), the effect of the DTP-polio vaccines could only be assessed against a background of BCG vaccination, and the observed result might better be described in terms of reducing the survival advantage associated with BCG vaccines than as increasing mortality (fig 2 on *BMJ*'s website).

Should we discard the results as unconvincing, or consider further what they might imply if true? If the latter, then we have hints of different, non-specific, short term effects on mortality associated with different vaccines in early life, in a population with high infant mortality. There are precedents for some such effects, in particular studies which have suggested non-specific reductions in childhood mortality associated with measles vaccines.² The extent and biological implications of that association are not yet clear. The issue of non-specific effects of infections and vaccines has become fashionable recently, in particular with reference to allergic phenomena, but even in this case the evidence is observational and not consistent.^{3 4} To attribute such effects to shifts towards Th1 or Th2 type immune responses is also fashionable but controversial and probably an oversimplification.⁵ In the broader context, a full assessment of benefits and risks of vaccines must take into account the diseases against which the vaccines are designed to protect and whose frequency may have been decreased by the vaccines.⁶

This paper may raise questions about the standards of evidence appropriate for publication of unexpected versus coherent effects of interventions. The findings reported here are not convincing in themselves though would be important if true. This problem has many facets, and appropriate studies, carefully designed and analysed, and thoroughly presented, are needed.

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Endpiece

A time honoured practice

In comparing various authors with one another, I have discovered that some of the gravest and latest writers have transcribed, word for word, from former works, without making acknowledgment.

Pliny the Elder, AD 23-79

Submitted by Fernando Lokschin, physician,
Porto Alegre, Brazil