

Commentary: Contrary findings from Guinea-Bissau and Papua New Guinea

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About four years ago, a study of routine immunizations in rural areas of Guinea-Bissau suggested that early BCG and measles vaccination (MV) were associated with reduced mortality, which was not explained by the prevention of TB or measles, but that early diphtheria-tetanus-pertussis (DTP) vaccine was associated with increased mortality.¹ Given the observational design and the potential for bias, a precise estimate of these effects could not be established, but it was noteworthy that different vaccines had opposite effects.^{1–3} Several studies from Bissau, Senegal, and Benin have found similar patterns of BCG and MV being associated with lower mortality and DTP with higher mortality.^{4–10} These effects are most marked immediately after vaccination and until the next vaccine is received. When DTP has been the last vaccine received, it has been associated with a higher mortality for girls.^{3–7,9} WHO withdrew high-titre measles vaccine (HTMV) because it was associated with increased female mortality;⁹ however, the higher mortality may have been because the measles vaccine was followed by DTP vaccine rather than any direct adverse effect of HTMV.

In response to the original paper on the non-specific effects of vaccines in Bissau,¹ WHO's Global Advisory Committee on Vaccine Safety (GACVS) sponsored four groups to re-analyse existing datasets to refute or replicate findings from Bissau. GAVCS has already announced that the four studies showed no negative effect of DTP and no difference in mortality between males and females.¹¹

The first of the studies sponsored by WHO is published in the present issue of IJE.¹² Lehmann and colleagues analysed data collected in Tari, Papua New Guinea (PNG) from 1989–1995, in connection with an effectiveness study of pneumococcal polysaccharide (PncPS) vaccine. This area had demographic surveillance between 1971 and 1995. The hospital and health centres in the area provided immunizations through monthly maternal and child health (MCH) clinics; vaccinations were noted on the child's card held at the health centre and on the health card held by the mother. Personnel from the PncPS study collected the health centre register once a month and computerized all information on consultations and immunizations. Of 213 deaths in the study, only 5 were attributed to vaccine-preventable diseases (4 measles and one pertussis, with no death from TB, diphtheria, or tetanus). Since these deaths could not explain the 6-fold reduction in mortality for BCG and DTP-vaccinated children, it is concluded that routine vaccinations were associated with a non-specific reduction in mortality during the first 2 years of life. Hence, the

contrast to findings from Guinea-Bissau is only about the effect of DTP. But has this study eliminated the possibility that DTP has non-specific negative effects on mortality?

As suggested by the authors, there are many reasons that the non-specific effects of vaccines might differ between Bissau and PNG. Infant mortality is much higher and malaria plays a greater role in rural Bissau. Furthermore, the PNG vaccination programme was totally different from Bissau. Pigbel vaccine was administered with DTP and OPV and the immunological effect of combining DTP and pigbel vaccines is unknown. MV was provided at 6 months of age, or even earlier during epidemics. In Bissau, the negative effect of DTP increased with the number of doses⁵ and was strongest at 6–8 months of age.^{5,7} In Tari, the duration of exposure to DTP as the last vaccine would have been limited because MV was administered early. At 8 months of age, most children received PncPS possibly providing herd immunity against pneumococcal disease. These differences make any comparison between PNG and Guinea-Bissau very difficult. However, there are more fundamental methodological differences, which also make the studies difficult to compare.

In Bissau, we used a survey design^{1–5}—the children being assessed as 'vaccinated' or 'unvaccinated' in a survey and then followed-up for 6 months until the next survey to evaluate their survival; children without information on vaccination status were not included in the analysis. This is admittedly a crude method that gives conservative estimates, because many initially unvaccinated children are vaccinated during the period of follow-up.¹ In effect, this survey design compares the relative advantage of being vaccinated early vs not-yet-vaccinated.^{4–8} In contrast, the PNG dataset was based on monthly registration of vaccinations, and was analysed in a Cox survival analysis with vaccination status as a time-dependent variable. If there was no vaccination linked to a child in the demographic database in Tari, it was assumed that the child had not been vaccinated. Hence, 'unvaccinated' is a default status. This would not be a problem in a system with perfect information on all vaccinations or assessment of vaccination cards of all children who die. But this was not the case in Tari where there were delays in the collection of information, so that vaccinations might have been preferentially registered among children followed-up intensively (children who survived), whereas vaccinations for children who travelled or died might be missing. As a consequence, vaccinated children who died may have been wrongly classified as unvaccinated, and the analysis might suffer from survival bias. Even limited misclassification has major effects for the estimated MR; for example, in a population with twice as many vaccinated as unvaccinated children, a mortality rate of 2.5% for unvaccinated children, and 25% misclassifications of vaccinated deaths as unvaccinated,

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a true mortality ratio (MR) of 2.0 for vaccinated children compared with unvaccinated children would result in a calculated MR of 0.76.

Although the PNG team tried very hard to register all vaccinations, they do not claim that the system was perfect. The focus was PncPS vaccinations and special data collection procedures were used for this vaccine; for example, PncPS vaccination information was collected for children who died or if the child was not registered to have received PncPS-vaccine before 2 years of age. The registration might have been less perfect for other vaccines, with delays in data collection in the beginning of the study and during periods of clan fighting; the BCG and HBV vaccines provided at birth were not registered unless a child attended an MCH clinic; and in contrast to 9–10% unvaccinated children in the first 5 years, the proportion of unvaccinated was 32% in the last year of the study (Table 1¹²) when mortality was also particularly high (Table 6¹²). More important, as would be expected if misclassification occurred, mortality was unusually high in the unvaccinated group (Table 3¹²): 1–5 month mortality was 233/1000 and the post-neonatal infant mortality 146/1000; these were surprisingly high rates in a community with a neonatal mortality of only 18/1000 (117/6665) and a general post-neonatal infant mortality of only 48/1000.^{12,13} A relevant unvaccinated group should not have higher mortality than in the pre-vaccination era. The post-neonatal infant mortality level in the present study is even higher than the rate reported from the 1920s and 1950s before any antibiotics or vaccinations were introduced.^{14,15} Furthermore, with age ‘unvaccinated’ children become an increasingly negatively selected group; the MR between unvaccinated and vaccinated children should therefore increase with age. However, as would be expected if misclassifications were reduced with longer follow-up and more information, the crude MR between unvaccinated and vaccinated children declined with age from 7.4 (5.1–11.0) at 1–5 months to 3.3 (1.3–8.6) at 12–23 months of age (Table 3¹²).

In addition, a survey design¹ will handle bias very differently from a survival analysis with change in vaccination status based on the date of vaccination.¹² Most studies suggest that vaccinated children have inherent advantages: they are healthier, have better nutritional status,¹ have mothers with better education,¹ better hygienic conditions¹ and higher income, live closer to a health centre, and have better access to hospital care and other health interventions such as malaria prophylaxis or vitamin A supplementation. Inequalities that are determined by known socioeconomic risk factors might be partly controlled in a multivariable analysis.¹ However, the likelihood of getting vaccination and the risk of mortality may also depend on more variable factors such as who happens to be sick, or to, travel. In a survey design, as used in Guinea-Bissau, comparing those vaccinated early with those not-yet-vaccinated, such variable factors would matter little if they were randomly distributed between vaccinated and unvaccinated children. However, if healthy children were vaccinated first, a survival analysis, as used in the PNG study, would maximize bias. At any given time, the healthier children who had received the next vaccine (say DTP) first would be compared with the more vulnerable children who had received only the previous vaccine (say BCG). There is no way of knowing how strongly heterogeneous mortality rates might have been associated with

age at vaccination in Tari. It is clear though that sick children were not vaccinated and that this bias is important is clearly illustrated in Table 4.¹² The authors attempt to control for bias by adjusting for a propensity score (PS) of being vaccinated and then stratifying their analysis by quintiles of PS. In the lowest PS quintile, the <2 year mortality of unvaccinated children was 14%, but with increasing PS quintiles, the mortality of unvaccinated children increased to 26%, 67%, and 100%, respectively (trend $\chi^2 = 61.1$). In other words, if the child should have been vaccinated according to its social propensity and did not, its likelihood of dying was totally different. Hence, this survival analysis seems to have compared not the mortality of unselected vaccinated and unvaccinated children but rather the mortality of vaccinated vs sick/moribund children. In effect, control for PS did not reduce bias; most MR estimates were more extreme in the model with adjustment (Table 5(a)¹²) than without adjustment (Table 5(b)¹²), particularly in the 1–5 month age group.

Lehmann *et al.* also controlled for access to health care by limiting the analysis to children who had at least received BCG. Contrary to the PS analysis, this did reduce the beneficial effect associated with DTP (Table 6¹²). Still, it is difficult to understand how a mortality rate for BCG-only of 3.8% between 1 and 5 months of age (Table 3¹²) and a rate of 3.1% for DTP with or after BCG could become a MR of 0.45 (0.2–0.9) for DTP (BCG + DTP) vs no DTP (BCG-only) unless age as time scale assured that the healthier DTP-vaccinated children were compared with the more vulnerable BCG-vaccinated children. When heterogeneous mortality rates are associated with age at vaccination, analytical models using age as time scale may not be the optimal choice.

Given the uncertainty about the completeness of data for children who died and the impact of bias, it is doubtful whether the Tari data has documented that DTP is associated with beneficial non-specific effects. However, there are other indications that vaccines might have had non-specific effects.¹⁶ In a previous analysis from Tari (1979–1983), infant mortality was higher for girls than boys (MR 1.38 (1.0–2.0)).¹³ In the present study, vaccinated children at 1–5 months of age had a crude female–male mortality ratio of 0.54 (0.3–1.1) compared with 1.02 (0.7–1.5) among unvaccinated children (Table 3¹²). This might well suggest that immunizations were associated with non-specific changes in the female–male mortality ratio as found in several other studies.^{3–9} The data on sex differences is limited and the presentation (Table 3¹²) does not take account of which other vaccines these children might have received during follow-up; if anything, both BCG and DTP were associated with lower female mortality, as found previously for BCG³ but in contrast to our observations on DTP.^{3–7,9} It is unclear whether these differences from previous observations¹³ are due to the combination of DTP with pigbel vaccine, the short duration of exposure to DTP as the last vaccine, herd immunity to pneumococcal infection from PncPS vaccination of older children, misclassification of dead children, or chance.

Vaccinations have been the most effective part of public health interventions in low-income countries,^{1,12} so it is unfortunate that so few studies have been published on the effects of vaccination in low-income countries. GACVS has recommended that vaccine studies use survival analyses with age as the underlying scale and vaccination status as a time dependent

variable.¹² As illustrated, such standard Cox survival analyses might suffer from survival bias, and they will make selection bias a continuous process over the period during which children are being vaccinated. In contrast, the survey design^{1,5} does not have survival bias and will be less affected by selection bias because only the difference between early and not-yet-vaccinated at the time of the survey will be relevant. Datasets with survival bias, or with heterogeneous mortality rates associated with the age at vaccination, will both give estimates to the benefit of the last vaccine received even when such effects do not exist. GACVS should take little assurance from such analyses.¹¹ To refute or replicate findings reported from Guinea-Bissau, we need documentation of both vaccination and non-vaccination status,^{1,7} and more imaginative observational study designs which minimize selection bias—such as when vaccines are missing,^{4,8} new vaccines are introduced^{5,17} the age of vaccination is changed⁹ or major changes in vaccination coverage occur—and randomized studies.¹⁶

Conflict of interest: The paper by Lehmann¹² is a response to our previous work.¹

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