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Commentary: an unexpected finding that needs confirmation or rejection

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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 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).

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 they would be important if true. There are thus many facets to this problem, and appropriate studies, carefully designed and analysed, and thoroughly presented, are needed.

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