Non-specific effects of BCG?

To the Editor—We would like to comment on the data presented by Aaby et al regarding their randomized trial of BCG in low-birth-weight children [1]. The authors designed their trial to test the hypothesis that among low-birth-weight infants, BCG vaccination at birth would reduce infant mortality by 25% compared with infants vaccinated later (on average, age 6 weeks). No significant difference was found between the infant mortality rates in the 2 groups. However, the authors conducted a number of secondary analyses, including stratifying deaths by age, and claim that there was an approximate 50% reduction in neonatal mortality, which was statistically significant. What is not evident in the article, but is clear in the supplementary table available online, is that the apparent reduction in mortality occurred entirely in the first 21 days of life. Indeed, it is stated that the tendency appeared “already during the first 3 days after BCG vaccination.”

In terms of mechanism, the authors suggest that “BCG might prepare the immune system to mount an effective response to infectious pathogens and therefore enhance survival.” It seems unlikely that an immunological mechanism could explain so rapid an impact on mortality. An alternative explanation for these results is that there was some inadvertent bias in the operation of the randomization procedure. An important aspect of all trials is concealment of the allocation prior to entry to the trial. Serious bias could have occurred if infants who looked particularly frail, as might have been the case for those destined to die in the weeks following vaccination, were either excluded from the trial if their random allocation was to the BCG group or were put into the control group without the investigators’ knowledge. Such a bias would be likely to create exactly the kind of difference in early mortality that is described in the article. It seems plausible that those responsible for administering BCG might have been reluctant to vaccinate such infants, especially because the current policy in Guinea-Bissau is to delay BCG vaccination in low-birth-weight infants. Thus, the mortality difference observed between the trial groups is exactly what would be expected if infants at highest risk of death were somehow selectively excluded from vaccination. Furthermore, because the trial was not blind, it is difficult to exclude the possibility that those who were vaccinated received slightly more attention from caregivers, and this may have had an impact on their risk of death.

In summary, we think the results of this trial are hard to explain in terms of immunology or physiology but may be plausibly explained in terms of a procedural flaw. We credit the authors for having attempted a very difficult trial, but they themselves acknowledge faulty randomization procedures at the start of the trial, which led to the exclusion of approximately the first third of infants entered into the trial. Furthermore, we note that the highlighted findings emerged as a result of secondary analyses, rather than from the hypothesis the trial was designed to test. For these reasons, we consider that the reported results should be treated with considerably more caution than is evident, either in the authors’ discussion or in the accompanying editorial [2].

Note

Potential conflicts of interest. All authors: No reported conflicts.