The Nonspecific Effects of Vaccines and the Expanded Program on Immunization

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There is now clear evidence that the simplistic conventional model of immunization is invalid [1]. We can no longer assume that a vaccine acts independently of other vaccines, or that it influences only infections caused by the target disease. Strong evidence from randomized trials suggests that bacillus Calmette-Guérin vaccine (BCG) reduces mortality from infections other than tuberculosis and that measles vaccine reduces mortality from infections other than measles [1–4]. However, there is worrying evidence that whole-cell diphtheria-tetanus-pertussis vaccine (DTP) may increase mortality from infections other than diphtheria, tetanus, or pertussis in high-mortality areas [1, 3–8]. These nonspecific effects of BCG, measles vaccine, and DTP are generally stronger in girls, appear to be maximal in the first 6 months after immunization, and are largely determined by the most recent vaccine administered [1].

Randomized trials show that measles vaccine has strong nonspecific effects. Providing it is not given after vitamin A or followed by DTP, measles vaccine reduces mortality from diseases other than measles by 45% (95% confidence interval [CI], 14%–65%) when given at 4.5 months of age [9], and by 47% (95% CI, 23%–63%) when given to girls at 9 to 10 months of age [1].

In this issue of the Journal, Aaby et al present further evidence, from Guinea-Bissau, that BCG has potent nonspecific effects on mortality [4]. Low-birth-weight neonates were randomized to receive BCG at birth or via the routine immunization program at an older age (median, 7.7 weeks). The biological effects of BCG are shown by the outcome during the first 4 weeks after randomization, before children in either group had been given DTP and when few children in the control group had received BCG. In this period, BCG reduced mortality by 45% (95% CI, 11%–66%); there were fewer deaths from sepsis and acute respiratory infection, and no deaths from tuberculosis (which is a rare cause of death at this age). This spectacular reduction in mortality is consistent with the results of 6 controlled trials performed in 45,662 children in the United States and the United Kingdom in the 1940s and 1950s, in which BCG reduced mortality from causes other than tuberculosis by 25% (95% CI, 6%–41%) [1, 2].

Although BCG reduced mortality in the first 4 weeks of life in the trial in Guinea-Bissau, investigators observed no difference in mortality after that age [4]. This is not surprising, because by 2 months of age 58% of the controls had received BCG and over 60% of children in both groups had received DTP. Consequently, BCG did not significantly reduce mortality in the first 12 months of life, the observed reduction being 17% (95% CI, −8% to 37%). This was the primary endpoint of the trial, which was underpowered because infant mortality was 101 deaths per 1000 live births, rather than 250 deaths per 1000 live births as predicted when the trial was designed. A lower-than-expected mortality often occurs when trial participants in a high-mortality area are offered free treatment, as in this study. This illustrates how difficult it is to do randomized trials in high-mortality areas, where we most need to obtain information about how to lower mortality.

A worrying finding in this trial was that children who had received DTP by 2 months of age had an increased mortality between 2 and 6 months of age: Mortality was increased 4.3-fold (95% CI, 1.5–12.2-fold) in the BCG-at-birth group and 1.7-fold (95% CI, 0.7–4.0-fold) in the control group [4]. DTP was observed to have similar effects in a randomized trial of revaccination with...
BCG at 19 months of age in Guinea-Bissau [3]. In that trial, 60% of the participants had not received their last dose of DTP (DTP4) at the time of enrollment, and many of these children were given DTP4 after entering the study. Children who received BCG had a lower mortality than controls if they had received DTP4 before enrollment (hazard ratio, .36; 95% CI, 13.99) but a higher mortality if they had not received DTP4 before enrollment (hazard ratio, 1.78; 95% CI, 1.04–3.04); the difference was highly significant \( (P = .006) \). Mortality was 0.36 deaths per 100 person-years if DTP4 had been given before BCG revaccination, 1.02 deaths per 100 person-years in controls who were not revaccinated with BCG (mortality was not affected by DTP4 status at enrollment), and 1.83 deaths per 100 person-years if DTP4 had not been given before BCG revaccination [3, 10]. These 2 studies suggest that BCG lowers mortality if it is given alone or after DTP, but that mortality may be increased if DTP is given after BCG as recommended in the schedule for the Expanded Program on Immunization (EPI) [3, 4]. The administration of DTP after BCG was not randomized in these studies, so the observed increase in mortality with DTP may have been caused by bias. However, this seems unlikely. In the trial of BCG in low-birth-weight babies [4], the infants who had received DTP by 2 months of age (and had increased mortality) were larger babies who would be expected to have a lower mortality in the absence of a nonspecific effect of DTP. In the trial of BCG revaccination at 19 months of age [3], mortality in the control group (no additional BCG) was not influenced by DTP4 status at the time of randomization, suggesting that this was not an independent risk factor.

Even in unimmunized communities, diphtheria, tetanus, and pertussis cause far fewer deaths than pneumonia, sepsis, and diarrhea [11]; despite reducing mortality from diphtheria, tetanus, and pertussis, DTP will, therefore, increase total mortality if it causes even a small increase in mortality from pneumonia, sepsis, and diarrhea in high-mortality areas [12]. When DTP was first introduced into Guinea-Bissau, despite the absence of herd immunity, mortality was 5.1 deaths per 100 person-years among children who did not receive DTP but 11.3 deaths per 100 person-years among children who did receive DTP (risk ratio, 2.03; 95% CI, 1.17–3.52) [7]. I know of no other study of the introduction of DTP in a high-mortality area with sufficient power to test the effect on total mortality.

No randomized trial has demonstrated that it is safe to give DTP to young infants in high-mortality areas, and there is now worrying evidence that DTP may increase mortality under these circumstances—especially when it is given after BCG as recommended in the EPI schedule [1, 3–8]. In 2002, 2003, and 2004, the WHO Global Advisory Committee on Vaccine Safety (GACVS) concluded that the evidence did not support an increased risk of mortality after DTP immunization [13]. However, the onus of proof is surely the reverse of this—we need clear evidence that a vaccine is safe when it is given routinely to all infants in high-mortality areas. In addition, the Committee based its conclusion on observational studies, all of which had one or more serious methodological problems [1, 5, 14–16]. First, any observational study (with nonrandom allocation of vaccines) may induce a spurious association between vaccination and survival [16]. Second, vaccination was often withheld in sick children, which causes selection bias in favor of DTP [5]. Third, many of the studies classified dead children as unvaccinated if there was no evidence they had been immunized; as some of these children will have been vaccinated, this causes survival bias in favor of DTP [1, 5, 14–16]. Fourth, most of the studies did not test the effect of the most recent vaccine received by each child over time: the first dose of DTP has different effects when given before, with, or after BCG [4, 5]; the last dose of DTP has different effects given before, with, or after measles vaccine [5, 6]; and the effects differ by sex [1]. Fifth, many children were given BCG at the same time as DTP, rather than at birth (6 weeks before DTP) as specified in the EPI schedule [5]. In 2008, GACVS finally endorsed the view that evidence for the safety of DTP is “unlikely to be obtained from observational studies” [17]. Given the very large number of lives at stake, it is disappointing that it took the Committee so long to decide that observational studies are unlikely to provide adequate evidence that it is safe to give DTP to infants who have been vaccinated with BCG at birth, and even more disappointing that international agencies have not funded randomized trials to test the effect of DTP on all-cause mortality in children in high-mortality areas [5, 18]. We could obtain this information while still immunizing against diphtheria, tetanus, and pertussis if we randomized children to receive the primary series of DTP at different ages, or to receive a booster dose of DTP at different ages [18, 19].

The current EPI schedule is BCG-poliomyelitis at birth; DTP-polio at 6, 10, and 14 weeks; and measles vaccine at 9 months—but tuberculosis, polio, diphtheria, tetanus, pertussis, and measles are not the main causes of death in children, even in unimmunized communities [11]. The main reason that the EPI program has been beneficial may not be because it protects against these infections, but because the nonspecific effects of BCG and measles vaccines reduce the very large number of deaths from pneumonia, sepsis, and diarrhea. It is exciting that we may be able to save several million more lives each year just by making better use of the current EPI vaccines in an improved schedule—we urgently need randomized trials of the effects of the EPI vaccines on total mortality to help us design the optimal schedule [5, 18].
References