Commentary

Nonspecific Effects of Vaccines and the Reduction of Mortality in Children

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ABSTRACT

There is now strong evidence that vaccines have substantial nonspecific (heterologous) effects in children in high-mortality regions. The hypothesis states that, until a different vaccine is given: (1) live vaccines induce a protective nonspecific immune response, whereas inactivated vaccines cause a harmful nonspecific immune response; (2) Bacillus Calmette-Guerin (BCG) vaccine approximately halves mortality from infections other than tuberculosis; (3) provided vitamin A was not given at birth, measles vaccine approximately halves mortality from infections other than measles (this effect may be stronger if the child still has maternal antibody); and (4) whole-cell diphtheria-tetanus-pertussis (DTP) vaccine increases mortality from infections other than diphtheria, tetanus, and pertussis (this effect is stronger in girls than boys). These observations suggest that minor modifications to the routine immunization schedule could reduce child mortality by at least 30%, and they have important implications for the design of randomized trials of vaccines in high-mortality regions. (Clin Ther. 2013;35:109–114) © 2013 Elsevier HS Journals, Inc. All rights reserved.

INTRODUCTION

There is now strong evidence that vaccines have substantial nonspecific (heterologous) effects in children in high-mortality regions.1,2 The first major study suggesting that vaccines have important nonspecific effects was published >11 years ago.3 This large cohort study from Guinea-Bissau in West Africa concluded that whole-cell diphtheria-tetanus-pertussis (DTP) vaccine may increase mortality—a finding that caused considerable controversy. Over the subsequent decade, many more observational studies were published, with conflicting results.1,4 However, analysis of data from observational studies of this issue is particularly difficult due to the potential for survival bias (which favors immunization) and because nonvaccinated children in observational studies from high-mortality regions tend to be disadvantaged, with an increased risk of death (which causes selection bias in favor of immunization).2,4,5 Consequently, the World Health Organization (WHO) concluded in 2008 that conclusive evidence about the nonspecific effects of vaccines is unlikely to be obtained from observational studies.6 Fortunately, we now have a substantial body of evidence from randomized controlled trials (RCTs) and it supports the hypothesis that, until the next vaccine is given, Bacillus Calmette-Guerin (BCG) and measles vaccines have potent beneficial nonspecific effects (Table).1,7–13

BCG VACCINE

In 6 controlled trials from the United States and the United Kingdom in the 1940–1950s, the mortality rate ratio (95% CI) for diseases other than tuberculosis (TB) was 0.75 (0.59–0.94) for BCG versus control (Table [line 1]).1

A randomized trial from Guinea-Bissau reported that, among children who had received a booster dose of DTP at 18 months, the mortality rate ratio after BCG was 0.36 (0.13–0.99) compared with controls (Table [line 2]).9

Two trials of similar design from Guinea-Bissau tested the effects of BCG vaccine administered at birth7,8; the combined result was that the neonatal mortality rate ratio was 0.52 (0.33–0.82) when BCG was given at birth in low-birthweight infants (Table [line 3]).8 Given that >50% of infant deaths occur in the neonatal period,14 it is good news indeed that giving BCG at birth approximately halved neonatal mortality in those studies. In the trials, BCG was

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associated with reduced mortality within 3 days of vaccination, with a total of 9 deaths in the BCG group and 21 deaths in the control group. The rapid onset of protection probably occurs because BCG causes methylation of histone, with an epigenetic effect on innate immune cells\textsuperscript{15}; in a murine model, BCG was associated with protection against vaccinia virus within 1 to 2 days.\textsuperscript{16}

Although the evidence presented here suggests that BCG halves neonatal mortality, <50% of neonates in high-mortality regions are given BCG during the neonatal period.\textsuperscript{17-19} Because BCG is usually supplied in 20-dose vials, many clinics delay opening a vial until they have 8 to 12 infants to vaccinate.\textsuperscript{8} Economic modeling may help decide whether to (1) supply small clinics with single-dose syringes of BCG or (2) change policy so that a multidose vial is used even if BCG is needed by only 1 child.\textsuperscript{20}

MEASLES VACCINE

In Gambia, Guinea-Bissau, Senegal, and the Sudan, the mortality rate ratio (95% CI) has been reported to be 0.53 (0.37–0.77) in girls randomly assigned to receive measles vaccine at 9 months of age (Table [line 4]).\textsuperscript{1} Girls in the control group had been immunized against measles at 5 months of age; so, the difference was not due to reduced mortality from measles.

In another study, provided vitamin A had not been given at birth, children in Guinea-Bissau who were randomly assigned to receive an extra dose of measles vaccine at 4.5 months had a mortality rate ratio (95% CI) of 0.59 (0.39–0.89) compared with children who received only 1 dose of measles vaccine at 9 months of age.\textsuperscript{10} When measles cases were censored, the mortality rate ratio was 0.65 (0.43–0.99) (Table [line 5]). The beneficial effect was greater in children who still had maternal antibody when measles vaccine was given.

DTP VACCINE

No randomized trials are available on the effect of DTP on all-cause mortality. Although WHO will accept evidence only from RCTs,\textsuperscript{6} it has also stated that it would be unethical to conduct an RCT of DTP vaccine. However, subset analyses of the data from RCTs of BCG strongly suggest that DTP increases mortality, especially in girls.\textsuperscript{2}

In the RCT of revaccination with BCG at 19 months of age (BCG2) in Guinea-Bissau (Table [line 2]),\textsuperscript{9} 60% of the participants had not received a booster dose of DTP (DTP4) at the time of enrollment, and many of

<table>
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<th>Vaccine/Study</th>
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<td>BCG (randomized trials)</td>
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<tr>
<td>1. US and UK, 1948–1961: 0–21 y\textsuperscript{1}</td>
<td>0.75 (0.59–0.94)</td>
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<td>2. GB, after DPT booster: 19–60 mo\textsuperscript{9}</td>
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<td>3. GB, low-birth-weight neonates: birth–4 wk\textsuperscript{7,8}</td>
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<td>4. Gambia, GB, Senegal, Sudan: girls 10–60 mo\textsuperscript{1}</td>
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<td>5. GB, no vitamin A and after DPT3: 4.5–36 mo\textsuperscript{10}</td>
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<td>DPT (not randomized)</td>
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<td>6. GB: BCG-then-DPT vs DPT-then-BCG, 19–60 mo\textsuperscript{9}</td>
<td>5.12 (2.01–16.7)*</td>
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<tr>
<td>7. GB, BCG at birth: DPT by 2 mo of age, 2–6 mo\textsuperscript{11}</td>
<td>4.33 (1.54–12.2)*</td>
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<tr>
<td>8. First use in GB: for 6 mo after immunization clinic\textsuperscript{12}</td>
<td>1.92 (1.04–3.52)</td>
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*Subgroup analysis within a randomized controlled trial; bias very unlikely.\textsuperscript{2}
those children were given DTP4 after entering the study. Children who received BCG2 had a lower mortality than did controls if they had received DTP4 before enrollment (hazard ratio [HR] = 0.36; 95% CI, 0.13–0.99) but had a higher mortality if they had not received DTP4 before enrollment (HR = 1.78; 1.04–3.04), giving an HR for BCG2-then-DTP4 compared to DTP4-then-BCG2 of 5.12 (2.01–16.7) (Table [line 6]). Mortality rates were 0.36/100 person-years if DTP4 had been given before BCG2, 1.02 in controls who did not receive BCG2, and 1.83 if DTP4 had not been given before BCG2 (BCG2-then-DTP4). It is very unlikely that the increase in mortality with BCG2-then-DTP4 was caused by selection bias, because mortality in the control group (no BCG2) was not influenced by DTP4 status at the time of randomization (see Roth et al,9 Table 2), suggesting that this was not an independent risk factor.

In low-birthweight neonates randomly assigned to receive BCG at birth in Guinea-Bissau, mortality was 4.33-fold (1.54–12.2) higher among children who had received DTP by 2 months of age (Table [line 7])11; this finding was unlikely to have been caused by selection bias, because the infants given DTP were heavier and would have been expected to have had a lower mortality rate than that of the smaller infants who did not receive DTP by 2 months of age.

In the only adequately powered study of mortality after the introduction of DTP (Table [line 8]), the mortality rate ratio (95% CI) was 1.92 (1.04–3.52) in children in Guinea-Bissau who received DTP.12 DTP approximately doubled mortality despite the fact that there was no herd immunity from previous pertussis immunization.

EVIDENCE OF NONSPECIFIC EFFECTS

Evidence of the nonspecific effects of vaccines comes from 18 countries. The randomized trials were from the Gambia, Guinea-Bissau, Senegal, Sudan, the United Kingdom, and the United States (Table), and the observational studies were from Bangladesh, Benin, Burkina Faso, Burundi, Ghana, Guinea-Bissau, Haiti, India, Malawi, New Guinea, the Philippines, Senegal, and Zaire.1,21,22

Recent evidence suggests that BCG confers nonspecific protection through an epigenetic effect on innate immunity mediated by methylation of histone15,16 and that DTP causes a harmful proinflammatory response.23 The recent discovery of the adaptive features of innate immunity has wide-reaching implications for the immunology of vaccines—their nonspecific effects in particular.15 Heterologous immunity has been studied by research groups based at the Australian National University,24 the University of Massachusetts Medical School,16,25 Imperial College London,26 the Medical Research Council Laboratories in the Gambia,23,27 and the Nijmegan Medical Centre in the Netherlands.15

EXPANDED PROGRAMME ON IMMUNIZATION SCHEDULE

In many low-income countries, the Expanded Programme on Immunization (EPI) vaccines target tuberculosis, polio, diphtheria, tetanus, pertussis, and measles, but these are not the leading causes of death in children, even in nonimmunized communities.28 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 the BCG and measles vaccines reduce the very large number of deaths from pneumonia and sepsis, which are the leading causes of mortality.

A key determinant of child mortality is the most recent vaccine administered; the BCG and measles vaccines reduce mortality, but DTP may increase mortality, especially in girls. The current EPI schedule is BCG–polio at birth; DTP–polio at 6, 10, and 14 weeks; measles vaccine at 9 months; and, in many countries, a booster dose of DTP at 18 months (Figure, part A).13 With this schedule, DTP (or penta or hexa) is the most recent vaccine for 50 of the 60 months between birth and 5 years of age. DTP would be the most recent vaccine for only 4 of the 60 months if the schedule were changed to BCG–polio at birth; DTP–polio at 6, 10, and 14 weeks; measles vaccine at 9 months; and, in many countries, a booster dose of DTP at 18 months (Figure, part B). The 2 extra doses of measles vaccine at 18 weeks and 19 months could reverse any adverse effects of DTP and provide substantial beneficial nonspecific effects. Vaccines would be given to children on 7 occasions—2 more than with the current schedule.

In the schedule shown in part C of the Figure, an extra dose of measles vaccine would be given at 14 weeks of age—4 weeks after DTP2 and replacing DTP3. Giving measles vaccine at 14 weeks rather than at 18 weeks further reduces the time of exposure to DTP as the most recent vaccine, and more children...
would have maternal measles antibody when they receive the measles vaccine (which may increase the beneficial nonspecific effects of measles vaccine). A primary course of only 2, rather than 3, doses of DTP is likely to provide similar protection against death from pertussis; there may be an increase in the incidence of nonfatal cases of pertussis, but total mortality may be substantially reduced (with little or no increase in mortality from pertussis, and a large reduction in mortality from pneumonia and sepsis, which cause more deaths than does pertussis). A booster dose of DTP would be given at 12 months of age, followed by a second dose of measles vaccine at 13 months. Vaccines would be given to children on 5 occasions, as with the current schedule. Randomized trials are needed to test this schedule.

If all neonates in high-mortality regions were given BCG at birth, and the revised immunization schedule shown in part B of the Figure were adopted, with extra doses of measles vaccine at 14 weeks and 19 months (at a cost of only US $0.60/dose delivered), ~1 million (30%) of the 3.2 million neonatal deaths each year might be prevented in developing countries, and 1.5 million (30%) of the 4.8 million deaths between 1 month and 5 years of age might be prevented (Table). This very large reduction in mortality in children <5 years of age would be achieved at a low cost using only vaccines that are already in the routine EPI schedule.

Current evidence suggests that the EPI schedule should be revised. Future research should test the effects of existing and new vaccines on all-cause mortality in high mortality regions. It might be important to continue to give the BCG and measles vaccines in high-mortality regions, even if the target disease were eradicated or subunit vaccines were developed. Unfortunately, policymakers have been all too ready to dismiss the nonspecific effects of vaccines as quirky findings based on flimsy evidence. Now that substantial evidence from randomized trials and immunologic studies suggests that these effects are important, it is time for strong international support for the conduct of randomized trials to test the effects of BCG, measles vac-

Figure. The current Expanded Programme on Immunization schedule, and modified versions that consider the nonspecific effects of vaccines. B = Bacillus Calmette-Guerin; D = diphtheria-tetanus-pertussis (DTP) or penta; M = measles vaccine; X = DTP most recent vaccine.
cine, and DTP on all-cause mortality in children in high-mortality regions.³¹

CONCLUSION
The available evidence suggests that minor modifications to the routine immunization schedule could reduce child mortality by at least 30%, and has important implications for the design of randomized trials of vaccines in high-mortality regions.

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CONFLICT OF INTEREST
The author has indicated that he has no conflicts of interest regarding the content of this article.

REFERENCES


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