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# Different Strains of Bacillus Calmette–Guérin Vaccine Have Very Different Effects on Tuberculosis and on Unrelated Infections

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(See the Major Article by Storgaard et al on pages 950–9.)

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Bacillus Calmette–Guérin (BCG) vaccine provides good protection against disseminated mycobacterial diseases such as miliary tuberculosis, tuberculous meningitis, and leprosy [1, 2] but weaker protection against pulmonary tuberculosis, especially in rural areas near the equator [3]. In high-mortality countries, until a different vaccine is given, BCG vaccine also provides nonspecific (heterologous) protection against diseases other than tuberculosis and leprosy (mainly respiratory infections and sepsis) [4]. In randomized trials in Guinea-Bissau, vaccination with BCG–Danish vaccine reduced neonatal mortality in low-birth-weight babies by 48% (95% confidence interval [CI], 18%–67%) [5, 6], and

revaccination reduced all-cause mortality by 64% (95% CI, 1%–87%) in children aged 19 months who had received a booster dose of diphtheria–tetanus–pertussis vaccine [7]. BCG vaccine may also have important nonspecific effects in high-income countries. In a cohort study in Spain, BCG–Danish vaccine reduced nontuberculous hospital admissions in infants by 32% (95% CI, 31%–34%) for respiratory infections and by 53% (95% CI, 44%–61%) for sepsis [8].

In this issue of *Clinical Infectious Diseases*, Storgaard and colleagues report the results of a study based on a remarkable surveillance system that has prospectively monitored a representative sample of rural Guinea-Bissau since 1990. This is an extraordinary database. The study found a scar in only 52% of children given BCG–Moscow vaccine, the same rate as BCG–Moscow vaccine in Uganda [9] but much lower than the 72%–97% scar rate after BCG–Danish vaccine was given in urban Guinea-Bissau [10–13]. The low scar rate in rural Guinea-Bissau may be due to the fact that the BCG–Moscow vaccine is less likely to produce a scar than the BCG–Danish vaccine (as suggested by the similar result in Uganda), but it may also be due to disruption of the cold chain in rural areas or poor vaccination techniques.

An important finding in the study in rural Guinea-Bissau was that among infants who had received BCG–Moscow vaccine, those with a scar had a 52% (95% CI, 10%–74%) lower mortality rate than those with no scar. The authors present evidence that the lower mortality was unlikely to be explained by healthier children being more likely to form a scar, and the results are consistent with previous studies showing a relationship between BCG–Danish vaccine scar and survival [10–13]. Clearly, it would be desirable to test whether revaccination with BCG vaccine reduces all-cause mortality in children who do not develop a scar after a single dose. In addition, in the randomized trial in Guinea-Bissau that showed reduced mortality after revaccination at age 19 months, 77% of the children had a scar [7]. Consequently, further randomized trials are needed to test the effects of revaccination on all-cause mortality in children who have a scar following BCG vaccination at birth, as well as those without a scar. Revaccination with BCG vaccine confers little or no extra protection against tuberculosis but it may improve protection against leprosy and increase the beneficial nonspecific effects of BCG vaccine [14].

Although the presence of a BCG vaccine scar is associated with reduced mortality from diseases other than tuberculosis, it

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does not predict susceptibility to tuberculosis [15]. Indeed, no laboratory test or clinical finding (such as BCG vaccine scar or Mantoux test) predicts susceptibility to tuberculosis after BCG vaccination, and animal models are not a reliable guide to the effectiveness of different strains of BCG [15]. Ninety-four years after it was first used in humans, we still have no way to determine which children are protected against tuberculosis following BCG vaccination, and we do not know how BCG vaccine protects against tuberculosis [16]. However, we do know that BCG vaccine protects against infections other than tuberculosis, at least in part, by an epigenetic effect mediated by methylation of histone that alters innate immunity in adults [17] and neonates [18]. It would be ironic if we were to discover that BCG vaccine protects against tuberculosis via a *nonspecific* effect mediated by innate immunity [16, 17]. We urgently need to know more about the mechanisms by which BCG vaccine protects against mycobacterial and nonmycobacterial infections.

The Expanded Program on Immunization (EPI) recommends that BCG vaccine be given at birth to all neonates in countries with a high prevalence of tuberculosis; the World Health Organization-approved vaccines are BCG–Danish, BCG–Tokyo, and BCG–Moscow. Are different strains of BCG equivalent? A large randomized trial in 303 092 neonates in Hong Kong found that the risk of tuberculosis with BCG–Pasteur vaccine was 45% (95% CI, 22%–61%) less than with BCG–Glaxo [19]. In a cohort study in Kazakhstan, vaccination of neonates reduced the risk of clinically diagnosed tuberculosis by 69% (95% CI, 61%–75%) after BCG–Tokyo vaccination, by 43% (95% CI, 31%–53%) after BCG–Serbia, and only by 22% (95% CI, 7%–35%) after BCG–Moscow [20]. These findings suggest that there are very large differences in effectiveness against tuberculosis between BCG strains. In 2014, United Nations Children’s Fund (UNICEF) supplied 86 million doses of BCG–Moscow

vaccine (the least effective strain in Kazakhstan), only 31 million doses of BCG–Tokyo (the most effective strain in Kazakhstan), and only 5 million doses of BCG–Danish (the strain that reduced neonatal mortality by 48% in Guinea-Bissau) [21]. However, UNICEF’s purchasing was constrained by limited supplies of BCG–Tokyo and BCG–Danish vaccines.

The nonspecific effects of BCG vaccine are greater when there is a scar following BCG–Danish or BCG–Moscow vaccination, and different strains of BCG have very different scar rates (usually >90% for BCG–Danish and BCG–Tokyo vaccines, but only 52% for BCG–Moscow vaccine in Guinea-Bissau and Uganda) [9–13]. Consequently, different strains are likely to have different nonspecific effects. It is therefore highly desirable that we compare both the specific and nonspecific effects of different strains of BCG. Comstock has suggested that protection against tuberculosis could be tested easily with an ABAB observational study [19]. In such a study, all neonates in a defined region would be vaccinated with one strain (A) of BCG for a year and another strain (B) the next year, with the alternation continued for another 2 years (AB). Providing tuberculosis were recognized similarly in odd and even years, this ingenious design would approach true randomization but at much lower cost.

In addition to the important genetic differences between the strains of BCG [22], there are genetic differences within some strains that can cause major differences in the characteristics of BCG vaccine produced from the same seed lot by different manufacturers [23] and between different batches from a single manufacturer [24]. BCG–Tokyo and BCG–Danish vaccines each contain at least 2 genotypes [25]. In 1983, Osborn suggested that BCG vaccines used for routine immunization should be prepared from seed lots derived from single colonies so that they have stable characteristics [23]. Unfortunately, this has not been done for BCG–Tokyo or

BCG–Danish vaccines. This can lead to problems with the production of these vaccines [21] and the potential for large variations in clinical effects [24].

BCG–Danish vaccine and probably BCG–Tokyo vaccine have potent nonspecific effects that substantially reduce mortality from diseases other than tuberculosis; however, these beneficial effects are not properly exploited at present. Although it is EPI policy for BCG vaccine to be given to all infants at birth in high-prevalence regions, less than half actually receive BCG vaccine in the first month of life, partly because health workers are told not to open a multidose vial until enough infants need BCG vaccine. A 10- or 20-dose vial costs UNICEF only \$0.75–\$2.74, and BCG–Danish vaccine given soon after birth reduced neonatal mortality by 48% (95% CI, 18%–67%) in randomized trials in Guinea-Bissau [5, 6]. Policy should change so that as many infants as possible receive BCG vaccine as soon as possible after birth, and a multidose vial should be opened even if only 1 infant needs BCG vaccine.

Over many years, substantial resources have been devoted to attempts to develop a new vaccine against tuberculosis, so far without success. This has distracted us from making optimal use of BCG vaccine, when some simple measures would almost certainly have improved both its specific and nonspecific effects. If a new vaccine against tuberculosis is developed, it will be important to test its effects on all-cause mortality as well as its effects on tuberculosis; we may need to continue to use BCG vaccine for its highly beneficial nonspecific effects.

The BCG vaccine is not a single vaccine; the different strains have very different properties, and there are different genotypes within strains. It is likely that we could substantially improve protection against tuberculosis and lower child mortality from other infections by manufacturing each BCG vaccine from a single genotype, comparing these vaccines to find which genotype has the strongest

effects against tuberculosis and against other infections, investigating the effect of revaccination on all-cause mortality, and ensuring that a high proportion of neonates are given BCG vaccine in the first few days of life. These measures are likely to yield very large benefits at minimal cost.

## Note

**Potential conflict of interest.** Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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