Changes in BCG Vaccination Policy Should Consider the Effect on Child Health

To the Editor—Tchakoute et al [1] assessed the BCG-specific T-cell proliferation and responsiveness following BCG vaccination at birth versus BCG vaccination at 8 weeks of age in human immunodeficiency virus (HIV)–exposed, uninfected infants. The authors concluded that the 8-week delay did not compromise the immunogenicity of BCG vaccination; in fact, the immunogenicity may have been even higher [1]. This is important because according to current World Health Organization (WHO) recommendations, whereas HIV-exposed children without symptoms should receive BCG vaccine at birth, HIV-infected infants and HIV-exposed infants with symptoms of HIV infection should not receive BCG vaccination, because of the risk of disseminated BCG disease (Table 1) [2]. Giving BCG vaccination to HIV-infected children is associated with an estimated risk of 417–992 cases of disseminated BCG disease per 100,000 vaccinations; with a case-fatality rate of 75% [3] this could mean around 1 death in 200 BCG vaccinations of HIV-infected children. Thus, if BCG administration to HIV-exposed infants can be delayed to 8 weeks, it would be possible to exclude many HIV-infected children and reduce the risk of disseminated BCG disease without compromising immunogenicity.

The authors should be commended for studying how BCG vaccination recommendations for HIV-exposed infants may be improved. However, neither the authors [1] nor the editorial commentary [3] consider the potential nonspecific effects of BCG.

Many observational studies have shown that BCG may have very positive heterologous nonspecific effects, increasing the general resistance to infectious diseases early in life. In randomized trials among low-birth-weight infants, administration of BCG vaccine at birth versus delayed vaccination as usual was associated with a 48% reduction in neonatal mortality [4, 5]. In 2014, the WHO Strategic Advisory Group of Experts on Immunization acknowledged that BCG vaccination may have beneficial nonspecific effects and recommended further research [6].

From a tuberculosis-prevention perspective, delaying BCG vaccination of HIV-exposed infants until 8 weeks of age may be a limited problem, and as shown by the authors, it may result in even improved immune response to the vaccine [1]. However, neonatal mortality constitutes a great proportion of deaths among children aged <5 years [7]. If BCG vaccination reduces neonatal mortality by around 40%, it is clear that, a delay in BCG vaccination to 8 weeks of age, among HIV-exposed children and irrespective of their symptoms, would yield >1 death among 200 recipients, compared with the mortality rate if they had received BCG vaccine at birth (Table 1). This difference will be even more pronounced with time: with reduced rates of mother-to-child transmission of HIV [8] and better treatment [3], disseminated BCG disease will be responsible for a decreasing fraction of deaths.

BCG vaccination is already markedly delayed in most African countries [9], preventing many children from benefiting from the nonspecific effects of BCG vaccination early in life. Emphasis on the immunological safety of delayed BCG vaccination may lead to further delays in BCG vaccination of HIV-exposed children and possibly also other children and may therefore do more harm than good. Larger studies assessing the impact on overall child survival are needed before recommending delayed BCG vaccination for HIV-exposed children.

Table 1. Current and Possible BCG Vaccination Policies

<table>
<thead>
<tr>
<th>Population</th>
<th>Current WHO Policy</th>
<th>Possible Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-unexposed infants</td>
<td>BCG vaccination at birth</td>
<td>BCG vaccination at birth</td>
</tr>
<tr>
<td>HIV-exposed infants with symptoms</td>
<td>No BCG vaccination</td>
<td>No BCG vaccination</td>
</tr>
<tr>
<td>HIV-exposed infants, no symptoms</td>
<td>BCG vaccination at birth</td>
<td>BCG vaccination at 8 wks of age</td>
</tr>
</tbody>
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Implications for HIV-exposed children
- Risk of disseminated disease in HIV-exposed infants without symptoms who turn out to have HIV infection (approximately 1 in 200 who are vaccinated)
- Beneficial nonspecific effects of BCG vaccination early in life (40% reduction in neonatal mortality)
- Reduced risk of disseminated disease in HIV-exposed infants without symptoms who turn out to have HIV infection (approximately 1 in 200 who are vaccinated)
- No beneficial nonspecific effects of BCG vaccination early in life

Abbreviations: HIV, human immunodeficiency virus; WHO, World Health Organization.

Notes

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