Adverse Effects of Bacille Calmette-Guérin Vaccination in HIV-Positive Infants

Sir—We refer to the recent article by Heseling et al. [1] on Danish bacille Calmette-Guérin (BCG) vaccine-induced disease in HIV-positive children. Although we do not wish to minimize the importance of exercising caution when administering BCG to HIV-exposed infants, we believe the main conclusion reached by the authors—namely, that “the Danish BCG strain poses a risk for localized and disseminated disease in infants who are infected with HIV” [1, p. 1232]—could imply that Danish BCG is more likely than other strains of BCG to cause disseminated disease in these infants. We contend that one cannot reach this conclusion on the basis of the data presented and because of the limitations of the study, particularly the lack of comparable data on other strains of BCG in HIV-infected children.

The fact that the authors found no isolates of Mycobacterium bovis BCG in infants and children immunized with the Tokyo M. bovis BCG strain may well relate to characteristics of the South African national immunization program before 2000, as well as to the relative pathogenicity of different BCG strains. Prior to 2000, percutaneous Tokyo M. bovis BCG vaccination was used. Kibel et al. [2] and Lunn [3] showed that the vaccination tool and method used led to a negligible number of local reactions and little evidence of penetration, because of blunt, bent, and retracted needles and questionable vaccination techniques. It was concluded that the vaccination device in question “fails to introduce adequate quantities of BCG” [3, p. 272]. If inadequate amounts of the Tokyo M. bovis BCG strain were being administered to South African infants between 1992 and 2000, that could be a major factor contributing to the failure to observe disseminated Tokyo BCG disease in these infants.

It is also our contention that the data presented leave room for some diagnostic uncertainty. It is true that patients A and B had intra-abdominal adenopathy, and patients A, B, D, and E all had hepatosplenomegaly. In all these cases, the findings are listed as possible manifestations of BCG disease, but, of course, there are other possible causes of hepatosplenomegaly, including disseminated Mycobacterium tuberculosis infection, which was present in patients B and E. Patients A and D did have definite evidence of disseminated BCG disease, as evidenced by isolation of M. bovis BCG from gastric washing specimens, but patients B, C, and E appear to have had local axillary adenitis, an adverse reaction to BCG vaccination, without definite evidence of dissemination, which is to be expected in a proportion of infants.

In a similar area of South Africa, we are performing follow-up for infants and children as part of a phase 4, randomized, controlled trial comparing the efficacy of percutaneous and intradermal Tokyo 172 BCG vaccination in the prevention of tuberculosis (TB). At the end of September 2003, a total of 8799 infants of a target number of 12,000 had received the vaccine. Active surveillance for vaccine-associated adverse events has, to date, identified 4 instances of ipsilateral axillary lymphadenitis (“regional disease,” according to Talbot’s classification; incidence, 0.045%). Blood samples for all 4 infants tested negative for HIV infection. The point is that the Tokyo M. bovis BCG strain can also cause severe local adverse reactions.

In addition, 663 infants and children enrolled in the trial who were either contacts of persons with TB or were suspected of having TB were evaluated for possible
tuberculous disease; 24 of these were HIV exposed. Evaluation involved admission to a hospital for obtaining of gastric washing and induced sputum specimens for TB smear and culture. Isolates from all positive TB cultures were then typed using biochemical and molecular techniques. Specimens from 105 patients produced results positive for TB. Six of these patients were HIV exposed. None of the isolates obtained to date has been typed as M. bovis BCG.

In the same area, as part of a separate evaluation completed this year, we performed follow-up for 100 HIV-exposed infants at 6-16 weeks of age. Of these 100, we found 16 who were HIV-PCR positive [4]. Approximately 50% of these infants had received vaccination with the Danish M. bovis BCG strain at birth; the rest received the Tokyo M. bovis BCG strain. None of the 100 infants had any evidence of regional, extraregional, or disseminated BCG disease.

In conclusion, we agree that BCG vaccine may have adverse effects in HIV-positive infants. However, the extent of this problem and the relative risk associated with different BCG strains, inoculation routes, and other variables still needs to be formally evaluated in well-designed, rigorous clinical studies.

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References

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Reply
Sir—We appreciate the comments from Hussey et al. [1] regarding our recent article [2]. Our main aim was to determine whether local and systemic complications from bacille Calmette-Guérin (BCG) vaccination do occur in HIV-infected infants. We therefore performed a retrospective study, which obviously has limitations. Our main conclusion was that these complications may occur in HIV-infected infants, and that this phenomenon should be studied in more detail in prospective studies.

Our aim was therefore not to compare adverse effects of different BCG vaccine strains. Only those infants vaccinated with the Danish Mycobacterium bovis BCG strain were found to have had BCG-disease complications. The risk and clinical presentation in this group of immunocompromised infants were described.

The reason Hussey et al. [1] propose for our finding of an absence of adverse effects following vaccination with the Tokyo BCG strain may be very plausible. However, differences in reactogenicity between BCG strains, and also between the Tokyo BCG strain and the Danish BCG strain, have been described [3, 4], suggesting that different rates of adverse events may also occur. Prospective, direct clinical comparisons of adverse effects following vaccination with different BCG strains are required to address this issue reliably. However, as intradermal vaccine with the Danish M. bovis BCG strain is now uniformly administered to both HIV-exposed and HIV-unexposed infants in South Africa, these findings are relevant.

We concur that clinical findings such as intra-abdominal lymphadenopathy and hepatosplenomegaly may allow variable interpretation, particularly in HIV-infected infants. Confirmation by deep-tissue biopsy was not always possible; therefore, we used the term “probable disseminated BCG disease” [5]. However, as pointed out by Hussey et al. [1], the Danish M. bovis BCG strain was detected in gastric aspirates of 2 patients, affirming a possible diagnosis of disseminated disease.

Further, we attempted to make a clear distinction between regional disease (e.g., ipsilateral adenitis) and systemic BCG disease.

The consequences of ipsilateral adenitis, as described in 3 patients, are unknown in immunocompromised, HIV-infected infants. However, in 1 patient, the initial presentation of ipsilateral adenitis was followed by systemic BCG disease. We pointed out the importance of clinical awareness and appropriate medical and/or surgical management of local complications. Of note, after the completion of our retrospective study, 2 additional cases of ipsilateral adenitis due to the Danish M. bovis BCG strain and 1 case of dual infection with M. tuberculosis and BCG were detected in severely immunodeficient, HIV-infected infants. The possible role of coinfection with M. tuberculosis was not discussed, as we still have inadequate data. However, immunocompetent infants with ipsilateral adenitis caused by BCG may indeed have a very different or minimal risk following local BCG complications, compared with severely immunodeficient infants.

We appreciate that Hussey et al. [1] share important preliminary data from their current, large vaccination studies. However, it is difficult to draw any comparisons between our retrospective hospital-based analysis, which describes Danish BCG-induced complications, and their population-based, randomized field trials.