Reply to Thysen et al

To the Editor—We thank Thysen et al for their cautionary perspective on BCG vaccination policy changes. Although we found improved immunogenicity of BCG vaccine in human immunodeficiency virus (HIV)–exposed infants vaccinated at 8 weeks of age, compared with immunogenicity among those vaccinated at birth [1], we do not recommend changes to vaccine-delivery services on the basis of these data. Nonetheless, our study contributes valuable data indicating that the immunogenicity of BCG vaccination is not negatively affected by delaying administration until 8 weeks of age, which is much needed in regions of high HIV prevalence where new tuberculosis vaccination strategies are undergoing clinical evaluation [2].

As highlighted by Thysen et al, previous trials have shown that BCG vaccination can improve all-cause mortality in West African children [3, 4], and in some cases, can improve innate and adaptive immunity to unrelated antigens [5, 6]. However, it is important to note the context in which these studies were performed. Gambia and Guinea-Bissau have poor healthcare infrastructures, high infant mortality [7], and considerably lower HIV infection and tuberculosis incidences than South Africa, where our trial was conducted. In such settings, the benefits associated with early BCG vaccination could outweigh any risks posed to HIV-infected infants, and delaying BCG vaccination could be detrimental to child survival. In settings with good integration of routine infant vaccination services, programs to prevent and treat tuberculosis, and services to prevent mother-to-child transmission of HIV, where infrastructure could support selectively delayed BCG vaccination for HIV-exposed infants, the risks due to delaying BCG vaccination would be lower.

Additional points to consider are that in the prior studies from Guinea-Bissau, BCG vaccination was combined with other interventions, including vitamin A administration, and the randomized trials studied delayed BCG vaccination in low-birth-weight infants only, in whom mortality is high and immunity less mature [3, 4]. In West Africa, routine infant immunization coverage is relatively low, and data on the causes of infant mortality in these studies are limited [8]. A recent systematic review of studies performed elsewhere did not show any clear evidence of beneficial nonspecific effects associated with BCG vaccination [9], which may be setting specific.

Furthermore, it is unclear whether there are any nonspecific protective effects from BCG vaccination in HIV-exposed infants, who have altered adaptive and innate immunity [10, 11]. One of the suggested mechanisms by which BCG vaccination improves immunity to pathogens other than the agents of tuberculosis is through monocyte reprogramming [5]. Monocyte responsiveness in HIV-exposed infants appears to be higher than that in unexposed infants, potentially implying differential epigenetics in this population [12]. In our randomized controlled trial in HIV-exposed infants [1], there were 2 deaths (mortality rate, 1.3%), both in infants who received BCG vaccine at birth and were not infected with HIV. In a recent randomized controlled trial of delayed BCG vaccination until 14 weeks of age in Khayelitsha, South Africa, we likewise found no difference in mortality between HIV-exposed infants receiving delayed BCG vaccination versus those vaccinated at birth [13]. All tuberculosis cases occurred between week 20 and month 18 of age; no investigations for tuberculosis were completed prior to 14 weeks of age. Therefore, in neither of these 2 South African studies did any infants receive a tuberculosis diagnosis before 14 weeks of age.

Thysen et al have not considered additional important complications of live BCG vaccination in HIV-infected infants apart from disseminated BCG, which is a rare complication. BCG adenitis, often occurring in the context of immune reconstitution inflammatory syndrome, occurs in 6.6% of infected infants, even in the setting of very early initiation of antiretroviral therapy [14]. The true number of BCG vaccine–associated adverse events

in HIV-infected infants is likely higher, given limited surveillance, and would again be setting specific. Finally, BCG vaccination leads to nonspecific $CD4^+$ T-cell activation in HIV-exposed infants, potentially making them more susceptible to HIV infection or disease progression if HIV infected [15]. All of these factors should be considered when implementing selectively delayed BCG vaccinations strategies in HIV-exposed infants.

We recommend that BCG vaccination strategies in research and routine care settings consider local factors, including the prevalence of HIV, the prevalence of tuberculosis, the healthcare infrastructure, and key indicators such as infant mortality rates. Further research is needed on BCG vaccination's risks and benefits in HIV-exposed infants before improved tuberculosis preventive vaccines are introduced.

Notes

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Christophe Toukam Tchakoute,[1,2,a] Anneke C. Hesseling,[3] Anna K. Blakney,[1,2,4] and Heather B. Jaspan[1,2,5,6,7]

[1]Division of Immunology, [2]Institute of Infectious Disease and Molecular Medicine, Department of Clinical Laboratory Sciences, University of Cape Town, and [3]Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; [4]Department of Bioengineering, [5]Seattle Children's Research Institute, [6]Department of Pediatrics, and [7]Department of Global Health, University of Washington, Seattle

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[a]Present affiliation: Columbia University, New York, New York.

Correspondence: Heather B. Jaspan, MD, PhD, Seattle Children's Research Institute, JMB-08 1900 9th Ave, Seattle, WA 98101 (hbjaspan@gmail.com).

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