EDITORIAL COMMENTARY

BCG Modulates Neonatal Innate Immune Cytokine Production

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(See the major article by Jensen et al on pages 956–67.)

Infection causes 0.6 million of the total 2.9 million neonatal deaths every year and devastates the lives of millions more who initially survive; it mercilessly seeks out those weakened by premature delivery and/or low birth weight (LBW), an unfortunate combination too frequently encountered all over the world but particularly so in low-income countries [1]. Reduction of neonatal mortality over the last decade has been slower than that for maternal and child mortality but slowest in the highest burden countries of Africa [2]. Given the scale and the scope of this problem, any intervention even remotely effective would save millions of lives as well as billions of dollars; but given the uneven global distribution, with neonatal infections most severely affecting the poorest regions of the world, such intervention has to be cheap to initiate and easy to sustain [3].

The article “Heterologous immunological effects of early BCG vaccination in low-birth weight infants in Guinea-Bissau: A randomized-controlled trial” by Jensen et al in this issue of the Journal presents data in support of bacillus Calmette-Guérin (BCG) being such a highly effective, cheap, and easy to sustain solution to tackle neonatal infection. Jensen et al identify that neonatal administration of BCG can induce an altered cytokine response in LBW newborns of Guinea-Bissau. More specifically, they show that BCG alters the cytokine response to antigen-specific but also to nonspecific stimuli as well as at baseline, that is, in unstimulated samples. These data expand on this group’s previous finding that innate immune cytokine production in blood correlates with neonatal survival [4]. They now show that the type of innate cytokine change induced by neonatal BCG vaccination could be expected to support enhanced Th-1 helper cell differentiation and/or be generally pro-inflammatory; and they conclude that a BCG-mediated “accelerated development of the neonatal innate immune system” may be partially responsible for the comprehensive protection against infectious mortality they had previously noted following neonatal BCG vaccination in Guinea-Bissau [5–7].

All live vaccines studied so far have been shown to reduce mortality more than can be explained by prevention of the targeted infection [8]. More specifically, the protective effect of BCG on neonatal survival, which has now been observed in several randomised trials in LBW infants, cannot be explained by reduction of the risk for infection with Mycobacterium tuberculosis or active tuberculosis [5–7] but is instead believed to be due to nonspecific (ie, not only targeting M. tuberculosis) immunomodulation by BCG [8].

The topic is very timely given the recent World Health Organization’s (WHO) acknowledgement of nonspecific effects of vaccines and the WHO’s urgent call for more research on this topic to identify the underlying mechanisms [9]. With respect to mechanisms, the findings presented by Jensen et al are in agreement with data obtained in adults indicating prolonged alteration of innate immunity following BCG administration [10, 11], a novel concept summarized under the term “innate immune memory” [12, 13]. The Jensen et al article is, however, the first time that a change of innate immune status following BCG has been documented in the neonatal age group, in which the protective effect of BCG on mortality had previously been identified. This article thus adds a key piece of information to this highly relevant field.

Note

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

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References