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EDITORIAL REVIEW
New developments in BCG vaccine: implications for tuberculosis control

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The efficacy of the conventional bacille Calmette-Guérin (BCG) vaccine is often questioned because of conflicting trial results [1]. In this context, a new BCG vaccine developed by Grode *et al*. [2] has been seen as a favourable development in tuberculosis (TB) control [3]. BCG vaccine development is a challenge for many reasons, not least of which is the complex immunology of mycobacterial infections. The pathogenesis of TB, and prevention of TB by BCG, is predominantly a function of cell-mediated immunity. *Mycobacterium tuberculosis* (MTB) and BCG are phagocytosed, but remain viable for some time within the phagosome. There, BCG antigens must be presented to major histocompatibility complex (MHC) class II molecules to activate CD4+ cells, and to MHC class I molecules to activate CD8+ cells [3]. However, both MTB and BCG fail to activate CD8+ cells sufficiently. The relative failure of activation of CD8+ cells is thought to be related to the enzyme urease, which keeps the intracellular pH high and thus inhibits presentation of antigens to T cells which would otherwise activate the CD8+ response. Grode *et al*. [2] have engineered a BCG strain which overcomes this problem and allows release of antigen into the cell and thereby stimulates a CD8+ cell response in addition to the CD4 response seen with conventional BCG. They did this first by engineering a strain of BCG which secretes listeriolysin (Hly), an enzyme from *Listeria monocytogenes* which perforates cell membranes. Second, they optimized the pH for Hly activity by making the BCG strain urease C-deficient. With the resultant lowering of intracellular pH, the BCG strain is able to better activate CD8 cells and antigen presentation. This new vaccine strain causes apoptosis of infected cells and release of BCG antigens, which are presented to CD8+ cells. The secretion of Hly and the engineered urease deficiency resulted in incrementally improved efficacy of the vaccine compared to conventional BCG, when tested in mice [2]. In severe combined immunodeficiency disease (SCID) mice tested, the modified BCG vaccine was less virulent than conventional vaccine, probably because of reduced intracellular persistence of the bacteria [2]. There are no published data yet on the use of this vaccine in humans, but phase 1 trials are being planned. Other approaches to modifying the BCG vaccine include a strain which secretes higher levels of MTB 30-kDa, a major secretory protein [4]. A combination of these approaches may result in even better efficacy, and may be the next step in vaccine development.

TB causes a high burden of disease in the developing world [5]. In sub-Saharan Africa in the pre-HIV era, the case fatality of TB is 41–48%, a figure which hardly differs from that of the pre-chemotherapy era of 50% mortality in 2 years [6, 7]. With HIV, the mortality became even higher. The increasing problem of multidrug-resistant TB [8], itself associated with high mortality rates and low survival time, makes vaccine development for TB a priority. BCG vaccination remains an important aspect of TB control, along with directly observed therapy, short course (DOTS) [9], in developing countries. However, BCG vaccine is only one strategy for prevention of TB.

Prevention of cases can be achieved by either reducing the risk of new infection, or by prevention of

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disease in those already infected. Prevention of new infections can be achieved by prompt diagnosis and treatment [10–13] and by good hospital infection control measures [14, 15]. Environmental factors such as ventilation and ultraviolet light may also play a role. BCG vaccine is used as primary prevention, and may prevent primary infection or subsequent haematogenous spread of TB [1]. Secondary prevention of disease in persons with asymptomatic infection can be reduced by screening and identifying persons at risk and giving them preventive therapy [16]. Effective treatment of comorbid conditions such as diabetes or HIV infection may also reduce the risk of reactivation. In developed countries, TB control efforts have centred on secondary prevention by screening with tuberculin and offering preventive therapy with isoniazid, rather than primary prevention by vaccination. This is due to a number of factors, including the low incidence of TB in most developed countries, perceived lack of effectiveness of BCG vaccine, difficulty in interpreting the tuberculin skin test in BCG-vaccinated people, and difficulty of implementing a targeted vaccination programme for infants at high risk.

BCG was developed from a live, attenuated strain of *Mycobacterium bovis* by Albert Calmette and Camille Guérin. Its widespread use in human populations began in the 1920s, without clear initial evidence of efficacy against prevention of TB. The first route of administration was oral, followed by subcutaneous and then intradermal. Throughout its history, several different strains of BCG have been used in clinical trials. The first trials of the vaccine, begun in Canada in 1925, used the Montreal strain. The United States in 1927 used the Park strain [17, 18]. While some of these early studies showed significant protective efficacy, the largest US trials using the Park strain and the Tice strain did not [19, 20]. Most trials conducted outside North America used the Copenhagen or Paris strains of BCG, including the largest published trial, the Madras trial, which included nearly 180 000 subjects [21]. The Madras trial showed lack of protection, and specifically showed no efficacy against pulmonary TB [21]. In the 1960s, the Glaxo strain was used in some trials [22].

The methods and study design of the many trials of BCG vaccine have also differed. Some, for example, included subjects with a positive tuberculin test, indicating latent infection with TB, while others used only uninfected subjects [23, 24]. If BCG vaccine is used in a population with a high prevalence of pre-vaccination tuberculous infection, the efficacy will be low [24]. In addition, there is a relationship between efficacy and geographical latitude and exposure to environmental mycobacteria, which is independent of vaccine strain [24–26]. The efficacy tends to increase with increasing latitude and with decreasing exposure to environmental mycobacteria.

The results of BCG vaccination trials have been widely divergent, with some showing efficacy against prevention of active TB as high as 80% and others none at all [1]. A meta-analysis by Colditz *et al.* in 1994 [1], which included clinical outcome data from all the major trials including the Madras trial, as well as observational studies, found that on average, BCG had 50% protective efficacy against active TB, and 71% efficacy against TB mortality. The studies included in this meta-analysis were heterogenous in many respects. This must be considered when interpreting the data, as averages, based as they are on different strains, populations and conditions, may be misleading. Most incident TB cases in the trials were pulmonary, so the protective efficacy was reported as being 'against predominantly pulmonary TB' [1]. This has been sometimes misunderstood to mean that the vaccine is not effective against extrapulmonary TB, or alternatively, the Madras trial is quoted as evidence that BCG has no efficacy against pulmonary TB, but the meta-analysis clearly showed effectiveness against both forms of TB. The variation in efficacy between trials was explained somewhat by geographical latitude, but not by vaccine strain [1]. A further meta-analysis of BCG trials in infants and children showed that the vaccine efficacy was 74% overall, and 83% if only laboratory-confirmed TB was considered [27]. BCG, therefore, has an efficacy in the same range as some routine childhood vaccines [28], but one that varies considerably, depending on factors such as geographical latitude, exposure to environmental mycobacteria, underlying prevalence of TB infection and possibly BCG strain. Sadly, it appears to be least effective in latitudes where the incidence of TB is highest [29].

In summary, despite conflicting and sometimes misinterpreted evidence from individual trials, it seems that conventional BCG is moderately effective. If the Grode vaccine proves to be highly efficacious in human trials, will it be the solution to the problem of global TB? There is undoubted value in the development of a new, more effective BCG vaccine, and the latest research by Grode *et al.* offers hope in this direction. If this vaccine continues to show promise in human trials, it may have an important role in TB

control in developing and developed countries. It is, however, possible that even if the vaccine shows high efficacy in human trials, it may be subject to the same variations in efficacy as seen with conventional BCG. That is, that the vaccine efficacy would vary by latitude and depend on prior infection with TB or exposure to environmental mycobacteria.

A more efficacious vaccine will be more useful in developed countries for targeted risk groups such as children of immigrants from high-risk countries and health-care workers, but is unlikely to be cost-effective as a universal vaccination programme [30]. In developing countries, primary prevention with a highly efficacious vaccine delivered through a national vaccination programme may be more cost-effective than current reliance on DOTS programmes as the mainstay of TB control efforts. BCG has been shown to be highly cost-effective for children in high-incidence areas [31]. The barriers to TB control have not been all related to intrinsic properties of the vaccine, therefore an effective vaccine is only one part of the solution. To achieve global control of TB, it is important to note that, even with a high efficacy vaccine, control can only be achieved with high vaccination coverage. In India, for example, BCG vaccination rates rose from 73% to 81% between 2001 and 2003, whereas in Nigeria it was 43% in 2003 [32]. Even the best new vaccine will not control disease unless coverage is adequate. Operational aspects of national TB programmes and vaccination programmes, as well as access to care, are probably as important in the global TB control efforts as is vaccine development. The best efforts for global TB control should include a strategic approach that considers all these issues.

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DECLARATION OF INTEREST

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