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SUPPLEMENT ARTICLE

BCG and New Preventive Tuberculosis Vaccines: Implications for Healthcare Workers

Mark Hatherill,[1] Thomas J. Scriba,[1] Zarir F. Udwadia,[2] Jai B. Mullerpattan,[2] Anthony Hawkridge,[3] Hassan Mahomed,[4,5] and Christopher Dye[6]

[1]South African Tuberculosis Vaccine Initiative, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa; [2]Department of Respiratory Medicine, P. D. Hinduja National Hospital, Mumbai, India; [3]Directorate of Health Impact Assessment, Western Cape Government Department of Health, Cape Town, [4]Division of Community Health, Faculty of Medicine and Health Sciences, Stellenbosch University, and [5]Metro District Health Services, Western Cape Government Department of Health, Cape Town, South Africa; and [6]Office of the Director General, World Health Organization, Geneva, Switzerland

Healthcare workers (HCWs) are at high risk of *Mycobacterium tuberculosis* (*Mtb*) infection and tuberculosis disease, but also play a crucial role in implementing healthcare. Preexposure tuberculosis vaccination, including revaccination with BCG, might benefit *Mtb*-uninfected HCWs, but most HCWs in tuberculosis-endemic countries are already sensitized to mycobacteria. A new postexposure tuberculosis vaccine offers greatest potential for protection, in the setting of repeated occupational *Mtb* exposure. Novel strategies for induction of mycobacteria-specific resident memory T cells in the lung by aerosol administration, or induction of T cells with inherent propensity for residing in mucosal sites, such as CD1-restricted T cells and mucosa-associated innate T cells, should be explored. The need for improved protection of HCWs against tuberculosis disease is clear. However, health systems in tuberculosis-endemic countries would need significantly improved occupational health structures to implement a screening and vaccination strategy for HCWs.

Keywords. tuberculosis; healthcare workers; vaccine; prevention.

It is widely recognized that healthcare workers (HCWs) worldwide carry a greater burden of latent *Mycobacterium tuberculosis* (*Mtb*) infection (LTBI) and are at greater risk for incident tuberculosis disease than the general population of the communities in which they live and work [1]. Cumulative risk for both LTBI and tuberculosis disease in HCWs depends partly on exposure to *Mtb* in these communities and added, often repeated, occupational *Mtb* exposure. A systematic review estimated the annual incidence of tuberculosis disease among HCWs in countries with low, intermediate, and high tuberculosis burdens as 67 per 100 000, 91 per 100 000, and 1180 per 100 000 persons, respectively [1]. These rates in HCWs compare to median incidence rates in the general population of 33 per 100 000, 82 per 100 000, and 311 per 100 000 persons, respectively, suggesting that 49%, 27%, and 81% of tuberculosis cases in HCWs could be attributed to occupational exposure [1].

The issue of occupational risk for tuberculosis is most acute among HCWs in low- and middle-income countries, where the average prevalence of LTBI in HCWs was estimated as 54%, with annual risk of infection ranging from 0.5% to 14%, and annual incidence of tuberculosis disease ranging from 69 to 5780 cases per 100 000 HCWs [2]. Prevalence rates of LTBI among HCWs in tuberculosis-endemic countries range from 10% (Malaysia) [3] to 41% (Colombia) [4], 47% (Vietnam) [5], 50% (India) [6], 55% (Georgia) [7], 57% (Uganda) [8], 63% (Brazil) [9], and 66% (Thailand) [10]. HCWs in certain tuberculosis hyperendemic "hot spots" are at elevated risk even within high-burden countries. The mean annual incidence of tuberculosis disease among HCWs in the KwaZulu-Natal Province of South Africa was 1133 cases per 100 000 persons, compared to contemporary community tuberculosis rates ranging from 316 to 782 per 100 000 (relative risk, 1.5–3.8) [11]. HCWs in specialist tuberculosis patient referral wards and hospitals are likely to be subject to the greatest risk of repeated *Mtb* exposure, including risk of multidrug (MDR) and extensively drug-resistant tuberculosis, despite tuberculosis-specific infection control measures [12, 13].

Although there is geographical heterogeneity in tuberculosis risk among HCWs, even among low- and middle-income countries, it is also clear that risk of occupational *Mtb* exposure varies considerably by work category, including not only direct providers of medical and nursing care, but also students, orderlies, and laboratory personnel [2, 14]. For example, the prevalence of LTBI, measured by interferon-γ release assay (IGRA), was 69% in professional and lay South African HCWs, compared to 15% in medical students, which likely reflects differences in age, socioeconomic status, and frequency of prior community and/or occupational exposure [15]. High risk of work-related exposure to *Mtb* is not limited to HCWs and is also a major problem for other occupations (eg, miners) [16]. The rationale for making protection of HCWs a priority includes the need to protect patients and coworkers from nosocomial transmission; although, based on the limited data available, transmission from HCW index tuberculosis cases to patients

Correspondence: M. Hatherill, Room 2.11, Wernher Beit South, University of Cape Town Faculty of Health Sciences, Anzio Road, Cape Town, South Africa (mark.hatherill@uct.ac.za).

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may be less common than in other settings [17]. However, the need to protect HCWs against tuberculosis, whether by vaccination, infection control, or preventive therapy, is especially important for national health systems, as HCWs have the specialized role of caring for patients. In the context of national tuberculosis programs, the entire tuberculosis control enterprise relies on implementation by HCWs who are trained, skilled, and healthy. The importance of protecting the health of HCWs is amplified in tuberculosis-endemic developing countries where overall HCWs are few and patient workload is great. The relative shortage of HCWs underlines the fact that efforts to protect HCWs against tuberculosis should also be broadly inclusive, to encompass rural and community health workers who play a pivotal role in the primary health systems of many countries, including early tuberculosis case detection, preventive therapy, and treatment adherence monitoring.

PREEXPOSURE VACCINATION

How might HCWs in tuberculosis-endemic countries be protected against nosocomial *Mtb* infection and disease? Historically, mass BCG vaccination of HCWs has been used effectively in some countries, particularly prior to the advent of isoniazid preventive therapy (IPT) [18, 19]. The work of Heimbeck and Scheel in Norway during the first half of the 20th century has particular relevance to the risk of tuberculosis infection and disease for modern-day HCWs in tuberculosis-endemic countries. Almost half of student nurses entering an Oslo nursing college between 1924 and 1936 were already *Mtb* infected, but of those who were tuberculin skin test (TST) negative on arrival, 100% became infected within 3 years. Nurses who were newly infected had 10-fold greater incidence of tuberculosis disease, with substantial mortality, compared to those with established LTBI. These investigators subsequently demonstrated in uncontrolled studies that a program of BCG vaccination targeting TST-negative nursing and medical students resulted in approximately 80% protection against development of tuberculosis disease [19].

Marcus and colleagues conducted a decision analysis of this issue, based on the assumption that HCWs with 1% annual incidence of *Mtb* infection might expect 235 tuberculosis disease cases per 100 000 and tuberculosis mortality of 9 per 100 000 over a 10-year period, in the absence of IPT [20]. BCG vaccination was expected to halve the number of tuberculosis cases in HCWs and to be more effective than annual TST screening and IPT in this scenario. Consistent with these findings, BCG vaccination of certain categories of HCWs is mandatory, or at least recommended, in several low-tuberculosis-burden European countries [21]. However, although the annual incidence of *Mtb* infection in HCWs is in excess of 1% in many countries, such as Thailand (4.8%) [10], this analysis assumes HCWs to be both BCG naive and *Mtb* uninfected at baseline, which is not the case in many tuberculosis-endemic countries.

Nevertheless, even in tuberculosis-hyperendemic countries such as South Africa, there is likely to be a small percentage of HCWs who are *Mtb* uninfected upon entering healthcare facilities; these *Mtb*-uninfected HCWs are at highest risk of tuberculosis morbidity and mortality upon encountering occupational *Mtb* exposure, especially those who are at increased risk due to human immunodeficiency virus (HIV) infection. It is this specific high-risk group, including *Mtb*-uninfected medical and nursing students and young trainees, for whom a targeted BCG revaccination strategy, or novel boost vaccine, might confer additional protection. Such a program would require universal TST or IGRA testing of all new HCWs entering healthcare facilities, a screening measure that is routine in many high-income countries, but which is not routine in most health systems in high-tuberculosis-burden countries.

BCG REVACCINATION

The majority of HCWs in tuberculosis-endemic countries would have received BCG vaccination in infancy [22]. It is debatable whether BCG revaccination of these HCWs would offer any additional protection against occupational *Mtb* infection or disease. Many, if not most adult HCWs in tuberculosis-endemic countries will have been exposed to *Mtb*, and also nontuberculous mycobacteria (NTM), and would already have become *Mtb* infected before starting work in healthcare facilities. For example, 60%–80% of healthy adults <40 years of age in rural and urban South African communities were found to be *Mtb* infected [23]. It follows that a vaccination program targeting HCW trainees or students in tuberculosis-endemic countries would necessarily involve BCG revaccination of many individuals with extensive mycobacterial sensitization and existing LTBI (ie, a postexposure vaccine strategy). BCG revaccination may have modest efficacy against tuberculosis disease in children and young adults who have had low-level prior exposure to *Mtb* and/or NTM, such that a program of BCG revaccination of IGRA/TST-negative adolescents might even be cost-effective in some settings [24–26]. Extended follow-up of the BCG-REVAC trial, a cluster randomized trial that included >200 000 children in Brazil, showed that BCG revaccination efficacy was higher in Salvador (19%) than in Manaus (1%), with the highest efficacy in children from Salvador aged <11 years at revaccination (33%) [25]. The authors suggest these findings are consistent with the hypothesis that BCG vaccination offers higher efficacy in areas with low NTM prevalence [25]. However, it is widely accepted, based on data from multiple controlled trials, that protection due to BCG is highly variable in adults (range, 0%–80%) and is most inconsistent and of shortest duration in persons with LTBI [27]. These are crucial exposure factors that highlight the likely differences in potential benefit from BCG (re)vaccination between modern HCWs and the trainee HCWs reported by Heimbeck in the early years of the 20th century [19, 27].

POSTEXPOSURE VACCINATION

HCWs may encounter repeated occupational *Mtb* exposure, and may thus develop tuberculosis disease as a result of reactivation or reinfection. The historical findings in TST-positive Norwegian nursing students support the notion, substantiated by later modeling studies and an extensive meta-analysis of published trials, that established LTBI offers almost 80% protection against reinfection tuberculosis disease [19, 28, 29]. It is tempting to suppose that established LTBI might offer some protection to HCWs in tuberculosis-endemic settings. Unfortunately, as the historical studies that gave rise to these data specifically excluded BCG-vaccinated individuals, there is no evidence from modern prospective studies that LTBI confers any additional benefit beyond that offered by prior BCG vaccination [19, 29].

Conversely, it has been proposed that prior mycobacterial exposure results in either masking of a beneficial immune response to subsequent BCG vaccination, or blocking of BCG vaccine "take" due to preexisting immune priming [30]. Both factors might play a role in limiting the additional benefit of postexposure vaccination strategies for latently infected HCWs in endemic countries, using either revaccination with the current licensed BCG, novel recombinant BCG vaccines, or other live attenuated mycobacterial vaccines in clinical development [31, 32]. Although there might be little immunologic benefit in offering BCG revaccination to HCWs with previous mycobacterial exposure, we have shown that BCG revaccination of *Mtb*-infected adults is safe, which implies that a mass campaign targeting HCWs would not necessarily need to conduct prevaccination or IGRA screening [33]. However, there are also safety concerns around the use of live mycobacterial vaccines, including BCG, in tuberculosis-endemic countries where HIV prevalence is high, and where BCG revaccination constitutes a potential safety risk for HIV-infected HCWs [34]. It is likely that a novel subunit or viral-vectored tuberculosis vaccine, if successful in inducing postexposure protective immunity, would hold the greatest potential as a tool to protect latently infected HCWs who are at increased risk of reactivation due to HIV infection, and subject to repeated occupational reexposure and reinfection tuberculosis disease.

IMMUNOLOGICAL CONSIDERATIONS

BCG-induced protection against pulmonary and extrapulmonary forms of tuberculosis, although highly variable on a global scale, is highest in infants and young children and gradually wanes as adolescence approaches [27, 35]. The limited duration of BCG-induced protection is hypothesized to result from a gradual loss of BCG-induced T-cell memory [36]. In line with this hypothesis, BCG appears to be poor at inducing long-lived central memory T cells, but preferentially induces interferon γ–expressing antigen-specific effector memory cells [36–38]. Given that effector memory cells are typically endowed with rapid effector function and ability to patrol peripheral tissues, including the airways and lungs, induction of effector memory responses by BCG revaccination of new, IGRA-negative HCW recruits may be particularly beneficial, especially in the short term. Indeed, induction and maintenance of antigen-specific persistent effector memory responses to new epitopes by chronic antigen stimulation appears to be a promising vaccination strategy against other chronic infections [39]. Efficacy of BCG revaccination of Brazilian schoolchildren, who had received their first BCG vaccination in infancy, was modest in Salvador, but absent in Manaus [40]. These data illustrate that environmental factors, such as sensitization to environmental mycobacteria, may play an important role in limiting efficacy of revaccination [27]. As a result, administration of BCG to persons with a history of previous vaccination in childhood is currently not recommended owing to "generally poor efficacy of BCG revaccination" [41].

Taking a forward view, vaccine efficacy in HCWs in the setting of high infection forces may be improved by deliberate targeting of the portal of *Mtb* infection, where lung-resident effector cells could provide immediate immunity against the inhaled bacillus before establishment of a productive infection. That prevention of *Mtb* infection may occur in natural infection is supported by the observation of reversion of positive TSTs or IGRAs in humans and animals (reviewed by Hawn et al) [42]. Several observational studies in children and adults also suggest that BCG vaccination may protect against *Mtb* infection [43–47]. Vaccine induction of local lung immune responses in the form of conventional CD4 and CD8 T cells with lung-homing capacity, tissue-resident T cells (Trm), mucosa-associated innate T cells (MAITs), or even mucosal antibodies, should therefore receive more attention. A particular advantage to induction of local immunity is that such strategies may be less prone to interference by prior mycobacterial sensitization, because prior intradermal BCG vaccination and/or exposure to environmental mycobacteria are not known to induce such local lung immune responses. Efficacy of aerosol vaccination may therefore be possible, even in HCWs with prior BCG vaccination or who live in settings of high exposure to environmental mycobacteria.

Recent results from a mouse model of herpes simplex virus showed that targeted induction of inflammation in skin or mucosa triggered recruitment of effector CD8 T cells that acquired the Trm phenotype [48]. These Trm cells remained in the local tissues and, upon challenge with herpes simplex virus, provided protection against viral challenge in skin and vagina. Importantly, protection by tissue-resident Trm cells was superior to circulating memory T cells [48]. Plausibility of a strategy for induction of mycobacteria-specific Trm cells in the airways or lung was recently demonstrated in a proof-of-concept trial of aerosol administration of MVA85A in BCG-vaccinated adults. In this trial, vaccination via the aerosol route was well tolerated and induced higher magnitudes of antigen-specific bronchoalveolar CD4

T cells compared with intradermal MVA85A vaccination [49]. As an alternative, vaccines that induce T cells with inherent propensity for residing in mucosal sites, such as CD1 T cells and MAITs, could be explored.

PROGRAMMATIC NEEDS (SOUTH AFRICAN PERSPECTIVE)

Given the extremely high burden of tuberculosis in South Africa [50], HCWs are at significant risk of *Mtb* exposure, both in the community and at work [51, 52]. There are also reports of HCWs in South Africa developing MDR tuberculosis, which has a high mortality [13]. In view of the relative shortage of skilled HCWs in South Africa, this is of enormous concern. Existing government policies seek to minimize the risk of transmission of *Mtb* in healthcare facilities. These policies focus on the traditional methods of infection control, such as administrative and environmental controls, and the wearing of personal protective equipment. These measures are only partially effective and there is consequently an ongoing high risk of tuberculosis exposure among HCWs in South Africa, even in primary healthcare settings [53]. If an effective tuberculosis vaccine was made available to high-burden countries such as South Africa, the question is whether health departments would be in a position to offer it to every HCW who might stand to benefit from it. Universal newborn BCG vaccination was introduced in South Africa in 1971. Existing policy does not include BCG revaccination as a preventive strategy, but it does set out a risk-rating approach, which could be used in the application of a putative new tuberculosis vaccine. A new tuberculosis vaccine is likely to be only partially effective in preventing tuberculosis disease, so augmenting existing control measures would remain crucial. Medical staff surveillance for tuberculosis is not a focus area and would need to be strengthened to monitor the effectiveness of implementation of any new vaccine.

The cost of any new tuberculosis vaccine for HCWs would also influence the feasibility of adopting tuberculosis vaccination on a national or provincial scale. For example, the Western Cape Provincial Health Department currently spends >$12 million annually on vaccines, primarily the 8 vaccines given to infants and young children and the human papillomavirus vaccine given to older children (A. Hawkridge, personal communication). If a new tuberculosis vaccine that required 2 doses were made available at approximately $2 per dose, immunizing the approximately 32 000 HCWs in the Western Cape Province would cost in the region of $128 000, which is around 1% of the annual immunization budget, and which many would consider justified and possibly affordable. The same may not apply in other South African provinces or other countries. In addition, staff attrition of around 5% per year and the added cost of TST or IGRA screening for new staff might influence the ability of health departments to afford a tuberculosis vaccine program for HCWs. IGRA testing for HIV-uninfected adults without additional risk factors is not currently routine, as current South African guidelines do not recommend INH prophylaxis for HIV-negative adults. However, if changes in South African national guidelines for tuberculosis screening led to a fall in the cost of IGRA testing, a screening and vaccination program for HCWs might be viewed as more feasible.

A proportion of HCWs are immunocompromised due to HIV infection, and are thus at higher risk of developing tuberculosis and are in greater need of a new, safe, and effective tuberculosis vaccine [34]. However, the effectiveness of such a vaccine might also be diminished in HIV-infected persons, a factor that might limit the benefit of the vaccine in controlling tuberculosis transmission among HCWs. Practical requirements for rolling out a new tuberculosis vaccine program among HCWs in South Africa would include an occupational health infrastructure that is not yet fully in place; a functional surveillance mechanism; the ability to manage cases of tuberculosis in HCWs; linkage to the existing induction program for new HCWs, including tuberculosis education; and a reliable supply chain management system for the vaccine product. These additional challenges would need to be overcome as part of any future HCW vaccination program against tuberculosis. National Core Standards, as enforced by the South African Office of Health Standards Compliance, currently include generic requirements for an occupational health infrastructure and medical surveillance for HCWs; and some of these measures are also required in terms of the Occupational Health and Safety Act.

PROGRAMMATIC NEEDS (INDIAN SUBCONTINENT PERSPECTIVE)

Occupational exposure of HCWs to *Mtb* infection in the Indian subcontinent is a major public health concern. HCWs in rural India showed LTBI prevalence of 40% [6]; prevalence in high-risk HCW groups, including interns, residents, and nurses, was almost 50% in another study [54]. The annual risk of infection in HCWs in India is about 5%, compared to the national average of 1.5%, with the additional risk being attributed to nosocomial transmission [6, 55, 56]. For example, in a study from Vellore among nurses, annual risk of infection was 7.8% [57]. Medical and nursing staff in India have relatively high workload, like many other low- to middle-income countries where healthcare facilities have far lower ratios of HCWs to tuberculosis patients than do high-income countries (median, 36 vs 6450 HCWs per 100 tuberculosis patients treated, respectively), leading to significantly higher tuberculosis exposure [2]. Many hospitals have no infection control policies in place and are overcrowded, and poorly ventilated hospital wards play a role in increasing the risk of nosocomial *Mtb* transmission. In a study from northern India, 2% of resident doctors working in hospitals developed tuberculosis, an incidence of 11 new cases per 1000 person-years of exposure, which is 10-fold higher than

the country incidence [54]. The risk factors for acquiring tuberculosis infection in Indian HCWs included working in laboratories, inpatient facilities, and emergency wards [54]. Pai et al showed that risk of LTBI in medical students increased approximately 1.5 times with each additional year of training [6]. It is also notable that poor baseline nutritional status (body mass index <19) of the HCW increased risk of LTBI [58].

There is clearly a need to improve screening of *Mtb* infection and disease in Indian HCWs, as the first step in controlling occupational *Mtb* transmission. There is currently no national policy in India for screening of HCWs for LTBI, and the standard National Tuberculosis Control Program guidelines, which recommend investigation of patients with >2 weeks of cough by a sputum test, are used to screen HCWs for tuberculosis disease. The current tuberculosis vaccine strategy for India is a single dose of BCG vaccine given at birth. The extended universal vaccination policy was implemented in 1985, and almost 87% of all children were administered BCG vaccine at birth in 2013 (World Health Organization Vaccine Preventable Diseases Monitoring System, 2014). However, there is currently no national recommendation for BCG revaccination of high-risk groups such as HCWs. There is an urgent need for an effective tuberculosis vaccine for high-risk populations in India, including HCWs, students, and support staff. A new tuberculosis vaccination strategy should complement, rather than replace, other tuberculosis preventive strategies, such as nutritional support and effective hospital infection control, which could be rolled out with immediate effect.

THE ROLE OF HCWs IN CLINICAL TRIALS OF NOVEL TUBERCULOSIS VACCINES

HCWs are, as a population group, at high risk of *Mtb* exposure, infection, and incident tuberculosis disease. They also have knowledge and insight into the importance of protection against tuberculosis and a personal stake in the development of a more effective tuberculosis vaccine. For these reasons, HCWs might play a role in clinical trials to test new tuberculosis vaccines; with the exception of HCWs with additional individual risk due to HIV infection or diabetes mellitus, HCWs as a group are not immunocompromised. As outlined above, new or trainee HCWs who are *Mtb* uninfected might take part in trials of new preexposure vaccines, including recombinant BCG or attenuated *Mtb* candidates [31, 32]. HCWs who are already *Mtb* infected, as expected, might be a suitable study population for new postexposure candidate vaccines [59, 60]. Given the high rates of *Mtb* exposure and incident tuberculosis disease, such clinical trials might be performed at a much smaller scale, and lower cost, than comparable community-based studies. However, although targeted inclusion of HCWs might be appropriate for the study population of experimental medicine or proof-of-concept efficacy studies, there is a theoretical but unproven risk that the degree of occupational *Mtb* exposure, in terms of infectious quanta, might exceed the protective ability of an otherwise efficacious tuberculosis vaccine [42].

CONCLUSIONS

HCWs are a population at high risk of *Mtb* infection and incident tuberculosis disease who also fulfill a crucial role in implementing healthcare in tuberculosis-endemic communities. The need for improved protection of HCWs against occupational and community-acquired tuberculosis disease is clear. However, with the exception of *Mtb*-uninfected HCWs who might derive some benefit from BCG revaccination—the minority in tuberculosis-endemic countries—the current state of tuberculosis vaccine development is such that the needs of HCWs must be met by a combination of infection control measures, tuberculosis preventive therapy, and regular symptom screening, combined with new rapid diagnostics and early treatment for disease [61]. It is also clear that health systems in tuberculosis-endemic countries would need improved occupational health structures to implement a program of tuberculosis vaccination linked to prior screening of HCWs for *Mtb* infection. Future development of an effective postexposure tuberculosis vaccine is the key to providing HCWs with long-standing protection against tuberculosis disease.

Notes

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