

Viewpoint paper:

CID Format guide:

- Word limit: 3000 words (excluding the abstract and references).
- Key points should be summarized on the title page in 40-words or less.
- References: 40 or less.
- Abstract: Up to 150 words, unstructured.
- Tables/Figures: Data in the text should not be repeated extensively in tables or figures.

Title:

Exposed, but not protected: more needed to prevent drug-resistant TB in healthcare workers and students

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Key Points:

- Healthcare workers and students are at increased risk of occupational DR-TB disease
- HCWs suffer high DR-TB associated morbidity and mortality
- Innovation, destigmatisation and better TB Infection Control implementation are key to reducing DR-TB transmission to HCWs and patients

Words: 38 (limit 40)

Abstract:

“Occupational MDR-TB”... “XDR-TB”... “Treatment-induced hearing loss”: three life-changing messages imparted over the phone. Three personal accounts are shared to highlight how many healthcare workers (HCWs) and students in low-resource settings falsely believe they are immune to tuberculosis (TB) despite high levels of exposure. This misconception reflects a lack of awareness of TB transmission and disease risk, compounded by the absence of accurate occupational TB estimates. As the global problem of drug-resistant TB (DR-TB) evolves, HCWs are increasingly infected and suffer considerable morbidity and mortality from occupational DR-TB disease. Similarly, healthcare students are emerging as a vulnerable and unprotected group. There is an urgent need for improved detection, preventive therapy, enhanced treatment and support for affected HCWs and those they care for as well as destigmatisation of all forms of TB. Finally, efforts to protect HCWs and prevent DR-TB transmission by universal implementation of TB Infection Control measures should be prioritized.

Words: 150 (limit 150)

Main piece - Total words: 2953 (limit 3000)

Introduction: From being a healthcare worker to becoming a patient

The continued and ominous global spread of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) poses a major threat to global TB control and global health security. [1] The WHO estimates that 480 000 cases were due to MDR-TB in 2013 with increasing prevalence being seen in Eastern Europe, Asia and Southern Africa. As many as 9% of these cases could have XDR-TB. [1] In South Africa, drug-resistant tuberculosis (DR-TB) consumes a third of the total national budget for tuberculosis, [2] with dismal cure rates despite admirable political and public health commitment: under 50% for MDR-TB and as low as 11% for XDR-TB. [3] DR-TB imposes devastating human suffering and isolation; not only upon patients and their communities, but also upon those called to care for them.

We share three personal accounts of occupational DR-TB to highlight how healthcare workers (HCWs) and students in low-resource settings falsely believe they are immune to tuberculosis (TB) despite high levels of exposure, and illustrate how developing DR-TB changed their perspectives on the dire need for better DR-TB prevention, treatment and de-stigmatisation.

Case history 1: The innocuous beep of the text message heralded the South African doctor's worst fear: "Bad news, high-frequency hearing loss." The sender, his wife and also a doctor, was sick with MDR-TB. After eight weeks of meticulously monitored MDR-TB therapy, she had begun losing her hearing. Alarm bells ring - will this progress to total deafness and also loss of her career? He was sick too, in bed during the past week with presumed primary pleural MDR-TB.

Case history 2: Fast forward a year and a half, a phone rings with similar news to that of the medical couple: "You need to go back to the clinic...you have MDR-TB." This time the message was delivered by a seemingly indifferent laboratory technician to a profoundly isolated and confused medical student. Her worst fear had been that the presumed drug-sensitive TB might have resulted in missing time from her studies. Now she worried for her life; a few years previously another student at her Medical School had tragically lost her battle with MDR-TB.

Case history 3: Fast forward another year and another doctor's phone rings with the message: "You have XDR-TB." Just like that, in the middle of a shopping mall, delivered by another laboratory technician with a pressing schedule – there were many more results to phone out.

Whilst the risk of contracting of TB in health care settings is well described, these young HCWs never expected that it would happen to them, let alone primary MDR/XDR-TB. They all shared the same profession, but were previously healthy and lacked the 'typical' risk factors for developing active TB disease. They all held the falsely reassuring belief that 'healthy' HCWs are unlikely to contract TB and that they were in fact 'TB Proof' (immune to developing TB disease). Another such false belief, that DR-TB is largely 'acquired' due to inadequate or interrupted treatment, has also been increasingly dispelled, with a systematic global review finding that up to three quarters of DR-TB cases were due to primary transmission (i.e. person to person spread, frequently in treatment naïve individuals). [4]

A threat to life and career

The harsh and largely unacknowledged reality is that globally HCWs are three times more likely to contract TB than the general population, [5] and in South Africa, are up to six times more likely to contract DR-TB. [6] The unexpected news of having been diagnosed with DR-TB can be devastating to HCWs who have full knowledge of the vexed problems associated with treatment: 1) The high mortality rate: up to a third of HCWs diagnosed with DR-TB may die [7,8]

2) The excess host inflammatory response which leads to permanent damage and long term functional disability. [9] 3) Coping with the lengthy treatment duration (of at least 20 months or more) with toxic drugs and (frequently irreversible) side-effects. Survivors often battle severe physical and psycho-social side-effects, [10] some of them career-ending like hearing loss, loss of vision and nerve damage among others. [11,12]

The husband got up and spent the next two hours on the phone. With the threat and implications of permanent hearing loss foremost in mind, they agonised over whether to stop the offending aminoglycoside drug or to continue the ototoxic therapy to have a better chance of cure. "Your life or your hearing?" What a terrible 'choice' to offer anybody, especially a colleague. A unique third choice, an application for compassionate use of the first new TB drug in more than 40 years to replace the aminoglycoside, had just been declined too.

The torment experienced during DR-TB therapy at the hands of outdated, ineffective TB 'treatment' has been well described. [13,14] Less well known is the sense of helplessness and even futility experienced by those battling a deadly disease that defies global attempts at control. Of the nearly half a million new MDR-TB cases in 2013, only 136 412 were diagnosed and even fewer (97 000) were started on appropriate therapy. Only about half of these individuals achieved treatment success - less than a tenth of all cases. The detection, management and outcomes for XDR-TB are even more dismal with only 7.5% enrolled on treatment (3 232 out of an estimated 43200 cases). The latest reported global cure rate was 22%. [1]

HCWs are a scarce resource in all countries of the world. Unfortunately many are lost or disabled by occupational TB disease in countries where they are needed most. This has a devastating effect on their families, colleagues and the patients they serve. A recent study from South Africa that screened 505 HCWs for latent TB infection (LTBI) at baseline and a year later found that the annual rate of LTBI was 38% using TST (Tuberculin Skin Testing), much higher than previously thought. [15] The situation for HCWs co-infected with HIV is even worse; they are often dead long before their DR-TB is even diagnosed. [16]

No DR-TB prophylaxis

The husband's disease was never conclusively diagnosed. The timing of symptoms and spike in interferon-gamma release assays (IGRAs) suggested primary transmission from his wife, but in the absence of any conclusive diagnostic results, and in the presence of very real and irreversible side-effects, he opted for an unconventional and rather 'un-medical' choice: doing nothing. His symptoms resolved after three weeks, but his IGRAs have remained doggedly inconclusive, fluctuating across the cut-off range, very much in keeping with the diagnostic uncertainty described in the latest literature. [17] And scarring in both his lung apices, frequently seen during routine screening of HCWs in high burden countries, attest to unrecognised encounters with TB.

The WHO cannot currently give any recommendation on preventive therapy for DR-TB contacts, because of a glaring lack of research and evidence in this field. [18] This poses a great challenge for families, friends and colleagues of HCWs that are diagnosed with this life-threatening disease. And even more so for the patients they serve: the wife had been working with neonates for six weeks before her mild, yet persistent cough was finally diagnosed as MDR-TB. There was no way of tracing all contacts, and the authorities never even tried.

Preventive therapy for children under five years of age is routinely given if a parent or close household contact is diagnosed with drug-sensitive TB, as the risk of children developing disease and the related morbidity and mortality are high. [19] The doctor diagnosed with XDR-TB was particularly concerned about her three year old daughter, but had no proven options for preventive therapy to protect her little one from such resistant disease. Every sniffle or cough from her child caused the mother concern for years after her diagnosis.

No safety net for students

In South Africa, in keeping with International Labour Organisation (ILO) regulations, [20] TB is classified as an occupational disease. This means a HCW who contracts the disease is eligible for compensation including medical expenses, income security and reimbursement for temporary or permanent disability and death. [21] For medical and other healthcare trainees or students, there is currently no law to enforce compensation.

Medical students have been found to have a higher rate of early TST conversion compared to other students in a high-burden country setting [22] and a higher prevalence of LTBI during their late clinical years, compared to preclinical and early clinical years. [23] A previous review also found a significantly higher risk for contracting TB amongst young HCWs compared to older HCWs. [24] Possible contributing factors to the high risk among junior HCWs and those in training include a greater amount of time spent with patients and decreased awareness of (and even control over) exposure to risk factors compared to senior colleagues. [10] Despite these risks, medical and other healthcare students receive no financial support for medical expenses, and frequently face discontinuation of their studies and loss of bursaries due to disease. The same untenable considerations apply to volunteers, unpaid (or 'supernumerary') trainees, as well as elective (visiting) students.

The medical student with MDR-TB experienced extreme social isolation, driven by a lack of understanding from family members, peers, as well as the medical school administrators. Fortunately she had access to free medical treatment through South African public clinics. The daily travel to the clinic to access excruciating intra-muscular injections and the progressively more debilitating side-effects soon meant that she had to discontinue her studies. She also heard of more students and colleagues who suffered permanent side-effects, like hearing loss and nerve damage, and of some who had even lost their lives to TB. This elicited intense fear of relapse or re-exposure, especially given the lack of infection control measures in the public healthcare facilities where she was training. This anxiety was further compounded by severe depression, a common side effect of DR-TB medication. Social isolation, treatment side effects, loss of career and stigma all contribute significantly to the high rates of suicide in DR-TB patients. [25,26]

A scarce resource globally

HCWs are in demand in almost every country of the world. Financial incentives and safer working conditions are some of the factors that drive migration. [27] Although most HCWs undergo X-ray screening before commencing work in a new country, a normal chest X-ray cannot exclude LTBI (or even active pulmonary disease in some cases). Some countries offer TSTs or IGRAs, but these cannot reliably estimate the risk of progression to active disease. A recent widely publicised case investigation in the United Kingdom (UK) tracked nosocomial transmission of MDR-TB from a South African HCW to a hospitalized patient, with a delay of disease manifestation in the patient of 49 months. [28] Following TB exposure, the risk of disease progression in contacts is highest in the first 2 years, moderate over five years and persists lifelong. [29] Predicting who will become sick and when is currently almost impossible.

There is currently also no way of determining whether HCWs with LTBI are infected with drug-sensitive (DS) or resistant (DR) strains, meaning that currently available treatment options for DS-LTBI would be ineffective for resistant strains at best, and harmful at worst. This uncertainty is compounded for HCWs living with HIV, since isoniazid preventive therapy (IPT) is recommended for up to 36 months to both treat existing latent infection and prevent new infections in all individuals with HIV in settings with a high TB transmission risk. [30] The ability of IPT to protect against transmission of DR-TB strains is not known and could inadvertently present a competitive transmission advantage to INH-resistant strains. The WHO recently highlighted the need for research to evaluate the risk of selecting for additional drug resistance following inappropriate LTBI treatment, stressing the need for studies evaluating efficacy of currently recommended treatment options in areas with high prevalence of DR-TB. [18]

HCWs could unwittingly contribute to the global spread of DR-TB, but to stigmatise them due to fear of contagion would only worsen the situation. HCWs in low-resource settings with possible TB symptoms are already wary of presenting for testing and treatment, because of stigma and career implications. [14] Such stigma is amplified for HCWs living with HIV, who are at a 20-50 fold higher risk of developing TB disease. [5,16,31] Fear of discrimination prevents disclosure and reduces the likelihood of HCWs accessing support and risk modification in the workplace.

Any delay in diagnosis could have catastrophic consequences for the HCW and for the patients that they serve. As described in a UK case investigation, three South African HCWs that were co-infected with HIV and MDR-TB lost their lives, even though they had treatable conditions. One of the HCWs presented very late, in a dire state of health, and authorities subsequently identified more than 500 potentially-infected contacts from this single source case. [32] The current lack of latent DR-TB diagnostic and treatment choices leave 'watchful (and lengthy) waiting' as the only highly unattractive 'option'.

Novel interventions for improved treatment outcomes

The current status quo of lengthy treatment duration with toxic drugs and poor treatment outcomes associated with DR-TB is not acceptable. There is an urgent need, not only for more effective and safer

drugs, [13] but also new innovations for shortening the duration of therapy, improving treatment outcomes, and repairing and preventing long term lung damage in DR-TB patients. [9] A wide range of Host-Directed Therapies (HDTs) have now been identified which have the potential to modulate protective innate and adaptive immune responses, reduce excess inflammation, repair or prevent tissue damage and enhance the effectiveness of DR-TB. [33] These include therapeutic vaccines and the use of the patient's own bone marrow derived stromal cells as adjunct therapy. However, the ultimate priority need is that of developing a preventive TB vaccine.

Why a new TB vaccine would make such a difference

It is estimated that a third of the world's population is infected with TB and an ever increasing number are latently infected with drug-resistant strains. There is a renewed sense of urgency to develop a vaccine that could prevent disease and halt this age-old pandemic that still ranks as the world's joint largest infectious killer. With a staggering 1.5 million people dying of this disease every year, [1] innovation is essential.

The *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) vaccine is the only TB vaccine currently in use. In infants it has been shown to reduce disseminated forms of TB, but has limited effectiveness in preventing pulmonary TB, especially in older children and adults. [34] Currently there is a shortage of surrogate biomarkers to assess the development of protection following vaccination, hampering clinical testing. New techniques for more effective vaccine delivery have shown promise, but further research into how the immune system responds to infection (initial and latent) and disease is needed to speed up vaccine development. [35]

However, to continue the search for vaccine candidates and promote ongoing research into new drug development, sustainable investment in research and innovations for TB will be required. [36] A recent report from the UK All-Party Parliamentary Group on Global Tuberculosis projected 75 million deaths from MDR-TB costing the global economy 16.7 trillion US dollars over the next three decades if we continue the status quo. [37]

What should we do today?

A novel vaccine and other new tools to reach the WHO's ambitious target of TB elimination will clearly not be available in the immediate future. [38] As evidence grows of TB transmission in health care facilities, both to patients and HCWs, [39,40] the need for full implementation of all recommended TB Infection Control (TB-IC) measures in all facilities should be a major focus of prevention efforts. Rigorous implementation of TB-IC can achieve reduction in TB transmission to HCWs and to people living with HIV. [41,42] In 2009, the WHO produced TB-IC guidelines outlining evidence-based and affordable measures (administrative, environmental and personal protective) to reduce the risk of TB transmission within hospitals and congregate settings. [43] At a global level a policy guideline for promoting access to care for HCWs, specifically focussed on TB and HIV, was published in 2010. [44]

Despite these guidelines and evidence for efficacy, poor implementation of TB-IC in health facilities persists. [45] Personal experiences of HCWs affected by TB reveal a need for improved educational and awareness programmes among all healthcare personnel, including facility managers. Additional suggestions of HCWs who survived TB include effective and sustained implementation of TB-IC measures, mandatory pre- and post-employment TB screening and a change in attitudes of senior healthcare colleagues and administrators. [46] Several studies have also noted that stigmatisation of TB and DR-TB creates a barrier to compliance with TB-IC best practice among HCWs who don't want to seem 'weak' or 'scared' and therefore refrain from wearing N95 respirators. We need to destigmatise TB by breaking down this myth of invincibility among HCWs, rooted in an apparent false sense of superior immunity, and through awareness campaigns targeting communities most affected by TB.

New interventions including an effective vaccine, safe treatment for all forms of latent and active TB, [13] active case finding, screening of contacts and increased advocacy for and education about TB-IC at both healthcare facility and community levels will accelerate our progress towards TB elimination. [47] And we need the political, financial and legislative commitments to effect real change. Without a strong healthcare workforce on the front line this battle cannot be won.

From patients to HCW advocates:

The wife's hearing and career were saved when her second compassionate use application succeeded. The student made a full recovery after missing two years of medical school and the mother has nearly completed her arduous two years of XDR-TB treatment. But the vast majority of our colleagues diagnosed with DR-TB are not as fortunate. Exposure without protection is simply not an option.

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