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Tuberculosis Healthcare Workers: There Goes My Hero

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Case identification, respiratory isolation, personal protective equipment (PPE), and contact investigation are recent additions to the national dialogue as a consequence of the Covid-19 pandemic. They are, of course, long-term components of the tuberculosis (TB) healthcare workers' (HCWs) vernacular. There are important differences between Covid-19 infection and TB but nosocomial transmission to HCWs is a critically important shared characteristic.

To minimize nosocomial transmission of Covid-19, the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) recommend several interventions including observing respiratory hygiene and cough etiquette, performing rapid triage and isolation if symptoms of Covid-19 are suspected, and wearing a face mask before entering a healthcare facility (1,2). Upon admission to a healthcare facility, patients should be placed in a single person room with a closed door, ideally with directional airflow. HCWs entering a room of a patient with known or suspected Covid-19 infection should wear personal protective equipment (PPE). These sensible and necessary interventions are unconditionally recommended even though randomized controlled trials (RCTs), PICO questions, or exhaustive literature reviews have not been done to confirm their effectiveness (1,2).

Preventing the spread of a disease transmitted by airborne droplets, be it Covid-19 or TB, requires interrupting the creation of infectious droplets, stopping dissemination from the source case or blocking inhalation of the infected droplets by the vulnerable individual. In the case of Covid-19, a new and highly contagious pathogen, WHO and CDC appropriately recommend an approach utilizing all available interventions for protecting HCWs.

Three decades ago, nosocomial TB transmission in the U.S., including MDR-TB, was a significant problem in hospitals and other congregate settings (3). Lax infection prevention and control (IPC) measures were important contributing factors. In retrospect, renewed and

comprehensive IPC efforts, similar to those recommended for Covid-19 and enforced by regulatory fiat, played a pivotal role in controlling the TB resurgence. It was stated in the 2005 CDC Guidelines for Preventing the Transmission of TB in Healthcare Settings that, "The TB infection-control measures recommended by CDC in 1994 were implemented widely in health-care facilities nationwide. As a result, a decrease has occurred in 1) the number of TB outbreaks in health-care settings reported to CDC and 2) health-care-associated transmission of *M. tuberculosis* to patients and health-care workers (HCWs)." (3)

Certainly, there are limits to the analogy between Covid-19 and TB. There is an immediate mortality threat posed by Covid-19 and a lack of effective treatment. The threat to HCWs posed by TB, albeit with a slower tempo, should not be forgotten or underestimated. Tuberculosis sickens 10 million people per year and is the number one infectious disease killer worldwide, even though it is treatable, curable and preventable (4). Global Covid-19 deaths continue to rise but optimistically, may decline again once safe and effective treatments and vaccines become available. Hopefully, Covid-19 deaths will not surpass the > 1.4 million TB attributable deaths globally *every year*. The Covid-19 threat to HCWs is well documented but the number of HCW TB deaths is impossible to know with certainty (5). HCWs can be exposed to multidrug-resistant (MDR) and extensively drug resistant (XDR) TB strains associated with treatment failure and death (6). Exposure to MDR- or XDR-TB without adequate protection is as alarming and unacceptable as inadequately protected exposure to Covid-19. It should be self-evident that TB HCWs require the same comprehensive protection as do Covid-19 HCWs.

Two systematic reviews that examine the evidence for the effectiveness of IPC measures to protect HCW from nosocomial TB transmission. are published in this issue of CID (7,8). The reviews were commissioned by WHO, and performed independently, to inform the 2019 WHO update for guidelines on tuberculosis infection prevention and

control (9). The authors performed comprehensive and rigorous systematic literature reviews to answer specific IPC intervention PICO questions. Karat et al concluded that evidence for effectiveness of triage, isolation, or effective treatment, alone or in combination, was indirect and low quality but that packages of IPC measures appeared to reduce *M. tuberculosis* transmission (7). This review did not show that the three interventions implemented individually would be effective for preventing TB transmission, but that when these measures were included with other IPC controls, such as, environmental measures and PPE, they seemed to be effective. Fox et al concluded that current evidence demonstrates that introducing a combination of administrative, engineering and personal respiratory protection measures reduces transmission of *M. tuberculosis* and TB disease in healthcare settings, although again, the contribution of any single intervention could not be determined (8).

The review process encountered major obstacles, due primarily to a limited evidence base for answering the PICO questions. Randomized controlled trials were absent. Most studies were retrospective cohort studies with a before-and-after design. It was not possible to estimate the effect of any individual intervention, because each intervention was introduced as a part of composite IPC measures. For example, determining the impact of respirators alone was not possible, given that respirator use is recommended as part of comprehensive respiratory protection. The studies could not prioritize interventions in terms of efficacy and cost-effectiveness, and the heterogeneity of the interventions precluded meta-analyses. According to the authors, the goal of the reviews was not to recommend the ideal combination of IPC interventions for practice, but rather to synthesize the evidence for the effectiveness of these interventions, individually and in combination, and present that to the WHO Guideline Development Group.

The WHO recommendations based on the reviews and PICO results are published in the 2019 WHO Guidelines (9). Triage of people with TB signs and symptoms or with TB disease, respiratory separation/isolation of people with presumed or demonstrated infectious TB, particulate respirators and ventilation systems are all described as a “conditional recommendation based on very low certainty in the estimates of effect”. Only prompt initiation of effective TB treatment and respiratory hygiene including cough etiquette are granted a “strong recommendation based on low certainty in the estimates of effect” for reducing TB transmission to HCW. While the authors note that the interventions described under each recommendation were not intended as stand-alone interventions, the PICO questions are posed in that way.

The PICO platform is intended to address answerable questions. This PICO question

is a representative example from the two studies. “In HCWs or other persons attending healthcare or congregate settings, can respiratory hygiene and/or cough etiquette reduce TB transmission when compared to settings where these interventions are not implemented?” There are no studies looking at the effects of a single intervention, only interventions in combination primarily as before and after analyses. There are no RCTs for any single intervention or combination of interventions. High quality, controlled intervention studies to answer any of the PICO questions are entirely lacking. The analyses succeed in demonstrating the lack of suitable studies for the posited PICO questions and in the process also demonstrate that the PICO questions were essentially unanswerable with the current evidence base. The conclusions from the analyses must be viewed in that context.

At best the findings support an aggregate benefit of multiple interventions but without prioritizing them or providing guidance on the optimal order of implementing them. At worst the GRADE nomenclature “conditional recommendation based on very low certainty” raises doubts about the efficacy of these strategies for interrupting TB transmission. GRADE methodology has been criticized for its grudging grading of evidence quality in high quality observational research, instead lumping all observational research into “low quality” and “very low quality” evidence bins. This classification differs from the original basis for evidence-based guidelines developed by the U.S. Preventive Services Task Force, which GRADE replaced, that did not minimize the value of research other than RCTs with such subjective terminology (10). There is also a science to communication that is not fully appreciated or utilized by proponents of strict GRADE methodology. Extending a questionably appropriate PICO analysis to the creation of specific WHO recommendations may legitimize them but also undermines confidence in the recommendations themselves

and therefore enthusiasm for adopting them.

Further, a “conditional” recommendation with “very low certainty in the estimates of effect” based on a rigorous examination of inadequate data, might do more to dissuade a skeptical or under-funded public health entity from implementing a simple intervention, more so than any real or potential untoward effect of that intervention. Given grossly inadequate public health budgets worldwide, tepid conditional recommendations based on very low certainty provides weak ammunition for public health officials to argue for funding of IPC measures when competing against other budget priorities. The spiritless recommendations dictated by GRADE classification of evidence challenge common sense, diminish their real-world value and do not adequately promote HCW protection.

The interventions evaluated in the studies are among the few practical and available ways to diminish droplet creation and transmission. In addition to economic concerns, it has been suggested that they may be accepted or applied inconsistently for cultural, social and religious reasons, but that cannot be the focus of WHO recommendations whose aim should be to promote practices that protect HCWs. Knowing that aggregate implementation of multiple interventions protects HCW and in the absence of data informing the contribution of each intervention, shouldn't the WHO guidance be to utilize as many interventions as practicable without reservation? There appears to be no reluctance to offer that type of guidance for Covid-19 HCWs.

The HCWs confronting the Covid-19 pandemic deserve all of the accolades, recognition and gratitude that they receive. They also deserve all the protection against Covid-19 transmission that can be provided. The tireless, selfless, and in some ways invisible HCWs who year after year confront the TB pandemic, deserve the same recognition and gratitude, but

more importantly and just like the Covid-19 HCWs, they unconditionally deserve all of the protection against TB transmission that can be provided.

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