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LETTER

How COVID-19 can instruct TB research: ensuring the safety of researchers exposed to infectious disease

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Dear Editor,

Although ethics is not currently a requirement of most institutional review boards, labour legislation or funders, we argue that the topic of ethics of health research should be expanded. Using TB and COVID-19 as examples, we suggest that an ethical approach should underpin all aspects of a research project, including making it mandatory to mitigate the risks of exposing both research and clinical staff to hazardous agents.

The current COVID-19 pandemic has served as a devastating reminder of the vulnerability of healthcare workers (HCWs) to airborne infections.[1,2] Awareness of the critical nature of personal protective equipment (PPE) has become the norm.[3] The value of N95 masks, already advised for those involved in clinical care of TB patients,[4] combined with appropriate hand sanitisation, has been established as crucial for protecting HCWs during the COVID-19 pandemic.[1,2]

TB is the leading contributor to the global infectious disease burden: in 2018, the estimated worldwide TB incidence was 10 million cases and associated mortality around 4,000 cases per day.[5] Unlike SARS-CoV-2, the infectious dose of TB is known: approximately 10 bacilli of *Mycobacterium tuberculosis* may cause infection.[4] Driven by the high HIV co-infection rate, sub-Saharan Africa has a high TB burden,[5] straining public health facilities and infrastructure. There is legitimate concern, moreover, that TB patients may be more vulnerable

to severe COVID-19 disease and death.[6,7] Focussing on the COVID-19 pandemic may derail current TB control programmes: a 50% decrease in testing was reported in South Africa between March and April 2020,[8] potentially increasing the prevalence of multidrug-resistant TB due to patient defaults. Management campaigns for TB patients have been adapted to avert treatment disruption while adhering to reasonable interventions to reduce SARS-CoV-2 transmission.[9]

TB is recognised as an occupational disease, and should be covered by labour legislation.[10] *M. tuberculosis* is classified as a Risk Group 3 pathogen, i.e., high individual, but low community risk, usually causing serious (human) disease, not easily spreading from one infected individual to another and for which effective treatment and preventive measures are available.[4] This classification does not address the acquisition of drug resistance by *M. tuberculosis* and challenges associated with treating resistant cases. HCWs in countries with high TB prevalence are particularly at risk: in crowded, confined settings, risk of TB transmission to close contacts increases. In South Africa, HCWs have a two-fold higher incidence of TB than that of the general population.[11,12] Conversely, high-risk procedures generating aerosols in the laboratory are offset by legislated comprehensive biocontainment procedures, minimising exposure risks.[4]

A HCW is defined as any person delivering care and services, including individuals conducting research on TB and other infectious diseases, who may be exposed to hazards (including airborne infections) in their specific research environment. Standardised and universally accepted methodologies determine the guidelines for identifying four levels of HCW protection.[4] The relative risk of exposure to TB in different research environments differ. The relevance of administrative, managerial, and environmental settings, and PPE, is determined by the relative risk of the environment, the programme's sustainability and cost-effectiveness of any intervention.

Research ethics on human participants are guided by the Nuremberg code and subsequent Helsinki Declaration, based on the principle of non-harm,[13] the predominant focus thus being to do no maleficence and respect patient confidentiality. Potential study participants should be informed of risks and benefits of participation and how their information will be safeguarded before enrolment. Clinical research studies on patients with pulmonary TB could also result in investigators operating unprotected in a high-exposure, high-risk environment: this exposure could occur over a prolonged period, thereby increasing the hazard. TB bacilli are not only exhaled or expectorated when the affected individual is coughing or sneezing, but aerosolised during normal breathing, a risk which is increased when sputum is collected from

the study subject. It is difficult to protect other people sharing the same contaminated environment in the absence of PPE.

As part of research methodology, protocols should include a plan on the ethics of protecting research teams in potentially hazardous environments. A risk assessment of the research environment should be a prerequisite, similar to those for TB exposure in the workplace. Appropriate measures, including training, monitoring individual exposure and individual responsibilities in ensuring staff safety should be specified. If the risk assessment shows low risk of exposure, it should be clarified that follow-up activities are unnecessary. If there are costs associated with protecting researchers, funders should be ethically obliged to require that a budget for this be included. By way of example, funding made available under the US President's Emergency Plan for AIDS Relief (PEPFAR) specifically mentions adherence to occupational health and safety measures for HCWs.[14] Although the South African Ministry of Health has developed a document on the ethics of health research which aims to "protect safety and other interests of researchers," this document does not cover the protection of researchers in institutional review board (IRB) ethics submissions.[15]

When study staff are recruited by the Tuberculosis Platform South African Medical Research Council, exposure risks for TB pertaining to an individual's work are discussed by a nurse or medical officer, inherent to the occupational health programme. This is confidential, and includes a baseline session with new incumbents (Table). If a staff member declines to participate, this refusal is documented in writing and the Director of the research unit is informed. All staff undergo an annual refresher course in biocontainment procedures for TB and basic principles of infection control, applicable to their specific research environment. New staff members must indicate in writing that they have received the necessary training. Similarly, laboratory staff participate in an induction programme appropriate to their responsibilities. At any stage of the study, concerned researchers are encouraged to request TB screening and specifically advised to do so whenever any symptoms are present (Table). The cost of the health monitoring plan is routinely included in grant application budgets. To date, funders have always accepted this additional cost.

We argue that research staff working in crowded public health facilities be independently trained in infection control, irrespective of the pre-existence of appropriate TB infection control measures, enabling them to perform risk assessment and follow personal protection procedures. Although it remains the employer's purview to provide training and relevant standard operating procedures in occupational health, training should ultimately ensure that each individual HCW has a responsibility to adhere to the risk assessment for each

specific research space. Specific statements on the risk of infection for researchers should be included in research protocols and budgets should itemise additional PPE or other interventions, if required. IRBs should require clarification on conditions under which researchers risking exposure to easily transmitted pathogens require protection, specifically including a statement if precautions are unnecessary, if this pertains to a particular project. As we progress to a post-COVID-19 world, equity in ethics demands protection of research staff, as much as clinical staff, from exposure to TB and other airborne pathogens.

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Table TB and COVID-19 Health Surveillance Programme offered to research staff working in high-risk airborne transmission public health settings

Investigations					
Medical examination for pulmonary TB			Integrated TB/COVID-19 screening		
Components	Practitioner	Interval	Components	Practitioner	Interval
Screening for symptoms and signs of TB: cough of any duration, weight loss, fever/night sweats, tiredness/fatigue	Sub-contracted to private sector medical practitioner to respect confidentiality	At onset of employment or start of a new research activity, annual and end of project or employment; quarterly for high-risk, TB-exposure employees	Screening for signs and symptoms of TB as previously: any cough, fever/night sweats, tiredness/fatigue, history of close contact with a COVID-19-positive individual, loss of taste or smell, flu-like symptoms	Performed by SA MRC TBP* nurse, refer for COVID-19 testing as per organisational occupational health procedures. If COVID-19-negative, monitor for a week and refer to medical doctor for TB/COVID-19 testing	Ad hoc, investigation initiated by employee or as mandated by the organisational occupational health procedures
TB: sputum for culture COVID-19: nasopharyngeal swab			Hotspot screening: any cough, fever/night sweats, close contact with a COVID-19-test-positive individual, tiredness/fatigue, loss of taste or smell, flu-like symptoms	Performed by SA MRC TBP nurse or organisational occupational health official	TB: daily for 3 days after initial consult COVID-19: two specimens taken 1 week apart
Latent TB investigation (IGRA)	On request, performed in a private pathology laboratory to respect confidentiality				

CXR	Read by a radiologist	
Health promotion advice on behavioural and or health risk factors for TB		
Costs included in grant applications		
Costs requested for pulmonary TB		Costs requested for integrated TB/COVID-19 screening
Quarterly screening for high-risk, TB-exposure staff such as front-line researchers		Ad hoc TB screening requested individually
Screening for symptoms and signs of TB: CXR, sputum specimens, reimbursement of medical practitioner		Screening for symptoms and signs of TB: cough of any duration, weight loss, fever/night sweats, fatigue; screening for COVID-19; reimbursement of medical practitioner

* As this individual is already employed by the SA MRC, no financial reimbursement is requested.

SA MRC TBP = South African Medical Research Council Tuberculosis Platform; IGRA = interferon-gamma release assay; CXR = chest X-ray