Tuberculosis transmission in South Africa: A need for a new paradigm?

Tuberculosis (TB) control is failing in South Africa (SA), with current notification rates as high as those reported in the early 1900s.[1,2] Adjusting for population size, SA remains ranked among the 10 countries with the highest incidence rate for TB, despite more than a century of TB control efforts and 75 years of combination TB therapy.[3]

The World Health Organization has endorsed an 'End TB Strategy' to end the TB global epidemic by 2035. As part of this global strategy, the SA TB control programme has proposed a programme incorporating three strategic pillars: 'find and link', 'treat and retain' and 'prevent and prepare'.[1] This approach is predicated on treatment as the major modality for TB control. However, there is little evidence of infectious epidemics being controlled by treatment of clinically symptomatic cases alone. Furthermore, the linkage between TB treatment and transmission is less than certain. In the early 20th century, prior to chemotherapy, TB incidence decreased by 75% in New York and London.[2] In contrast, in Cape Town, one of the first cities to introduce compulsory TB notification, the incidence remained high over the early 20th century.[4] While the introduction of TB therapy markedly decreased TB case fatality equally in each setting, it had little impact on TB notification rate.[2]

TB transmission has been believed to be necessarily linked to sputum-positive TB disease. However, a minority of transmission events in high-burdened settings can be linked to identified sputum-positive TB cases, indicating that most TB transmission events result from unrecognised sources.[5-7] An active case-finding programme using mass miniature radiography (MMR) to identify subclinical TB was implemented in Cape Town between 1948 and 1994. The programme performed 2.6 million MMRs.[8] In the 1950s, MMR screening reached 12% of the city's population annually, yielding 14 cases per 1 000 radiographs, and identified up to 20% of TB notifications. However, the impact of MMR on transmission was modest, with TB notifications briefly dipping beneath 400 per 100 000 in the 1960s and 1970s. TB notifications returned to levels above 500 per 100 000 in the 1980s and 1990s, paralleling the wind-down of MMR, with further increases due to the HIV-epidemic.[8]

Recent experiences of the HIV and COVID-19 epidemics have highlighted the role of asymptomatic transmission, making population control particularly difficult. The study of asymptomatic TB carriage is technically and ethically challenging. In the pre-treatment era, *Mycobacterium tuberculosis* (Mtb) was transiently found in gastric washings of adults with normal chest radiographs.[9] '*Mirage de tuberculose*', a historically reported condition in which transient positive sputum cultures were observed in clinically well individuals, has been reviewed.[10] Recent studies using sensitive detection methods identified aerosol shedding of Mtb organisms and DNA sequences from subclinical and asymptomatic individuals in high-burdened settings. A study of patients in a Pretoria hospital detected Mtb by quantitative polymerase chain reaction (PCR) from face mask samples in subclinical TB cases.[11] Mtb was identified by IS6110 PCR assay from electrostatically captured organisms from cough sampling of 10 randomly selected asymptomatic Brazilian prisoners who remained TB disease free over 12 months of follow-up.[12] Viable Mtb organisms have been detected using microscopy and a fluorescent salvatochromic probe in exhaled breath of 30 subclinical GeneXpert sputum-negative TB suspects attending TB clinics, who remained disease free for 6 months without antitubercular treatment.[13] Furthermore, this latter study showed that Mtb shedding could be controlled without TB therapy. The same collection and detection system identified persistent low shedding of viable Mtb organisms in 80% of randomly selected residents of a high-burdened Cape Town township.[14] Cryptic shedding of viable Mtb organisms may explain transmission in high-burdened settings not linked with clinical or subclinical TB cases.

The separation of TB transmission from TB disease raises both challenges and opportunities. Mtb has co-evolved with *Homo sapiens* for thousands of years, and its evolutionary survival is more dependent on successful ongoing transmission than an ability to cause disease. Additionally, the finding of asymptomatic Mtb carriage implies that Mtb may be necessary but not sufficient to cause TB disease. Asymptomatic carriage of Mtb may be due to the organism living within an immune-privileged site or by phenotypic adaptation to avoid immune recognition. Immune activation can result in both symptoms and tissue damage.[15] Specific cytokines such as tumour necrosis factor (TNF) alpha have been strongly associated with cachexia, a pathognomonic symptom of consumptive TB.[16]

Studies of the specifics of the immune recognition of Mtb necessary for development of disease could result in novel diagnostic biomarkers and targets for host-directed therapies. The triggers for the change from asymptomatic carriage to inflammatory disease may be host, pathogen or externally driven. Host factors such as diabetes, HIV infection and immune suppression have been recognised as TB risk factors.[17] Mtb complex has also been recognised to change its phenotype in response to its environment.[18] It has been speculated that the seasonality of TB might be related to other seasonal respiratory infections.[19]

The change of focus from identification of subclinical, sputum-positive individuals who have not presented to the health system to include larger populations of potential transmitters will require novel strategies. Low efficiency transmission by a large proportion of the population identifies a novel target population. Low organism shedding from this population could be expected to be highly sensitive to social and environmental conditions, as illustrated by the longstanding difficulty of TB control in prisons and other overcrowded environments.[20] The reduction in the amount of Mtb bioaerosol shedding in symptomatic but untreated TB suspects is potentially important in limiting TB prevalence. Replication of this host-related clearance of bioaerosol shedding by a vaccine could lead to a novel vaccine strategy targeting TB transmission control in current endemic settings.

Our understanding of a disease is dependent on the assays and tools available to study it. Sputum-based diagnostics have held centre stage over the last century, but recent detection of Mtb in aerosols challenges the current TB transmission paradigm. Better understanding of TB transmission may help explain past failures and help re-address the greatest infectious disease challenge to our country.

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