What lies beneath - beware of the iceberg of TB disease

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The global burden of tuberculosis (TB) disease remains stubbornly high. Population surveys estimate 14 million individuals have prevalent TB disease, reflecting around 10 million incident cases a year, of which around six million are diagnosed and treated. Finding the remaining 'missing millions', i.e. closing the gap between estimated incidence of TB disease and those receiving care, is a key component of global and national TB care and prevention policies.[1]

Such policies however assume we actually know the full burden of TB disease, which is almost certainly untrue. Instead, current TB estimation likely measures the proverbial tip of a much larger iceberg, missing potentially millions of additional individuals with prevalent (i.e. current) TB disease beneath the surface.

Our approaches to estimating prevalent TB disease look to measure the amount of 'active pulmonary TB disease', which is defined as 'bacteriologically-confirmed TB' from two sputum samples, analysed for the presence of *Mycobacterium tuberculosis* (*Mtb*) by culture or PCR-based tests.[2] A statistical adjustment is then made to include paediatric and extra-pulmonary TB disease, based on modelling of limited data.[3,4]

The problem lies in the threshold chosen for pulmonary TB disease. It should cover all individuals whose treatment would benefit the individual, population, or both. Instead, the current threshold reflects TB disease contributing to *Mtb* transmission, which is assumed to usually be accompanied by symptoms, and captured by two sputum cultures (**Figure - Measured**).[2,5] However, those assumptions are demonstrably incorrect.

Aside from the emergence of sputum-positive subclinical TB disease, which is currently detected[6], we know that increasing the number or type (induced, broncho-alveolar lavage) of samples will identify additional sputum bacteriologically-confirmed TB, be it clinical or subclinical.[7] More importantly, systematic bio-aerosol sampling with face masks has found sputum-negative individuals exhaling *Mtb* in large numbers, and likely contributing to transmission (**Figure - Missed - yellow**).[8] If our TB disease threshold is *Mtb* transmission, our burden estimation should probably include all individuals actively spreading *Mtb* into the air.[8]

However, using *Mtb* transmission as a disease threshold still dismisses individuals with ongoing inflammatory pathology, sometimes extensive, before onset of infectiousness or recognisable symptoms.[9–11] As a consequence, current TB measurement effectively assumes that individuals negative on sputum examination do not have pulmonary TB disease, regardless of radiological evidence suggestive of active TB pathology on imaging e.g. by chest Xray (CXR) or computed tomography (CT) ± Positron emission tomography (PET/CT). Classifying this non-infectious TB phenotype as merely 'latent infection' instead of 'disease' is short-sighted.

We know this non-infectious population is sizeable. Although CXR is an imperfect tool with relatively low specificity, detailed evaluations of mass-CXR screening suggest even the number of 'TB-suggestive' CXRs exceeds the bacteriologically-confirmed disease 1.5-10 times **(Figure – Missed – green)**.[6,11] Furthermore, follow-up in a Cambodia population survey found 18% of individuals with 'TB-suggestive' CXRs had developed classic infectious, sputum bacteriologically-confirmed TB over two years. [11]

Such data make clear that non-infectious TB disease affects large populations, which remains uncounted towards the burden of TB. Aside from the immediate health costs, such

individuals would be at risk of post-TB sequelae, regardless of whether they recover or receive treatment at a later stage.[12] In addition, as the Cambodia data shows, individuals with non-infectious TB are likely to contribute to *Mtb* transmission later, highlighting a missed opportunity for treatment which would truly prevent, rather than merely interrupt, transmission.

A broadening of the definition of TB disease will need to be accompanied by a practical method to measure its burden. While the diagnostic tools to do so exist (see **Figure**), many are not practical at scale. In addition, current prevalence surveys are already at the edge of feasibility in terms of costs and time investment, which means extending the scope and screening tools within surveys is not realistic.

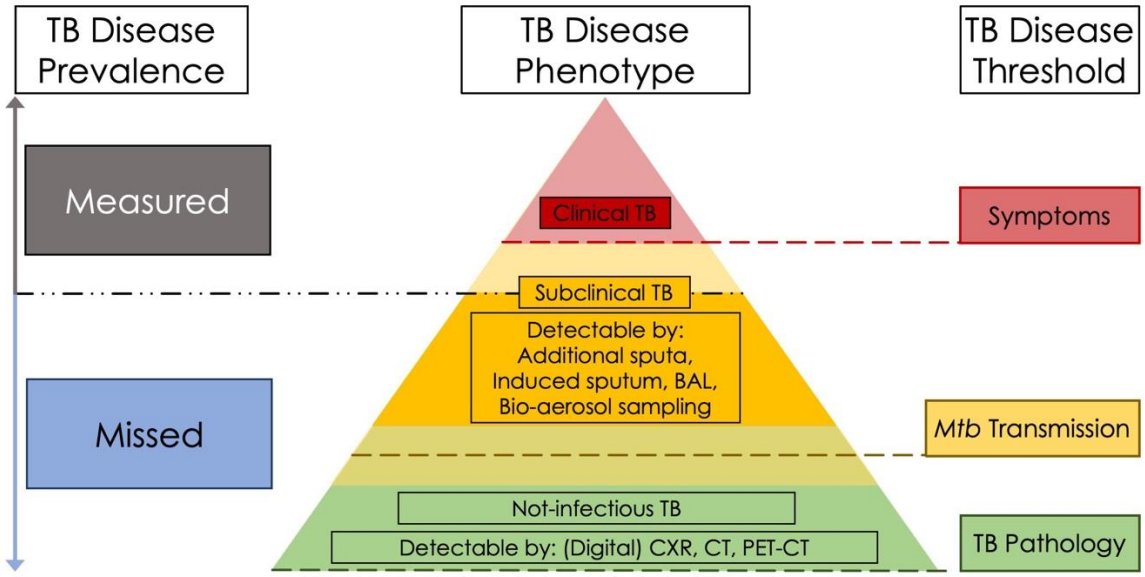
As an alternative, prevalence surveys should be supplemented by a programme of detailed studies across different geographies using current best available tools. Such studies can provide estimates for the relative size of the extended TB phenotypes, but also assess how those ratios vary by epidemiological setting (e.g. level of HIV co-infection), and how phenotypes overlap depending on diagnostics used (**Figure – shaded area above non-infectious TB**). For example, we should recognise that non-infectious disease, be it pulmonary or extra-pulmonary, can also present with symptoms depending on the extent of pathology.[10]

Prevalence surveys in their current form, which measure adult sputum-positive pulmonary TB would serve as a starting point. Similar to the process whereby symptomatic paediatric and extrapulmonary disease are added, we could then estimate the prevalence of TB disease for all phenotypes.

Further challenges with shifting the thresholds for TB disease include developing diagnostic and treatment guidelines for these groups, and a quantification of progression, persistence, recovery, and resultant sequelae from each disease phenotype. While beyond the scope of this commentary, the necessary discussions will benefit from ongoing advancements in thinking and technology in TB diagnostics and treatment.[13,14]

As the TB community focuses on ‘finding the missing millions’ with TB disease, we argue millions more are being missed, and unless we change our TB disease thresholds, they will remain unmeasured, underserved and continue to perpetuate *Mtb* transmission.

Figure: The iceberg of prevalent tuberculosis disease



BAL = Broncho-Alveolar Lavage; CXR = Chest X-Ray; CT = Computerised Tomography; PET-CT = Positron Emission Tomography-Computed Tomography. Figure shows the iceberg of prevalent TB Disease, divided into what is currently 'Measured' (grey box, left) and 'Missed' (blue box, left) by TB burden estimation. Boxes on right show TB disease thresholds, which are conceptual. Actual relative proportions will vary on the diagnostic sample and/or tool used, as indicated by shaded areas. Relative size of areas reflects conservative estimates of additional individuals potentially contributing to Mtb transmission (i.e. bio-aerosol positive, sputum negative - yellow) and with TB pathology (on CXR – green).

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