Spotting the old foe – revisiting the case definition for TB

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Disease case definitions are important instruments for clinical care, interventional research, and surveillance. In light of this, it is concerning that the current case definitions for tuberculosis (TB) remain underscored by the classic paradigm of binary states of latent infection and active disease, with a stepwise, linear transition under which symptoms, bacteriological positivity and disease pathology are assumed to emerge broadly together (figure, top row).\(^1\) This has resulted in a reliance on symptom screening to distinguish these two states. However, in recent prevalence surveys 40-79% of bacteriologically-positive TB occurs in absence of patient-recognised TB symptoms.\(^2\) Rather than explicitly addressing this discordance, TB case definitions are often ambiguous with regard to TB symptoms, or internally inconsistent.

We propose a new perspective on the case definition of pulmonary TB, one that resolves the current ambiguity of TB symptoms and recognises the presence and dynamics of subclinical TB.\(^3\) Under this paradigm, individuals with subclinical TB, also referred to as the ‘Walking well’, have *M. tuberculosis* (Mtb) bacteriologically-positive pulmonary lesions and are thus able to transmit Mtb intermittently or persistently through symptoms they are not aware of, don’t acknowledge, or attribute to alternative conditions (figure, middle row).\(^4\) Crucially, some of these individuals may never advance to clinical TB disease, but instead persist at subclinical level for an unknown period, or regress and self-cure (figure, bottom row).

Allowing for case definitions that recognise distinct disease phenotypes has wide precedent. For example, both HIV and malaria have well-established definitions for infectious, but not clinically ill individuals (e.g. people living with HIV\(^6\) and (sub)patent malaria infections\(^7\). In TB, the implications of current practices are wide ranging. Below we highlight consequences in the areas of clinical care, trials as well as TB surveillance and policy, and suggest potential actions to facilitate resolution.

Currently all individuals diagnosed with drug-sensitive TB disease receive the same six month, fourdrug treatment regimen. While this simplification has enabled the roll-out of DOTS, which has saved millions of lives,\(^8\) it ignores the difference in treatment requirements that may exist between individuals diagnosed passively based on self-reported symptoms and those actively identified in absence of any clinical signs. Historically, treatment regimens have differed depending on clinical severity, and trials of bacteriologically-negative individuals with minimal Xray lesions showed similar efficacy of four months treatment as six months treatment in bacteriologically-positive individuals.\(^9\) Explicit differentiation in the case definition may therefore enable development of trials for more personalized, and potentially shorter regimens.

The TB case definitions used in research, trials in particular, can be ambiguous with regard to the requirement of symptoms, and are often inconsistent between entry and follow-up. As a consequence, disease prevention trials enrolling individuals based on absence of symptomatic disease only may underestimate the efficacy of the intervention if the initial period during which incident cases of TB disease are not counted is short.\(^10\) In addition, taking bacteriologically-positive symptomatic TB disease as the primary outcome will miss subclinical TB, which not only limits the trial’s statistical power but also its ability to differentiate the effect of the intervention on preventing or detecting subclinical versus classic clinical TB. For example, it will be important to understand whether a candidate TB vaccine protects against any disease (thus interrupting transmission) or only against clinically overt disease, leaving subclinical cases to sustain transmission. We note that during
the recent M72/AS01E trial all endpoints were based on clinical presentation, thus providing limited insight as to where in the development of disease the vaccine has an effect. We propose that case definitions in TB trials are expanded to enable detection of differential effect of the intervention on subclinical and clinical TB disease. One option is to complete follow-up with a symptom-agnostic culture-based test in all participants, which would have resource implications, but would also identify subclinical TB, and enable the required analyses. Here, regulatory agencies could drive change, and specify at what point in development a product’s impact needs to be evaluated on the full spectrum of bacteriological positive TB, rather than the symptomatic subset, e.g. at phase 2B.

On a policy level, there are inconsistencies in the case definitions used to estimate the incident burden of TB. For example, for many high-burden countries, incidence is extrapolated from prevalence surveys, which include both (asymptomatic) subclinical and (symptomatic) clinical bacteriologically-positive TB, whereas for others it is primarily based on notifications which predominantly reflect individuals who self-reported to clinics with symptomatic TB. Since in most settings the incidence to notification ratio (i.e. the ‘case detection rate’) is used to estimate programme performance, this inconsistency in case definition is problematic. In addition, global and National TB programmes should acknowledge that up to 80% of individuals with likely infectious TB present in their population will not be detected by the symptom-dependent case-finding strategies which still dominate TB policy. By recognising that bacteriologically-positive and symptomatic TB often overlap only partially, a set of symptom-agnostic case-finding approaches can be developed that are potentially effective. Such changes should also be reflected in what surveillance systems report, e.g. mode of detection, and presence of clinical symptoms to enable more refined analysis of notification data and programme performance. Guidance in this area falls to policy bodies, in particular the Global TB Department at WHO, which should also ensure that sufficient specificity is retained to avoid an increase in false-positive TB diagnoses.

Even if our proposed changes to distinguish symptomatic and non-symptomatic disease are adopted, many challenges will remain. For example, the detected size of the subclinical TB population will vary depending the sampling approach, timeframe and the microbiological techniques used. Yet if we are to achieve meaningful reduction of the burden of TB in our lifetime, we need to interrupt transmission, which will require addressing all bacteriologically-positive TB, including subclinical. Recognising this disease state in our TB case definitions, and removing the current ambiguity, will provide a better understanding of current epidemiology and enable more effective control policy. We hope our proposals can advance discussions and enable much needed progress.
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**Figure: Progression of individual after initial Mtb infection**

Progression of individuals after infection with *Mycobacterium tuberculosis* and associated TB case definitions. a) Classic TB case definition, which assumes an individual’s incubation and pre-infectious period simultaneously transition into clinical disease and becoming infectious. b) Addition of a subclinical or ‘Walking well’ stage leads to infectious period now preceding clinical disease. c): Addition of non-progression or self-cure from subclinical stage will introduce a discrepancy between measured prevalence and estimated incidence. Mtb = *Mycobacterium tuberculosis*
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