the impact this has on transmission dynamics within communities are rarely appreciated. The intensity of the infection pressure that exists in some endemic areas is evidenced by the frequency of disease caused by re-infection and/or multiple strain infection. Case density is a variable that describes the proximity of cases in space and time. From a transmission perspective, case density provides a measure of transmission overlap. Mathematical models using hypothetical scenarios assign a fixed number of secondary infections to each source case. By diagnosing and treating the source case it is assumed that a fixed number of secondary infections will be prevented. However, in endemic areas with high case densities the elimination of a single source case has limited impact on secondary infections among close contacts due to significant transmission overlap. Therefore, if we hope to develop mathematical models that are more robust and predictive of the situation in endemic areas, it seems relevant to adjust for case density. It should also be noted that, with transmission overlap, contacts are at risk of being infected multiple times by different source cases. The effect of repeated infections remains poorly understood, but multiple infectious challenges may "overwhelm" host immunity and predispose to the development of active disease.

Transmission saturation

Most source cases have fairly fixed circles of social interaction. This implies that once the majority of close contacts have been infected, the risk of infecting new people may decline even though the source case remains highly infectious. This phenomenon is referred to as transmission saturation. Transmission saturation illustrates the importance of early diagnosis and immediate institution of effective treatment. In this respect, the traditional focus on the most infectious sputum smear-positive cases, although clearly warranted, may not be the optimal strategy to limit the spread of disease within communities if it implies diagnostic delay beyond the point of transmission saturation. With delayed diagnosis, the transmission impact of ultimate treatment is greatly reduced. Current targets do not reflect the importance of limiting diagnostic delay and more sensitive diagnostic tools are required to achieve this.

There is a need to reconsider the accuracy and applicability of current mathematical models and to identify pragmatic ways of quantifying additional factors that may be at play in endemic areas. The incorporation of case density and transmission saturation in future mathematical models may assist the identification of more stringent, albeit more realistic, performance targets for global TB control.

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BJ Marais & PD van Helden

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Author reply
Marais & van Helden provide an important historical context for the role of mathematical modelling in formulating performance targets for tuberculosis (TB) control. Furthermore, they appropriately highlight that such models serve as simplifications of a far more complex reality, in which M. tuberculosis is transmitted in heterogeneous fashion. They mention two key factors – case density and transmission saturation – that contribute to such heterogeneity. However, there are many more, including nosocomial transmission clusters, strains of different fitness, social determinants of TB transmission and complex interactions with the HIV co-pandemic. Ultimately, no model can account for all potentially relevant aspects of TB transmission. Thus, we need simple models capable of distilling key components of transmission dynamics into clear messages. However, more complex models can be created to try to show us where – and to what degree – simple models may go wrong. Models exploring case density and transmission saturation could have an important role to play in this regard, and we welcome such efforts.

Ultimately, we must also remember that mathematical models are but one component of a broader TB research agenda that is sorely in need of expansion. While refining our models, we must not lose sight of the fact that approaches over the past 20 years have failed to stem the tide of ongoing TB transmission and that a broad-based, concerted effort – including an expanded research agenda, relentless improvements in case detection and development of better tools for TB diagnosis and treatment – will be required to meet current goals for TB control. Over the next 20 years, the value of TB mathematical models may be measured less by their ability to accurately describe the dynamics of TB transmission, and more by their power to galvanize support and inform appropriate policy.

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