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Study finds high prevalence of *Mycobacterium tuberculosis* aerosol release in Cape Town community

Since the discovery of *Mycobacterium tuberculosis* (*Mtb*) as the bacterial cause of tuberculosis (TB) in the late 1800s, it has generally been assumed that advanced disease and severe symptoms are prerequisites for airborne bacterial transmission between infected host and uninfected recipient.

A team of researchers based in the University of Cape Town's (UCT) Institute of Infectious Disease and Molecular Medicine (IDM) has studied the generation of *Mtb* aerosols since 2013. They have been using the custom-built Respiratory Aerosol Sampling Chamber (RASC), a highly sensitive personal clean-room that captures all respiratory matter released by individuals in aerosols, including live *Mtb* bacilli.

In a new study, the team utilised the RASC to determine the prevalence of *Mtb* aerosol release in Masiphumelele, a heavily TB-burdened community in Cape Town. They collected aerosol samples from 89 randomly selected inhabitants recruited into two consecutive cohorts. The first was a cross-sectional community survey comprising 39 participants, and the second was a longitudinal observational study in which 50 individuals consented to be serially sampled at three separate time points over two months: baseline, two weeks and two months.

Reporting their findings in the journal *iScience*, the team found that, across both cohorts, the baseline prevalence of *Mtb* aerosol release was 80%. "That means, at any given moment, random sampling of the community yields approximately 80% *Mtb* aerosol positivity, albeit at very low bacterial counts per individual. Surprisingly, this high prevalence bioaerosol-positivity occurs independently of standard bacteriological and immunological assays for detecting *Mtb* infection," said Dr Ryan Dinkele, the study's lead author.

Longitudinal follow-up revealed that most individuals were persistently or transiently infected with *Mtb*, with only one participant returning negative results at all three visits across the two-month study duration. Despite temporal fluctuations in *Mtb* release per individual, there was no overall trend for the whole cohort, supporting the inference that low-level *Mtb* bioaerosol positivity is common and fluctuates transiently across apparently healthy individuals in the community.

Dr Dinkele commented: "The inclusion of new tools in TB research has facilitated insights that question well-accepted models of *Mtb* pathogenicity. For example, there is an

increasing awareness that TB disease may not be as important for *Mtb* transmission as initially predicted.

"Our results further this understanding by revealing a potentially vast and undetectable reservoir of *Mtb* transmission potential. Importantly, these observations imply that targeting interventions to disrupt *Mtb* transmission at individuals diagnosed with active disease will fail to curtail the TB epidemic."

The findings challenge prevailing models of *Mtb* pathogenicity and TB aetiology, said Dinkele. "Although infection with *Mtb* is a prerequisite for TB, it is insufficient to cause disease. Elucidating the suite of host, bacterial, and environmental factors constituting the sufficient cause(s) of disease is therefore essential in developing novel interventions for TB."

Dinkele noted that the high prevalence of *Mtb* bioaerosol release is driven by a homeostatic interaction between the human host and the mycobacterium, either through a high turnover of infection and clearance, or through sustained infection occluded from immune detection.

"It is important to bear this observation in mind when designing new vaccines and deciding who to vaccinate. Are vaccines aiming to prevent or clear infection or to perpetuate this homeostatic interaction? Moreover, our findings suggest that the presence of *Mtb* infection is a poor prognostic for risk of disease. It is critical, therefore, that further research is performed to elucidate the causes of disease and to develop more accurate prognostics," he said.

Dinkele shared that the significance of the findings for TB control and the attributable transmission risk from this population remained to be demonstrated definitively.

"Nevertheless, the implications are provocative. I hope that, rather than dismissing these findings, other researchers will be inspired to re-evaluate previous assumptions in the TB field."

According to Dinkele, TB is an ancient disease that continues to confound researchers despite the investment of significant (though not enough) resources in national TB control programmes, TB diagnostics, anti-TB vaccine and drug development, and fundamental research. "Reevaluating the disease from a fresh perspective may shed light on why TB remains recalcitrant to biomedical interventions and will hopefully benefit the millions of people who suffer from TB each year," he said.

Professor Digby Warner, Director of the IDM, said: "It's both surprising and exciting – this latest instalment in a series of studies which, in addition to questioning some of the assumptions about TB aetiology and risk in our high-burden setting, exemplifies the benefits of locally-driven, innovative, multi-disciplinary research that is enabled in the IDM."

Emeritus Professor Robin Wood, a full member of the IDM, said: "Our understanding of any disease is limited by the set of tools through which we view it. By adding the RASC to our tool box, we have only just begun to describe the earliest interactions between the host and *Mtb*. We aim to expand on these findings in the years to come in the hopes of transforming our understanding of the aetiology of TB."

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