Threat from *Mycobacterium orygis*-associated tuberculosis in south Asia

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South Asia is a hotspot of tuberculosis with an estimated annual incidence of 3·7 million cases, accounting for 37% of the global tuberculosis incidence in 2019.[1] The southeast Asia region, which includes south Asia, has a high burden from zoonotic tuberculosis, with an estimated 43 000 (31·76%) new cases in 2016; however, as the causative agent of this zoonotic tuberculosis has not been fully defined, the true incidence could be underestimated.[2] Reports of tuberculosis caused by *Mycobacterium orygis* in animals and humans in south Asia, and the discovery of *M orygis* in south Asian migrants, highlights an overlooked threat from *M orygis* in south Asia and beyond.

M orygis is a genetically distinct animal-adapted subspecies of the *Mycobacterium tuberculosis* complex that causes tuberculosis in animals and humans.[3] It has been isolated from a range of animals in south Asian countries, across livestock farms, zoos, and free-ranging wild animals, suggesting endemicity in the region.[3–6] Direct evidence of *M orygis* transmission between livestock and humans has been reported from an Indian immigrant working in a cattle farm in New Zealand.[7] *M orygis* in migrants from India, Nepal, and Pakistan who live in the USA and Norway, indicate that the origin of such *M orygis* infections is in south Asia.[8,9] The US study found that the eight cases of *M orygis* did not belong to an epidemiological transmission cluster, suggesting that the infections were independently acquired. The only epidemiological risk factor in all cases was that patients emigrated from south Asia.[8] Similarly, in the study from Norway, the authors concluded that all *M orygis* isolates were uniquely imported to Norway from south Asian migrants at various time points, and no transmission of *M orygis* occurred in Norway during the patients' residence there.[9] In a comprehensive molecular epidemiological survey of 940 mycobacteria-positive cultures from clinical patients, mainly from different states of India and some from Nepal and Bangladesh, seven *M orygis* isolates but no *Mycobacterium bovis* isolates were reported, prompting the authors to argue that *M bovis* should be reconsidered as a sole proxy for zoonotic tuberculosis as per the WHO definition.[10] These seven cases of *M orygis* were reported from four different states in northern and southern India, and six of them were associated with extrapulmonary tuberculosis, as in the typical case of zoonotic tuberculosis. These reports of *M orygis* from across humans, livestock, and wildlife in south Asia suggest that *M orygis* is endemic and a causative agent of animal and zoonotic tuberculosis in the region. In-depth epidemiological surveillance should be conducted across humans, livestock, and wildlife to understand the unique epidemiological, ecological, and pathogenomic drivers of distribution, risk factors, and transmission dynamics of *M orygis* in south Asia.

South Asia is a biodiversity hotspot and home to many iconic endangered animals such as tigers, rhinoceros, and elephants. *M orygis* was reported to originate from a free-ranging rhinoceros at the Chitwan National Park in Nepal, a transboundary national park between Nepal and India.[5] Furthermore, *M orygis* was reported in zoo animals in Nepal originally from Chitwan National Park, suggesting unknown maintenance hosts of *M orygis* in and around the national park.[6] The case of *M orygis* in an endangered rhinoceros in Nepal and many unreported cases of tuberculosis in wild animals in zoo and captive facilities of south Asian countries suggest an unexplored threat of tuberculosis, perhaps due to *M orygis*, to wildlife conservation in the region.

The emphasis on diagnosis and control of tuberculosis in south Asia is given to human tuberculosis, particularly multidrug-resistant tuberculosis. Commonly used diagnostic methods, such as those that make use of clinical signs, Ziehl-Neelsen staining, and cultures, cannot identify the particular species of the *M tuberculosis* complex. Similarly, the popular GeneXpert MTB/RIF test does not differentiate between species of the *M tuberculosis* complex, so the true burden of zoonotic tuberculosis is unknown because of inaccurate diagnosis. Furthermore, the real burden of animal tuberculosis in the region is unknown as there are no livestock or wildlife tuberculosis control programmes being implemented. In the light of WHO's End TB Strategy to diagnose and cure every tuberculosis case to end the epidemic by 2030, the threat from

M orygis in south Asia must be recognised at national and international levels, and the appropriate control programmes implemented.

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