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Drug-resistant tuberculosis – primary transmission and management

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Summary The DOTS strategy assisted global tuberculosis (TB) control, but was unable to prevent the emergence and spread of drug-resistant strains. Genomic evidence confirms the transmission of drug-resistant *Mycobacterium tuberculosis* strains in many different settings, indicative of epidemic spread. These findings emphasise the need for enhanced infection control measures in health care and congregate settings. Young children in TB endemic areas are particularly vulnerable. Although advances in TB drug and vaccine development are urgently needed, improved access to currently available preventive therapy and treatment for drug resistant TB could reduce the disease burden and adverse outcomes experienced by children. We review new insights into the transmission dynamics of drug resistant TB, the estimated disease burden in children and optimal management strategies to consider.

Introduction

The World Health Organization (WHO) estimates that 10.4 million people developed tuberculosis (TB) in 2015, resulting in 1.8 million deaths; more deaths than attributed to HIV/AIDS and malaria combined.[1] An estimated 580,000 TB cases had rifampicin or multidrug resistant (MDR; resistance against isoniazid and rifampicin) TB, with the majority of cases found in the Indian sub-continent and China.[1] With sputum smear microscopy as the only diagnostic tool in many TB endemic settings, drug resistant TB was able to "travel under the radar" for many decades. Improved access to rapid molecular tests, such as the Xpert MTB/RIF® assay, and results from representative prevalence surveys are slowly providing a more accurate picture.

Seminal observations by Oestreicher and Middlebrook in the 1950s suggested that isoniazid resistant strains have greatly reduced "fitness",[2] which induced a sense of complacency that these strains will not be able to sustain epidemic spread. Although Fox and Sutherland noted isoniazid resistant disease in close contacts of TB cases treated with isoniazid,[3] indicative of transmitted drug resistant disease, this observation never received the attention it deserved. Since then, the detection of paediatric cases wherever

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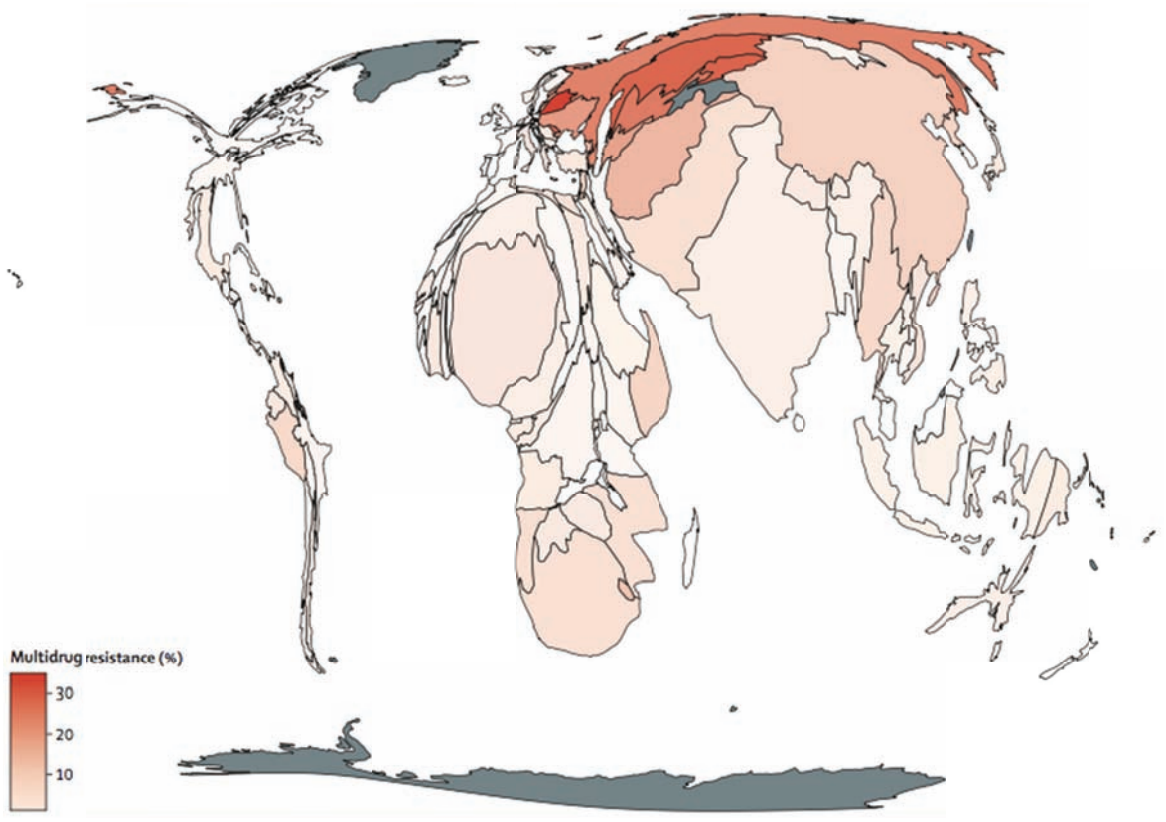

Figure 1 Estimated country-specific burden of paediatric MDR-TB. Used with permission.[30]

adult MDR-TB cases were identified provided a strong signal of MDR-TB transmission; the presence of paediatric MDR-TB cases have now been identified in nearly every country where adult MDR-TB cases have been diagnosed.[4]

In China, a drug resistant TB prevalence survey conducted in 2007 found MDR-TB among 6% of new and 26% of re-treatment TB cases,[5] with high rates of concurrent fluoroquinolone resistance.[6] A recent assessment of 100 paediatric cases with culture confirmed TB suggests active MDR-TB transmission within the community;[7] supported by high drug resistance rates in adults with tuberculous meningitis.[8] In China, the TB epidemic is dominated by *Mycobacterium tuberculosis* strains of the Beijing lineage.[9] Traditional molecular typing methods provide insufficient resolution to differentiate transmission clusters among highly monomorphic Beijing lineage strains, but a study using highly discriminatory whole genome sequencing (WGS) in Shanghai, found that at least 73% of MDR-TB cases represented primary MDR-TB transmission.[10,11] No detailed drug resistance profiles were reported in the Shanghai study, but data from northwest China[8] and neighbouring Mongolia[12] demonstrate high rates of pan-resistance against all first-line drugs, including streptomycin. There is evidence that even with good adherence to multi-drug therapy, variable drug concentrations within complex tuberculosis lesions and differences in pharmacokinetics, may lead to sub-optimal drug exposures and the development of drug resistance.[13] However, empiric use of the retreatment regimen, which adds streptomycin to standard first-line drugs, offers the most likely explanation for drug resistance amplification and ongoing transmission from inadequately treated MDR-TB cases in parts of the world where this is routinely used.

The identification of young children with culture confirmed MDR-TB provide clear evidence of transmission, which supports modelling,[14–16] laboratory[17,18] and epidemiological[19–22] data demonstrating fitness restoration and successful transmission of drug resistant *Mycobacterium tuberculosis* strains. Beijing lineage strains seem to have a particular preponderance to develop drug resistance[23] and are over-represented among paediatric MDR-TB cases.[24] The clustering of MDR-TB cases along the trans-Siberian railway line offers a prescient reminder that MDR-TB is "on the move",[25] which has relevance beyond the worst affected areas since tuberculosis does not respect national borders.[21] The possibility of future epidemic replacement where drug resistant strains might pre-dominate, is illustrated by places like Minsk, Belarus, where almost 50% of new and more than 75% of previously treated TB cases have MDR-TB.[26] Young and vulnerable children are particularly at risk in settings with poor epidemic control.[27] We briefly review the estimated global burden of MDR-TB in children and optimal management strategies to consider.

MDR-TB disease burden in children

Childhood TB remains substantially under-diagnosed due to diagnostic challenges and limitations in recording and reporting practices.[28] These challenges are most pronounced in children with MDR-TB, since this is essentially a bacteriological diagnosis. Two modelling studies that used different approaches to assess the global MDR-TB burden in children, suggest that around 30,000 children develop MDR-TB every year.[29,30] Figure 1 reflects country-specific disease burdens, demonstrating large case numbers in the Indian