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## Healthy survival after tuberculosis

WHO estimates that 1.6 million people die each year before or during tuberculosis treatment. In *The Lancet Infectious Diseases*, Kamila Romanowski and colleagues<sup>1</sup> meta-analysis showed that tuberculosis survivors have approximately three-times to four-times greater mortality than their local populations, including among younger adults. These transformative findings show that tuberculosis, already the most frequent cause of death from a single infectious agent, is associated with even greater mortality than current estimates. This excessive tuberculosis-associated mortality and the proposed pathways that might explain it are summarised in the figure.

Each year, millions of tuberculosis cases are believed to be missed and, globally, 18% of tuberculosis treatments are unsuccessful, explaining some of the tuberculosis-associated deaths.<sup>2</sup> Tuberculosis recurrence is a potential pathway to mortality after tuberculosis, regardless of apparent treatment success or whether recurrence is diagnosed and treated. Recurrence due to relapse is especially probable when treatment is inadequate because of non-completion, intermittent adherence, or inappropriate treatment with drugs to which a patient's tuberculosis is resistant.<sup>3</sup> Recurrence might also be caused by reinfection in households, communities, or health-care facilities.<sup>4</sup> These issues emphasise the importance of global efforts to increase case-finding, treatment success, rapid drug-susceptibility testing, and infection control.<sup>2,5</sup>

Although tuberculosis diagnosis and assessment of cause of death are notoriously unreliable in the resource-constrained settings where most tuberculosis cases occur,<sup>6</sup> the available data suggest that most deaths after tuberculosis are not caused by recurrence.<sup>1</sup> Sequelae of tuberculosis, such as residual or secondary lung diseases, might cause death<sup>7,8</sup> independently of apparent treatment success. These deaths could occur either

directly through respiratory failure, indirectly through cardiovascular effects (such as pulmonary hypertension),<sup>9</sup> or through as-yet uncharacterised mechanisms that might explain increased ischaemic heart disease and cancers after tuberculosis.<sup>10</sup>

Comorbidities and social determinants (eg, HIV infection, smoking, and poor living conditions) predispose to tuberculosis recurrence and sequelae,<sup>11</sup> and also often cause death by mechanisms completely unrelated to tuberculosis, potentially explaining much of the excess mortality during and after tuberculosis.<sup>12</sup> Furthermore, comorbidities and social determinants are often worsened by the psychosocial and economic challenges of tuberculosis illness, treatment, and associated catastrophic costs, constituting a vicious cycle leading to, and being worsened by, tuberculosis.<sup>13</sup>

Tuberculosis treatment has saved millions of lives,<sup>2</sup> but drug toxicity also contributes to excess mortality after treatment, as evidenced by the harmful effects of months of multidrug treatment on liver, kidney,



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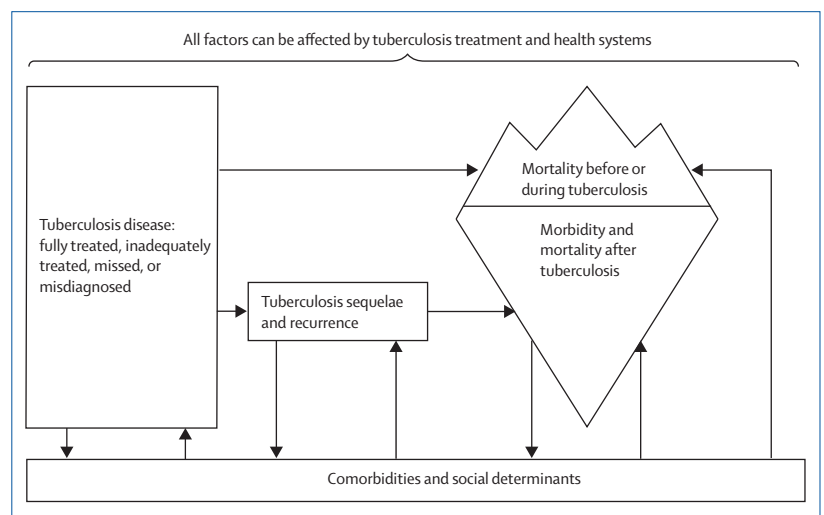


Figure: Schematic indicating potential pathways explaining tuberculosis-associated mortality

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hearing, and vision, especially in the treatment of drug-resistant forms of tuberculosis.<sup>14</sup>

Current estimates of deaths before or during tuberculosis treatment appear to be the tip of the iceberg of tuberculosis-associated mortality. Only two-thirds of the global estimate of 10 million tuberculosis cases per year were notified cases, and only approximately half of these notified cases were laboratory-confirmed tuberculosis.<sup>2</sup> Therefore, some deaths after tuberculosis treatment probably occurred in people who never actually had tuberculosis and whose misdiagnosis might have denied them potentially life-saving treatment.<sup>15</sup> Conversely, autopsy studies have consistently shown that many people die from tuberculosis without having been diagnosed before death.<sup>6</sup> Like most causes of death, especially in low-income and middle-income countries, mortality before, during, and after tuberculosis treatment is inadequately quantified.

Although this meta-analysis focuses on mortality after tuberculosis,<sup>1</sup> the overall burden of disability and morbidity after tuberculosis probably affects even more people and is very poorly characterised. Like mortality after tuberculosis, morbidity after tuberculosis is also probably caused by a combination of tuberculosis recurrence, sequelae, comorbidities, social determinants, and treatment toxicity. Although a tuberculosis elimination perspective might emphasise treatment, a patient-centred approach must also prioritise quality of life and healthy survival during and after tuberculosis. This approach should also include consideration of the patient's household members, especially their care givers, who are often profoundly affected by the illness, impoverishment, and stigma associated with tuberculosis.

The need for follow-up after completing treatment for many conditions is clear and Romanowski and colleagues' meta-analysis highlights the need for tuberculosis survivors to be provided with continuing care after treatment.<sup>1</sup> This continuing care is not only a medical need, but also a chance to prevent other morbidity and mortality. Follow-up should include assessing and treating morbidity after tuberculosis, providing surveillance for recurrence and sequelae, and addressing risk factors for preventable mortality, including comorbidities and social determinants. This meta-analysis identified considerable heterogeneity in study methods and findings, and a dearth of evidence, raising many questions. Therefore, it should also be considered as a call for action, highlighting

that morbidity and mortality after tuberculosis and the interventions and health systems needed to reduce them are priorities for research and funding.<sup>1</sup> These issues will be the focus of the First International Post-Tuberculosis Symposium in South Africa (July 22–23, 2019). It seems inevitable that to effectively reduce morbidity and mortality after tuberculosis, interventions must be multidisciplinary, addressing psychosocial, economic, and biomedical factors.<sup>16</sup>

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## Better surveillance to protect mothers and infants from Zika



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In *The Lancet Infectious Diseases*, Sarah Hill and colleagues<sup>1</sup> report their multi-component investigation of the Zika virus outbreak in Angola. The authors make a compelling argument that the Asian lineage of Zika virus caused the outbreak, recognition of which was substantially delayed. Phylogenetic analyses of the viral genome suggest that isolates from Angola were closely related to Zika viruses circulating in Brazil, and that the virus was introduced to Angola between July, 2015, and June, 2016. They estimated that Zika virus had been circulating in Angola for 17–28 months, and reported that the virus could have been circulating for up to 18 months before local detection in December, 2016 (local transmission of Zika virus was reported to WHO in January, 2017).<sup>1,2</sup> The timing of the birth of the first infant with suspected microcephaly that was potentially attributable to Zika virus infection in January, 2017, provides additional evidence that the virus was probably circulating in early 2016.<sup>3,4</sup> Such delays in recognition of Zika virus are not unusual in countries with little surveillance of arboviral diseases or birth defects. For Zika virus, the absence of adequate surveillance could lead to severe consequences—specifically, infants with congenital Zika syndrome.

Surveillance of transmission of Zika virus is difficult because most cases are mild or asymptomatic; clinical signs and symptoms, when present, are similar to those of other common infections; and there is no reliable diagnostic test outside the 1–2 weeks after initial infection.<sup>5</sup> Careful genomic epidemiological studies in the WHO Region of the Americas have shown probable prolonged local transmission and multiple introductions of Zika virus before detection even in areas with well established arboviral surveillance systems,<sup>6,7</sup> emphasising the challenge facing countries with less developed surveillance, particularly those with close travel and trade links with countries where Zika virus or other arboviruses are circulating.

The 2015–16 Zika virus outbreak in the Americas also showed the devastating fetal effects associated with the Asian lineage of Zika virus. Animal studies<sup>8</sup> suggest that the African lineage, which was identified in Uganda more than 70 years ago and has probably been circulating across the continent since, could be equally or more harmful to the developing fetus. However, the absence of surveillance for both the virus and adverse pregnancy outcomes in most African countries means that potential effects of Zika virus infection could have gone undetected for decades.<sup>8</sup> A 2006 March of Dimes report<sup>9</sup> on the global burden of birth defects estimated that Angola had one of the highest prevalences of birth defects worldwide. Because there is no surveillance infrastructure for birth and few health-care personnel trained in public health surveillance, affected babies in Angola are unlikely to be detected or to receive appropriate care.

To improve capacity for surveillance of birth defects, the US Centers for Disease Control and Prevention (CDC), the International Clearinghouse for Birth Defects Surveillance and Research, ministries of health, and other relevant country-specific government entities have collaborated on in-country and regional training. This training has focused on increasing awareness of the importance of birth defects surveillance; the establishment of a programme to collect complete, accurate, and timely data; and ensuring referral to services to improve quality of life for children affected by birth defects. Training materials, including a surveillance manual and an atlas of selected congenital anomalies, to help countries to launch surveillance programmes and monitor birth defects in low-income and middle-income countries are publicly available.

Development, implementation, and maintenance of high-quality surveillance of birth defects and vector-borne disease are difficult and costly, but can aid in

For the International Clearinghouse for Birth Defects Surveillance and Research see margin link to [www.icbdsr.org](http://www.icbdsr.org)

For training materials see [http://www.who.int/nutrition/publications/birthdefects\\_manual/en/](http://www.who.int/nutrition/publications/birthdefects_manual/en/)