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Importance of tuberculosis control to address child survival

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Tuberculosis commonly affects young children (<5 years) in countries that have high rates of child mortality.[1] The global public health focus to control tuberculosis has traditionally aimed to reduce transmission through early case-finding and effective treatment of the most infectious cases. Young children have historically been excluded from this focus, since their contribution to tuberculosis transmission is believed to be small. In the past decade, national tuberculosis programmes in high-burden settings have given increased attention to the challenges of childhood tuberculosis.[2] In 2012, World TB Day focused on children for the first time. This attention is likely to increase further as the WHO Global Tuberculosis Programme's ambitious post-2015 tuberculosis control strategy seeks to engage the entire health sector, including maternal and child health.

Within the Millennium Developmental Goal (MDG) framework, tuberculosis control and its related targets are framed within MDG 6, and yet are also relevant to MDGs 4 and 5 (child and maternal mortality) and MDG 1 (undernutrition). Improvement of child survival is a major global health priority but tuberculosis is not regarded as important in that context. However, we believe that the relevance of tuberculosis to child survival will become increasingly apparent over the next decade, especially in countries where tuberculosis control remains difficult and high rates of *Mycobacterium tuberculosis* transmission are sustained. Recognition of the relevance and challenges of tuberculosis to child survival is growing.[3]

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For more on the WHO Global Tuberculosis Programme's post-2015 tuberculosis control strategy see http://www.who.int/tb/post2015_strategy/en/

Contributors

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Declaration of interests

We declare that we have no competing interests.

The 2012 WHO Global Tuberculosis Report[4] was the first edition of this report to provide global estimates of the burden of childhood tuberculosis. The difficulties in provision of accurate estimates of childhood tuberculosis are widely acknowledged and include challenges of case detection, diagnostic accuracy, and poor recording and reporting practices. Vital registration data, in which causes of death are coded according to the two latest revisions of the International Classification of Diseases (ICD; underlying cause of death: ICD-10 A15–A19, equivalent to ICD-9: 010–018), were used to produce a global estimate of childhood mortality attributed to tuberculosis in children not infected with HIV, with the most recent estimate of 74 000 deaths in 2012.[5] Because these deaths represent only about 1% of the estimated total deaths in children globally in 2012, tuberculosis is not regarded as a major contributor to child mortality.

However, there are important limitations to the estimate of 74 000 child deaths from tuberculosis. First, tuberculosis is also an important cause of death in children living with HIV,[6] but for these deaths HIV is registered as the underlying cause and tuberculosis as a contributory cause. Since a third of countries with vital registration systems report only the underlying causes of death and not contributory causes to WHO, vital registration data cannot be used to estimate the number of tuberculosis deaths in people living with HIV. Further, vital registration data are available for only 3% of global child deaths and are not available in most tuberculosis-endemic countries.[5]

The risk of death due to tuberculosis in children is highest for those younger than 5 years.[7,8] However, accurate characterisation of tuberculosis-related deaths in young children can be challenging because the clinical features of tuberculosis are not specific. Tuberculosis in young children is usually a clinical diagnosis that is not confirmed microbiologically, especially in tuberculosis-endemic areas with scarce resources. Therefore, estimation of the contribution of tuberculosis to deaths in young children that have been attributed to pneumonia or malnutrition, either as the direct cause or as comorbidity, is a challenge.

Findings from clinical studies show that tuberculosis is common in African children with severe pneumonia.[9,10] Investigators of a study from Uganda of 270 children with WHO-defined severe pneumonia reported that 19% had a clinical diagnosis of tuberculosis and 6% had culture-confirmed tuberculosis.[10] Pooled analysis of autopsy studies from five African countries of children who died with respiratory disease showed that 11% of 473 children with HIV and 8% of 338 children not infected with HIV had tuberculosis.[11] The findings need to be interpreted with caution because of possible sample bias. These clinical and autopsy studies were mainly from tertiary urban centres representing the most critically ill children, and the direct cause of death in these children is difficult to ascertain. However, the findings suggest that tuberculosis could be a more common cause of morbidity and mortality in children with pneumonia than is recognised. 1.3 million children were estimated to have died from pneumonia in 2011, and almost half of these deaths were children in Africa.[6] If then, for example, around 10% of child pneumonia-related deaths were due to tuberculosis, the present estimates of deaths in children due to tuberculosis would more than double.

Tuberculosis can cause substantial weight loss, but data to quantify its contribution to childhood malnutrition are scarce. Investigators of studies from Bangladesh and South

Africa report very similar results,[12,13] despite representing low and high HIV-endemic settings. Tuberculosis was microbiologically confirmed in 4–6% of children with severe malnutrition and clinically diagnosed in an additional 16–17%.[12,13] In 2011, an estimated 500 000 deaths in children were associated with severe wasting, and infectious diseases, such as pneumonia, were the immediate causes of these deaths.[14]

Infants and young children are at increased risk of disseminated tuberculosis and meningitis compared with older children and adults, and tuberculosis is known to be an important cause of meningitis in children.[15,16] Tuberculous meningitis is associated with very high case-fatality rates (as high as 50%) and a high likelihood of severe disability in survivors.[15] In a state-sponsored vaccination programme that includes *Haemophilus influenzae* type b and pneumococcal conjugate vaccines, *M tuberculosis* is now the most common cause of bacterial meningitis in children in Cape Town, South Africa.[16]

The large increased risk of tuberculosis and tuberculosis-related death in children with HIV compared with children not infected with HIV is well recognised. In the era before early treatment for HIV, autopsy studies commonly showed that tuberculosis was not recognised before death in children and adults with HIV who died in hospitals in Africa.[11] 159 000 deaths due to AIDS were reported in children younger than 5 years in 2010, but what proportion might also have been due to tuberculosis is not known.[6] The numbers of deaths due to tuberculosis in children living with HIV is probably falling because of prevention of mother-to-child transmission and early treatment for HIV.[17,18] However, the coverage of treatment for HIV in children remains low (recent estimate of 28% globally) and is only half of that for adults living with HIV.[19]

Finally, it is also important to consider the indirect effects of tuberculosis on child survival. WHO estimates that globally there are 9.7 million orphans as a result of tuberculosis.[20] Death of a parent in a resource-poor setting, particularly the death of the mother of an infant or young child, is a major predictor for the child's mortality. All-cause mortality of children from households with an adult with tuberculosis in Guinea-Bissau was significantly greater than was all-cause mortality in children living in tuberculosis-free households; all-cause mortality was eight-times greater when the mother had tuberculosis than for children living in households with no tuberculosis contact.[21] Tuberculosis is a common cause of maternal mortality especially in women with HIV, and maternal tuberculosis is associated with transmission of tuberculosis to the infant, low birthweight, and infant mortality.[22]

We have presented data from small-scale studies and a rationale that suggests that the number of deaths attributable to tuberculosis in children could in fact be higher than present estimates, but larger and more representative studies are needed to confirm this. The relative prominence of tuberculosis in these contexts could increase over the next decade, if the impressive progress in child survival achieved in recent decades is maintained while gains in tuberculosis control remain modest. As sepsis and meningitis, common causes of child pneumonia, become less common after wider implementation of bacterial conjugate vaccines, *M tuberculosis* is likely to become a more notable causative pathogen—one that is treatable and preventable if adequate diagnostic and service delivery channels are in place.

The major challenge limiting widespread recognition that tuberculosis control is important for child survival and to improve outcomes is the difficulty to establish a diagnosis with a high degree of certainty, especially in settings with high rates of child mortality. Improvements in diagnostic yield over traditional techniques in young children, such as in sputum collection and more rapid molecular testing, are encouraging but still lack sensitivity for children.[23] Continued investment is needed in additional diagnostic break throughs that have a high sensitivity, use child-friendly sampling techniques, and can be widely applied in resource-limited settings.

The *Roadmap for childhood tuberculosis: towards zero deaths* recognises diagnostic challenges as crucial to provide more accurate estimates of disease burden and improve care.[3] The Roadmap also emphasises the need to better use the methods and resources that already exist to address the wide gap between policy and practice. Substantial progress could be made if child health services and national tuberculosis programmes were to work together to support improved diagnosis and care; optimise inclusion and management of tuberculosis within existing maternal and child health services, including those providing care for HIV and malnutrition; implement screening of children who have been in contact with people with tuberculosis to further improve case detection and provide preventive therapy; and ensure that all child tuberculosis cases are registered with the national tuberculosis programme. As Edith Lincoln, a pioneering paediatrician who originally observed the natural history of infection and tuberculosis in children, said: “There are many contributions which the paediatrician can make to the tuberculosis control program. First the negativism about tuberculosis so prevalent in paediatrics must be overcome…Wherever there are tuberculous adults there are infected children. No one is immune. No child will be even relatively safe from tuberculous infection and some of its dread sequelae until tuberculosis is diminished to the point where it is no longer a public health problem.”[24]

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