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EDITORIAL

Childhood tuberculosis in 2017: Where do we go from here?

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The last decade has brought remarkable advancements in the science of childhood tuberculosis. After several decades of a paucity of study, the rate of development of new knowledge has sped up rapidly over the past 10 years. Among the advances, many of which are outlined in this publication, are: improved modeling of the epidemiology of childhood tuberculosis; standardization of treatment regimens for both drug-susceptible and drug-resistant tuberculosis in children; development, study and roll-out of Xpert MTB/RIF, which performs much better for children than sputum acid-fast smear for the rapid diagnosis of tuberculosis disease; the development of the interferon-γ receptor assays (IGRAs), the blood tests that will likely soon replace the tuberculin skin test in high income countries because of their much higher specificity and positive predictive values, especially for children who have received a bacillus Calmette-Guérin (BCG) vaccination; and the availability of several different treatment regimens for tuberculosis infection that have reduced the number of doses required for a good effect from 180-270 (for isoniazid), to 120 (for rifampin) to 12 (for the combination of isoniazid and rifapentine). Currently, many of these advances are out-of-reach in the countries and areas with the highest tuberculosis burdens, but there is hope that the cost can be reduced and the required technology simplified enough to make them more available where they are needed the most. We are still seeking the "Holy Grail" of an accurate and sensitive point-of-care test for tuberculosis disease in a child.

I practice in a low tuberculosis burden setting. Some aspects of childhood tuberculosis can be studied and understood more readily in low burden settings because of the absence of background tuberculosis "noise" in the community that makes analysis of individual cases more difficult. In my setting, every case of childhood tuberculosis is considered to be a sentinel event and for each case we ask, "How could this case have been prevented?" In low burden settings, tuberculosis can be seen as a series of clusters or collection of mini-outbreaks. The value of contact tracing to identify children who are infected and are at high risk of developing disease can be established. We can determine settings at high risk of transmission by determining infection rates among children; this allows for the identification of less common modes and locations of transmission. In this setting the effectiveness of treating young children who are infected or exposed has been established. We also have been able to establish the lack of contagiousness of the vast majority of children with pulmonary tuberculosis by testing in schools and children's hospitals[1]. Some lessons learned in a low burden environment include:

1. Prevention of tuberculosis in children requires a system with central coordination and community activity
2. Linking a child to a source case improves the accuracy of diagnosis and effectiveness of treatment
3. Analysis of childhood tuberculosis is a window into the effectiveness of tuberculosis control programs
4. Most childhood tuberculosis can be prevented with very little cost but requires organization and emphasis
5. Migrating children are at high risk for tuberculosis and have difficulty accessing central and community services, especially if they lack health insurance

Unfortunately, the news in 2017 is not all good. Prior to 2012, the World Health Organization (WHO) did not issue estimates of the number of tuberculosis cases in children because it did not have an adequate, validated model to do so. The first

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estimate of annual cases in children less than 15 years of age made in 2012 was 490,000 cases, using the same methodology for estimating the burden of adult cases, but the WHO and childhood tuberculosis experts knew this method was flawed. Over the past 5 years, sophisticated modeling studies have been published showing the number of cases to be much higher[2,3]. The WHO now estimates that there are about 1 million annual cases of tuberculosis disease in children, and 210,000 deaths[4]. However, only about 30% of the cases are actually reported and recorded. The modeling studies also suggest that there are ~ 54 million children with untreated tuberculosis infection in just the 22 highest burden countries; this is the pool from which many future cases of tuberculosis disease will arise[3].

A recent paper by Helen Jenkins and colleagues[5] in *Lancet Infectious Diseases* analyzed the results of published papers and other datasets to compare the mortality of childhood tuberculosis among the pre-treatment era, the pre-BCG vaccine era and modern times. They showed that, in the pre-treatment era, the pooled fatality ratio was 21.9% and was significantly higher in children aged 0-4 years than in those aged 5-14 years (43.6% [95% Cl 36.8-50.6] *vs* 14.9% [11.5-19.1]. By contrast, in studies published since 1980, the pooled case fatality ratio was 0.9% and only 2.0% in children aged 0-4 years. However, according to the WHO estimates, the current case fatality ratio of tuberculosis for children ages 0-14 years is 21%, almost identical to that determined by Jenkins and colleagues in the *pre-chemotherapy era*! The Americas have a case fatality ratio of 8% and the rate ranges from 2% in Europe to 34% in Africa[4]. Clearly, we are failing at protecting children from the ravages of tuberculosis[6]. Clinical and autopsy studies demonstrate that, in high tuberculosis burden regions, many cases of childhood tuberculosis are misdiagnosed as bacterial or viral pneumonia[7].

The major problem is that a large proportion of cases of childhood tuberculosis are not being detected and thus some children are dying undiagnosed and untreated. There are many reasons why childhood tuberculosis has not received adequate attention from child health and tuberculosis programs. One is the difficulty of microbiologically confirming tuberculosis in a child. Traditional diagnosis and reporting of tuberculosis in adults has relied almost exclusively on microbiologic testing. While the large majority of adult tuberculosis cases can be confirmed microbiologically via acid-fast smear, Xpert MTB/RIF and culture, microbiologic confirmation of tuberculosis disease in children can be attained in, at best, 30% to 40% of cases. I have seen many children who have immigrated to the United States with obvious pulmonary tuberculosis, but the family was told during immigration screening that the child did not have tuberculosis because she did not have a positive acid-fast sputum smear. Chest radiography is essential for a childhood tuberculosis program, but it remains unavailable in many high and middle burden settings. Many years ago I attended a meeting of several tuberculosis program managers in African countries designed to teach them about childhood tuberculosis. As the course progressed and they realized the importance of the chest radiograph, many of them said that they could make it available but they had not because it was not considered essential for the diagnosis of adult pulmonary tuberculosis (which relied on sputum studies). Because childhood tuberculosis is difficult to confirm and children are rarely contagious to others, many local and national tuberculosis programs have paid little attention to children and the subsequent case notifications have been woefully inadequate.

There are several settings where one might expect to find a particularly high number of childhood tuberculosis cases. Tuberculosis diagnosis and management is lacking in many childhood HIV programs. One survey of pediatric antiretroviral therapy programs in Africa, Asia, the Caribbean and Central and South America documented a low utilization of tuberculosis diagnostic and screening services in these programs[8]. While sputum microscopy and chest radiography were available in every program, among 146 children diagnosed with tuberculosis chest radiography was used in 86%, sputum microscopy in 52%, culture in 17% and Xpert MTB/RIF in 8% of children. Only 86% of sites provided treatment for tuberculosis and 30% never provided treatment for tuberculosis infection to HIV-infected children. Although WHO guidelines recommend integration of TB/HIV activities into Prevention of Mother-to-Child Transmission (PMTCT) programs, this integration is inadequate or totally lacking in most high tuberculosis burden countries and regions.

Another high risk setting is malnutrition programs. Malnutrition in regions with a high tuberculosis burden is a predictor of tuberculosis disease and worse outcomes. One prospective study of pneumonia in malnourished children in Bangladesh showed that of 1,482 malnourished children, 405 had respiratory symptoms and an abnormal chest radiograph; tuberculosis was confirmed microbiologically in 7% and clinically in 16%[9]. Pulmonary tuberculosis in young children frequently presents as acute or chronic pneumonia but the diagnosis is often not even considered until the disease is far-advanced. Unfortunately, screening for tuberculosis at child nutritional rehabilitation centers is often lacking, even in high burden countries. One study in India showed that a standardized tuberculosis diagnostic algorithm was followed for only 37% of the children and operational challenges included non-availability of a pediatrician, non-functioning X-ray equipment, use of an inferior tuberculin skin test solution and poor training of the staff in tuberculosis[10].

There are also institutional reasons why childhood tuberculosis has been neglected. The child survival movement has not embraced tuberculosis as an important issue because of the previous lack of accurate estimates demonstrating the true and enormous burden of disease and mortality. There was a circular argument: without evidence of under-reporting there was no justification to provide additional resources for

diagnosis, treatment and prevention of childhood tuberculosis; however, the resources to adequately determine the true burden of childhood tuberculosis - the evidence - were not made available. Tuberculosis services in most low- and middle-income countries, including access to drugs and diagnostic tests, are restricted to national tuberculosis programs so, understandably, little activity in the diagnosis, treatment and prevention of tuberculosis has been undertaken by child health programs. As a result, there has been little advocacy for child tuberculosis services by pediatricians and child health experts. Unfortunately, most national tuberculosis programs in high burden countries have also neglected childhood tuberculosis. Many national tuberculosis programs do not have a comprehensive plan for childhood tuberculosis. As a result, effective and inexpensive prevention measures that are standard in low burden countries have not been implemented in high burden countries. For several decades, in low resource settings, the WHO has recommended evaluating children living in a household with a potentially contagious person with tuberculosis; children with symptoms should be evaluated further for disease, and children less than 5 years of age without symptoms should receive 6 months of isoniazid therapy. However, this simple, safe intervention is rarely utilized and regions with the highest childhood tuberculosis mortality have the lowest proportion of exposed children undergoing therapy.

So, where do we go from here? In 2013, in recognition of the severity of the childhood tuberculosis problem and the many missed opportunities for its diagnosis and prevention, WHO, UNICEF and several other organizations wrote and release the Roadmap for Childhood Tuberculosis[11]. This document set the goal of zero childhood tuberculosis deaths, and recognized that reaching that goal will require, "sustained advocacy, greater commitment, mobilization of increased resources, and a joint effort by all stakeholders involved in providing health care for children and in tuberculosis control". The document outlined 10 basic steps that will be necessary:

1. Include the needs of children and adolescents in research, policy development and clinical practice
2. Collect and report better pediatric data, including data on tuberculosis prevention
3. Develop child-specific training and reference materials for healthcare workers
4. Foster local expertise and leadership in childhood tuberculosis, especially among pediatricians
5. Do not kiss critical opportunities for intervention - individuals and organizations
6. Engage all key stakeholders at all levels
7. Develop integrated *family-centered* and community-centered strategies for children
8. Address research gaps in childhood tuberculosis: diagnosis, treatment, prevention
9. Meet funding needs for childhood tuberculosis
10. Form coalitions and partnerships to improve diagnosis and management of childhood tuberculosis

More recently, the WHO has issued its End TB Strategy. This sets ambitious goals for the reduction and eventual elimination of tuberculosis-related mortality and morbidity, and the financial burdens placed on families and patients. One of the cornerstone of this strategy is patient-centered care, putting the emphasis on the needs of the patients and not on those of the programs. However, for children this strategy does not go far enough. For children, *family-centered care* is essential. For children, the family household and closely related places are where most *Mycobacterium tuberculosis* is transmitted. The key activity to find exposed and infected children, as well as those with early tuberculosis disease, is contact tracing. Knowing that a child has been exposed recently to someone with tuberculosis significantly increases the positive predictive value of the the TST and IGRAs, the chest radiograph, and consistent clinical signs and symptoms. By identifying recently exposed and infected children, one can: prevent establishment of infection; prevent infection from progressing to disease; detect early disease which is easier to treat and cure; and prevent further dissemination of infection. Many contact tracing studies from both low and high tuberculosis burden counties have established the importance and high yields of this activity for both early treatment and prevention of childhood tuberculosis. In addition, contact tracing may be the only way to establish the presence of drug resistance for children with infection or those with disease from whom the organism cannot be cultured. The many benefits of contact tracing include:

1. Benefit for the individual: accurate diagnosis and appropriate treatment
2. Benefit for the family: access to directly observed therapy and other support services, the psychological effect of preventing tuberculosis in loved ones, and empowerment over the disease
3. Benefit for society: preventing future disease and mortality
4. Benefit for the tuberculosis program: accurate and more complete case-finding, prevention, cost-containment

A *family-centered* approach to tuberculosis control is essential for children. In their 2013 editorial, Graham and Triasih stated, "We have the policy, the evidence and the tools we need to implement [contact tracing]; even the political will is beginning to emerge, but [recent studies] highlight the consequences and missed opportunities of continued neglect". The ultimate solutions for the prevention of tuberculosis in children will be local, so national and regional tuberculosis programs, along with government and community programs

and organizations, will need to develop plans and provide resources for this effort. However, an essential element will be for the community of pediatricians, other child health providers and child support organizations to develop the political will to finally address the scourge of tuberculosis in children.

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