Adolescent tuberculosis

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Adolescence is characterised by a substantial increase in the incidence of tuberculosis, a known fact since the early 20th century. Most of the world's adolescents live in low-income and middle-income countries where tuberculosis remains common, and where they comprise a quarter of the population. Despite this, adolescents have not yet been addressed as a distinct population in tuberculosis policy or within tuberculosis treatment services, and emerging evidence suggests that current models of care do not meet their needs. This Review discusses up-to-date information about tuberculosis in adolescence, with a focus on the management of infection and disease, including HIV co-infection and rifampicin-resistant tuberculosis. We outline the progress in vaccine development and highlight important directions for future research.

Introduction

Following mid-childhood (5–9 years) when tuberculosis cases drop substantially compared with early childhood (0–4 years), adolescence represents a period of increased susceptibility to tuberculosis, when both the prevalence of *Mycobacterium tuberculosis* infection and the incidence of tuberculosis rise considerably.[1–5] The reasons for the increase in the disease are not completely understood, although sex hormones, changing social contact patterns, and immunological changes are thought to each have a role.[1] An estimated 1·8 million adolescents and young adults (10–24 years) worldwide develop tuberculosis each year (figure 1), a burden that has been elucidated only recently (first estimates for 2012 were published in 2018) because of a historical focus within tuberculosis surveillance on children (aged 0–14 years) and adults (aged ≥15 years), neglecting adolescents (aged 10–24 years) entirely.[6] In high-burden settings, adolescents make up a sizeable proportion of both the general population and patients with tuberculosis.[6] Accordingly, there is a major need for high-quality tuberculosis services that are accessible and acceptable to adolescents, both to facilitate timely diagnosis, and support medication adherence and treatment completion. Despite the growing recognition of adolescence as a period of escalating risk and increasing burden of tuberculosis, to date, adolescents have not been addressed as a distinct population within tuberculosis control efforts.

This Review aims to summarise up-to-date information about tuberculosis in adolescents from both a clinical and public health perspective, and highlights important knowledge gaps. In this Review, adolescence is defined as 10–24 years of age, consistent with evidence that many developmental processes continue between 18 years and 24 years.[7] We define young adolescents as those aged 10–14 years, older adolescents as 15–19 years, and young adults as 20–24 years. *M tuberculosis* infection (also known as latent tuberculosis infection) refers to an asymptomatic state before the development of disease, whereas tuberculosis refers to the presence of radiographical, and clinical signs and symptoms attributable to tuberculosis, although these might be better understood as two points on a spectrum rather than two entirely distinct states.[8]

Clinical management

Tuberculosis

Adolescents might present to tuberculosis services in one of three ways (figure 2). Firstly, they might be identified following exposure to *M tuberculosis* as part of a contact tracing investigation. Secondly, they might present with symptoms or signs that could be consistent with a diagnosis of tuberculosis. Finally, they might be referred following results from an investigation that then requires

Key messages

- The historic focus on children (<15 years) and adults (≥15 years) in tuberculosis control has meant that there has been little attention to tuberculosis incidence, diagnosis, management, and outcomes among adolescents (aged 10–24 years)
- The prevalence of *Mycobacterium tuberculosis* infection and incidence of tuberculosis rise substantially during adolescence, driven in part by shifting social contact patterns and immunological changes connected to puberty
- Tuberculosis diagnosis can be complex in adolescents, with younger adolescents (aged 10–14 years) often presenting with paucibacillary disease, which is difficult to confirm with microbiological tests
- Successfully engaging adolescents requires careful attention to the accessibility and acceptability of services, staff attitudes, and age-appropriate models of care; adherence support is crucial for this age group, particularly for those with HIV or drug-resistant tuberculosis
- Adolescents with tuberculosis might have additional and important health needs, particularly related to mental health, substance use, or sexual and reproductive health, and health services should identify and respond to these needs
- More evidence is needed regarding the burden of *M tuberculosis* infection and tuberculosis in this age group in different settings; effective prevention including novel vaccines; high-quality age-appropriate models of care; treatment outcomes; and the long-term sequelae of tuberculosis

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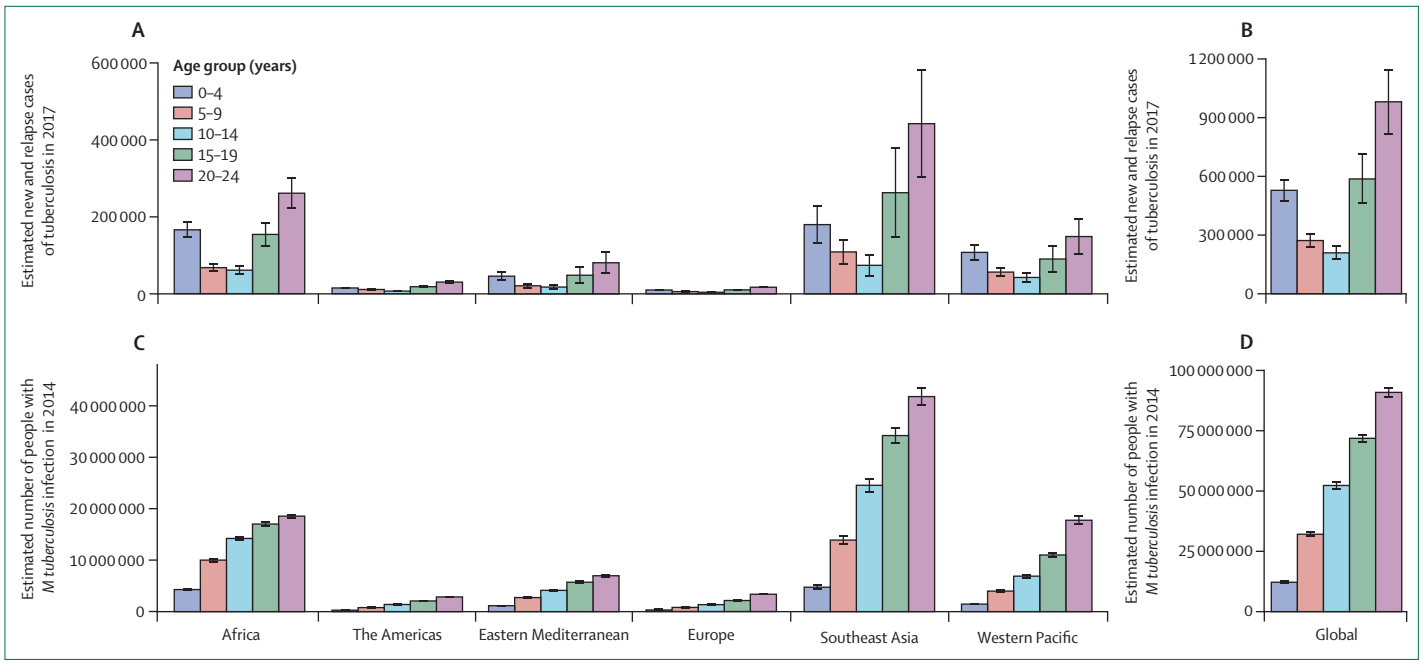

Figure 1: **Estimated numbers of people developing new or relapse tuberculosis (A, B)[6] and people living with *Mycobacterium tuberculosis* infection (C, D)[5]**
Per capita figures and the estimated number of people living with *M tuberculosis* infection across the entire age range are provided in the appendix (p 1). Unfortunately the same estimation process is not yet possible for tuberculosis.

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See Online for appendix

evaluation for tuberculosis, which commonly includes imaging results in which tuberculosis is in the list of differential diagnoses, or positive immune-based tests such as interferon-γ release assays (IGRAs) or the tuberculin skin test (TST).

In each of these scenarios, the first step for the healthcare worker is to evaluate the adolescent for tuberculosis using a combination of history and examination, together with radiological and microbiological tests (smear microscopy, mycobacterial culture, or polymerase chain reaction testing [eg, Xpert MTB/RIF; Cepheid, Sunnyvale, CA, USA]). Most adolescents have intrathoracic tuberculosis, defined as either parenchymal lung disease (infiltrates, cavities, miliary disease), pleural effusions, or intrathoracic (hilar, mediastinal) lymphadenopathy.[9] Common symptoms include cough, fever, and weight loss. Findings on chest radiographs reflect the changes in pathogenesis that occur with age; adolescents more commonly present with cavitation and pleural effusions, and less commonly with intrathoracic lymphadenopathy or miliary disease, as seen in younger children.[10–13] Parenchymal changes are more likely to be apical, as in adults. We have listed the major sites of disease and prevalence of confirmed disease in case series of adolescents with tuberculosis identified during this Review (table).[10–12,14–24]

Although peripheral (most commonly cervical) lymphadenopathy is often reported as the next most common site of disease in adults, it has infrequently been reported in adolescents. Up to 4% of adolescents in two series had tuberculous meningitis,[11,16] which might be explained by selection bias resulting from those with more severe forms of tuberculosis being more likely to be identified and correctly diagnosed. The prevalence of symptoms, pulmonary disease, and microbiological confirmation are likely to be overestimated in most case series for the same reasons. When resources are available, radiological evaluation for extrathoracic tuberculosis might include ultrasonography, CT, or MRI to identify enlarged lymph nodes, typical intracranial features, or involvement of bone or soft tissue.

Unlike for young children (aged 0–4 years), in whom gastric aspirates or induced sputum are required to obtain respiratory samples, adolescents are usually able to expectorate sputum. The use of saline to induce coughing has been associated with increased culture yields compared with spontaneously produced samples in children and young adolescents.[25] Adolescents with pulmonary tuberculosis commonly have bacteriologically confirmed disease (ie, positive for smear, culture, or polymerase chain reaction),[9–11,16,19,25,26] although paucibacillary disease remains common and negative test results do not rule out tuberculosis. Yields from multiple samples (usually two samples) collected on the same day have been shown to be similar to samples collected on separate days in children, potentially making sample collection less burdensome and more feasible.[27] The new generation Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, CA, USA) has greater sensitivity than the previous test, Xpert MTB/RIF.[28] Many adolescents with pulmonary disease are able to transmit *M tuberculosis*, and because of the high number of social

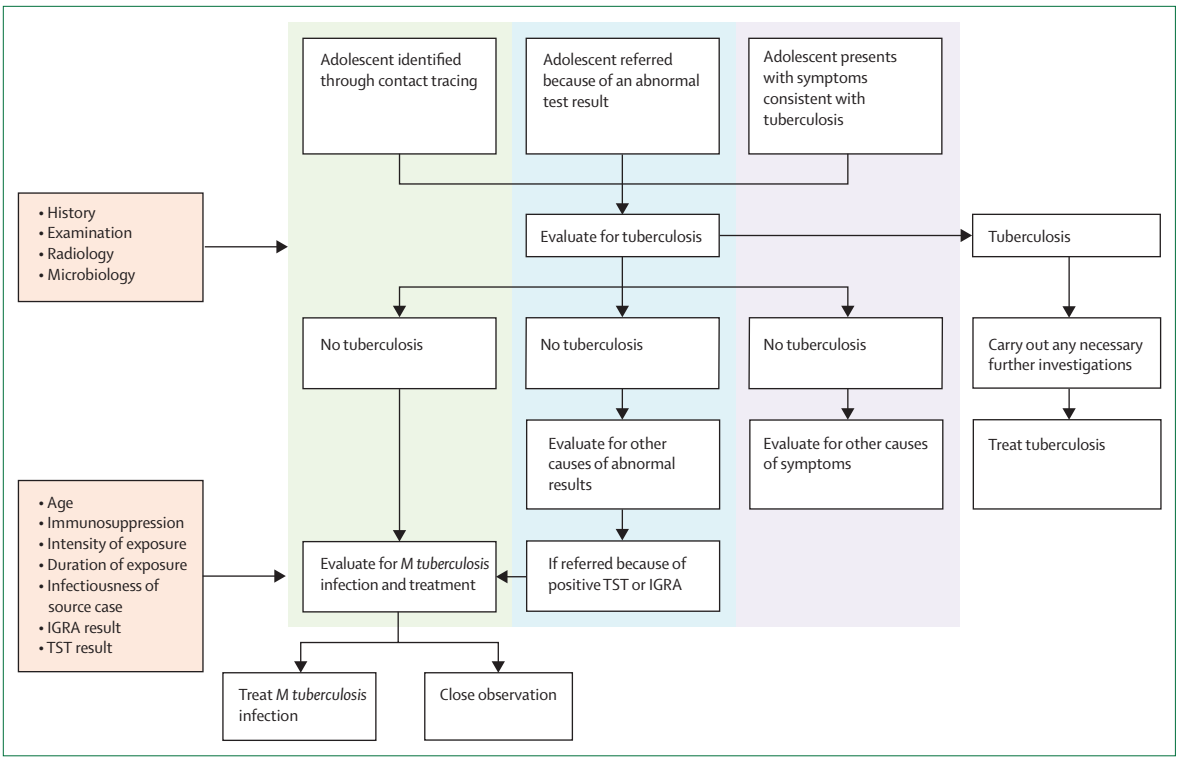

Figure 2: **A suggested algorithm for the evaluation of adolescents who are referred for possible tuberculosis**
IGRA=interferon-γ release assays. *M tuberculosis=Mycobacterium tuberculosis*. TST=the tuberculin skin test.

contacts made by adolescents (including outside the home, in schools, and peer networks), contact investigation around adolescent patients should be a priority.

In those adolescent patients with large pleural effusions, pleural taps or biopsies can be undertaken for microbiological and biochemical examination. An adenosine deaminase concentration greater than 40 IU/L has high sensitivity to distinguish tuberculosis from other causes of effusion in children and young adolescents; however, yields from molecular tests and culture done on pleural fluid vary widely.[29] For adolescents with extrathoracic disease, confirming the diagnosis can be challenging. Lymph node aspiration biopsy is safe, feasible, and associated with good sensitivity and specificity in adolescents.[30] Microbiological confirmation of abdominal, renal, genitourinary, meningeal, and musculoskeletal tuberculosis generally requires more invasive sampling, and yields from culture and molecular testing are lower than for thoracic disease.

The recommended drug therapy for tuberculosis in adolescents is the same as that for younger children and adults, although adjusting the dose on ideal or lean weight might be appropriate for obese adolescents.[31] Data are sparse on adverse events in adolescents (table); however, asymptomatic elevated liver transaminases are seen relatively commonly.[12] Likewise, few studies report any aspect of adherence to tuberculosis treatment in adolescents, including those with *M tuberculosis* infection, for whom lack of symptoms makes adherence even more challenging.[32] Several studies have investigated tuberculosis treatment outcomes in adolescents, and comparative studies show more loss to follow-up than children and adults in the same settings.[15,19] However, premature disengagement from care lies at one extreme end of the adherence spectrum; partial adherence is more common than non-adherence in most other conditions. In one study from South Africa, 58 (41%) of 142 adolescent patients treated in the community took fewer than 80% of the prescribed doses of their tuberculosis treatment.[20]

The principles underpinning adherence-promoting interventions for adolescents are well established for HIV, diabetes, and other chronic diseases; however, they are completely absent for tuberculosis. A crucial issue is the adolescent-friendliness of services. A systematic review synthesised the evidence about young people's priorities in health care, which identified the importance of respectful attitudes among technically competent staff and the delivery of clinically appropriate care in environments that are age-appropriate, clean, and welcoming.[33] Adolescents on tuberculosis treatment who are no longer contagious might benefit from peer support groups, which have been shown to help adolescents with HIV to remain engaged with care.[34] Computer-based interventions and text messaging have also been shown to improve adherence and retention in care for adolescents with HIV, and offer

	Country	Years of study	Sample size (n)	Age range (years)	Percentage symptomatic (%)	Disease manifestations*	Disease confirmation (%)	Adverse events	Outcomes
Tuberculosis									
Berry et al (2019)[14]	South Africa	2010–15	17 640	10–24	NR	84% pulmonary	Smear positive in 22% of 10–14 year olds, 51% of 15–19-year olds, and 51% of 20–24 year olds	NR	91% success in young adolescents, 86% success in older adolescents, and 82% success in young adults
Cruz et al (2013)[11]	USA	1987–2012	145	12–18	79%	79% intrathoracic of whom cavitary disease (26%), peripheral adenopathy (6·9%), and CNS (4·1%)	43%†	4%; 2 with elevated ALT (1%)	92% success
de Pontual et al (2006)[12]	France	2000–04	52	12–18	Fever (77%); weight loss (73%); asthenia (71%); cough (53%)	53% pulmonary; 31% pulmonary and extrapulmonary; 17% extrapulmonary	52% confirmed; 29% smear positive gastric aspirates	ALT elevated in 14%	98% success; 1 adolescent lost to follow-up (2%)
Enane et al (2016)[15]	Botswana	2012–14	330	10–24	NR	83% pulmonary tuberculosis	77% smear positive	NR	86% success in 10–19 year olds; 88% success in 20–24 year olds
Lotfian et al (2016)[16]	Iran	2006–11	143	10–18	96·5%	93% intrathoracic of whom cavities (29%), peripheral adenopathy (0·7%), and CNS (2·8%)	80% confirmed; 69% smear positive	ALT elevated in 6·2%	Reported outcomes in 61%, of these 80% success
Mulongeni et al (2019)[17]	South Africa	2009–13	23 737	10–24	NR	86% pulmonary	NR	NR	92% success in 10–14 year olds; 87% success in 15–19 year olds; 82% success in 20–24 year olds
Reif et al (2018)[18]	Haiti	2011–14	1005	10–24	Restricted to those with symptoms	NA	Restricted to confirmed disease	NR	89% success in 10–15 year olds; 77% success in 16–19 year olds; 77% success in 20–24 year olds
Sant'anna et al (2013)[10]	Brazil	1996–2003	907	10–19	NR	All had intrathoracic disease; cavities seen in 27·6% (aged 10–15 years) and 36·1% (aged 16–19 years)	NR	NR	NR
Snow et al (2017)[19]	South Africa	2011	2616	10–19	NR	87% intrathoracic	Smear positive: 40% of 10–14 year olds; 58% of 15–19 year olds	NR	91% success in patients who were HIV-negative; 80% success in patients who were HIV-positive
Weber et al (2000)[20]	South Africa	1987–92	338	10–18	NR	88% intrathoracic	78% smear or culture positive (37% of 11 year olds; 89% of 18 year olds)	1 case of fatal liver failure	41% took less than 80% of doses; 7% absconded from in-patient facility; success NR
Ziemele et al (2017)[21]	Latvia	2011–14	95	10–17	34%	86% pulmonary; all with x-ray abnormalities consistent with tuberculosis	39% confirmed: 8% smear positive; 26% culture positive; 20% Xpert MTB/RIF assay positive	NR	98% success
Multidrug-resistant tuberculosis									
Isaakidis et al (2013)[22]	India	2007–13	11	10–19	NR	54% exclusively pulmonary (all HIV-positive)	82% (9 of 11) confirmed MDR tuberculosis	100% had at least 1 adverse event; 3 severe (2 psychosis; 1 convulsion); 3 moderate (1 hypokalaemia; 2 gastrointestinal).	4 died before or just after treatment initiation (3 lost to follow-up, of whom 2 later died); 4 treated successfully or alive on treatment
Moyo et al (2014)[23]	South Africa	2008–13	71	10–19	NR	NR	NR	NR	Data available for 44 patients: 36% treated successfully, 43% lost to follow-up, 9% died, treatment not successful in 11%
Tierney et al (2016)[24]	Peru	1999–2002	90	10–19	NR	NA	Restricted to confirmed pulmonary multidrug-resistant tuberculosis	NR	76% success; 11% died; 9% lost to follow-up

NR=not reported. ALT=alanine aminotransferase. *Radiographic findings used percentages of adolescents in whom chest radiographs were obtained as the denominator and intrathoracic disease was defined as parenchymal lung disease (including infiltrates, cavities, and miliary disease), pleural effusions, and intrathoracic lymphadenopathy. †Acid-fast smear or culture or PCR positive.

Table: **Studies showing the clinical manifestations of tuberculosis and multidrug-resistant tuberculosis in adolescents**

tools to assist with therapeutic adherence.[35] Educational interventions (including efforts to reduce stigma), behavioural interventions, and peer support might also have a role, and involvement of supportive family members can be helpful.

M tuberculosis infection

Adolescents might be referred for assessment for *M tuberculosis* infection through contact tracing, or because of a positive result on a TST or IGRA test. When deciding whether to treat *M tuberculosis* infection, the risk of future progression to disease needs to be evaluated together with the individual and public health benefits of prevention and weighed against the risk and burden of treatment. Although treatment of *M tuberculosis* infection is relatively safe, adverse events do occur.[36] Risk factors for progression include recent exposure, any degree of immunosuppression[37] (especially HIV),[38] low body-mass index,[39] and a positive IGRA or TST.[40] WHO recommends that testing and treatment for *M tuberculosis* infection can be offered to all close contacts of people with bacteriologically confirmed pulmonary tuberculosis, regardless of their age or HIV status.[41] Although having a positive TST or IGRA is associated with an increased risk of future disease progression compared with a negative test, most of those with positive tests will never develop tuberculosis (especially in high-burden settings where the background prevalence of infection is higher), necessitating treatment of many adolescents with infection to prevent each case of disease. Conversely, false-negative TSTs and IGRAs can occur,[40] and a negative result does not necessarily indicate that preventive treatment is unwarranted.

Isoniazid, taken daily for 6 or 9 months, is associated with a reduction in risk of future tuberculosis in all age groups, and has been the mainstay of treatment for *M tuberculosis* infection for 50 years.[42] Newer alternatives to the 6 or 9 month isoniazid regimen include 3 months of daily therapy with both isoniazid and rifampicin,[43] 3 months of weekly isoniazid and rifapentine,[44] 4 months of daily rifampicin,[45] and 1 month of daily isoniazid and rifapentine.[46] Compared with 9 month regimens, shorter regimens are associated with improved adherence, a particular issue in adolescents,[47] and at least equivalent efficacy, with no increase in adverse events.[36,45]

Tuberculosis prevention has been historically neglected in high tuberculosis burden settings because of resource constraints.[48] The Sustainable Development Goals place new emphasis on prevention, as shown in both the *End TB Strategy*[49] and in the WHO or UNICEF *Roadmap Towards Ending Tuberculosis in Children and Adolescents*.[50] Although preventive therapy is standard practice in high-income countries, the updated WHO guidelines[41] on treatment for *M tuberculosis* infection are a substantial expansion of current policies in low-income and middle-income countries, with direct relevance to adolescents. High-quality evidence on how to address health systems and other barriers to facilitate wider administration of treatment for *M tuberculosis* infection in children, adolescents, and adults are needed in diverse settings.[48,50] The issue is yet more complex in the case of preventive therapy for children and adolescents exposed to multidrug-resistant tuberculosis, which is the subject of clinical trials.

Rifampicin resistant tuberculosis

Rifampicin-resistant tuberculosis includes multidrug-resistant (resistance to at least rifampicin and isoniazid) and extensively drug-resistant tuberculosis (multi-drug resistant with additional resistance to at least one fluoroquinolone and at least one second-line injectable agent). A confirmed diagnosis of rifampicin-resistant tuberculosis relies on microbiological confirmation from clinical samples or cultured isolates, with genotypic or phenotypic drug susceptibility tests, which can be challenging in children and young adolescents.[51] In the absence of rapid molecular drug susceptibility tests, or in the case of patients with culture-negative tuberculosis, a clinical diagnosis of rifampicin-resistant tuberculosis can be made in symptomatic adolescents on the basis of exposure to an index patient with bacteriologically confirmed rifampicin-resistant tuberculosis, or lack of clinical improvement (ie, symptom resolution and weight gain) after at least 2 months of first-line therapy with good adherence (provided the risk of misdiagnosis of another chronic lung condition is low).[52]

Composition and duration of second-line treatment regimens for adolescents with adult-type disease and bacteriological confirmation of rifampicin-resistant tuberculosis is generally the same as for adults. The 2019 WHO recommendations[53] for the use of novel drugs in rifampicin-resistant tuberculosis treatment also apply to adolescents, as available pharmacokinetic data indicate that delamanid and bedaquiline can be given to children as young as 3 years and 6 years of age, respectively.[53] For younger adolescents with paucibacillary disease that is clinically diagnosed without bacteriological confirmation of drug susceptibility, regimen composition should consider the adolescent's exposure history and the drug susceptibility results of the likely index patient, if known. Young adolescents with culture-negative, non-severe rifampicin-resistant tuberculosis have been shown to have excellent outcomes with total treatment duration of 12 months.[54]

Few reports have characterised the frequency and effect of adverse effects of rifampicin-resistant tuberculosis treatment in adolescents. A small case series from India reported that five of eight adolescents with HIV who were treated for multidrug-resistant tuberculosis, had a moderate or severe adverse event during their tuberculosis treatment (table), including psychosis, convulsions, hypokalaemia, and gastrointestinal intolerance.[22] A review of eight case reports of 18 children and young adolescents receiving linezolid-based regimens suggests that haematological toxicity and neuropathies

occur less commonly than in adults.[55] QT prolongation is a concern for patients receiving bedaquiline, delamanid, clofazimine, or fluoroquinolones, but data are scarce in adolescents.[56] In 16 children aged 8–17 years receiving delamanid, one had clinically significant adverse effects, including QT prolongation.[57] In 27 adolescents receiving bedaquiline-containing regimens, five had clinically significant QT prolongation, which was managed without withdrawal of bedaquiline.[58] Skin discolouration is a common adverse effect of clofazimine.[59] Skin hyperpigmentation has been associated with poorer perceived quality of life in younger adults (aged <35 years),[60] which is likely to be distressing and stigmatising for adolescents, and might lead to decreased adherence and treatment discontinuation.

Delayed diagnosis, treatment refusal, and loss to follow-up were common and serious issues in two rifampicin-resistant tuberculosis case series from South Africa and India (table).[22,23] Several adolescents in both studies were diagnosed so late that they died either before or shortly after initiation of treatment, and several more died after being lost to follow-up during treatment. These sobering experiences highlight the intense vulnerability of many adolescents with rifampicin-resistant tuberculosis and the challenges of successfully engaging them in care.

HIV-associated tuberculosis

Globally, HIV is the second leading cause of death for adolescents aged 10–19 years, and HIV-related deaths have tripled in this age group since 2000.[61] The increase in deaths occurred predominantly in the African region, where 90% of the world's children and adolescents with HIV live, and during a period when HIV-related deaths were decreasing in all other age groups. HIV mortality in adolescents has largely been driven by delayed diagnosis and treatment of perinatally-acquired infection, as HIV infection acquired during adolescence will usually progress to severe disease only after many years.[62] Because of suboptimal coverage of HIV diagnosis in early infancy, many children infected perinatally have been diagnosed only in older childhood and adolescence, when they were already severely immunosuppressed.[63,64] The scale-up of antiretroviral therapy (ART) since 2003 has had a profound effect on tuberculosis incidence, morbidity, and mortality, but each of these remain higher in adolescents with HIV than the general adolescent population.[65] Adherence to HIV treatment often drops in adolescence, and HIV viral suppression is lower in adolescents than in other age groups,[66,67] which increases the risk of immunosuppression and with it, the risk of developing tuberculosis.

Adolescents living with HIV should be assessed for initiation of both ART and treatment for *M tuberculosis* infection. The updated and consolidated WHO guidelines[41] for programmatic management of *M tuberculosis* infection recommends treatment of the infection for adolescents living with HIV, and an unknown or a positive TST result, provided they are assessed as being unlikely to have tuberculosis.[41] Treatment for *M tuberculosis* infection should be given irrespective of the degree of immunosuppression, ART, or history of previous tuberculosis treatment. Clinicians administering both ART and treatment for the infection should be aware of potential drug interactions and follow appropriate guidelines to manage these. This is particularly important given the increasing use of rifamycins for treatment, which can adversely affect ART metabolism.

Tuberculosis remains the main cause of mortality in adolescents living with HIV.[68] The presence of HIV co-infection compounds the well recognised challenges of reaching a definitive diagnosis in children and adolescents with suspected tuberculosis.[69] Extrapulmonary and disseminated disease patterns are more common, tuberculosis is typically paucibacillary, and chest radiographic appearances are not typical.[70] Notably, studies have reported a high prevalence of chronic respiratory disease in adolescents with long-standing HIV, even in those taking ART.[71] Chronic lung disease in the context of HIV infection might be a sequela of previous respiratory tract infections including tuberculosis, or HIV itself. In low-income settings where pulmonary diagnostics such as high-resolution CT and lung function testing are not readily available, these symptoms often result in misdiagnosis of tuberculosis and unnecessary empirical tuberculosis treatment, particularly in children and adolescents, who tend to have chronic, non-specific abnormalities on chest radiography.[72,73]

If not already on ART, any adolescent with HIV diagnosed with tuberculosis should be started on ART when it is practically possible, following the start of tuberculosis treatment.[74] Waiting for a short period of time is common to allow the individual to become accustomed to tuberculosis treatment before starting ART, but this period should not be more than a few weeks. Treatment of tuberculosis in HIV is further complicated by the risk of immune reconstitution syndrome, pharmacokinetic interactions, and overlapping toxicities between ART and antituberculous drugs, particularly when second-line ART or rifampicin-resistant tuberculosis regimens are required.[75] For example, concurrent administration of isoniazid preventive therapy with nevirapine resulted in high hepatotoxicity in children and adolescents living with HIV.[76]

Tuberculosis and HIV both represent major threats to public health. However, the historical neglect of adolescents as a key population within HIV control might be one reason why there has been little change in HIV mortality in their age group.[77] Recent recognition of the importance of adolescents within HIV control efforts is a positive change. Research is urgently required to inform evidence-based management of tuberculosis and HIV in adolescents, including development of appropriate diagnostic algorithms, optimal approaches to tuberculosis prevention, and best practices for adherence support.

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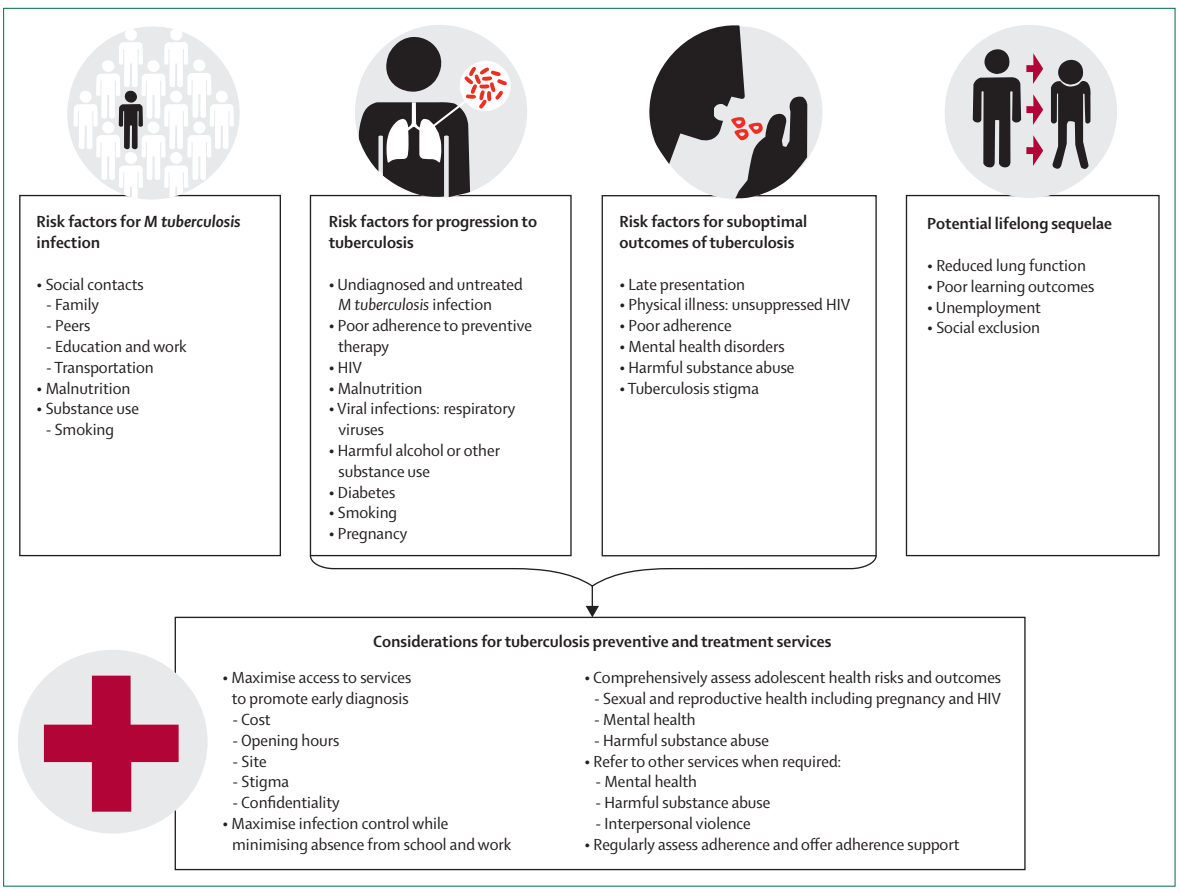

Figure 3: **General and adolescent-specific risk factors associated with *Mycobacterium tuberculosis* infection, progression to tuberculosis, and suboptimal outcomes**

Specific considerations for adolescents during tuberculosis treatment

The developmental period of adolescence can be challenging for paediatric and adult providers alike. In part, this challenge is due to adolescents' desire for autonomy, and their prioritising short-term social benefits over potential long-term health gains.[78] Several topics need to be broached with adolescents before initiating therapy (figure 3), including adherence with appointments and medication, the effect of health-compromising behaviours (including substance use), interruption of education and employment, and the effects of social (and medical) isolation and stigma. The legal circumstances of the adolescent might need to be explored if they have an uncertain or precarious immigration status or face other structural barriers to accessing health care.

Medication adherence and loss to follow-up are serious concerns for health professionals managing adolescents with tuberculosis, especially in those with HIV co-infection or rifampicin-resistant tuberculosis.[22,23] Adherence support is of the utmost importance in this age group, particularly for adolescents with rifampicin-resistant tuberculosis, who endure more adverse effects and longer duration of treatment than those treated for drug-susceptible disease, or those with complex comorbidities such as HIV, diabetes, or substance dependence. Children and adolescents with rifampicin-resistant tuberculosis report social isolation, stigmatisation, depression, and poor self-esteem, highlighting the importance of psychosocial support during tuberculosis treatment.[79,80]

Adolescents with pulmonary tuberculosis might require isolation until they cease to be contagious, which should be closely monitored during treatment. This public health reality can temporarily prevent adolescents attending school or work, leading to short-term and long-term economic ramifications. However, some adolescents might also be unnecessarily excluded from school because of unfounded concerns about infection risks (eg, those with exclusively extrapulmonary disease). Unnecessary exclusion from school and other regular activities should be avoided, and adolescents who cannot attend school should receive appropriate educational support until they can return.

Tuberculosis treatment should be delivered with full knowledge of other health issues, medications (including contraception), and behaviours such as harmful substance use that might increase side-effects or limit the

efficacy of the treatment. Although a polysubstance-using adolescent is unlikely to stop using all substances, adolescents need guidance on which substances are most problematic during tuberculosis treatment. They should be informed that alcohol use is particularly harmful as it can increase problematic side effects including hepatotoxicity,[81] and might increase the risk of adverse treatment outcomes.[82] Providers also need to discuss which methods of substance use would be more likely to transmit *M tuberculosis*, such as sharing water pipes or so-called bongs when using marijuana, and shotgunning (a practice of inhaling smoke and then exhaling it into another person's mouth), so that patients can adjust their usage habits to protect their peers.[83] Substance dependence should be addressed through referral to appropriate evidence-based services, such as medication-assisted treatment for adolescents with opioid dependence.

Providers should counsel adolescent girls on non-hormonal contraception options (eg, intrauterine devices or condoms), which are not adversely affected by rifamycins, as hormonal contraception cannot be relied upon during tuberculosis treatment.[84] Pregnancy testing should be done before provision of therapy so that pregnant adolescents can be appropriately referred for prenatal care. Testing for other sexually transmitted infections should be offered at the time adolescents are tested for HIV infection, as these age groups have the highest incidence.[85] To improve quality care for adolescents, provision of tuberculosis care should include the opportunity for confidential consultations as adolescents are less likely to accurately report their sexual activity, substance use, and mental health status when parents or caregivers are present.[86]

Sequelae after tuberculosis

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Adolescence is a crucial period for physical, psychosocial, and cognitive development—all of which might be affected by tuberculosis (figure 3). Yet little is known about the long-term consequences of tuberculosis on health and wellbeing in this age group. For example, there are no studies of the extent and consequence of school absence in relation to tuberculosis treatment. A few published studies describe neurological sequelae after tuberculosis meningitis, which occurs in 54–66% of successfully treated patients (≤18 years),[87,88] and irreversible hearing loss due to injectable agents in patients treated for rifampicin-resistant tuberculosis.[89]

No studies have evaluated post-tuberculosis lung health in adolescents or children. In adults, pulmonary tuberculosis is a well established risk factor for chronic airflow obstruction and bronchiectasis;[90] however, extrapolating data from adults to adolescents is suboptimal for several reasons. Unlike adult lungs, adolescent lungs are still growing in volume and developing gas exchange capability, which might make them especially vulnerable.[91] Understanding post-tuberculosis lung function has important clinical implications, but in most high-burden settings people who complete tuberculosis treatment receive minimal follow-up. Adult patients with previous tuberculosis with residual lung abnormalities have been shown to have diminished quality of life,[92] and such patients can benefit from supportive measures, such as pulmonary rehabilitation.[93]

The long-term psychosocial effect of tuberculosis in adolescence is also undocumented. In addition to interrupting education and employment, tuberculosis and its treatment can disrupt relationships with family and peers. Adolescents are intensely sensitive to social exclusion, and the effect of stigma and discrimination during adolescence can be profound and long lasting. For example, in South Asia, young women with tuberculosis report diminished marriage prospects.[94] Qualitative and mixed methods research around the breadth of developmental issues that tuberculosis might affect—including schooling, work, relationships, and mental health—would be of great value.

Tuberculosis vaccines

As of September, 2019, BCG is the only vaccine available to prevent tuberculosis. There is clear evidence of a strong protective effect (90%) of initial BCG vaccination against disseminated tuberculosis in infants, and moderate protection (60–75%) against pulmonary disease in children and young adolescents.[95] Large-scale trials of BCG done by the UK Medical Research Council in the 1960s involved adolescents aged 14–15 years, and found that the BCG vaccine was 87% protective against disease, and 74% protective 20 years later.[96] This effect was, however, only seen in those who had not yet been sensitised to *M tuberculosis* or non-tuberculous mycobacteria. Mycobacterial sensitisation, measured with the TST, was suspected to limit any additional protection provided by the BCG vaccine.

As the search for a more protective vaccine continues, greater attention is being given to adolescents both with and without evidence of exposure to *M tuberculosis*. Population groups at increased risk of *M tuberculosis* infection and disease, such as adolescents, are ideal participants to include in clinical trials, as primary endpoints can be achieved with smaller sample sizes. In addition, modelling suggests that a vaccine targeted to adolescents would have the most rapid and cost-effective outcome on the global tuberculosis epidemic.[97]

Several clinical trials of new vaccine candidates are enrolling adolescents. In a phase 2 trial (HYVAC4),[98] 990 HIV-negative, BCG-vaccinated, and IGRA-negative adolescents aged 12–17 years living in a tuberculosis endemic setting, were randomly assigned to receive either the H4:IC31 vaccine, BCG revaccination, or placebo. Results suggested that the BCG revaccination provided 45% protection against sustained *M tuberculosis* infection, whereas the effect of the H4:IC31 vaccine to prevent sustained infection did not reach statistical significance. Concomitant laboratory data showed that

Search strategy and selection criteria

This Review was an analysis of the literature on adolescent tuberculosis, informed by expert opinion and clinical experience. We reviewed English and Spanish language literature for studies on adolescent tuberculosis to identify case series documenting clinical presentation and treatment outcomes. We searched PubMed on Aug 19, 2019, and our search terms included "tuberculosis" and "adolescent". The search returned 210 results, of which 11 were eligible for inclusion, and we identified three additional studies from reference lists, giving a total of 14 studies. We excluded studies reporting solely on prevalence or where data from adolescents was aggregated with those of younger children or adults. Data were extracted regarding major sites of disease, percentage of adolescents with microbiologic confirmation, adverse drug reactions, and final treatment outcomes.

BCG revaccination was found to significantly boost BCG-specific CD4 T-cell responses. Although the result is disappointing for the HYVAC4 vaccine candidate, the findings suggest that BCG revaccination of quantiferon-negative adolescents might provide additional benefit, leading to renewed interest in BCG revaccination in adolescence.[99]

Another phase 2b controlled trial randomly assigned 3575 HIV-negative individuals aged 18–50 years with evidence of *M tuberculosis* infection in 11 centres in South Africa, Kenya, and Zambia, to either the M72/AS01E vaccine or placebo.[100] The candidate vaccine showed significant efficacy in the prevention of tuberculosis, with an overall vaccine efficacy of 54%. In prespecified subanalyses, vaccine efficacy varied considerably by age, with an 84·4% efficacy in participants aged 18–25 years, compared with 10·2% in those older than 25 years. The importance of the previous BCG vaccination and *M tuberculosis* sensitisation on the efficacy of the M72/AS01E vaccine is yet to be defined. However, if generalisable, the results suggest that the vaccine is likely to be effective when administered to adolescents.

Conclusion

Important questions remain regarding many biological, clinical, and psychosocial aspects of tuberculosis in adolescence. Most tuberculosis literature divides the population into only two age groups, children (0–14 years) and adults (≥15 years). However adolescence is defined, adolescents have been ignored using this classification, resulting in a data void. There is an urgent need to better understand tuberculosis epidemiology, prevention, and management in adolescents, including those with HIV or drug-resistant disease. However, much is already known about effective tuberculosis control and how to provide high-quality health services for adolescents with complex health conditions. The ambitious goals for tuberculosis control in the coming decades demand a comprehensive response. Success in the fight to end tuberculosis will hinge in large part on whether we can meet the needs of the current generation of adolescents for effective prevention, diagnosis, and management of this disease.

Contributors

KJS, SMS, and KK conceptualised the review. KJS and KK coordinated the review, wrote the introduction, section on knowledge gaps, and conclusion with input from SMS, and collated and edited the manuscript. KJS and ATC searched the literature. ATC and JAS drafted the section on clinical management for tuberculosis and *M tuberculosis* infection with input from SSC and SMG. JAH and SSC drafted the section on rifampicin-resistant tuberculosis with input from JAS and SMG. SSC drafted the section on sequelae with input from RAF and SMG. BK drafted section on the vaccines. RAF drafted the section on HIV with input from KK. RMH and PJD drafted the epidemiology content with input from KJS and JTD. JTD provided input on all figures. SMS collated the specific considerations section and provided input on all sections and figures. All authors contributed to editing and approved the final version of the manuscript.

Declaration of interests

BK has a patent for diagnostic biosignature issued. All the other authors declare no competing interests.

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References

1 Seddon JA, Chiang SS, Esmail H, Coussens AK. The wonder years: what can primary school children teach us about immunity to *Mycobacterium tuberculosis*? *Front Immunol* 2018; **9:** 2946.
2 Marais BJ, Gie RP, Schaaf HS, et al. The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis* 2004; **8:** 278–85.
3 Styblo K. Surveillance of tuberculosis. *Int J Epidemiol* 1976; **5:** 63–68.
4 Dodd PJ, Looker C, Plumb ID, et al. Age- and sex-specific social contact patterns and incidence of *Mycobacterium tuberculosis* infection. *Am J Epidemiol* 2016; **183:** 156–66.
5 Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med* 2016; **13:** e1002152.
6 Snow KJ, Sismanidis C, Denholm J, Sawyer SM, Graham SM. The incidence of tuberculosis among adolescents and young adults: a global estimate. *Eur Respir J* 2018; **51:** 1702352.
7 Sawyer SM, Azzopardi PS, Wickremarathne D, Patton GC. The age of adolescence. *Lancet Child Adolesc Health* 2018; **2:** 223–28.
8 Delogu G, Goletti D. The spectrum of tuberculosis infection: new perspectives in the era of biologics. *J Rheumatol Suppl* 2014; **91:** 11–16.
9 Cruz A. Tuberculosis in adolescents. In: Starke JR, Donald PR, eds. Handbook of child and adolescent tuberculosis. Oxford: Oxford University Press, 2016: 217–30.
10 Sant'anna CC, Schmidt CM, March MF, Pereira SM, Barreto ML. Tuberculosis among adolescents in two Brazilian State capitals. *Cad Saude Publica* 2013; **29:** 111–16 (in Portuguese).
11 Cruz AT, Hwang KM, Birnbaum GD, Starke JR. Adolescents with tuberculosis: a review of 145 cases. *Pediatr Infect Dis J* 2013; **32:** 937–41.
12 de Pontual L, Balu L, Ovetchkine P, et al. Tuberculosis in adolescents: a French retrospective study of 52 cases. *Pediatr Infect Dis J* 2006; **25:** 930–32.

13 Wong KS, Huang YC, Lai SH, Chiu CY, Huang YH, Lin TY. Validity of symptoms and radiographic features in predicting positive AFB smears in adolescents with tuberculosis. *Int J Tuberc Lung Dis* 2010; **14:** 155–59.

14 Berry KM, Rodriguez CA, Berhanu RH, et al. Treatment outcomes among children, adolescents, and adults on treatment for tuberculosis in two metropolitan municipalities in Gauteng Province, South Africa. *BMC Public Health* 2019; **19:** 973.

15 Enane LA, Lowenthal ED, Arscott-Mills T, et al. Loss to follow-up among adolescents with tuberculosis in Gaborone, Botswana. *Int J Tuberc Lung Dis* 2016; **20:** 1320–25.

16 Lotfian F, Bolursaz MR, Khalilzadeh S, Baghaie N, Hassanzad M, Velayati A. Features of adolescents tuberculosis at a referral TB's hospital in Tehran, Iran. *Mediterr J Hematol Infect Dis* 2016; **8:** e2016005.

17 Mulongeni P, Hermans S, Caldwell J, Bekker L-G, Wood R, Kaplan R. HIV prevalence and determinants of loss-to-follow-up in adolescents and young adults with tuberculosis in Cape Town. *PLoS One* 2019; **14:** e0210937.

18 Reif LK, Rivera V, Bertrand R, et al. Outcomes across the tuberculosis care continuum among adolescents in Haiti. *Public Health Action* 2018; **8:** 103–09.

19 Snow K, Hesseling AC, Naidoo P, Graham SM, Denholm J, du Preez K. Tuberculosis in adolescents and young adults: epidemiology and treatment outcomes in the Western Cape. *Int J Tuberc Lung Dis* 2017; **21:** 651–57.

20 Weber HC, Beyers N, Gie RP, Schaaf HS, Fish T, Donald PR. The clinical and radiological features of tuberculosis in adolescents. *Ann Trop Paediatr* 2000; **20:** 5–10.

21 Ziemele B, Ranka R, Ozere I. Pediatric and adolescent tuberculosis in Latvia, 2011–2014: case detection, diagnosis and treatment. *Int J Tuberc Lung Dis* 2017; **21:** 637–45.

22 Isaakidis P, Paryani R, Khan S, et al. Poor outcomes in a cohort of HIV-infected adolescents undergoing treatment for multidrug-resistant tuberculosis in Mumbai, India. *PLoS One* 2013; **8:** e68869.

23 Moyo SJ, Furin J, Hughes J, et al. Outcomes in adolescents undergoing treatment for drug-resistant tuberculosis in Cape Town, South Africa. *Arch Pediatr Infect Dis* 2014; **2:** e17934.

24 Tierney DB, Milstein MB, Manjourides J, Furin JJ, Mitnick CD. Treatment outcomes for adolescents with multidrug-resistant tuberculosis in Lima, Peru. *Glob Pediatr Health* 2016; published online Oct 26. DOI:10.1177%2F2333794X16674382.

25 Detjen AK, DiNardo AR, Leyden J, et al. Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: a systematic review and meta-analysis. *Lancet Respir Med* 2015; **3:** 451–61.

26 Rachow A, Clowes P, Saathoff E, et al. Increased and expedited case detection by Xpert MTB/RIF assay in childhood tuberculosis: a prospective cohort study. *Clin Infect Dis* 2012; **54:** 1388–96.

27 Al-Aghbari N, Al-Sonboli N, Yassin MA, et al. Multiple sampling in one day to optimize smear microscopy in children with tuberculosis in Yemen. *PLoS One* 2009; **4:** e5140.

28 Nicol MP, Workman L, Prins M, et al. Accuracy of Xpert MTB/RIF ultra for the diagnosis of pulmonary tuberculosis in children. *Pediatr Infect Dis J* 2018; **37:** e261–63.

29 Fischer GB, Andrade CF, Lima JB. Pleural tuberculosis in children. *Paediatr Respir Rev* 2011; **12:** 27–30.

30 Coetzee L, Nicol MP, Jacobson R, et al. Rapid diagnosis of pediatric mycobacterial lymphadenitis using fine needle aspiration biopsy. *Pediatr Infect Dis J* 2014; **33:** 893–96.

31 Geiseler PJ, Manis RD Jr, Maddux MS. Dosage of antituberculous drugs in obese patients. *Am Rev Respir Dis* 1985; **131:** 944–46.

32 Starr M, Sawyer S, Carlin J, Powell C, Newman R, Johnson P. A novel approach to monitoring adherence to preventive therapy for tuberculosis in adolescence. *J Paediatr Child Health* 1999; **35:** 350–54.

33 Ambresin A-E, Bennett K, Patton GC, Sanci LA, Sawyer SM. Assessment of youth-friendly health care: a systematic review of indicators drawn from young people's perspectives. *J Adolesc Health* 2013; **52:** 670–81.

34 Child Survival Working Group. Providing peer support for adolescents and young people living with HIV. Geneva: World Health Organization, 2018.

35 Navarra AD, Gwadz MV, Whittemore R, et al. Health technology-enabled interventions for adherence support and retention in care among US HIV-infected adolescents and young adults: an integrative review. *AIDS Behav* 2017; **21:** 3154–71.

36 Cruz AT, Starke JR. Completion rate and safety of tuberculosis infection treatment with shorter regimens. *Pediatrics* 2018; **141:** e20172838.

37 Zhang Z, Fan W, Yang G, et al. Risk of tuberculosis in patients treated with TNF-α antagonists: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open* 2017; **7:** e012567.

38 Dodd PJ, Prendergast AJ, Beecroft C, Kampmann B, Seddon JA. The impact of HIV and antiretroviral therapy on TB risk in children: a systematic review and meta-analysis. *Thorax* 2017; **72:** 559–75.

39 Koethe JR, von Reyn CF. Protein-calorie malnutrition, macronutrient supplements, and tuberculosis. *Int J Tuberc Lung Dis* 2016; **20:** 857–63.

40 Rangaka MX, Wilkinson KA, Glynn JR, et al. Predictive value of interferon-γ release assays for incident active tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2012; **12:** 45–55.

41 WHO. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization, 2018.

42 Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev* 2004; published online Jan 26. DOI:10.1002/14651858.CD000171.pub2.

43 Assefa Y, Woldeyohannes S, Hamada Y, Getahun H. 3-month daily rifampicin and isoniazid compared to 6- or 9-month isoniazid for treating latent tuberculosis infection in children and adolescents less than 15 years of age: an updated systematic review. *Eur Respir J* 2018; **52:** 1800395.

44 Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011; **365:** 2155–66.

45 Diallo T, Adjobimey M, Ruslami R, et al. Safety and side effects of rifampin versus isoniazid in children. *N Engl J Med* 2018; **379:** 454–63.

46 Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Omoz-Oarhe A. One month of rifapentine/isoniazid to prevent TB in people with HIV: BRIEF-TB/A5279. Conference on Retroviruses and Opportunistic Infections; Boston, MA; March 4–7, 2018.

47 Chang SH, Eitzman SR, Nahid P, Finelli ML. Factors associated with failure to complete isoniazid therapy for latent tuberculosis infection in children and adolescents. *J Infect Public Health* 2014; **7:** 145–52.

48 Graham SM. The management of infection with *Mycobacterium tuberculosis* in young children post-2015: an opportunity to close the policy-practice gap. *Expert Rev Respir Med* 2017; **11:** 41–49.

49 WHO. The end TB strategy. Geneva: World Health Organization, 2015.

50 WHO. Roadmap towards ending TB in children and adolescents. Geneva: World Health Organization, 2018.

51 Chiang SS, Swanson DS, Starke JR. New diagnostics for childhood tuberculosis. *Infect Dis Clin North Am* 2015; **29:** 477–502.

52 Chiang SS, Park S, White EI, et al. Using changes in weight-for-age z score to predict effectiveness of childhood tuberculosis therapy. *J Pediatric Infect Dis Soc* 2019; published online Feb 1. DOI:10.1093/jpids/piy138.

53 WHO. WHO Consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization, 2019.

54 Seddon JA, Hesseling AC, Godfrey-Faussett P, Schaaf HS. High treatment success in children treated for multidrug-resistant tuberculosis: an observational cohort study. *Thorax* 2014; **69:** 458–64.

55 Garcia-Prats AJ, Rose PC, Hesseling AC, Schaaf HS. Linezolid for the treatment of drug-resistant tuberculosis in children: a review and recommendations. *Tuberculosis (Edinb)* 2014; **94:** 93–104.

56 Harausz E, Cox H, Rich M, Mitnick CD, Zimetbaum P, Furin J. QTc prolongation and treatment of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2015; **19:** 385–91.

57 Tadolini M, Garcia-Prats AJ, D'Ambrosio L, et al. Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: early experiences and challenges. *Eur Respir J* 2016; **48:** 938–43.

58 Achar J, Berry C, Herboczek K, et al. Multidrug-resistant tuberculosis in child successfully treated with 9-month drug regimen. *Emerg Infect Dis* 2015; **21:** 2105–06.

59 Schaaf HS, Garcia-Prats AJ, McKenna L, Seddon JA. Challenges of using new and repurposed drugs for the treatment of multidrug-resistant tuberculosis in children. *Expert Rev Clin Pharmacol* 2018; **11:** 233–44.

60 Maymone MBC, Neamah HH, Wirya SA, et al. The impact of skin hyperpigmentation and hyperchromia on quality of life: a cross-sectional study. *J Am Acad Dermatol* 2017; **77:** 775–78.

61 WHO. Health for the world's adolescents: a second chance in the second decade. Geneva: World Health Organization 2014.

62 Morgan D, Whitworth J. The natural history of HIV-1 infection in Africa. *Nat Med* 2001; **7:** 143–45.

63 Wettstein C, Mugglin C, Egger M, et al. Missed opportunities to prevent mother-to-child-transmission: systematic review and meta-analysis. *AIDS* 2012; **26:** 2361–73.

64 Ferrand RA, Munaiwa L, Matsekete J, et al. Undiagnosed HIV infection among adolescents seeking primary health care in Zimbabwe. *Clin Infect Dis* 2010; **51:** 844–51.

65 Dye C, Williams BG. Tuberculosis decline in populations affected by HIV: a retrospective study of 12 countries in the WHO African Region. *Bull World Health Organ* 2019; **97:** 405–14.

66 Bygrave H, Mtangirwa J, Ncube K, Ford N, Kranzer K, Munyaradzi D. Antiretroviral therapy outcomes among adolescents and youth in rural Zimbabwe. *PLoS One* 2012; **7:** e52856.

67 Nachega JB, Hislop M, Nguyen H, et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in southern Africa. *J Acquir Immune Defic Syndr* 2009; **51:** 65–71.

68 Ferrand RA, Bandason T, Musvaire P, et al. Causes of acute hospitalization in adolescence: burden and spectrum of HIV-related morbidity in a country with an early-onset and severe HIV epidemic: a prospective survey. *PLoS Med* 2010; **7:** e1000178.

69 Venturini E, Turkova A, Chiappini E, Galli L, de Martino M, Thorne C. Tuberculosis and HIV co-infection in children. *BMC Infect Dis* 2014; **14** (suppl 1)**:** S5.

70 Munthali L, Khan PY, Mwaungulu NJ, et al. The effect of HIV and antiretroviral therapy on characteristics of pulmonary tuberculosis in northern Malawi: a cross-sectional study. *BMC Infect Dis* 2014; **14:** 107.

71 Attia EF, Miller RF, Ferrand RA. Bronchiectasis and other chronic lung diseases in adolescents living with HIV. *Curr Opin Infect Dis* 2017; **30:** 21–30.

72 Metcalfe JZ, Mason P, Mungofa S, Sandy C, Hopewell PC. Empiric tuberculosis treatment in retreatment patients in high HIV/tuberculosis-burden settings. *Lancet Infect Dis* 2014; **14:** 794–95.

73 Pitcher RD, Lombard CJ, Cotton MF, Beningfield SJ, Workman L, Zar HJ. Chest radiographic abnormalities in HIV-infected African children: a longitudinal study. *Thorax* 2015; **70:** 840–46.

74 WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, 2nd edn. Geneva: World Health Organization, 2016.

75 Lawn SD, Meintjes G, McIlleron H, Harries AD, Wood R. Management of HIV-associated tuberculosis in resource-limited settings: a state-of-the-art review. *BMC Med* 2013; **11:** 253.

76 Mudzviti T, Shamu T, Chimbetete C, Munengerwa T, Bote S, Pascoe M. Tolerability of isoniazid preventive therapy in an HIV-infected cohort of paediatric and adolescent patients on antiretroviral therapy from a resource-limited setting: a retrospective cohort study. *Drugs Real World Outcomes* 2019; **6:** 37–42.

77 UNAIDS. HIV prevention, treatment, care and support for adolescents and youth. Geneva: Joint United Nations Programme in HIV and AIDS, 2014.

78 Sawyer SM, Aroni RA. Sticky issue of adherence. *J Paediatr Child Health* 2003; **39:** 2–5.

79 Franck C, Seddon JA, Hesseling AC, Schaaf HS, Skinner D, Reynolds L. Assessing the impact of multidrug-resistant tuberculosis in children: an exploratory qualitative study. *BMC Infect Dis* 2014; **14:** 426.

80 Treatment Action Group, the Sentinel Project. We can heal: prevention, diagnosis, treatment, care, and support: addressing drug-resistant tuberculosis in children. New York, NY: Treatment Action Group, 2013.

81 Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; **174:** 935–52.

82 Volkmann T, Moonan PK, Miramontes R, Oeltmann JE. Tuberculosis and excess alcohol use in the United States, 1997–2012. *Int J Tuberc Lung Dis* 2015; **19:** 111–19.

83 Oeltmann JE, Oren E, Haddad MB, et al. Tuberculosis outbreak in marijuana users, Seattle, Washington, 2004. *Emerg Infect Dis* 2006; **12:** 1156–59.

84 Simmons KB, Haddad LB, Nanda K, Curtis KM. Drug interactions between rifamycin antibiotics and hormonal contraception: a systematic review. *BJOG* 2018; **125:** 804–11.

85 Torrone EA, Morrison CS, Chen PL, et al. Prevalence of sexually transmitted infections and bacterial vaginosis among women in sub-Saharan Africa: an individual participant data meta-analysis of 18 HIV prevention studies. *PLoS Med* 2018; **15:** e1002511.

86 Ford CA, Millstein SG, Halpern-Felsher BL, Irwin CE Jr. Influence of physician confidentiality assurances on adolescents' willingness to disclose information and seek future health care: a randomized controlled trial. *JAMA* 1997; **278:** 1029–34.

87 Chiang SS, Khan FA, Milstein MB, et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2014; **14:** 947–57.

88 Duque-Silva A, Hampole V, Cheng YN, Flood J, Barry PM. Outcomes of pediatric central nervous system tuberculosis in California, 1993–2011. *J Pediatric Infect Dis Soc* 2018; published online Sept 4. DOI:10.1093/jpids/piy084.

89 Seddon JA, Thee S, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS. Hearing loss in children treated for multidrug-resistant tuberculosis. *J Infect* 2013; **66:** 320–29.

90 Ehrlich RI, Adams S, Baatjies R, Jeebhay MF. Chronic airflow obstruction and respiratory symptoms following tuberculosis: a review of South African studies. *Int J Tuberc Lung Dis* 2011; **15:** 886–91.

91 Nève V, Girard F, Flahault A, Boulé M. Lung and thorax development during adolescence: relationship with pubertal status. *Eur Respir J* 2002; **20:** 1292–98.

92 de la Mora IL, Martínez-Oceguera D, Laniado-Laborín R. Chronic airway obstruction after successful treatment of tuberculosis and its impact on quality of life. *Int J Tuberc Lung Dis* 2015; **19:** 808–10.

93 Jones R, Kirenga BJ, Katagira W, et al. A pre-post intervention study of pulmonary rehabilitation for adults with post-tuberculosis lung disease in Uganda. *Int J Chron Obstruct Pulmon Dis* 2017; **12:** 3533–39.

94 Hatherall B, Newell JN, Emmel N, Baral SC, Khan MA. "Who will marry a diseased girl?" Marriage, gender, and tuberculosis stigma in Asia. *Qual Health Res* 2019; **28:** 1109–19.

95 Mangtani P, Abubakar I, Ariti C, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. *Clin Infect Dis* 2014; **58:** 470–80.

96 Hart PD, Sutherland I. BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life. *BMJ* 1977; **2:** 293–95.

97 Dye C. Making wider use of the world's most widely used vaccine: Bacille Calmette-Guerin revaccination reconsidered. *J R Soc Interface* 2013; **10:** 20130365.

98 Nemes E, Geldenhuys H, Rozot V, et al. Prevention of *M. tuberculosis* infection with H4:IC31 vaccine or BCG revaccination. *N Engl J Med* 2018; **379:** 138–49.

99 Roy A, Eisenhut M, Harris RJ, et al. Effect of BCG vaccination against *Mycobacterium tuberculosis* infection in children: systematic review and meta-analysis. *BMJ* 2014; **349:** g4643.

100 Van Der Meeren O, Hatherill M, Nduba V, et al. Phase 2b controlled trial of M72/AS01E vaccine to prevent tuberculosis. *N Engl J Med* 2018; **379:** 1621–34.