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Snow, K.J., Cruz, A.T., Seddon, J.A. et al. (10 more authors) (2020) Adolescent tuberculosis. The Lancet Child & Adolescent Health, 4 (1). pp. 68-79. ISSN 2352-4642

https://doi.org/10.1016/s2352-4642(19)30337-2

Adolescent Tuberculosis

Author's submitted version.
Published in Lancet Child and Adolescent Health, 18 Nov 2019

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Keywords
Adolescents, young adults, tuberculosis, HIV, multi-drug-resistance, quality healthcare

Summary

Adolescence is characterised by a dramatic increase in the incidence of tuberculosis, a fact that has been appreciated since the early 20th century. The majority of the world's adolescents live in low and middle-income countries where tuberculosis remains common, and where they comprise one 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 article reviews current knowledge about tuberculosis in adolescence with a focus on the management of infection and disease, including HIV co-infection and rifampicin-resistant tuberculosis. Recent progress in vaccine development is outlined and important directions for future research are highlighted.

Search strategy and selection criteria

This was a narrative review of the literature on adolescent tuberculosis, informed by expert opinion and clinical experience. We reviewed the English- and Spanish-language literature for studies on adolescent tuberculosis to identify case series documenting clinical presentation and treatment outcomes. We searched PubMed with the following string on 19 August 2019: ('tuberculosis'[Title]) AND ('adolescent'[TIAB]). The search returned 210 results, of which 11 were eligible for inclusion (Table 1), and we identified three additional studies from reference lists, for a total of 14 studies. Studies reporting solely on prevalence or where data from adolescents was aggregated with those of younger children or adults were excluded. Data were extracted regarding major site(s) of disease, percent of adolescents with microbiologic confirmation, adverse drug reactions, and final treatment outcomes.

Introduction

Following the "golden years" of mid-childhood where tuberculosis cases drop significantly compared to early childhood, adolescence represents a period of increased susceptibility to tuberculosis, when both the prevalence of *Mycobacterium tuberculosis* (*M.tb)* infection and the incidence of tuberculosis disease rise considerably.[1-4] The reasons for this are not completely understood, although it is thought that sex hormones, changing social contact patterns and immunological changes may each have a role.[1] An estimated 1.8 million adolescents and young adults around the world develop tuberculosis disease each year, a burden which has been elucidated only recently due to a historical focus within tuberculosis surveillance on "children" (aged 0-14 years) and "adults" (aged ≥15 years), neglecting adolescents entirely.[5] In high-burden settings, adolescents make up both a substantial proportion of the general population, and a substantial proportion of patients with tuberculosis.[5] This creates a major need for high-quality tuberculosis services which are accessible and acceptable to adolescents, both to facilitate timely diagnosis and to 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 current knowledge about tuberculosis in adolescents from both a clinical and public health perspective, while also highlighting important knowledge gaps. In this review, adolescence is defined as 10-24 years of age, consistent with evidence that many developmental processes continue between age 18 and 24.[6] We use "young adolescents" to refer those aged 10-14 years, "older adolescents" to refer to those aged 15-19, and "young adults" to refer to those aged 20-24. '*M.tb* infection', also known as 'latent tuberculosis infection', refers to an asymptomatic carrier state prior to development of disease, whereas 'tuberculosis' refers to the presence of radiographic and clinical signs and symptoms attributable to tuberculosis disease, although these may be better understood as two points on a spectrum rather than two entirely distinct states.[7] Figure 1 shows the estimated incidence of tuberculosis disease (panels A and B) and prevalence of M.tb infection (panels C and D) in children and adolescents around the world, from previous studies.[5,8] Per capita figures are provided in the supplementary materials (Figure S1). Supplementary figure 2 shows the estimated number of people living with M.tb infection

across the entire age range; unfortunately the same estimation process is not currently possible for tuberculosis disease.

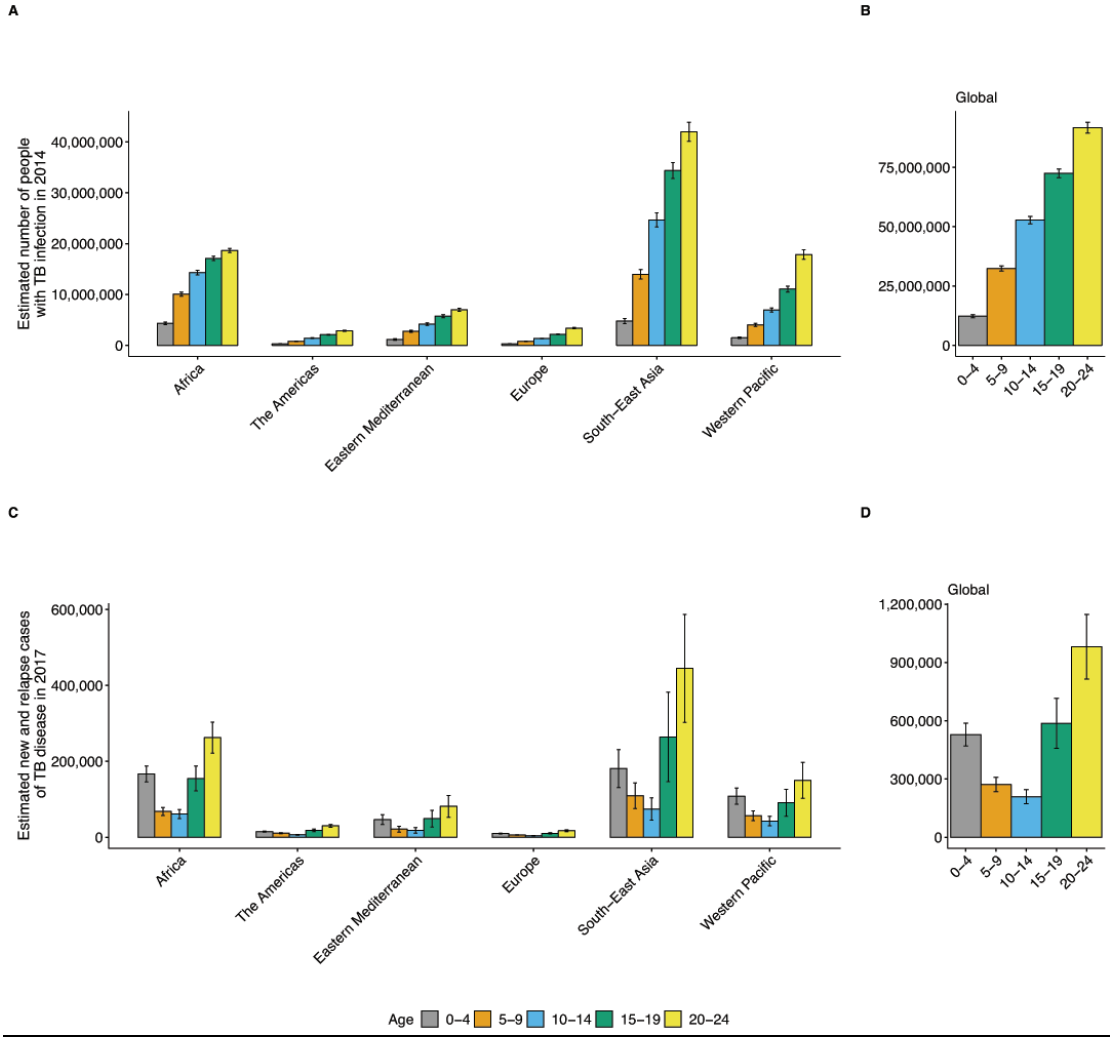


Figure 1: Estimated numbers of people living with *M.tb* infection (panels A and B)[8] and developing new or relapse tuberculosis disease (panels C and D)[5].

Clinical Management

Tuberculosis

Adolescents may present to tuberculosis services in one of three ways (Figure 2). First, they may be identified following exposure to *M.tb* as part of a contact tracing investigation. Second, they may present with symptoms or signs that could be consistent with a diagnosis of tuberculosis. Third, they may be referred following results from an investigation that then requires evaluation for tuberculosis disease. Commonly this includes imaging results in

which tuberculosis is in the list of differential diagnoses, or positive immune-based tests such as interferon gamma release assays (IGRAs) or the tuberculin skin test (TST).

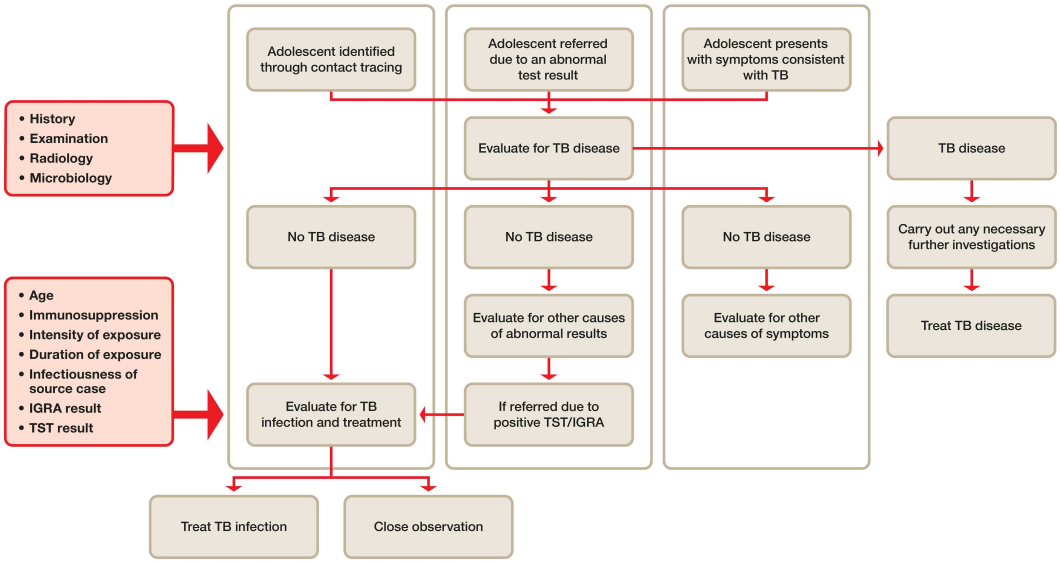


Figure 2: A suggested algorithm for the evaluation of adolescents who are referred for possible tuberculosis.

In each of these three 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, and/or polymerase chain reaction (PCR) testing, e.g. MTB/Rif). Most adolescents have intrathoracic tuberculosis, defined as either parenchymal lung disease (infiltrates, cavities, miliary disease), pleural effusions, or intra-thoracic (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 intra-thoracic lymphadenopathy or miliary disease, as seen in younger children.[10-13] Parenchymal changes are more likely to be apical, as in adults. Table 1 shows the major sites of disease and prevalence of confirmed disease in case series of adolescents with tuberculosis identified during this review.[10-12,14-24]

While 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] although this may 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 microbiologic confirmation are likely overestimated in most case series for the same reasons. When resources are available, radiological evaluation for extra-thoracic tuberculosis might include ultrasonography, computerised tomography or magnetic resonance imaging to identify enlarged lymph nodes, typical intracranial features or involvement of bone or soft tissue.

Unlike for young children, in whom gastric aspirates or induced sputum are required to obtain respiratory samples, adolescents are usually able to expectorate sputum. Using saline to induce coughing has been associated with increased culture yields compared to spontaneously produced samples in children and young adolescents.[26] Adolescents with pulmonary tuberculosis commonly have "bacteriologically confirmed" disease (i.e. smear, culture or PCR positive),[9-11,16,19,26] although paucibacillary disease remains common and negative test results do not rule out tuberculosis. Yields from multiple samples (usually two) 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 has greater sensitivity than the previous test, Xpert MTB/RIF.[28] Many adolescents with pulmonary disease are able to transmit *M.tb*, and due to the high number of social contacts made by adolescents (including outside the household, in schools and peer networks), contact investigation around adolescent patients should be a priority.

In those with large pleural effusions, pleural taps or biopsies can be undertaken for microbiological and biochemical examination. An adenosine deaminase level 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 performed on pleural fluid vary widely.[29] For adolescents with extra-thoracic disease, confirming the diagnosis can be challenging. Lymph node aspiration biopsy is safe, feasible and associated with good sensitivity and specificity in adolescents.[30] Microbiologic 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 for younger children and adults, although it may be appropriate to dose on ideal or lean weight in obese adolescents.[31] There are very sparse data on adverse event rates in adolescents (see Table 1), 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.tb* infection, for whom lack of symptoms makes adherence even more challenging.[32] Several studies have investigated tuberculosis treatment outcomes among adolescents, and comparative studies show higher rates of 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, 41% of 330 adolescent patients took fewer than 80% of the prescribed doses of their tuberculosis treatment.[20]

At present, evidence for tuberculosis-specific adherence support interventions for adolescents is completely absent. However, the principles underpinning adherence–promoting interventions for adolescents are well established for HIV, diabetes, and other chronic diseases, which equally apply to adolescents with tuberculosis. A critical issue is the 'adolescent-friendliness' of services. A recent systematic review synthesised the evidence about young people's priorities in healthcare, 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 may benefit from peer support groups, which have been demonstrated 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 tools to assist with therapeutic adherence.[35] Educational interventions (including efforts to reduce stigma), behavioural interventions and peer support may also have a role, and involvement of supportive family members can be helpful.

M.tb Infection

Adolescents may be referred for assessment for *M.tb* infection through contact tracing, or due to a positive result on a TST or IGRA test. When deciding whether to treat *M.tb*

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. While treatment of *M.tb* 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] The World Health Organization (WHO) now recommends that testing and treatment for *M.tb* infection can be offered to all close contacts of people with bacteriologically confirmed pulmonary tuberculosis, regardless of their age or HIV status.[41] While having a positive TST or IGRA is associated with increased risk of future disease progression compared to a negative test, the vast majority of those with positive tests will never develop disease (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 results does not necessarily indicate that preventive treatment is unwarranted.

Isoniazid, taken daily for six or nine months, is associated with a reduction in risk of future tuberculosis disease in all age groups and has been the mainstay of treatment for *M.tb* infection for fifty years.[42] Newer alternatives to the six or nine month isoniazid regimen include three months of daily therapy with both isoniazid and rifampicin,[43] three months of weekly isoniazid and rifapentine,[44] four months of daily rifampicin[45] and one month of daily isoniazid and rifapentine.[46] Compared to nine-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 due to resource constraints.[47] The Sustainable Development Goals place new emphasis on prevention, as demonstrated in both the End TB Strategy[48] and in the WHO/UNICEF Roadmap Towards Ending Tuberculosis in Children and Adolescents.[49] While standard practice in high-income countries, the updated WHO guidelines on treatment for *M.tb* infection are a substantial expansion of current policies in low- and middle-income countries, with direct relevance to adolescents. High quality evidence on how to address health system and other barriers to facilitate wider administration of treatment for *M.tb* infection in children, adolescents and adults is needed in diverse settings.[49] This 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 current clinical trials.

Rifampicin Resistant Tuberculosis

Rifampicin-resistant (RR) tuberculosis includes multidrug-resistant (MDR; resistance to at least rifampicin and isoniazid) and extensively drug-resistant tuberculosis (XDR; MDR with additional resistance to at least one fluoroquinolone and at least one second-line injectable agent). A confirmed diagnosis of RR tuberculosis relies on microbiological confirmation from clinical samples or cultured isolates, using genotypic or phenotypic drug susceptibility tests (DSTs), which can be challenging in children and young adolescents.[51] In the absence of rapid molecular DSTs, or in the case of patients with culture-negative tuberculosis, a clinical diagnosis of RR tuberculosis can be made in symptomatic adolescents based on exposure to an index patient with bacteriologically confirmed RR tuberculosis, or lack of clinical improvement (i.e. symptom resolution and weight gain) after at least two 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 RR tuberculosis is generally the same as for adults. The 2019 WHO recommendations for use of novel drugs in RR tuberculosis treatment also apply to adolescents, as available pharmacokinetic data indicate that delamanid and bedaquiline may be given to children as young as three and six 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 RR tuberculosis disease have been shown to have excellent outcomes with total treatment duration of 12 months.[54]

Few reports have characterised the frequency and impact of adverse effects of RR tuberculosis treatment in adolescents. A small case series from India reported that 5 of 8 HIV-positive adolescents treated for MDR tuberculosis experienced a moderate or severe adverse event during their TB treatment (see Table 1), including psychosis, convulsions, hypokalemia, and gastrointestinal intolerance.[22] A review of eight case reports of 18 children and young adolescents receiving linezolid-based regimens suggests that haematologic

toxicity and neuropathies occur less commonly than in adults.[55] QT prolongation is a concern among patients receiving bedaquiline, delamanid, clofazimine, and/or fluoroquinolones, but data are limited in adolescents.[56] Among 16 children aged 8-17 years receiving delamanid, one experienced clinically significant adverse effects, including QT prolongation.[57] Among 27 adolescents receiving bedaquiline-containing regimens, five experienced clinically significant QT prolongation; these events were 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] so this effect is likely to be distressing and stigmatising for adolescents and may lead to decreased adherence and treatment discontinuation.

Delayed diagnosis, treatment refusal and loss to follow-up were common and serious issues in two RR tuberculosis case series from South Africa and India (see Table 1).[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 RR tuberculosis and the challenges of successfully engaging them in care.

HIV-associated Tuberculosis

Globally, HIV is the second leading cause of death among 10-19 year old adolescents, and HIV-related deaths have tripled in this age-group since 2000.[61] This increase 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 population 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] Due to suboptimal coverage of HIV diagnosis in early infancy, many perinatally-infected children 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 impact on tuberculosis incidence, morbidity and mortality, but these each remain higher in adolescents with HIV compared to the general adolescent population.[65] Adherence to HIV treatment often drops in adolescence, and HIV viral suppression rates are

lower in adolescents than in other age-groups.[66,67] This 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.tb* infection. The updated and consolidated WHO guidelines for programmatic management of *M.tb* infection recommend treatment of *M.tb* infection for adolescents living with HIV and an unknown or a positive TST result, provided they are assessed as being unlikely to have tuberculosis disease.[68] Treatment for *M.tb* infection should be given irrespective of the degree of immunosuppression, ART, history of previous tuberculosis treatment and pregnancy. Clinicians administering both ART and treatment for *M.tb* infection should be aware of potential drug interactions and follow appropriate guidelines to avoid these. This is particularly important given the increasing use of rifamycins for *M.tb* infection treatment, which can adversely affect ART metabolism.

Tuberculosis disease remains the main cause of mortality among adolescents living with HIV.[69] The presence of HIV co-infection compounds the well-recognised challenges of reaching a definitive diagnosis in children and adolescents with suspected tuberculosis.[70] Extrapulmonary and disseminated disease patterns are more common, tuberculosis is typically paucibacillary, and chest radiographic appearances are not typical.[71] Notably, in recent years, studies have reported a high prevalence of chronic respiratory disease in adolescents with long-standing HIV, even among those taking ART.[72] Chronic lung disease in the context of HIV infection may be a sequela of previous respiratory tract infections including tuberculosis, or HIV itself. In low-income settings where pulmonary diagnostics such as high resolution computed tomography 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.[73,74]

If not already on ART, any adolescent with HIV diagnosed with tuberculosis should be started on ART as soon as is practically possible, following the start of tuberculosis treatment.[75] It is common to wait a short period of time to allow the individual to become accustomed to tuberculosis treatment before starting ART, but this should not usually be more than a couple of weeks. Treatment of tuberculosis in HIV is further complicated by the risk of immune reconstitution syndrome, and pharmacokinetic interactions and overlapping

toxicities between ART and anti-tuberculous drugs, particularly when second-line ART or RR tuberculosis regimens are required.[76] For example, concurrent administration of isoniazid preventive therapy with nevirapine resulted in high rates of hepatotoxicity among children and adolescents living with HIV.[77]

Tuberculosis and HIV both represent major threats to public health. Yet the historical neglect of adolescents as a key population within HIV control may be one reason why there has been little change in HIV mortality in this age group.[78] 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 this age group, including development of appropriate diagnostic algorithms, optimal approaches to tuberculosis prevention, and best practices for adherence support.

Specific Considerations for Adolescents during Tuberculosis Treatment

The developmental period of adolescence can be challenging for paediatric and adult providers alike. In part this is due to adolescents' desire for autonomy, and their prioritising short-term social benefits over potential long-term health gains.[79] Several topics need to be broached with adolescents prior to 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 may need to be explored if they have an uncertain or precarious immigration status, or face other structural barriers to accessing healthcare.

Medication adherence and loss to follow-up are serious concerns for health professionals managing adolescents with tuberculosis, especially in those with HIV co-infection and/or RR tuberculosis.[22,23] Adherence support is of the utmost importance in this age group, particularly for adolescents with RR tuberculosis, who endure more adverse effects and longer duration of treatment than those treated for drug-susceptible disease, or those with complex co-morbidities such as HIV, diabetes, or substance dependence. Children and adolescents with RR tuberculosis report social isolation, stigmatisation, depression, and poor self-esteem,[80,81] highlighting the importance of psychosocial support during tuberculosis treatment.

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

Tuberculosis treatment must 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 treatment. While it is unlikely that a polysubstance-using adolescent will stop using all substances, adolescents need guidance on which substances are most problematic during tuberculosis treatment. Adolescents should be informed that alcohol use is particularly harmful, as it can increase problematic side effects including hepatotoxicity,[82] and may increase the risk of adverse treatment outcomes.[83] Providers also need to discuss which modalities of substance use would be more likely to transmit *M.tb,* such as sharing water pipes or “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.[84] Substance dependence should be addressed through referral to appropriate evidence-based services, for example medication-assisted treatment for adolescents with opioid dependence.

Providers should counsel adolescent girls on non-hormonal contraception options (e.g. intrauterine devices or condoms) which are not adversely affected by rifamycins, as hormonal contraception cannot be relied upon during tuberculosis treatment.[85] Pregnancy testing should be performed prior to 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 incidence rates are usually highest in this age group.[86] To improve quality care for adolescents, provision of tuberculosis care must therefore include the opportunity for confidential consultations; adolescents are less likely to accurately report their sexual activity, substance use and mental health status when parents or caregivers are present.[87]

Sequelae post tuberculosis

Adolescence is a critical time for physical, psychosocial, and cognitive development—all of which may be impacted 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 connection with tuberculosis treatment. A few published studies describe neurological sequelae after tuberculosis meningitis, which occur in 54-66% of successfully treated patients ≤18 years,[88,89] and irreversible hearing loss due to injectable agents in patients treated for RR tuberculosis.[90]

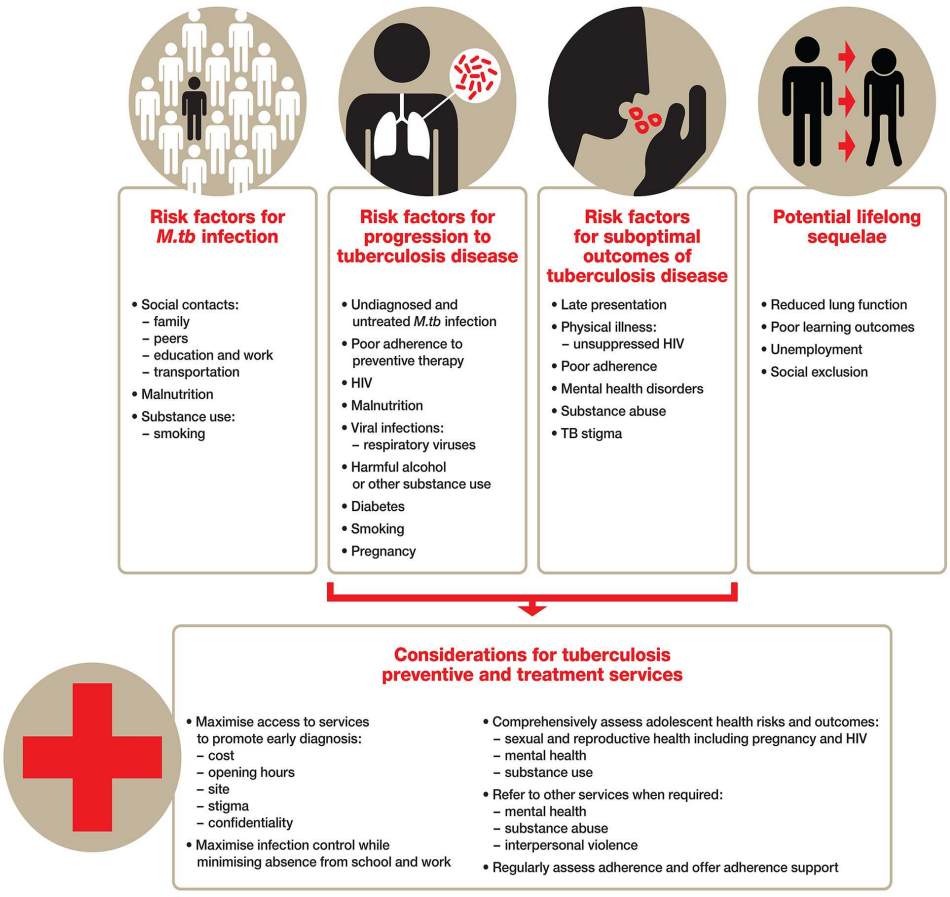


Figure 3: Tuberculosis in the life course: general and adolescent-specific risk factors associated with *Mycobacterium tuberculosis* infection, progression to tuberculosis disease, and outcomes.

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,[91] 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 may make them especially vulnerable.[92] Understanding post-tuberculosis lung function has important clinical implications, but in most high-burden settings people who complete tuberculosis treatment receive minimal follow-up. It has been shown that former adult tuberculosis patients with residual lung abnormalities experience diminished quality of life,[93] and such patients can benefit from supportive measures, such as pulmonary rehabilitation.[94]

The long-term psychosocial impact of tuberculosis in adolescence is also undocumented. In addition to interrupting education and employment, tuberculosis disease and its treatment can disrupt relationships with family and peers. Adolescents are intensely sensitive to social exclusion, and the impact 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.[95] 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

Bacillus Calmette–Guérin (BCG) is the only vaccine currently available to prevent tuberculosis. There is clear evidence of a strong protective effect (90%) of initial BCG vaccination against disseminated TB in infants, and moderate protection (60-75%) against pulmonary disease in children and young adolescents.[96] Large-scale trials of BCG conducted by the British Medical Research Council in the 1960s involved 14-15 year old adolescents and found that the BCG vaccine was 87% protective against disease, and 74% protective 20 years later.[97] This effect was, however, only seen in those who had not yet been sensitised to *M.tb* or nontuberculous mycobacteria. Mycobacterial sensitisation, measured using 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 paid to adolescents both with and without evidence of exposure to *M.tb*. Population groups at

increased risk of *M.tb* 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.[98]

Several clinical trials of new vaccine candidates are enrolling adolescents. In the recently published Phase 2 HYVAC4 trial, 990 HIV-negative, BCG-vaccinated, IGRA-negative adolescents between the ages of 12 and 17 years living in a tuberculosis endemic setting were randomly assigned to receive the H4:IC31 vaccine, BCG revaccination, or placebo.[99] Results suggested that BCG revaccination provided 45% protection against sustained *M.tb* infection, while the effect of the H4:IC31 vaccine to prevent sustained infection did not reach statistical significance. Concomitant laboratory data showed that BCG revaccination was found to significantly boost BCG-specific CD4+ T-cell responses. Whilst disappointing for the HYVAC4 vaccine candidate, the findings suggest that BCG revaccination of QFT-negative adolescents may provide additional benefit, leading to renewed interest in BCG revaccination in adolescence.[100]

Another recent Phase 2b controlled trial randomised 3,575 HIV-negative individuals aged 18-50 years with evidence of *M.tb* infection in 11 centres in South Africa, Kenya, and Zambia to the M72/AS01E vaccine or placebo.[101] The candidate vaccine showed significant efficacy in the prevention of tuberculosis disease, with an overall vaccine efficacy of 54%. In pre-specified sub-analyses, vaccine efficacy varied considerably by age: vaccine efficacy was 84.4% in 18-25 year old participants, compared to 10.2% in those older than 25. The importance of previous BCG vaccination and previous *M.tb* sensitisation on the efficacy of this vaccine candidate remains 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 two age groups: “children” 0–14 years and “adults” aged ≥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

among 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.

Acknowledgements

KJS is supported by the Centre for Research Excellence in Tuberculosis (TB-CRE), funded by the National Health and Medical Research Council of Australia. JAS is supported by a Clinician Scientist Fellowship jointly funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement (MR/R007942/1). RAF is funded by the Wellcome Trust (Grant no (206316/Z/17/Z). SSC is supported by the U.S. National Institutes of Health (K01TW010829). BK is funded by the MRC (MC_UP_A900/1122, MR/K011944/1, MR/P024270/1). RMGJH received funding from the European Research Council under the European Union's Horizon 2020 research and innovation programme (grant agreement no 757699). PJD is funded by a fellowship from the UK Medical Research Council (MR/P022081/1). The funders had no role in decision to publish, or preparation of the manuscript.

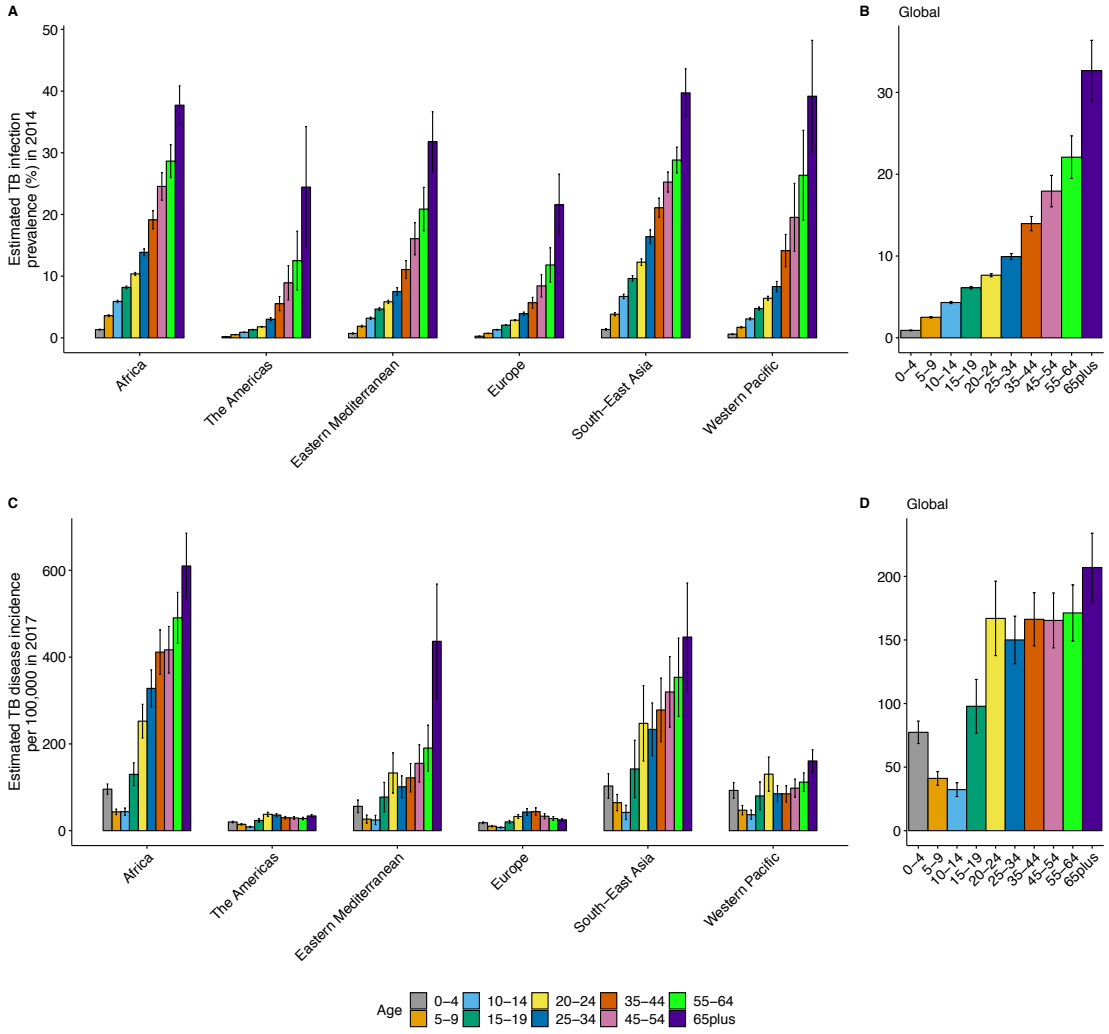
Authors' contributions

KJS, SMS and KK conceptualised the review. KJS and KK coordinated the review, wrote the introduction, knowledge gaps section and conclusions with input from SMS, and collated and edited the manuscript. KS and AC conducted the literature search. ATC and JAS drafted the section on clinical management for tuberculosis and *M.tb* infection with input from SSC and SMG. JH and SSC drafted the RR tuberculosis section with input from JAS and SMG. SSC drafted the section on sequelae with input from RAF and SMG. BK drafted the vaccines section. RAF drafted the HIV section with input from KK. RMGJH and PJD drafted the epidemiology content with input from KS. 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.

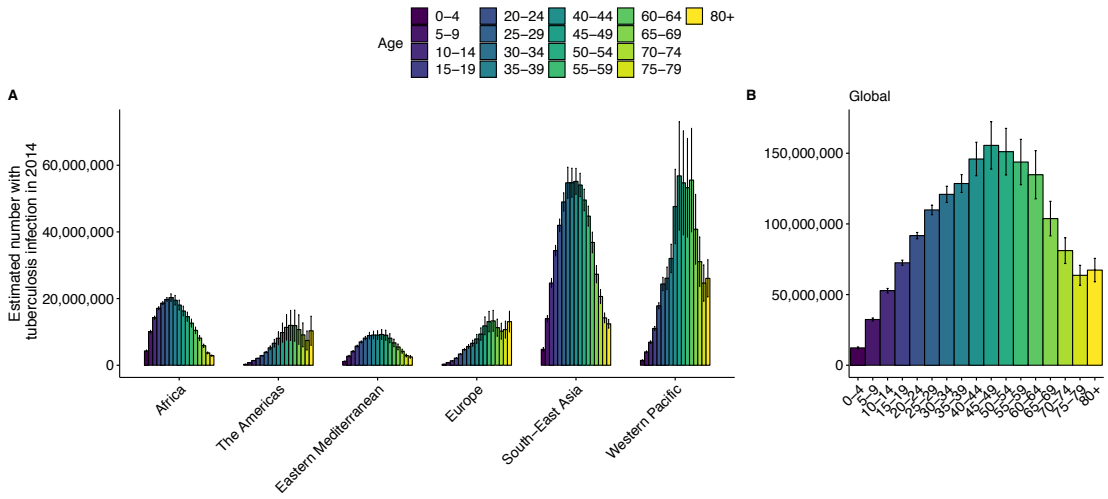
Declaration of interests

BK has a patent for diagnostic biosignature issued. The other authors declared no conflicts of interest.

Supplementary Figures



Supplementary figure 1: Estimated numbers of people living with *M.tb* infection (panels A and B)[8] and developing new or relapse tuberculosis disease (panels C and D)[5], per 100,000 population.



Supplementary figure 2: The estimated number of people living with *M.tb* infection in each WHO region and globally, disaggregated by five-year age band.[8]

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