Incidence and prevalence of bacteriologically confirmed pulmonary tuberculosis among adolescents and young adults: a systematic review

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Abstract

The burden of tuberculosis (TB) among adolescents and young adults in endemic settings is poorly characterised. This study aimed to review published and unpublished estimates of the incidence and prevalence of bacteriologically confirmed TB among young people aged 10–24 years. We searched PubMed and World Health Organization archives for publications and unpublished data from population-based epidemiologic studies reporting confirmed pulmonary TB among young people, conducted from January 2000 onwards. We identified 27 publications and unpublished data from two national surveys, representing a total of 26 studies in 19 countries. The prevalence of bacteriologically confirmed TB ranged from 45 to 799 per 100 000 in the Asia-Pacific region and from 160 to 462 per 100 000 in African settings. We did not identify any epidemiologic studies of confirmed TB among adolescents living with human immunodeficiency virus (HIV). Many studies were excluded due to absent or inadequately reported age-specific data. Adolescents and young adults living in many endemic settings appear to be at substantial risk of developing active TB. There is a pressing need to improve the routine reporting of age in epidemiologic studies of TB, and to generate high-quality epidemiologic data regarding TB among adolescents living with HIV.

Introduction

Tuberculosis (TB) in children has received increasing attention in recent years, with the World Health Organization (WHO) being particularly interested in improving the estimates of the burden of child morbidity and mortality from TB and its contribution to the global burden of TB [1–4]. It is widely recognised that infants and young children (<5 years of age) are at high risk of progression to active disease following infection with *Mycobacterium tuberculosis* and are particularly prone to severe, disseminated forms of TB [5, 6]. While the risk of active disease is much lower in the 5–9-year-old age group, early epidemiological observations in the pre-human immunodeficiency virus (HIV) era reported a sharp increase in risk again through the adolescent and young adult years (ages 10–24) [5, 7, 8]. As adolescents and particularly young adults who develop TB often present with 'adult-type' pulmonary TB that is sputum smear-positive [5], they are far more likely than younger children to contribute to on-going transmission in the community. Furthermore, evidence is emerging that adolescents and young adults ('young people') with TB may have complex adherence support needs [9], and may be at elevated risk of treatment discontinuation relative to both children and to adults [10, 11]. As such, young people (aged 10–24) arguably constitute an important but neglected group within global TB control.

It is increasingly appreciated that the adolescent and young adult years are a time of rapidly changing burden of disease, which presents new opportunities for public health interventions [12, 13]. The International Roadmap for Childhood TB explicitly called for the attention of the needs of adolescents at risk of TB in research, policy development and clinical practices, with the first step of a suggested framework being to 'know your epidemic' [2]. With regard to TB among adolescents and young adults, this is challenging for a number of reasons. At present, data on TB burden are routinely reported by national TB programmes to the WHO disaggregated into broad age groups (5–14, 15–24 years) which complicates burden of disease estimation among young people [3]. A recent analysis of global TB surveillance data suggests that between 1.2 and 3.0 million adolescents and young adults develop TB each year, with the

considerable uncertainty around the estimates due to limitations in available data [14]. Adolescent-specific data are rarely reported in publications, despite the presence and adolescents and young adults in many clinical cohorts. Similar challenges pervade reporting on other communicable diseases such as HIV, obscuring our understanding of the major causes of morbidity and mortality in adolescents and young adults as a distinct group [15].

TB among young people is epidemiologically complex and may require specialised health system responses with regards to prevention and management, but currently, even the most basic epidemiological information regarding the burden of TB in adolescence and young adulthood – estimates of incidence and prevalence – are lacking. The primary aim of this systematic review was to identify direct estimates of the incidence and prevalence of bacteriologically confirmed pulmonary TB among adolescents and young adults aged 10–24 years, as measured using active case finding approaches.

Methods

We searched PubMed with the following string on 14 June 2014 and again on 20 August 2017: ('tuberculosis'[Title]) AND ('adolescent'[MeSH Terms] OR 'adolescent'[All Fields] OR 'adolescents'[All Fields]) AND ('epidemiology'[Subheading] OR 'epidemiology'[All Fields] OR 'incidence'[All Fields] OR 'incidence'[MeSH Terms] OR 'prevalence'[All Fields] OR 'prevalence'[MeSH Terms]). We also hand-searched archives maintained by the WHO's Global TB Programme for written reports and unpublished data on national prevalence surveys supported by the WHO global task force on TB impact measurement [16].

The review questions and search strategy were decided *a priori*. KS and LN independently screened the PubMed search results and identified studies for full-text retrieval. Disagreements were resolved through discussion with CS. KS retrieved the full texts, confirmed eligibility and extracted the data. We contacted authors of prospective studies and national prevalence surveys that included adolescents but did not report adolescent-specific estimates to request additional data.

Inclusion criteria

Inclusion and exclusion criteria were defined so as to limit the risk of bias due to unrepresentative sampling or diagnostic criteria with low-specificity. Studies were eligible for inclusion if they:

- Reported data for an observation period that began during or after January 2000;
- Reported age-specific observations of incidence or prevalence in an age group with a minimum lower bound of 10 years and a maximum upper bound of 24 years (e.g. 12–17 years, 15–24 years);
- Used at least one of sputum smear microscopy, culture or the Xpert MTB/RIF® assay to confirm suspected TB;
- Included at least 100 participants in an age group of interest, drawn from a representative sample of the source population.

Exclusion criteria

- Publications reporting exclusively on passively collected surveillance data were excluded. National surveillance data are summarised in WHO's global TB database, which is publicly available online [17]. This review was restricted to primary research data collected through active case finding, to address the issues of underdiagnosis and underreporting which can occur through passive case detection and surveillance.
- Studies reporting on broad age groups that included adolescents or young adults but did not differentiate them from younger children or older adults (e.g. 10–35 years) were not included.
- Studies reporting exclusively on non-representative population sub-groups (e.g. remote Indigenous communities, migrants, prisoners) were excluded unless the study reported on a sample of young people living with HIV.

Data analysis

Age-specific incidence and prevalence estimates were extracted from each eligible paper. Where possible, missing parameters (e.g. 95% confidence intervals) were calculated from the data presented using Stata 13 (StataCorp, Texas, USA).

National estimates of TB caseload in the relevant age groups were derived from national prevalence survey data and United Nations Population Division estimates for the relevant age groups in the nearest calendar year to the survey (2000, 2005, 2010 or 2015), where *estimated TB caseload = TB prevalence per 100 000 * (population in age group/100 000)*. National estimates were not calculated from sub-national studies, as studies conducted in subnational areas cannot be assumed to represent entire nations. No meta-analysis was performed as the resulting pooled estimate would be determined by the settings of the included studies and would not represent the average value worldwide.

Risk of bias within studies was assessed using a customised checklist assessing the sampling strategy, screening algorithm, diagnostic criteria and statistical adjustment for clustering and missing data within the age bracket. Risk of bias across studies was assessed with regard to both geographic representativeness and the epidemiological characteristics of the included studies in aggregate.

Results

Search results

Our initial PubMed search returned 3540 results, of which 449 full texts were screened and 12 were found eligible for inclusion. Studies rejected at the title review stage were most often rejected due to ineligible study designs (e.g. case series, reports on routine surveillance data). Studies rejected after abstract or full-text screening were most often rejected because they did not include young people, because they were not population-based studies (e.g. surveys of army recruits) or because they did not present age-specific data for an appropriate age group (see Fig. 1). The updated search identified 475 results, of which 12 full texts were screened and four found eligible for inclusion. An additional 11 publications or reports were identified in WHO records.

Among the 27 included publications only two pertained to prospective studies; the remainder reported the results of cross-sectional prevalence surveys. Two prevalence surveys resulted in two publications each, as did one cohort study, resulting in a total of 27 publications from 24 studies. Data from a further two national prevalence surveys were obtained prior to the publication of their reports.

No epidemiological studies reporting laboratory-confirmed TB in adolescents or young people living with HIV were identified. A small number of clinical cohort studies pertaining to children
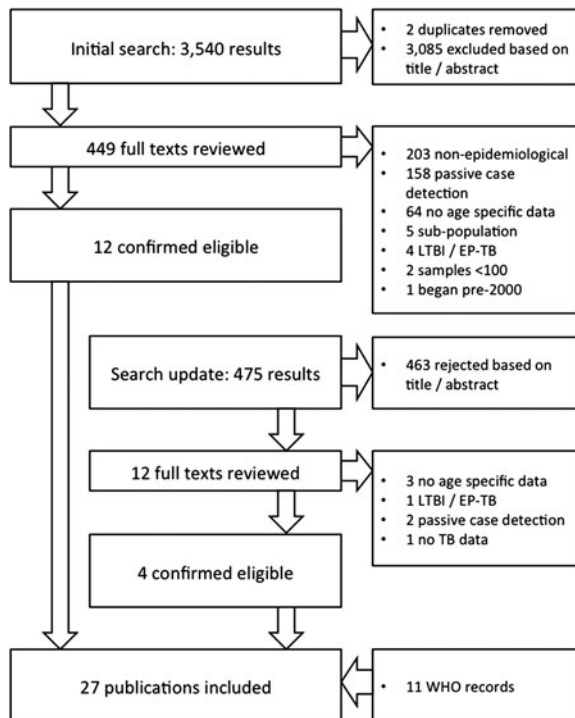
Fig. 1. PRISMA flowchart of study selection process.

engaged in clinical care for HIV were screened. None of these studies included adolescent-specific data, and all used a clinical case definition of TB without laboratory confirmation, highlighting the persistent challenges with diagnostic confirmation in this group.

Of studies excluded after review of the full text, 68 had included adolescents in the study but did not present TB incidence or prevalence disaggregated by age group. Among the authors who responded to our requests for disaggregated data, one was able to provide case numbers of bacteriologically confirmed TB in adolescents in South Africa [18]. Additional age-disaggregated data were obtained from WHO records on national prevalence surveys in China [19], Nigeria [20], Ethiopia [21, 22], Cambodia [23], Pakistan [24, 25], Ghana [26], Thailand [27], the Philippines [28], Bangladesh (report in preparation) and Kenya (report in preparation).

Of the 30 countries that WHO defines as high TB burden [29], 15 were represented in at least one of the identified studies. In several of the remaining 15 countries, WHO-supported national TB prevalence surveys are either completed, underway or planned [30].

Study results

Prevalence estimates from studies using both smear and culture ranged from 45 per 100 000 in China [19] to 241 per 100 000

in Pakistan [24] in the Asia-Pacific region, and from 160 per 100 000 in Basuoga, Uganda [31] to 462 per 100 000 in Lusaka, Zambia in sub-Saharan Africa [32]. Two studies from Bangladesh using smear microscopy only reported observed prevalence of smear-positive disease of 39 and 45 per 100 000 [33, 34]. The most recent national prevalence survey in the Philippines utilised the Xpert MTB/RIF® assay in addition to smear and culture, resulting in a prevalence estimate of 799 per 100 000 [28] (Tables 1–3, Fig. 2).

Estimated TB prevalence was lowest in China at 45 per 100 000 population aged 15–24. However, as China is home to an estimated population of 237 million people aged 15–24, the estimated prevalent caseload in China remains very substantial at an estimated 106 000 prevalent cases among 15–24-year olds in 2012 (Fig. 3). Pakistan, the Philippines, Ethiopia and Nigeria all have both high prevalence and substantial estimated caseloads owing to high prevalence rates in large populations, while Laos, Cambodia and Thailand each have fewer than an estimated 15 000 prevalent cases, despite each having prevalence rate estimates in excess of 100 cases per 100 000 population.

Risk of bias

Given our restrictive exclusion criteria, the risk of bias within most included studies is considered to be low. Most studies used multiple screening strategies (most commonly symptom screening and chest X-ray), which should have moderate to high sensitivity in this age group, followed by laboratory confirmation using both smear and culture, which should provide high specificity. Four studies used symptom screening alone in some or all clusters [33, 34, 42, 45], which could reduce sensitivity and may lead to underestimates of prevalence [47]. Almost all studies used both smear and culture for bacteriological confirmation; two studies used smear without culture [33, 34], which would have reduced sensitivity and resulted in an underestimate of the prevalence of all active pulmonary TB in their setting, Bangladesh [47].

Most studies used random sampling methods within clearly defined geographic areas, although the two cohort studies enrolled adolescents from high schools [31, 35, 43], who may not be representative of out-of-school adolescents in the community. As recorded in Table 2, not all studies presented age-specific estimates adjusted for both non-participation and clustering, although in studies where both crude and adjusted age-specific estimates were presented, the differences were usually not substantial.

Risk of bias across studies is considered to be low; publication bias should be minimal, although the delay between the undertaking and the publication of large prevalence surveys is often lengthy, and some completed studies may not yet be represented in the literature. Unsurprisingly, all the included studies were conducted in moderate or high TB transmission settings in Asia and Africa – population-based epidemiological studies of TB are not

Table 1. Incidence of confirmed TB among young people in prospective cohort studies

Author, year	Setting	Study period	Age group (years)	Person-years	Cases	Incidence per 100 000 (95% CI)
Mahomed, 2013 [35]	Worcester, South Africa	2005–2007	12–18	14 635	67	450 (349–571)
Waako, 2013 [31]	Basuoga, Uganda	2009–2011	12–18	5532	13	235 (125–402)

Table 2. TB prevalence among young people in national prevalence surveys

Author, year	Setting	Study period	Age group (years)	Participants	Cases	Prevalence per 100 000 (95% CI)
Smear only						
Zaman, 2012 [33]	Bangladesh	2007–2009	15–24	15 275	7	45 (18–94)
Smear or culture						
In preparation[a]	Bangladesh	2015–2016	15–24	27 182	28	103 (65–152)[b]
National Tuberculosis Control Program, 2012 [23]	Cambodia	2010	15–24	10 568	14	130 (74–227)[b]
Wang, 2014 [19][a]	China	2010	15–24	N/R	N/R	45 (16–75)[b]
Ministry of Health, 2011/Kebede, 2014 [21, 22]	Ethiopia	2010–2011	15–24	14 978	36	292 (194–390)[b]
Bonsu, 2015 [26][a]	Ghana	2013	15–24	17 089	29	184 (104–265)[b]
In preparation[a]	Kenya	2015–2016	15–24	17 578	54	360 (242–478)[b]
National Tuberculosis Centre, 2014 [36]	Laos	2010–2011	15–24	9879	14	142 (78–237)
National Tuberculosis Program, 2014 [37]	Myanmar	2009–2010	15–24	11 899	11	92 (42–165)
Department of Public Health, 2014 [20]	Nigeria	2012	15–24	11 956	19	274 (130–419)[b]
Qadeer, 2013, 2016 [24, 25]	Pakistan	2011	15–24	33 693	60	241 (169–313)[b]
Tropical Disease Foundation and Department of Health, 2008 [38]	Philippines	2009	10–19	6280	11	175 (87–313)
Ministry of Health, 2015 [27][a]	Thailand	2012	15–24	4516	7	155 (70–342)[b]
Hoa, 2010 [39]	Viet Nam	2006–2007	15–24	20 935	10	55 (22–88)[b]
Kapata, 2016 [40]	Zambia	2013–2014	15–24	14 702	32	285 (157–412)
Ministry of Health and Child Welfare, 2015 [41][a]	Zimbabwe	2014	15–24	9798	11	129 (48–210)[b]
Smear, culture or Xpert MTB/RIF® assay						
Department of Health, 2017 [28][a]	Philippines	2016	15–24	11 381	72	799 (586–1011)

N/R, not reported.
[a]Personal communication of adolescent-specific data, Irwin Law (World Health Organization).
[b]Adjusted for clustering and for missing data using inverse probability weighting [16].

feasible in lower transmission settings, including many South American settings, as the denominators required become prohibitively large as prevalence falls.

It should be noted that sub-national studies should not be interpreted as representing the true prevalence of TB among all adolescents and young adults in the nation. India, in particular, is both very large and epidemiologically diverse with regard to TB, and estimates pertaining to the single districts in which the two Indian studies were conducted may not be nationally representative [42, 45]. Likewise, the South African studies intentionally targeted high transmission urban communities [18, 35, 43]. At the time of writing, national TB prevalence surveys were planned in India and underway in South Africa (Law, personal communication).

Table 3. Confirmed TB prevalence among young people in sub-national prevalence surveys

Author, year	Setting	Study period	Age group (years)	Participants	Cases	Prevalence per 100 000 (95% CI)
Ayles, 2009 [32]	Lusaka, Zambia	2005	15–24	3244	15	462 (259–762)
Chadha, 2012 [42]	Nelamangala, India	2008–2010	15–24	15 602	9	58 (26–109)
Mahomed, 2013 [43]	Worcester, South Africa	2005	12–18	5682	16	282 (156–443)
Marais, 2005 [18][a]	Cape Town, South Africa	2002	10–14	476	1	210 (5–1164)
Nduba, 2015 [44]	Nyanza, Kenya	2010	12–18	5004	16	320 (190–450)
Rao, 2012 [45]	Jabalpur, India	2009–2010	15–24	29 747	25	84 (54–124)
Van't Hoog, 2011 [46]	Nyanza, Kenya	2006–2007	15–24	6562	19	289 (174–450)
Waako, 2013 [31]	Basuoga, Uganda	2009	12–18	5000	8	160 (69–315)
Zaman, 2006 [34]	Matlab, Bangladesh	2001	15–24	15 555	6[b]	39[b] (14–84)

[a]Personal communication of adolescent-specific data, Ben Marais (University of Sydney).
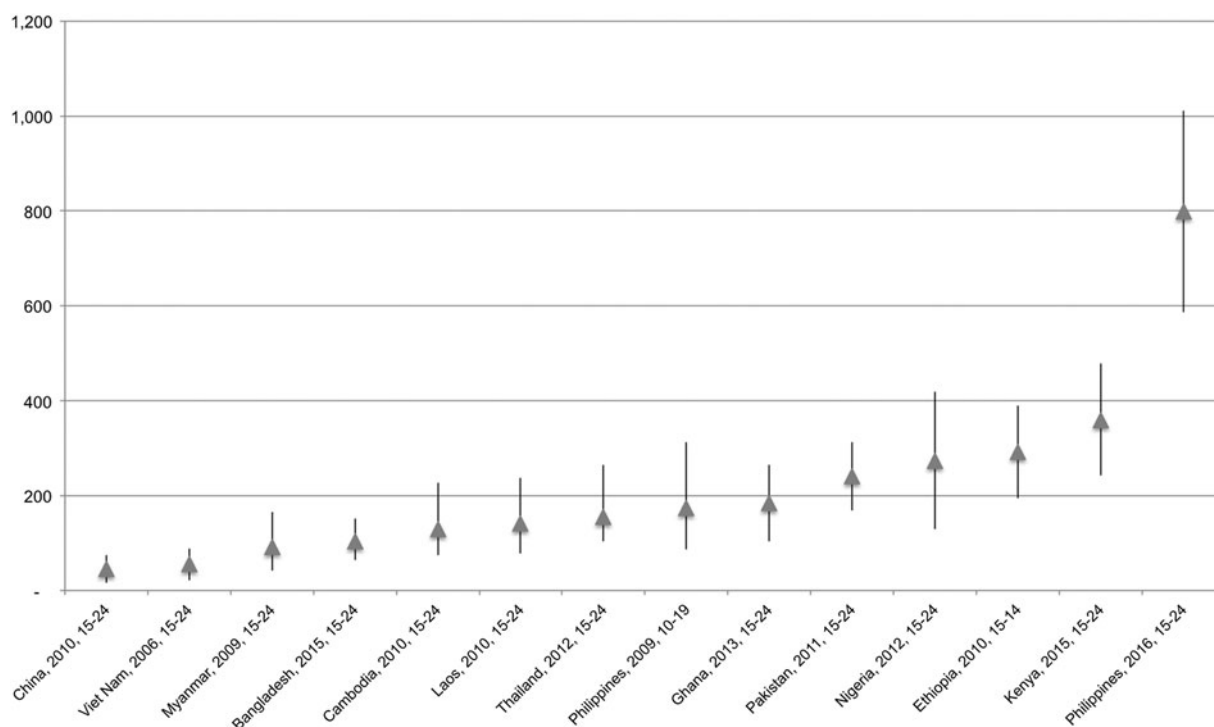[b]Smear-positive TB only.

Fig. 2. Estimated national TB prevalence among adolescents and young people (per 100 000), from national TB prevalence surveys (country, survey start year, age group).

Discussion

This project reviewed published and unpublished data on TB incidence and prevalence among young people around the world. The identified studies were conducted in a variety of moderate- and high-transmission settings in the Asia-Pacific region and sub-Saharan Africa. The results presented demonstrate that young people in many high transmission settings currently experience a substantial burden of TB. Adolescents are often considered by both paediatric and adult clinicians to be at 'low risk' of TB, which may reflect the clinical experience that adolescents represent a low proportion of patients accessing either child or adult health services for TB treatment. However, results from southern Africa and the Philippines, in particular, demonstrate that although young people may be at lower risk than adults in the same country, the absolute magnitude of the risk they face in high-transmission settings can be very substantial. Further, owing to sizeable populations of people aged 10–24 years, very large numbers of young people in the Asia Pacific region are likely living with TB, even in countries such as Pakistan and China where per capita prevalence is only moderate. This is consistent with recent estimates that 1.2–3.0 million adolescents and young adults develop TB each year, a majority of whom live in the WHO African and South East Asian regions [14]. These findings imply a need for improved TB prevention and management in this age group, as well as consideration of their role in unfolding TB epidemics around the world.

TB prevention

While infants and young children are often exposed to TB in the household by caregivers, adolescents spend more time outside the household, where they may face an increased risk of exposure to an infection with *M. tuberculosis* [5]. Unlike young children, adolescents are at risk of exposure to disease by same-age peers

[5, 48], a risk amplified in some settings by classroom overcrowding and poor ventilation [49]. Historical data suggest that there may be a second peak in the risk of progression to active TB after infection during the adolescent years [7], although one smaller modern study among migrants did not observe the same phenomenon [50]. Whether it is due to increased risks of infection, progression, or both, it is consistently observed that burden of disease increases with advancing age throughout adolescence [8, 51]. The prevalence of major risk factors for TB such as HIV, smoking, diabetes and pregnancy likewise increase with age across adolescence and young adulthood [12].

Notwithstanding the recognised escalation in TB risk during the adolescent years, little has been written regarding effective TB prevention interventions in the adolescent age group. There is currently no effective vaccine to prevent pulmonary TB, although several novel candidates are currently in clinical trials [52]. Contact tracing and TB preventive therapy are currently routinely recommended for children under 5, but are rarely implemented even for this highly vulnerable group in moderate- and high-incidence countries [53]. If the risk of progression to disease is indeed elevated during the adolescent years, preventive therapy for this age group might also be an efficient public health intervention; however, this is currently routinely implemented only in high-income countries in response to household contact or school-based outbreaks.

TB management

After disease develops, adolescents and their guardians may need to negotiate the space between child and adult health services [13], which can complicate the diagnostic pathway depending on whether child or adult algorithms are used. This will be doubly true in low- and moderate-incidence settings, where a variety of other respiratory diseases may be more common than TB,
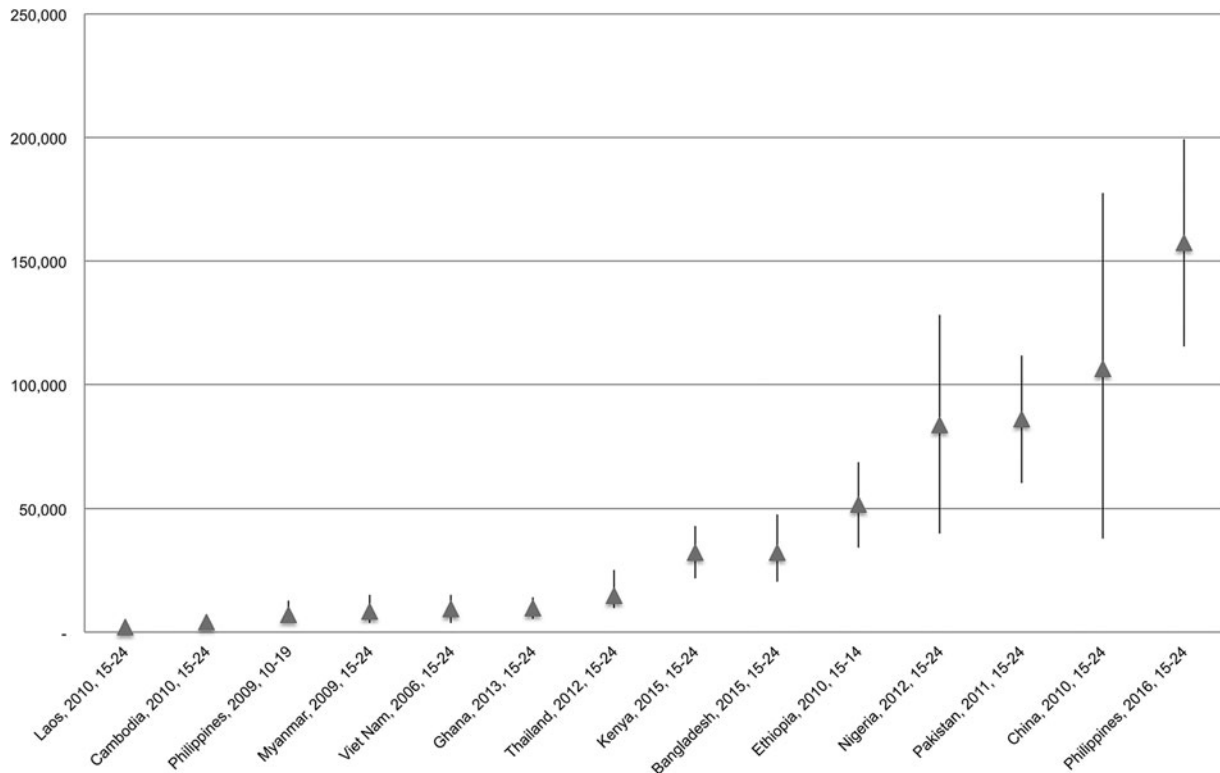
Fig. 3. Estimated number of adolescents and young adults with prevalent pulmonary TB, based on national prevalence survey data (country, survey start year, age group).

complicating differential diagnosis for clinicians who may see TB in adolescents only infrequently.

Once the diagnosis is achieved, treatment can be initiated; however, a wide variety of health services are challenged by engaging adolescents and young adults in on-going care [54]. Supporting adherence among young people is appreciated to require specialised approaches, especially with regard to stigmatised and complex conditions, such as HIV [54, 55]. Comparatively little has been written regarding support for young people receiving treatment for TB: two recent studies in southern Africa have documented elevated risks of treatment discontinuation among young people with TB compared to children and adults [10, 11], and an additional study from India documented complex psychosocial support needs among adolescents with multidrug-resistant TB/HIV co-infection [9]. In settings where clinic-based direct observation of therapy remains the standard of care, TB treatment may disrupt schooling or vice versa. Infection control concerns can also result in adolescents with TB being excluded from school after treatment is initiated, sometimes unnecessarily. Although the needs of young people with TB are beginning to be appreciated, evidence on optimal models of care for TB among this group is currently absent from the literature. Lessons may be learned from other chronic conditions, where dedicated programmes targeting young people are more commonly implemented [54, 55].

Long-term implications

In addition to suffering a substantial burden of disease at present, our findings also imply that young people in some high-transmission settings likely have a high prevalence of *M. tuberculosis* infection, which may become an active disease in the distant future. Given what is known with regard to disease progression

risk in this age group [5, 50], the prevalence of latent infection is likely to be 6–20 times higher than the prevalence of active disease. Some young people currently acquiring *M. tuberculosis* infection will ultimately contribute to TB incidence in their communities as adults over the coming decades, should they develop reactivation disease. The dramatic fall in under-five mortality in the last decade is resulting in many more children reaching adolescence [56], creating the largest generation of young people in human history [57]. The significance of this generation of young people is particularly striking in countries in the African region, where they comprise up to 30% of the population of some countries [58]. The future course of the global TB epidemic will be determined to a significant extent by the success or failure of TB control efforts among this generation, including the prevention of both TB infection and disease.

Limitations

In spite of the widely recognised significance of age in TB epidemiology, we encountered widespread failures to report age-specific data appropriately. A large number of studies were excluded from this review because they did not report any age-stratified data. Many studies reported the age of participants simply as a mean and standard deviation, including studies targeting paediatric populations; given that the age of young TB patients often has a bimodal distribution due to the fall in incidence after early childhood and the subsequent rise during adolescence [5, 8, 11], this is almost universally statistically inappropriate. Some studies reported age in seemingly arbitrary age groups (possibly quartiles) without explanation. Still others did not report on upper and lower bounds of age, simply referring to participants as 'children' or 'adults'. This is unfortunately

consistent with recent experience in reviews related to HIV in adolescents [55, 58], and hampers our understanding of the epidemiology of these two important diseases in this age group. Reporting age in standard 5-year age groups (0–4, 5–9, 10–14 and so on) in all studies of paediatric and adolescent TB and HIV, and in standard 10-year age groups for population-based studies, would address this issue.

In addition to the paucity of published age-specific data, the major limitation of the included studies and consequently of this review itself is the statistical precision of the estimates. Even national prevalence surveys with participants numbering in the tens of thousands are not powered to provide high-precision estimates of TB prevalence within narrow age bands. This is unfortunately an unavoidable issue in population-based epidemiological studies of pulmonary TB, as prevalence rarely exceeds 0.5% of a population [29].

The major strengths of this study were the broad search strategy, which should have identified a majority of relevant publications, and the inclusion of previously unpublished age-specific data from WHO records.

It was striking that we identified no eligible studies of the incidence or prevalence of confirmed TB among young people living with HIV, although the difficulties with microbiological confirmation of TB in this group present a considerable challenge to both clinicians and researchers (Rashida Ferrand, personal communication). Adolescents living with perinatally-acquired HIV infection are likely to be a high-risk group of particular importance. The generation of children born after ART became available in high HIV prevalence settings are now passing through adolescence [55, 58], with significant implications for healthcare provision. Is it estimated that there are over 2 million adolescents living with HIV around the world and that HIV-associated mortality is currently rising in this age group even as it falls in all others [59]. A key challenge among perinatally-infected young people is the risk of disengagement from HIV care if they are inadequately supported through the transition from paediatric to adult HIV services [54, 55, 58]. Inconsistent or interrupted access to ART for adolescents who fail to make this transition successfully is likely to increase their risk of TB. That we did not identify a single epidemiological study of confirmed TB in this group is cause for concern. Existing cohort studies planned TB prevalence surveys and other opportunities should be explored to fill this information gap, especially as higher sensitivity tests for paucibaccilary disease (e.g. the Xpert MTB/RIF assay) are now in routine use in many settings. In the meantime, for children and adolescents receiving HIV treatment and care, recommended routine TB screening activities could generate data on TB incidence and prevalence.

Conclusion

Age-specific data regarding TB epidemiology are inconsistently reported; however, several studies documented a substantial burden of TB among young people in settings in Asia and southern Africa. There is a need to improve standardised reporting of age-specific data in epidemiological studies of TB. Given the burden of disease documented in many studies included in this review, TB prevention and management in young people living in many high TB transmission settings merits increased attention.

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