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Tuberculosis as a cause or comorbidity of childhood pneumonia in tuberculosis-endemic areas: a systematic review

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Pneumonia is a major cause of morbidity and mortality in infants and children worldwide, with most cases occurring in tuberculosis-endemic settings. Studies have emphasised the potential importance of *Mycobacterium tuberculosis* in acute severe pneumonia in children as a primary cause or underlying comorbidity, further emphasised by the changing aetiological range with rollout of bacterial conjugate vaccines in high mortality settings. We systematically reviewed clinical and autopsy studies done in tuberculosis-endemic settings that enrolled at least 100 children aged younger than 5 years with severe pneumonia, and that prospectively included a diagnostic approach to tuberculosis in all study participants. We noted substantial heterogeneity between studies in terms of study population and diagnostic methods. Of the 3644 patients who had culture of respiratory specimens for *M tuberculosis* undertaken, 275 (7.5%) were culture positive, and an acute presentation was common. Inpatient case-fatality rate for pneumonia associated with tuberculosis ranged from 4% to 21% in the four clinical studies that reported pathogen-related outcomes. Prospective studies are needed in high tuberculosis-burden settings to address whether tuberculosis is a cause or comorbidity of childhood acute severe pneumonia.

Introduction

Pneumonia is the leading cause of death in children aged 1–59 months, accounting for an estimated 18% of under-5 mortality worldwide in 2011.¹ In 2010, roughly 120 million episodes of pneumonia, 14 million severe pneumonia episodes, and 1.3 million deaths due to pneumonia in infants and children aged younger than 5 years were recorded.^{1–3} Most (81%) of these deaths occurred in the first 2 years of life. The epidemiology of child pneumonia varies widely between different regions of the world in terms of disease incidence, severity, and associated mortality, and the contribution of causative pathogens and prevalence of risk factors (table 1, figure 1).^{4,5} Liu and colleagues² report that most pneumonia episodes in children younger than 5 years occurred in southeast Asia (39%) and Africa (26%), with sub-Saharan Africa accounting for 43% of pneumonia deaths, despite only constituting 19% of the world's under-5 population.

An understanding of the common causative pathogens in high-burden settings is important to inform case-management and potential preventive strategies, such as vaccine development and delivery. Case-management and immunisation strategies have been informed by studies done in the 1980s which identified *Streptococcus pneumoniae* and *Haemophilus influenzae* as the most common bacterial pathogens causing pneumonia in children.^{6,7} These studies also showed that most pneumonia-related deaths were due to bacterial rather than viral pneumonia, with the exception of measles. However, even in the case of measles-associated pneumonia deaths, 47–55% were associated with bacterial superinfection with *S pneumoniae* identified in 30–50% of confirmed bacterial co-infections.⁸ The diagnostic techniques used in these studies restricted identification of pathogens to bacteria and known common viruses.^{7,9} They did not use diagnostics specific to the identification of *M tuberculosis*, atypical bacteria, or opportunistic pathogens

such as *Pneumocystis jirovecii* or cytomegalovirus. Furthermore, most previous studies did not highlight the potential importance of co-infections, as manifested by a high prevalence of pneumococcal-respiratory viral co-infections (roughly 33%), which has since been observed in children admitted to hospital with pneumonia in low-income, middle-income, and high-income settings.^{10,11} Furthermore, the studies were done before the worldwide spread of the HIV epidemic.

The HIV epidemic has had a major effect on the burden and mortality of pneumonia in children; bacterial pneumonia is more common and more severe in HIV-infected children compared with uninfected children.⁵ *P jirovecii* pneumonia (PCP) is frequently fatal in HIV-infected infants not receiving co-trimoxazole preventive therapy and co-infections (concurrent

Key messages

- Tuberculosis is not often reported in young children presenting with acute severe pneumonia in tuberculosis-endemic settings
- Tuberculosis might be a direct cause of severe pneumonia or might be an underlying comorbidity that increases the risk of secondary bacterial pneumonia
- Clinical and autopsy studies have confirmed tuberculosis in children that have died with severe pneumonia
- Restrictions of tuberculosis diagnostic techniques in children hinder estimation of actual burden and improved case detection
- Data on tuberculosis in children with acute severe pneumonia are from a small number of studies in mainly large urban-based hospitals with marked heterogeneity in diagnostic approaches
- The non-specific clinical presentation of pulmonary tuberculosis in infants and young children highlights the urgent need for improved diagnostic instruments

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bacterial, mycobacterial, fungal, or viral) are common in HIV-infected children.¹² Additionally, the HIV epidemic has substantially increased the incidence and transmission of tuberculosis in HIV endemic settings, particularly in young women, greatly increasing the risk of tuberculosis in their infants.¹³ Reversal of the burden of HIV in infants has been encouraging, with increasing coverage of prevention of mother-to-child transmission of HIV, early antiretroviral therapy, and co-trimoxazole prophylaxis for HIV-infected and HIV-exposed infants.¹⁴

Potential contribution of tuberculosis to childhood pneumonia

Although tuberculosis is a curable and preventable disease, it is the second leading cause of death from an infectious agent after HIV. In 2013, about 9·0 million new cases of tuberculosis occurred, with 1·5 million deaths worldwide, and most of the cases were from Asia and Africa.¹⁵ Roughly 550 000 of the new cases were in children, with 80 000 deaths in those who were HIV-uninfected.^{15,16} This number might be an underestimate owing to the challenges of establishing the diagnosis of tuberculosis in children. There is a growing awareness that children have a high burden of tuberculosis-related disease that is often not reported as such.¹⁷

Previous studies of pneumonia in infants and young children might also have underestimated the contribution of tuberculosis as a direct cause or comorbidity of acute community-acquired pneumonia in children because of the difficulties of microbiological confirmation in this age group, especially in resource-restricted tuberculosis-endemic settings.⁵ These settings are the ones that have the highest incidence of childhood pneumonia and pneumonia-related mortality (figures 1, 2).^{3,4,16} Additionally, these settings have the highest prevalence of childhood malnutrition and HIV infection worldwide, both common comorbidities that increase the risk and the mortality of tuberculosis and of pneumonia in young children.^{17–19} Furthermore, the relative interaction with tuberculosis as a cause or contributor to childhood pneumonia in tuberculosis endemic areas is likely to be changed with increasing global uptake of vaccines that protect against

other causes of pneumonia, including measles vaccine, *H influenzae* type b (Hib), and pneumococcal conjugate vaccines.^{17,20,21} Tuberculosis needs specific treatment (in contrast to many respiratory viruses) and treatment outcomes in young children are usually excellent.

The contribution of tuberculosis to the burden of pneumonia and death in childhood as a direct cause or underlying contributing factor is still poorly quantified. Cause-specific mortality estimates are usually modelled from vital registration data with historical assumptions and allow only the reporting of a single cause of death, which in the context of respiratory disease is not pathogen-specific. Additionally, the fact that children with acute pneumonia symptoms might have microbiologically confirmed tuberculosis contradicts traditional teaching and standard case management, in which tuberculosis is only considered in children with prolonged persistent symptoms. The concept that tuberculosis might increase susceptibility to secondary bacterial pneumonia in young children is also not widely appreciated.

To assess the association of tuberculosis with childhood pneumonia in tuberculosis-endemic areas, we did a systematic review of published literature reporting the causes of severe pneumonia in infants and young children that prospectively evaluated these children for multiple infectious causes, including *M tuberculosis*. By reviewing the available data on prevalence, clinical presentation, diagnostic approaches, co-infection, and outcome, we aimed to provide an overview of knowledge gaps and a resource for future research and advocacy.

Search strategy and selection criteria

We included studies of any design that were done in a tuberculosis-endemic setting (country incidence ≥ 50 new cases per 100 000 people per year at the time of the study); enrolled at least 100 children aged younger than 5 years who had a diagnosis of pneumonia or respiratory tract infection (defined as clinical evidence of severe or very severe pneumonia according to WHO criteria of acute respiratory infection,²² or radiological evidence of lobar or patchy consolidation); and included a tuberculosis diagnostic workup and described the diagnostic approach in sufficient detail. We included studies that reported additional comorbidities such as HIV or malnutrition as long as a lower respiratory tract infection provided the main point of entry into the study. Case reports or series, studies with older populations, and those done in high-income countries not endemic for tuberculosis (incidence < 50 new cases per 100 000 people per year) were excluded. The primary outcomes considered were the numbers and proportions of tuberculosis cases diagnosed clinically or culture-confirmed in children aged younger than 5 years with pneumonia.

We recognised studies as potentially highly heterogeneous but did not exclude any because of perceived low quality (STROBE checklist).²³ Heterogeneity included study population, study setting and diagnostic methods

	Population aged <5 years (2010)	Incidence per child-year	Total episodes ($\times 10^6$)	Total deaths ($\times 10^3$)
Africa	133 340 762	0·27 (0·14–0·63)	36·4 (18·2–84·4)	540·6 (43·8–627·3)
Americas	76 995 700	0·08 (0·04–0·18)	6·4 (3·3–14·5)	23·9 (22·6–35·6)
Eastern Mediterranean	72 151 965	0·23 (0·11–0·53)	16·4 (8·2–38·0)	168·4 (147·3–217·1)
Europe	54 605 243	0·03 (0·02–0·04)	1·6 (1·3–2·1)	18·1 (14·7–23·4)
Southeast Asia	179 956 087	0·26 (0·13–0·61)	47·4 (23·7–109·8)	443·8 (336·7–534·2)
Western Pacific	116 411 580	0·11 (0·05–0·24)	12·2 (6·2–28·2)	61·9 (50·7–78·0)
World	633 461 337	0·19 (0·10–0·44)	120·4 (60·8–277·0)	1256·8 (1053·2–1482·9)

The data in parentheses are uncertainty ranges. Adapted from Walker and colleagues.¹

Table 1: Pneumonia disease burden estimates by WHO region in children aged 0–4 years (2011)

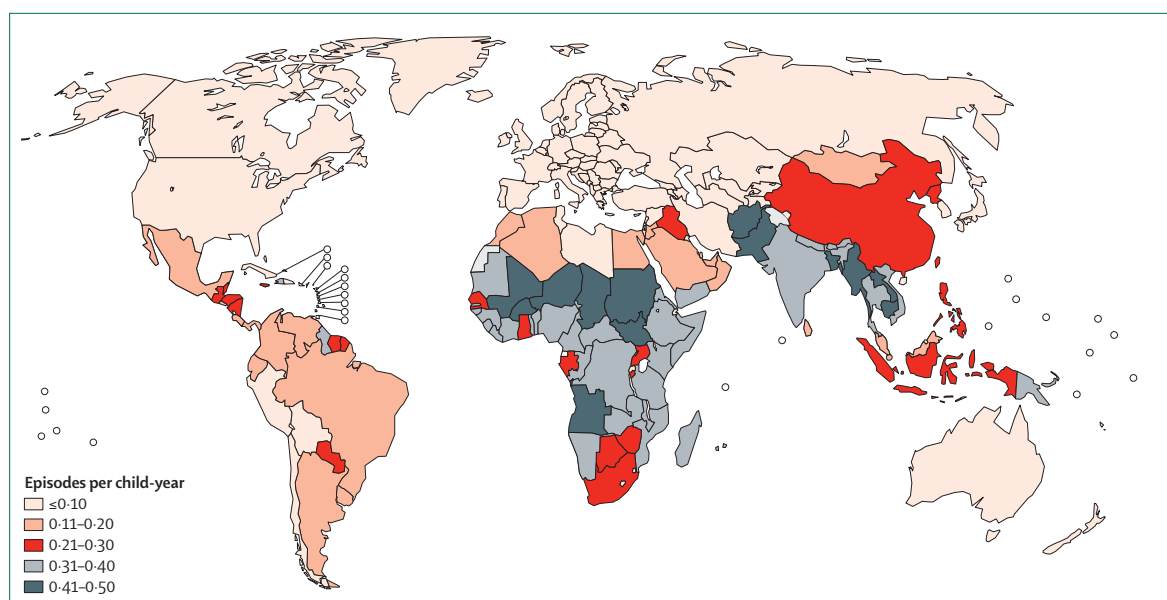


Figure 1: Incidence of clinical pneumonia in children less than 5 years of age (2012)*

Figure adapted from the World Health Organization (WHO) with permission. Small circles represent island populations.

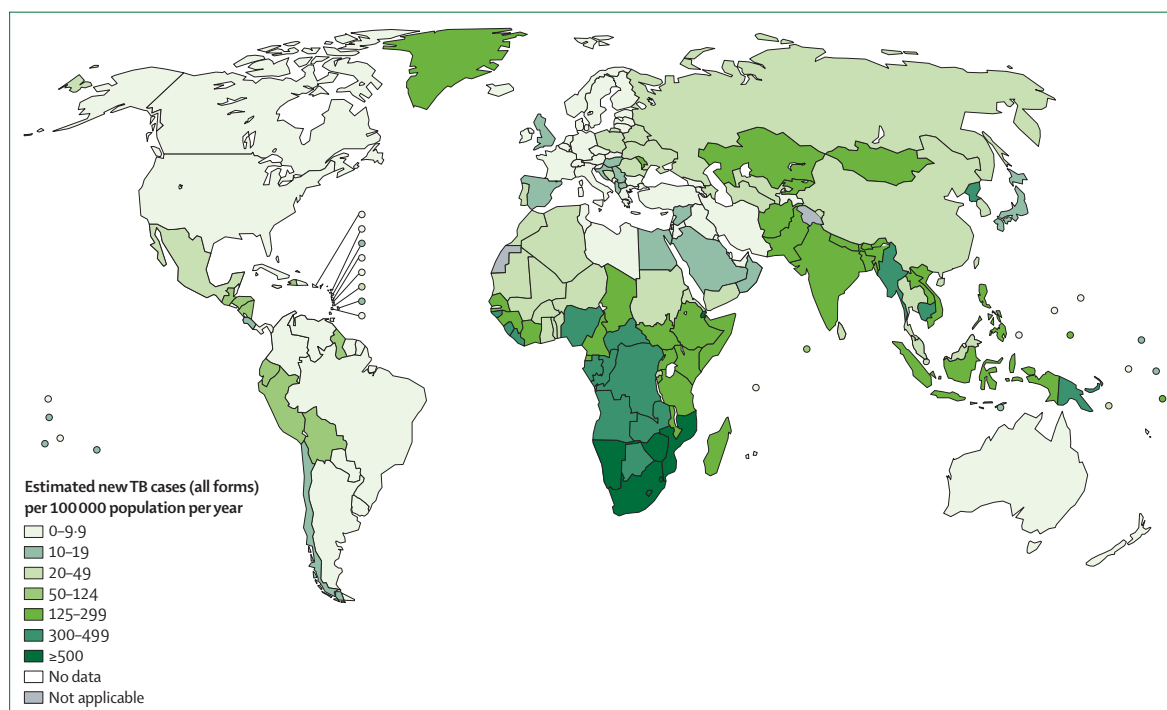


Figure 2: WHO estimated tuberculosis incidence estimates per country (2013)¹⁶

Figure adapted from the World Health Organization (WHO) with permission. Small circles represent island populations.

used to clinically diagnose or microbiologically confirm tuberculosis, and all recognised factors that have a risk of bias across studies for detection of the primary outcome of the review and for mortality. Assessment of the risk of bias of individual studies identified potential sampling bias in many of the clinical studies (appendix). The substantial heterogeneity and recognised risk of bias

across and within studies did not allow for pooled estimates or meta-analysis of variables. Rather, the main characteristics for individual studies were listed. The gold standard for tuberculosis diagnosis is culture confirmation and so the principal summary measures that we aimed to report were the pooled numbers of culture-confirmed tuberculosis and as a proportion of

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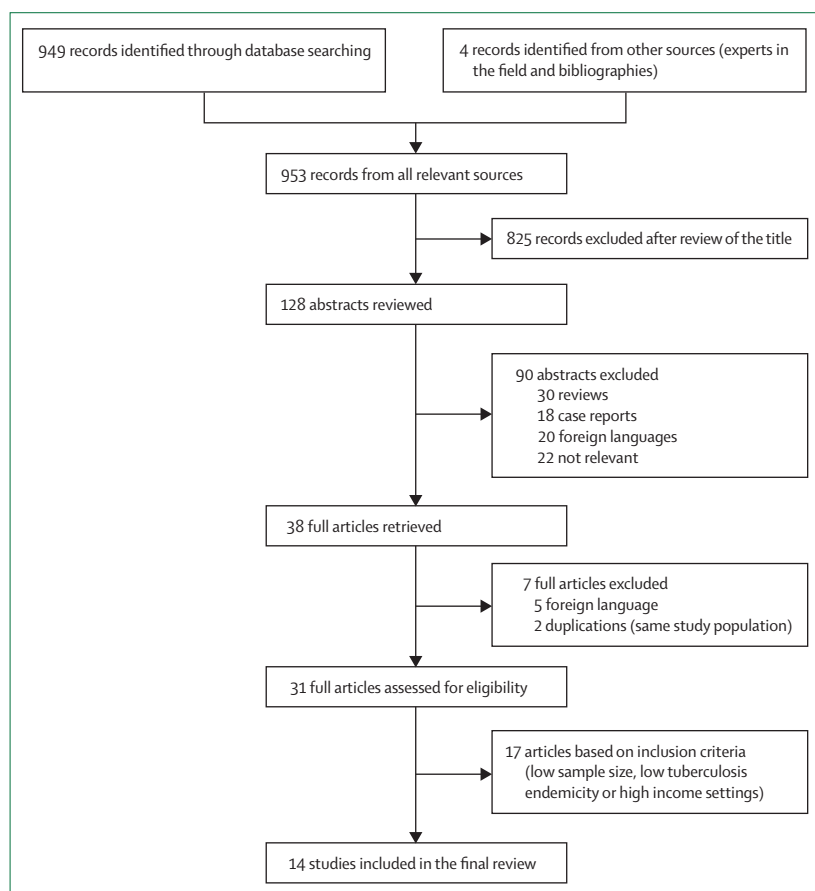


Figure 3: PRISMA flow diagram of studies included in the Review

those that had respiratory specimens cultured, with risk of bias explicitly acknowledged. We deemed the risk of bias of individual studies for reporting of inpatient deaths negligible.

Findings

Study overview

Our search identified 14 articles that were eligible for the final analysis: 11 prospective clinical studies and three autopsy studies (figure 3, table 2).^{24–37} We noted substantial heterogeneity between studies in terms of factors that would potentially affect yield of tuberculosis diagnosis in children with pneumonia such as inclusion criteria, study setting, background tuberculosis incidence at the time of the study, prevalence of comorbidities such as severe malnutrition, and techniques used for sputum collection and microbiological confirmation. The 11 clinical studies of children treated in hospital included a total of 6504 infants and children with a clinical or radiological diagnosis of pneumonia that were aged younger than 5 years.

Six of these studies were done in large urban-based hospitals in South Africa and Malawi, which are very high-burden tuberculosis settings (reported incidence ≥ 300 cases per 100 000 population per year) with high

rates of HIV infection.^{26,31–33,36,37} The other five were studies of children treated in hospital from a wide range of high-burden tuberculosis settings (reported incidence 50–299 cases per 100 000 population per year) including rural Africa, and low-HIV-prevalence settings in Asia, namely Bangladesh and China.^{24,25,27,29,35} The three autopsy studies were also from southern African countries with very high tuberculosis incidence (South Africa, Zambia, and Zimbabwe).^{28,30,34}

Tuberculosis diagnosis

Studies were done in hospitals with varying capabilities to microbiologically confirm tuberculosis, and not all studies included mycobacterial culture for microbiological confirmation. Diagnostic approaches for each study are summarised in table 2. Potential sampling bias occurred within studies; four studies^{25,27,31,33} collected samples for culture for *M tuberculosis* in all study participants, whereas four studies^{24,26,32,35} collected samples for culture in a subset of participants, in which criteria for selection were not clearly mentioned. One study used Xpert MTB/RIF (Cepheid, CA, USA) additionally to culture in 214 children.²⁷ Most of the 3644 samples taken for culture or Xpert MTB/RIF were sputum samples obtained by induced sputum technique or gastric lavage, with an additional 94 samples from a direct lung aspirate. One study reported multiplex PCR results from a nasopharyngeal sample.²⁹

Chest radiographs were done as part of the diagnostic evaluation for pneumonia in all the studies but only three of the studies^{27,30,31} compared radiological findings with those with a diagnosis of tuberculosis and those without. In a study of severely malnourished children in Bangladesh,²⁷ no differences were noted except that one of the 27 confirmed tuberculosis cases had a milary pattern. In the South African autopsy study of HIV-infected children,³⁰ no differences were noted in radiological patterns between those with tuberculosis and those with other HIV-related lung diseases.³⁰ The clinical study by Zar and colleagues reported that hilar or mediastinal adenopathy was significantly more common in children with tuberculosis than in those without (43% vs 12%).³¹

Contribution of tuberculosis to pneumonia

The proportion of pneumonia cases that were diagnosed with tuberculosis ranged from 1% to 23%. The proportion of culture-confirmed tuberculosis in children with pneumonia also varied widely between the nine studies that included *M tuberculosis* culture, with five studies^{25–27,31,32} reporting culture-confirmed rates of 5–8%. One study reported culture-confirmed rates of 15%.³³ Overall, of the infants and young children with pneumonia who had culture of respiratory specimens for *M tuberculosis* performed, 7.5% (275 of 3644) were culture positive. The proportion of culture positive cases was higher in settings with a very high tuberculosis burden at the time of the study (incidence of ≥ 300 cases per 100 000 population per

	Country (setting)	Tuberculosis population incidence per 100 000 per year ^{38*}	Participants (age)	Duration of symptoms on presentation for tuberculosis cases	Inclusion criteria	Tuberculosis diagnosis	Tuberculosis cases (% of enrolled)	Case-fatality rate and other characteristics of tuberculosis cases	HIV prevalence (number of HIV-infected over number of tuberculosis cases tested for HIV)
Very-high-burden settings (tuberculosis incidence ≥300 cases per 100 000 people per year)									
Graham ³⁷ (2005–06)	Malawi (urban and peri-urban)	328	288 of under-5's (median 5 months [range 2–59])	Not reported	WHO severe or very severe pneumonia	Clinical†	5 (1.7%)	20% (1 of 5) died aged 5 months	40% (2 of 5)
Moore ²⁶ (1998–2006)	South Africa (urban)	406	2439 (3–59 months)	77% of cases had cough for <10 days duration	Admission to hospital for lower respiratory tract infection	Culture of sputum in 1334 children when tuberculosis clinically suspected	421 (17%) of 2439 enrolled; 90 (7%) of 1334 sputum samples culture confirmed	376 first and 45 recurrent episodes; 4% (4 of 90) of culture-confirmed cases died in hospital; 49% (206 of 421) cases discharged following response to empirical antibiotics and not initiated on tuberculosis treatment	64% (241 of 376)
McNally ³³ (2001–02)	South Africa (urban)	780	358 (median 4.8 months [IQR 2.7–13])	85% of cases had symptoms for <2 weeks	WHO severe or very severe pneumonia	Culture of sputum	53 (15%), all culture confirmed	64% (34 of 53) of cases were aged <1 year; 11 (21%) died; maternal tuberculosis associated with poor outcomes	72% (38 of 53)
Zar ³¹ (1998)	South Africa (urban)	406	250 (median 6 months [IQR 3–16])	Enrolment criteria: cough <14 days duration	WHO severe or very severe pneumonia	Culture of sputum	20 (8%), all culture confirmed	15% (3 of 20) died	55% (11 of 19)
Madhi ³² (1997–98)	South Africa (urban)	406*	1215 (2–59 months)	Enrolment criteria: cough for <14 days duration	WHO severe or very severe pneumonia	Culture of sputum in 858 children when tuberculosis clinically suspected	69 (6%); 69 (8%) of 858 culture confirmed	58 (84%) aged <2 years; 7 (10%) also had bacteraemia	52% (36 of 69)
Graham ³⁶ (1996)	Malawi (urban and peri-urban)	479	150 (median 5 months [IQR 2–59])	Not reported	WHO severe or very severe pneumonia	Clinical†	9 (6%)	All cases had close tuberculosis contact and poor response to antibiotics	89% (8 of 9)
High-burden settings (tuberculosis incidence 50–299 cases per 100 000 people per year)									
Nantongo ³⁵ (2011)	Uganda (urban)	193	231 (median 15 months [IQR 7–36])	37% of cases had cough for <2 weeks	WHO severe or very severe pneumonia	Clinical; culture of sputum	37 (16%) cases; 12 (5%) culture-confirmed	24 (65%) aged <2 years; young age (<1 year) and contact history associated with confirmed tuberculosis	28% (14 of 51)
Chisti ²⁷ (2011–12)	Bangladesh (urban)	225	385 (median 10 months [IQR 2–59 months])	Median duration of cough for cases: 7 days (IQR 4–8)	Severely malnourished; radiological consolidation	Clinical†; culture (n=385) and Xpert [‡] (n=214) of sputum	8 (23%); 27 (7%) culture or Xpert [‡] confirmed	4 (5%) died within 3 months	Not tested; low HIV prevalence setting
Hammit ²⁴ (2010)	Kenya (rural)	298	810 (1–59 months)	Not reported	WHO severe or very severe pneumonia	Clinical†; culture of sputum (n=108)	5 (0.6%); 2 (2%) of 108 sputum sampled culture confirmed	108 investigated for tuberculosis were selected from 810 severe pneumonia cases	Not reported for tuberculosis cases; 10% for severe pneumonia cases
Wang ²⁹ (2004–05)	China (urban)	92	100 (mean 15.7 months)	Not reported	Radiological evidence of pneumonia	Multiplex PCR of nasopharyngeal specimens; culture not done	1 (1%)	<i>S pneumoniae</i> and <i>M tuberculosis</i> identified in same specimen	Not tested; low HIV prevalence setting
Adegbola ³⁵ (1990–92)	The Gambia (urban and peri-urban)	189	278 (3–58 months)	Not reported	WHO severe or very severe pneumonia; radiological consolidation	Culture of lung aspirate (n=94) or induced sputum (n=26)	5 (1.8%); 2 (2%) of 120 sampled culture confirmed	All 5 cases were severely malnourished; 2 cases also had bacteria cultured from lung aspirate	2% (3 of 155) malnourished subgroup

(Table 2 continues on next page)

	Country, (setting)	Tuberculosis population incidence per 100 000 per year ^{38*}	Participants (age)	Duration of symptoms on presentation for tuberculosis cases	Inclusion criteria	Tuberculosis diagnosis	Tuberculosis cases (% of enrolled)	Case-fatality rate and other characteristics of tuberculosis cases	HIV prevalence (number HIV-infected over number of tuberculosis cases tested for HIV)
(Continued from previous page)									
Autopsy studies									
Chintu ³⁴ (1997–2000)	Zambia (urban and peri-urban)	645	264 (1–192 months)	Not reported	Death from respiratory disease in hospital	Histopathology including Ziehl-Neelsen stain	54 (20%); pulmonary tuberculosis in 42 cases and miliary tuberculosis in 12 cases	35 (65%) aged <18 months; 12 cases had concurrent pyogenic pneumonia	59% (32 of 54)
Rennert ³⁰ (1998–99)	South Africa (urban)	406	93 (mean 10.5 months [range 1.5–69.8])	No case had cough for >1 week	HIV-related death with antemortem lung disease	Histopathology including Ziehl-Neelsen stain and culture	4 (4%)	3 (13%) of 23 deaths in children of 1 year or older were tuberculosis cases	All HIV-infected
Ikeogu ³⁸ (1992–93)	Zimbabwe (urban and peri-urban)	362	184 (mean 11.1 months [range 1–55])	Not reported	Dead on arrival or shortly thereafter	Microscopy and culture of lung tissue	8 (4%); 4 disseminated and 4 pulmonary tuberculosis	All severely malnourished; 6 cases had concurrent pyogenic pneumonia	75% (6 of 8)

^{*}Tuberculosis incidence per 100 000 population at time of study from World Bank Estimates.³⁸ +“Clinical” included history of contact, response to antibiotics, chest radiograph, and tuberculin skin test. ‡Xpert MTB/RIF (Cepheid, CA, USA).

Table 2: Studies assessing the contribution of tuberculosis to pneumonia in children aged younger than 5 years in tuberculosis-endemic areas

year; 232 (8%) of 2800 pneumonia cases in which samples were available for culture) than in studies done in high tuberculosis burden settings (incidence of 50–299 cases per 100 000 people per year; 43 (5%) of 844 pneumonia cases in which samples were available for culture).

Relation to vaccine coverage

The national immunisation programme in six of the study sites included Hib conjugate vaccine in early infancy.^{24–27,33,37} The only study²⁶ that included children who received a pneumococcal conjugate vaccine reported follow up of a randomised placebo-controlled trial of the nine-valent pneumococcal conjugate vaccine in South African infants. The main aim of the study was to assess protective efficacy against invasive pneumococcal disease and all-cause radiological confirmed pneumonia during the first 2 years of life. A post-hoc vaccine-probe analysis from this study²⁶ estimated that 43–47% of treatment in hospital for culture-confirmed tuberculosis in HIV-infected and HIV-uninfected children in this setting could be due to superimposed pneumococcal co-infection.

Symptoms associated with tuberculosis

The duration of respiratory symptoms such as cough before admission was acute in most patients with tuberculosis when this feature was reported in the study (table 2),^{26,27,31–33} with the exception of the Ugandan study²⁵ that reported persistent cough of more than 2 weeks' duration was more common in pneumonia cases with tuberculosis compared with those without. One study noted that 49% of patients with tuberculosis responded to first-line empirical antibiotic treatment for community-acquired pneumonia and were well enough to discharge

with antituberculosis treatment started later once culture results became available.²⁶

Association with HIV infection

HIV co-infection was common (28–89%) in children diagnosed with tuberculosis in the HIV-endemic settings of eastern and southern Africa.^{25,26,32,33,36,37,39} One study³² reported a 23-fold (95% CI 13–48) higher incidence of admission to hospital with culture-confirmed tuberculosis presenting as acute severe pneumonia in HIV-infected children aged younger than 2 years (1470 cases per 100 000 per year) than in HIV-uninfected children (65 per 100 000 per year). However, the proportion of patients that were culture positive for *M tuberculosis* was similar between HIV-infected and HIV-uninfected children treated in hospital for acute pneumonia in studies in HIV-endemic settings.^{25,26,32,33,39}

Mortality

Mortality in children with pneumonia and diagnosis of tuberculosis was not consistently reported. In those studies that reported inpatient deaths in tuberculosis cases from HIV-endemic African settings, case-fatality rates ranged from 4% to 21%.^{26,31,33,37} The study of severely malnourished Bangladeshi children²⁷ followed all children until 12 weeks after discharge and reported deaths in four (four of 86 [5%] patients with tuberculosis that were discharged; note, one patient died of tuberculosis in hospital) of the patients with tuberculosis. Autopsy studies provide additional data on the contribution of tuberculosis to pneumonia-related deaths in children. This contribution ranged from 4% to 20% in children who died from respiratory disease in three settings with

very high tuberculosis incidence rates.^{28,30,34} These autopsy studies were also done at the peak of the HIV epidemic and before the rollout of preventive measures, such as co-trimoxazole preventive therapy and universal antiretroviral therapy for HIV-infected children. The selection criteria in these studies were highly variable and only one study³⁰ provided antemortem clinical data (table 2). Disseminated tuberculosis was common, as were co-infections of tuberculosis with pyogenic pneumonia in children (most were younger than 5 years of age) dying from respiratory disease. Polymicrobial infections were also noted to be common and associated with a worse outcome in one of the clinical studies,³³ with *M tuberculosis* identified in 18% of HIV-infected and 29% of HIV-uninfected infants with acute pneumonia who failed empirical first-line antibiotic therapy.

Discussion

Pneumonia is a major cause of under-5 mortality worldwide, and tuberculosis is a treatable and preventable disease in young children that most often presents as a lower respiratory tract disease. This Review provides evidence of the prevalence of tuberculosis in infants and young children admitted to hospital with predominantly acute pneumonia in a range of tuberculosis-endemic settings. The findings of this Review should, however, be interpreted with caution because of the heterogeneity of study populations and diagnostic approaches between studies, the sampling bias for diagnosis within some studies, and the acknowledged difficulties of diagnosis of tuberculosis in children. In view of the poor specificity of clinical features of tuberculosis in young children,⁴⁰ the most robust data are provided by studies that sought culture confirmation. An important finding was that 275 of 3644 (7.5%) of patients with severe pneumonia in whom respiratory specimens were collected for *M tuberculosis* culture had culture-confirmed disease (especially because culture has low diagnostic sensitivity in young children with intrathoracic tuberculosis at about 30–60%, dependent on the specific disease manifestation).^{41,42} Our findings also show that tuberculosis might be an important contributor to pneumonia-related deaths in young children because of underdiagnosis or comorbidity predisposing to bacterial co-infection.^{11,26,31,33,34}

The findings from these studies are not likely to be representative of the epidemiology of childhood pneumonia in tuberculosis-endemic areas in general. First, four of the studies were from large urban hospitals in South Africa,^{26,31–33} a country that is highly endemic for tuberculosis and HIV, with routine access to conjugated Hib and pneumococcal vaccines at the time of the studies. Second, the studies from Bangladesh and The Gambia focused on tuberculosis diagnosis in malnourished children with respiratory symptoms.^{27,35} Although the bidirectional association between tuberculosis and malnutrition is well recognised, surprisingly few data on the prevalence of tuberculosis in malnourished children

have been reported, with or without respiratory disease, and clinical diagnosis is especially challenging in this group.⁴³ Third, many of the studies were in HIV-endemic settings before the rollout of interventions that have substantially reduced HIV prevalence in young children in those settings and reduced the susceptibility to tuberculosis of children that are living with HIV. Although we noted the prevalence of tuberculosis in patients with pneumonia being similar between HIV-infected and HIV-uninfected children,^{25,26,31–33} the risk of tuberculosis was increased in HIV-infected children not receiving antiretroviral therapy.^{32,44} Finally, the two studies from Malawi relied on clinical suspicion, such as a positive contact history and poor response to antibiotics, and reported the lowest prevalence of tuberculosis of studies from the highly endemic countries.^{36,37} Relying solely on clinical criteria for the diagnosis of tuberculosis might overestimate rather than underestimate the prevalence of the disease;⁴⁵ however, this issue might not be the case in children with tuberculosis who present to hospital when they have an acute bacterial pneumonia because they might respond to antibiotics and the underlying tuberculosis might be missed, as noted in the study that followed the pneumococcal conjugate vaccine study cohort.²⁶

Case-management guidelines often advise health workers to consider the diagnosis of tuberculosis in infants and children with chronic cough. Tuberculosis is known to be common in studies of children with persistent cough in tuberculosis-endemic settings.^{46,47} However, in this Review we noted that many of the confirmed tuberculosis cases presented with acute cough.^{25–27,31–33} Furthermore, many of the study participants were infants. Although tuberculosis can directly cause severe pneumonia and disseminated disease, especially in infants, many of these children are likely to present to hospital with a bacterial pneumonia complicating underlying pulmonary tuberculosis. Many of the studies reported bacterial–tuberculosis co-infection.^{28,29,32–35} One study reported that 10% of culture-confirmed tuberculosis cases also had bacteria isolated from blood culture, despite this being a test of low sensitivity (5–15%) for bacterial pneumonia.³² Furthermore, tuberculosis cases improved with antibiotics for community-acquired pneumonia, and admission to hospital with tuberculosis was significantly less common in children who had received the pneumococcal conjugate vaccine compared with placebo.²⁶ A seasonal correlation between invasive pneumococcal disease and tuberculosis cases that is particularly pronounced in HIV-infected individuals has been reported by the same group in Johannesburg.⁴⁸ On the basis of the results from the pneumococcal conjugate vaccine-probe design and clinical response to empirical antibiotic treatment against bacterial pneumonia, the scarce evidence shows that almost half the children with culture-confirmed tuberculosis were admitted to hospital because of bacterial (and particularly pneumococcal) pneumonia.²⁶

Search strategy and selection criteria

We searched PubMed, clinical trials register, Cochrane reviews, DARE, Embase, and CINAHL for articles published in English between April 30, 1949 and May 27, 2014 with the MeSH search terms "child*", "infan*", "paediatric", "pediatric", "tuberc*", "TB", "MTb", "mycobact*" (restrict to pulmonary TB), "pneum*", "ARI" (acute respiratory tract infections), "LRTI" (lower respiratory tract infections), "mortality", "death", "morbidity", "infect*", "inciden*", "preval*". Search terms used included "tuberculosis OR mycobacter* AND pneumonia AND child OR children OR paediatric OR pediatric" and "tuberculosis [MeSH Terms] OR tuberculosis [All Fields] AND pneumonia [MeSH Terms] OR pneumonia [All Fields] AND child [MeSH Terms] OR child [All Fields] OR child* [MeSH Terms] OR child* [All Fields] OR children [All Fields] OR paediatrics [MeSH Terms] OR paediatrics [All Fields] OR paediatric [All Fields] OR paediatrics [MeSH Terms] OR pediatric [All Fields] OR pediatric [All Fields]". Additionally, we reviewed the reference lists of original studies and review papers and contacted experts in the field of child tuberculosis in an attempt to include all relevant publications.

The key information abstracted from included papers were study characteristics including year of study, country and setting, tuberculosis incidence at the time of the study, study sample size and age range, inclusion criteria, diagnostic approach, reported outcomes, and HIV prevalence in tuberculosis cases (when available).

The mortality associated with a diagnosis of tuberculosis is a concern. In view of the high prevalence of comorbidities and co-infections in these children, differentiation between children that died with underlying tuberculosis, which was complicated by concurrent or superimposed infections, from those that died directly because of tuberculosis is not possible. The autopsy studies suggest that bacterial co-infections are important causes of death in children with tuberculosis.^{28,30,34} The autopsy studies included in this Review all had large sample sizes but did not necessarily represent the full range of children dying with pneumonia, because consent for autopsy was less than 25% in the studies in Zambia and Zimbabwe,^{28,34} whereas the South African study only included HIV-infected children.³⁰ Only one study reported antemortem clinical data.³⁰ Small autopsy studies were not included in this Review, such as a study from Botswana that reported tuberculosis prevalence of 21% in children dying with respiratory disease in Francistown.⁴⁹ Additionally, an autopsy study from Bangladesh reported tuberculosis prevalence of 3% in children who died from pneumonia.⁵⁰ A review of autopsy studies of deaths due to respiratory infections in Africa reported that about 8.5% of all cases in children had pulmonary tuberculosis, which was statistically more prevalent in HIV-uninfected cases.⁵¹

This Review shows the need for improved diagnostics for tuberculosis in infants and young children, including those presenting with acute severe pneumonia. The clinical presentation and radiological features frequently overlap and even a clinical response to antibiotics does not necessarily exclude a diagnosis of tuberculosis, which might be the underlying cause predisposing to susceptibility for acute bacterial pneumonia treatment in hospital. If an infant develops tuberculosis, infection of the infant by a close contact who has tuberculosis (which might or might not have been diagnosed) is very likely, and so this information should always be carefully sought after.

The first step is for clinicians managing infants and young children with severe pneumonia in tuberculosis-endemic countries to be aware that tuberculosis might be a cause or contributor. At present, this recognition is not the case and an aim of this Review is to improve awareness. Improved diagnosis will probably depend on the future development of a point-of-care test that does not rely on sputum sampling. This test is now an important focus of research.^{52,53} Studies also need to be done in a wider range of settings than has been the case so far, such as rural-based, secondary-level care settings that include a sufficient period of follow up after discharge to appropriately manage suspected or culture-confirmed tuberculosis.

In conclusion, this Review suggests that tuberculosis is important in the pathogenesis of acute childhood pneumonia in countries with a high incidence of tuberculosis, either as a direct cause or as an underlying risk factor that increases susceptibility to bacterial pneumonia. Interpretation of findings from previous studies is restricted by recognised diagnostic challenges and substantial heterogeneity between studies with risk of bias. Prospective studies from several epidemiological settings that use optimum diagnostic techniques are needed to better understand the contribution of tuberculosis to child pneumonia and to improve clinical management.

Contributors

All authors contributed to the concept and plan for this Review. JNO and JMK did the literature review and analysis with input from BJM and SMG. JNO, BJM, and SMG developed the first draft and all authors provided major contributions to the final manuscript. JNO abstracted the data and JMK, BJM, SAM, and SMG verified accuracy. JNO and JMK independently screened the titles and abstracts of all papers identified by the search and applied the predefined study selection criteria to identify eligible studies.

Declaration of interests

SAM has received honoraria, but not linked to this work, from GlaxoSmithKline, Pfizer, Novartis, and Sanofi Pasteur. The other authors declare no competing interests.

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