Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis

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Objectives: Tuberculosis (TB) is estimated to be the leading cause of HIV-related deaths globally. However, since HIV-associated TB frequently remains unascertained, we systematically reviewed autopsy studies to determine the true burden of TB at death.

Methods: We systematically searched Medline and Embase databases (to end 2013) for literature reporting on health facility-based autopsy studies of HIV-infected adults and/or children in resource-limited settings. Using forest plots and random-effects meta-analysis, we summarized the TB prevalence found at autopsy and used meta-regression to explore variables associated with autopsy TB prevalence.

Results: We included 36 eligible studies, reporting on 3237 autopsies. Autopsy TB prevalence was extremely heterogeneous (range 0–64.4%), but was markedly higher in adults [pooled prevalence 39.7%, 95% confidence interval (CI) 32.4–47.0%] compared to children (pooled prevalence 4.5%, 95% CI 1.7–7.4%). Post-mortem TB prevalence varied by world region, with pooled estimates in adults of 63.2% (95% CI 57.7–68.7%) in South Asia ($n = 2$ studies); 43.2% (95% CI 38.0–48.3) in sub-Saharan Africa ($n = 9$ studies); and 27.1% (95% CI 16.0–38.1%) in the Americas ($n = 5$ studies). Autopsy prevalence positively correlated with contemporary estimates of national TB prevalence. TB in adults was disseminated in 87.9% (82.2–93.7%) of cases and was considered the cause of death in 91.4% (95% CI 85.8–97.0%) of TB cases. Overall, TB was the cause of death in 37.2% (95% CI 25.7–48.7%) of adult HIV/AIDS-related deaths. TB remained undiagnosed at death in 45.8% (95% CI 32.6–59.1%) of TB cases.

Conclusions: In resource-limited settings, TB accounts for approximately 40% of facility-based HIV/AIDS-related adult deaths. Almost half of this disease remains undiagnosed at the time of death. These findings highlight the critical need to improve the prevention, diagnosis and treatment of HIV-associated TB globally.

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Keywords: AIDS, autopsy, death, HIV, mortality, post mortem, prevalence, resource-limited settings, tuberculosis

Introduction

Tuberculosis (TB) is estimated to be the leading cause of HIV/AIDS-related deaths globally, with 1.1 million cases of HIV-associated TB and 360 000 deaths in 2013 [1]. It is further estimated that TB accounted for approximately 25% of all HIV/AIDS-related deaths worldwide in 2013, and that sub-Saharan Africa accounted for almost 80% of

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this burden of morbidity and mortality [1,2]. This is despite steady improvements in the implementation of comprehensive strategies to reduce the burden of HIV-associated TB [1,3], which are estimated to have saved 1.3 million lives between 2004 and 2012 [2]. However, estimates of TB disease burden and associated deaths are largely based on modelling of data originally derived from clinical records, death certificates, notification data and verbal autopsies, all of which are inaccurate [4].

Early in the HIV epidemic, autopsy studies played a key role in establishing the range and frequency of opportunistic infections and other diseases [5], and autopsy still remains the gold-standard method of ascertaining causes of death. Marked discordance between pre-mortem and post-mortem diagnoses has been observed in HIV-infected patients even in high-income settings [6]. This discrepancy is likely to be even more marked in resource-limited settings due to limitations in laboratory facilities and radiological capacity. Diagnosis of TB is particularly difficult in the context of HIV co-infection due to atypical, non-specific clinical presentation and reduced sensitivity of widely used routine diagnostic tests [7]. Autopsy studies therefore have a key role in determining the frequency of TB as a cause of death in HIV-infected patients.

Although a growing number of autopsy studies have been conducted over the past 20 years to determine causes of death in HIV-infected individuals in resource-limited settings, and narrative reviews of studies from Africa have been published [8,9], this literature has not previously been reviewed systematically and synthesized quantitatively using meta-analysis. The purpose of this systematic review and meta-analysis was to summarize prevalence of TB found in health facility-based autopsy studies of HIV-infected patients in low and middle-income settings worldwide. We further aimed to explore how prevalence varied by age (adults versus children), geographic region and contemporary estimates of both national TB and HIV prevalence and study year [the latter being used as a proxy for antiretroviral therapy (ART) scale-up]. We also sought to summarize the anatomic sites of TB disease found in these studies and the proportions of TB cases that remained undiagnosed at the time of death.

Methods

Search strategy

We searched Medline and Embase databases for autopsy studies done in HIV-infected adults and/or children in low and middle-income countries (as defined by the World Bank on 23 December 2013) and published by December 2013. The search strategy (Supplementary Table 1, http://links.lww.com/QAD/A748) was pre-specified in the review protocol. In brief, three search sets were created and then combined using 'and'; these included comprehensive search terms for autopsy, for HIV/AIDS and for TB. References of individual studies and review articles were also hand-searched, and experts in the field were consulted to suggest additional articles. In addition, abstract books from the International Union Against Tuberculosis and Lung Disease were hand-searched for a 10-year period (2004–2013), and abstracts from the International AIDS Society Conferences on HIV Pathogenesis and Treatment and International AIDS Conferences were electronically searched from 2001 to 2013. Studies identified by the searches were compiled into a database and duplicates were removed. Citations were initially screened by title and abstract to assess for potential eligibility. Full-texts of those deemed potentially eligible were then obtained and reviewed. This review was conducted with adherence to the PRISMA checklist [10]. Research Ethics Committee permission was not required as this was a secondary analysis of published anonymized data.

Study selection

Studies identified in the literature search were eligible for inclusion if they entailed at least 10 autopsies (either full or limited) of HIV-infected adults or children, if they reported the prevalence of TB amongst those autopsied and were conducted in a low or middle-income country. Studies were excluded if patients were pre-selected according to a specific clinical ante-mortem diagnosis (e.g. TB) or if they studied specific sub-populations with potentially limited generalizability (e.g. deaths among pregnant women or among mine workers). Single-organ autopsy studies were only included if this organ was the lung. If multiple reports were derived from the same study population, only the largest study was included. Authors of studies which reported on both HIV-infected and uninfected patients were contacted to provide data disaggregated by HIV status; studies for which disaggregated data were not obtained were excluded. Non-English articles were included if they had an abstract in English that provided sufficient information to meet the above inclusion criteria. Authors of studies that reported aggregated data from both adults and children or that did not specify the ages of the study participants were contacted and asked to provide appropriately stratified data.

Data extraction

Data were extracted directly into a spreadsheet that included the following variables: title, authors, year of study, year of publication, location, estimates of the prevalence of TB and of HIV in country at time of study [using WHO and Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates], study setting, study population, need for consent for autopsy; the total number of deaths potentially available for autopsy; the autopsy rate (the proportion of eligible subjects in whom an autopsy was done); the number of HIV-positive adults autopsied, number of HIV-positive children autopsied; demographics of patients; $CD4^+$ cell counts and ART status. The following were also recorded regarding the autopsy methods and findings: autopsy type and methods, post-mortem TB case definition, proportion of patients with TB found at autopsy, proportion of patients in whom TB was identified as the primary cause of death, organs involved with TB at autopsy and correlation of clinical and autopsy diagnoses.

The primary outcome was the prevalence of TB at autopsy. Other outcomes of interest included the anatomical site of TB disease, and the proportion of autopsy-confirmed TB cases that were undiagnosed pre mortem. Study quality was assessed using a pre-specified, graded checklist (Supplementary Table 2, http://links.lww.com/QAD/A748); studies were considered to be of 'good quality' if they scored at least 70% of points; 'medium quality' if they scored 40–69%; and 'lower quality' if they scored below 40%.

Analyses

Forest plots displaying the prevalence of TB at post mortem were generated for all included studies and then for studies stratified by age and geographical region. Pooled estimates were obtained using a random-effects model, and heterogeneity of outcomes was assessed through calculation of I-squared statistics for each of the groups of studies. A fixed continuity correction was used for studies which had 0 or 100% outcomes. When meta-analysis was not appropriate to use, summary measures were calculated instead as medians and ranges. Scatter plots and meta-regression were used to examine the relationships between the post-mortem TB prevalence found in each study and the estimated national TB prevalence and national HIV prevalence at the time the study was conducted, along with the year at the midpoint of the study (the latter serving as a proxy for ART scale-up). All analyses were done using Stata 13.0 (StataCorp, College Station, Texas, USA).

Results

Characteristics of studies included

A total of 36 studies (reported in 32 papers and four conference abstracts) were included (Fig. 1). Of these, 16 reported on adult patients only, others reported on children only ($n = 10$) and the remainder either reported on both adults and children or on patients of unspecified age ($n = 10$) (Table 1). Among the latter, disaggregated data were provided by the authors of one of these studies; however, since only six of 46 patients were children, only the adult data were included in these analyses [11]. This review includes data from a total of 3237 autopsies. Of these, 1562 autopsies were of adults, 704 were of children, and a further 971 autopsies were of patients whose age remained unclassified.

Of the 36 studies included, 20 were done in sub-Saharan Africa, eight in the Americas, four in East Asia and four in South Asia (Table 1). The population prevalence of TB at the time of the studies ranged between 87 and 851 cases per 100 000 population, and HIV prevalence ranged from 0.1 to 26.8% (Table 1). Autopsies were primarily done in patients who died as hospital in-patients (29 studies); a small proportion of studies included some community-based deaths ($n = 2$) [12,13], but this variable was unspecified in five studies.

Consent (from families or patients prior to death) was required for autopsy in 18 of 36 (50%) of the included studies. The total number of deaths considered for possible autopsy was stated in 15 studies, allowing the autopsy rate to be calculated (median 28.8%; range 4–97.5%). The mean/median age of patients autopsied was specified in 22 studies, ranging from 31.3 to 40 years in adults and from 3 months to 5.9 years in children. Only five studies reported the $CD4^+$ cell counts of patients, with the mean/median ranging from 50 to 87 cells/μl. In each of four studies [14–17], a proportion of patients was receiving ART at the time of death (range 17–100%).

Autopsy methods were specified in 32 studies (Table 1); 13 did full autopsies, including the brain; eight others did full autopsies, but did not specify whether the brain was examined; another study did full autopsies, but excluded the brain and 10 studies performed limited autopsies. The method of confirming TB at autopsy was specified in 29 studies. TB diagnosis in 26 of these studies was based on histopathological appearances and staining for acid-fast bacilli (AFB) (six of these studies additionally used TB culture and/or TB PCRtesting); 2 studies made TB diagnoses using case conference reviews of the clinical history, autopsy and microbiology data [14,17]; 1 study used AFB microscopy and culture only [16]. The median number of autopsies in each study was 62 (range 16–250). A total of 11 studies were assessed as being of good quality, 15 of medium quality and 10 of lower quality (Table 1).

Prevalence of tuberculosis at autopsy

The prevalence of TB in HIV-infected patients at autopsy was extremely heterogeneous, ranging from 0 to 64.4% (median 27.7%) (Fig. 2a). A stratified plot shows that TB prevalence was strongly associated with age category (Fig. 2b). We used meta-analysis to generate pooled summary prevalence estimates for adults [39.7%, 95% confidence interval (CI) 32.4–47.0%] and for children in whom pooled prevalence was much lower (4.5%, 95% CI 1.7–7.4%). Of note, the pooled summary proportion of TB cases among adults who remained undiagnosed pre mortem was 45.8% [95% CI 32.6–59.1%).

Among studies reporting on adults, the prevalence of TB at autopsy varied markedly by geographic region. The pooled prevalence was 63.2% (95% CI 57.7–68.7%)

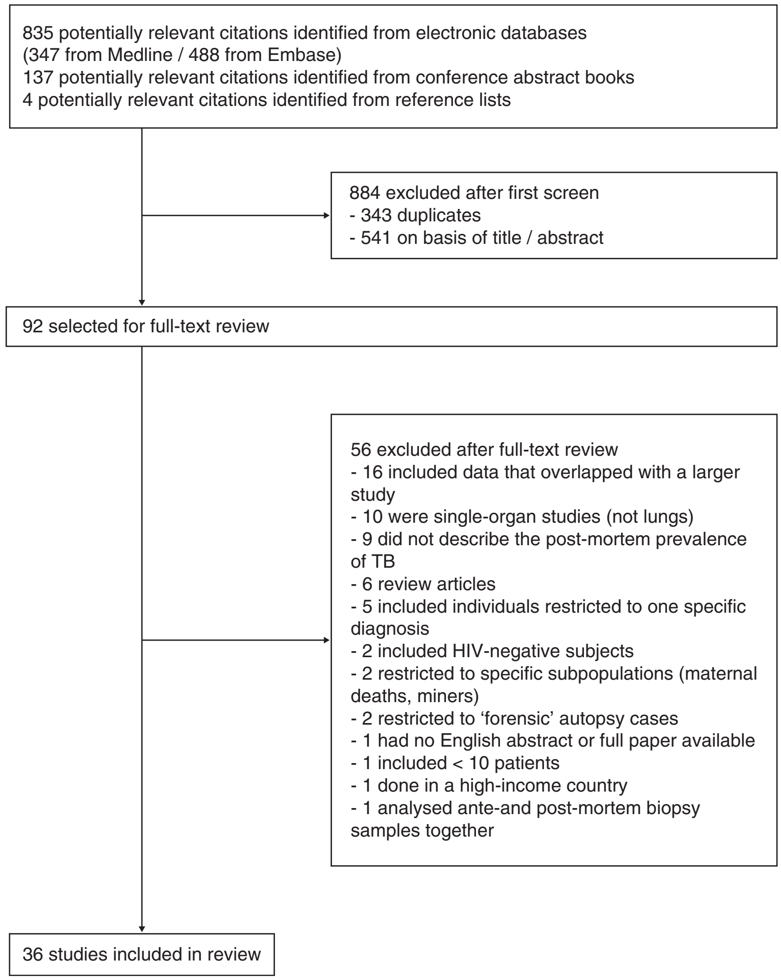

Fig. 1. Flow diagram showing study selection process and reasons for exclusions.

for studies in South Asia ($n = 2$); 43.2% (95% CI 38.0–48.3%) in studies in sub-Saharan Africa ($n = 9$), 27.1% (95% CI 16.0–38.1%) in studies in the Americas ($n = 5$) and 12.5% in a single study from East Asia (Fig. 2c). Among studies of children, just two reported a TB prevalence that exceeded 10% (11 and 18%), and both of these were from the southern African region [18,19].

Meta-regression analyses

Using meta-regression analysis, higher prevalence of TB at autopsy was found to be positively associated with a greater national population TB prevalence estimate at the time of the study (Fig. 3a). In crude analysis, an increase in national TB prevalence of 200 per 100 000 was associated with a 6.5% (95% CI 0.3–12.7%, $P = 0.04$) increase in post-mortem TB prevalence. Similarly, autopsy TB prevalence tended to be higher in studies done in countries with higher HIV prevalence, but this relationship did not reach statistical significance (Fig. 3b). In studies done in sub-Saharan Africa in adults, autopsy TB prevalence tended to increase over the 20-year period between 1992 and 2012 (Fig. 3c), with an approximately 5% greater post-mortem prevalence for an increase in each 10-year period (5.6%, 95% CI 0.0–11.3%, $P = 0.05$). Studies with higher-quality assessment scores also tended to report higher autopsy TB prevalence (Fig. 3d), with a 4.7% greater TB prevalence for every 4 points higher score, but this relationship did not reach statistical significance ($P = 0.37$).

Sensitivity analysis for potential selection bias in autopsy studies

Bias in autopsy studies during selection of individuals for study inclusion could potentially have enriched the proportion with TB. We examined studies from Africa ($n = 4$) in which the medical in-patients studied were considered to be at very low risk of selection bias. Among these, the pooled post-mortem prevalence of TB was 48.1% (95% CI 39.1–57.1%) [14,16,20,21], which did not differ from the pooled summary estimate of 43.2% (95% CI 38.0–48.3) for all studies of adults in Africa ($n = 9$).

Tuberculosis dissemination

A total of 12 studies (Table 2) described the proportion of adult TB cases in which disease was disseminated (pooled

Table 1. Characteristics of studies included in the systematic review.

Authors	Setting (study dates)	Setting prevalence of HIV and TB at time of study: HIV (%)	TB (per 100 000)	Study population and selection for autopsy	Autopsy rate	Adults or children?	Mean/median age (range)	Autopsy type	Post-mortem TB diagnostic methods	Quality assessment score (/10)	Notes
Studies in adults											
Abouya *et al.* (1992) [22]	Abidjan, Ivory Coast, Africa (1989)	3.4	394	Consecutive deaths on pulmonary ward	75%	Adults	NS	NS ('lungs + extrapulmonary')	Histopathology + AFB stain	6.5	Pulmonary ward patients
Amarapurkar and Sangle (2005) [23]	Mumbai, India, South Asia (1991-2003)	0.3	459	Hospital in-patients - selection for autopsy unclear	NS	Adults	32.1 (19–35)	Full (brain not specified)	Gross organ examination. Histopathology and AFB stain (liver only)	2.5	Focus on liver histology
Ansari *et al.* (2002) [24]	Francistown, Botswana, Africa (1997–1998)	24.5	851	Medical in-patient deaths, including dead on arrival patients.	18.4%	Adults	35 (14–87)	Full including brain	Histopathology + AFB stain	8.5	Emphasis on those without a diagnosis, those with unexpected deterioration, those with pulmonary disease, and suspected PCP
Borges *et al.* (1997) [25]	Uberlandia, Brazil, Americas (1989–1996)	NS	123	Medical in-patient deaths – selection for autopsy unclear	NS	Adults	32.5 (15–54)	Full (brain not specified); partial in 7 cases	Histopathology + AFB stain	4.5	
Cohen *et al.* (2010) [16]	KwaZulu-Natal, South Africa, Africa (2008–2009)	18.9	761	Consecutive, unselected in-patient deaths	24.1%	Adults	33 (20–45)	Limited – lungs, liver, spleen using saline lavage and needle biopsies	Microscopy, liquid culture	8.5	94% were HIV-positive; disaggregated data obtained. 17/110 TB cases were multidrug-resistant.
Cox *et al.* (2012) [15]	Kampala, Uganda, Africa (2009)	6.8	222	Consecutive deaths on infectious disease/ gastroenterology ward	NS	Adults	38	Full including brain	Histopathology + AFB stain	6	
Cury *et al.* (2003) [26]	Sao Paulo, Brazil, Americas (1993–2000)		98	Hospital in-patients – selection for autopsy unclear	NS	Adults	34.8 (19–68)	Full (brain not specified)	Histopathology + AFB stain	3.5	Describes 'mycobacteriosis' rather than TB specifically
Eza *et al.* (2006) [27]	Lima, Peru, Americas (1999–2004)	0.5	253	In-patient deaths – selection bias for autopsy of those with unclear cause of death	NS	Adults	33.5 (19–62)	Full including brain in 12, excluding brain in 4	Histopathology + AFB stain	6	3 other cases had 'possible' TB. Only 1.4% of HIV-infected deaths had autopsies
Hsiao *et al.* (1997) [28]	Taiwan, East Asia (1986–1996)		165	Medical in-patient deaths – selection for autopsy unclear	5.1%	Adults	40 (25–52)	Full including brain	Histopathology + AFB stain	7	Small sample of deaths autopsied
Jessurun *et al.* (1990) [29]	Mexico City, Mexico, Americas (-1988)	0.1	145	Consecutive, unselected in-patient deaths	81.7%	Adults	31.3	Full including brain	Histopathology + AFB stain	10	Included in preference to larger Mohar *et al.*'s [30] study, which included children with no disaggregation
Lanjewar (2011) [31]	Mumbai, India, South Asia (1988–2007)	0.3	459	Medical in-patient deaths – selection for autopsy unclear	NS	Adults	NS (>18)	Full including brain	Histopathology + AFB stain	6	Nonreactive histological pattern noted
Lucas *et al.* (1993) [20]	Abidjan, Ivory Coast, Africa (1991)	3.9	435	Consecutive, unselected in-patient and community deaths	24.2%	Adults	NS (>14)	Full including brain	Histopathology + AFB stain (culture in subset)	9.5	Selection bias towards HIV-2. Nonreactive, multi-bacillary pattern noted. Unselected medical inpatient deaths ($n=247$) included only

Table 1 (*continued*)

Authors	Setting (study dates)	Setting prevalence of HIV and TB at time of study: HIV (%)	TB (per 100 000)	Study population and selection for autopsy	Autopsy rate	Adults or children?	Mean/median age (range)	Autopsy type	Post-mortem TB diagnostic methods	Quality assessment score (/10)	Notes
Marques *et al.* (1996) [11]	Rio, Brazil, Americas (years NS)		98	Medical in-patient deaths – selection for autopsy unclear	NS	Adults	28.9 (9–49)	NS	Histopathology + AFB stain	4.5	Focus on renal disease. Study included adults and children; disaggregated data obtained
Nelson *et al.* (1993) [32]	Kinshasha, Zaire, Africa (1988–1991)	4.4	323	Medical in-patient deaths with AIDS on death certificate and unknown cause of death	NS	Adults	34.4 (16–59)	Full excluding brain (brain done in 2)	NS	5	Only individuals with AIDS on death certificate or on chart with sufficient information to apply WHO AIDS criteria included. <10% acceptance noted
Rana *et al.* (2000) [21]	Nairobi, Kenya, Africa (1996–1997)	10.8	198	Consecutive, unselected in-patient deaths	48.4%	Adults	33	Full including brain	Histopathology + AFB stain + culture	8.5	Non-reactive, multi-bacillary histopathology noted
Siika *et al.* (2012) [17]	Eldoret, Kenya, Africa (2012)	6.1	299	Patient receiving ART – selection for autopsy unclear	NS	Adults	40 (>14)	Full (brain not specified)	Conference review	2.5	Presented proportion of cases with TB as cause of death only
Wong *et al.* (2012) [14]	Johannesburg, South Africa, Africa (2009)	18.9	795	Consecutive, unselected in-patients receiving ART or eligible for ART	NS	Adults	36 (>18)	Limited – lungs, liver, spleen, kidney, bone marrow, lymph nodes, skin, CSF using ultrasound-guided needle biopsies	Conference review	7	
Studies in children											
Ansari *et al.* (2003) [19]	Francistown, Botswana, Africa (1997–1998)	24.5	851	Consecutive, unselected paediatric inpatient deaths	27.8%	Children	7 months (1 month - 13 years)	Full including brain	Histopathology + AFB stain + culture	9.5	
Bhoopat *et al.* (1994) [33]	Chiang Mai, Thailand, East Asia (years NS)	2.1	216	Paediatric in-patients - selection for autopsy unclear	NS	Children	NS	Lungs only	Histopathology + AFB stain	3	
Chakraborty *et al.* (2002) [13]	Nairobi, Kenya, Africa (1997–2000)	10.4	225	Orphanage deaths – selection for autopsy unclear	NS	Children	5.9 (7 months–13 years)	Full including brain	Histopathology + AFB stain + culture	6	
Chintu *et al.* (2012) [18]	Lusaka, Zambia, Africa (1997–2000)	14.7	555	Consecutive paediatric deaths dying from respiratory disease	16.5%	Children	NS	Limited – chest cavity including lungs and lymph nodes only	Histopathology + AFB stain	5.5	
Drut *et al.* (1997) [34]	Argentina, Brazil, Mexico, Americas (1992–1994)	0.1	100	Deaths from multiple South-American sites – selection for autopsy unclear	NS	Children	2.7 (0–16)	Full (brain not specified)	NS	2.5	
Ikeogu *et al.* (1997) [12]	Bulawayo, Zimbabwe, Africa (1992–1993)	18.6	297	Community paediatric deaths (death on, or shortly after, arrival in hospital). Selection for autopsy unclear	55%	Children	10.4 months (1 month–5 years)	Limited – lung needle aspirates and blood	Histopathology + AFB stain	5	May have included pre-mortem TB diagnoses (gastric washings)
Jeena *et al.* (1996) [35]	Durban, South Africa, Africa (1993–1994)	2	461	Consecutive paediatric ICU deaths	95.8%	Children	4.3 months (1–18 months)	Limited – lung and liver needle biopsies	Histopathology + AFB stain	7	Young population with severe respiratory disease

Lucas *et al.* (1996) [36]	Abidjan, Ivory Coast, Africa (1991–1992)	3.9	435	Mortuary based – consecutive, unselected paediatric deaths	97.5%	Children	18 months (1 month–12 years)	Full including brain	NS	8	Mortuary-based
Nathoo *et al.* (2001) [37]	Harare, Zimbabwe, Africa (1995)	26.8	295	Consecutive paediatric pneumonia in-patient deaths	4%	Children	3 months	Limited – lung needle biopsies only	Histopathology + AFB stain + TB PCR	5	67% had evidence of PCP
Rennert *et al.* (2002) [38]	Soweto, South Africa, Africa (1998–1999)	11.3	443	Consecutive paediatric in-patient deaths with lung disease	85.30%	Children	10.5 (1.5–69.8 months)	Limited – lung and liver needle biopsies	Histopathology + AFB stain + liquid culture + TB PCR	7	
Studies in adults and children or with unclear age range											
Ayisi *et al.* (1997) [39]	Ghana, Africa (1995)	1.8	301	Unclear	NS	Unclear	NS	Full including brain	NS	3	
Carrilho *et al.* (2012) [40]	Maputo, Mozambique, Africa (2010)	11.2	541	Medical in-patient deaths – selection for autopsy unclear	28.8%	Both	NS (1 month–72 years)	Full (brain not specified)	NS	5	Abstract only; only 2% of patients were children. Presented proportion of cases with TB as cause of death only
Deshmukh *et al.* (2003) [41]	Pune, India, South Asia (1993–2002)	0.3	459	Unclear	NS	Unclear	NS	Full (brain not specified)	NS	1.5	Conference abstract only
Garcia-Jordan *et al.* (2010) [42]	Eastern Cape, South Africa, Africa (2000–2008)	18.3	736	Medical in-patient deaths – selection for autopsy unclear	NS	Both	NS	Full including brain	Histopathology + AFB stain	5	12% of patients <1 years
Liu and Lin (1996) [43]	China, East Asia (years NS)		186	Unclear	NS	Unclear	NS	NS	Histopathology + AFB stain	1	Abstract only (full text Chinese)
Satyanarayana *et al.* (2003) [44]	Delhi, India, South Asia (1998–1999)	0.3	454	Unclear	NS	Unclear	NS	Limited – needle biopsies and aspirations of lungs, heart, liver, spleen, abdomen, lymph nodes, kidneys, testes, CSF, brain	Histopathology, AFB stain, solid culture	4	No lung samples in 32/44 cases
Soeiro *et al.* (2008) [45]	Sao Paulo, Brazil, Americas (1990–2000)		103	Deaths from acute respiratory failure; selection for autopsy unclear	NS	Unclear	36	Full (brain not specified)	Histopathology, AFB stain, solid culture	3.5	
Souza *et al.* (2008) [46]	Manaus, Brazil, Americas (1996–2003)		87	Unclear	NS	Unclear	NS	NS	NS	0	Full text Portuguese - abstract only included. Presented proportion of cases with TB as cause of death only
Viriyavejakul *et al.* (2002) [47]	Bangkok, Thailand, East Asia (years NS)	1.7	280	Medical in-patient deaths – selection for autopsy unclear	NS	Unclear	NS	Limited – needle biopsies of variable organs in each patient (≥2 in each)	Histopathology	4	Variable organs sampled

AFB, acid-fast bacilli; ART, antiretroviral therapy; CSF, cerebrospinal fluid; NS, not specified; PCP, pneumocystic jiroveci pneumonia.

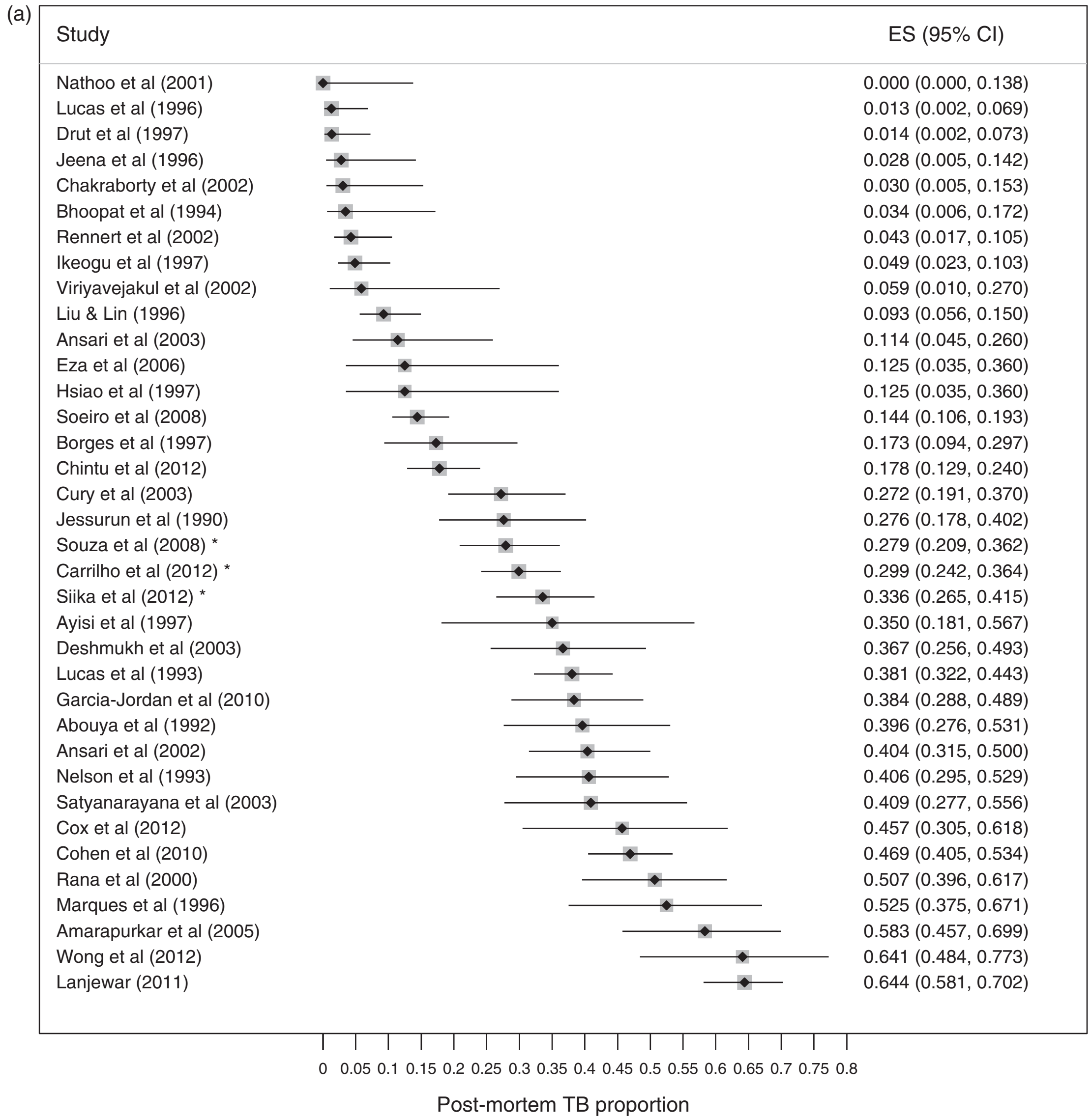

Fig. 2a. Forest plots showing post-mortem prevalence [% (95% CI)] of tuberculosis (TB) in the following as given in the legend. Fig. 2(a). All studies included in the review ordered by prevalence ($n = 36$ studies; 3237 autopsies included).
(b) All studies stratified by age category of patients: adults/children/mixed or unspecified (n 36 studies; 3237 autopsies included).
(c) Studies of adults only, stratified by world region: Africa/South Asia / East Asia / Americas ($n = 17$ studies; 1562 autopsies included). Pooled summary estimates generated by using a random-effects meta-analysis are shown for each of the three age classifications ('adults', 'children' and 'mixed or unspecified') and for each of the four geographic regions (Africa, South Asia, East Asia and the Americas). CI, confidence interval. (*) Studies that presented the proportion of patients in which TB was regarded as the primary cause of death at autopsy.

summary proportion 87.9%, 95% CI 82.2–93.7%), but specific details of which organs were involved was inconsistently reported (Table 2). The organs most frequently involved were the lungs (median 85% of TB cases; range 56–98%; $n = 4$ studies), spleen (median 83% of TB cases; range 81–84%; $n = 5$ studies), liver (median 79% of TB cases; range 69–88%; $n = 5$ studies), and lymph nodes (median 75% of TB cases; range 56-86%; $n = 4$ studies). The central nervous system was less frequently involved with a median of 20% of TB cases (range 10–25%; $n = 5$ studies).

Tuberculosis as primary cause of death

A total of 12 studies overall described 'both' the prevalence of TB at autopsy and the proportion of patients in whom TB was the primary cause of death (Table 2). Among 10 studies of adults, TB was the primary cause of death in a pooled proportion of 91.4% (95% CI 85.8–97.0%) of cases where it was present. The overall proportion of HIV-related deaths for which TB was identified as the primary cause of death was reported by 10 studies done in adults (pooled summary proportion 37.2%, 95% CI 25.7–48.7%).

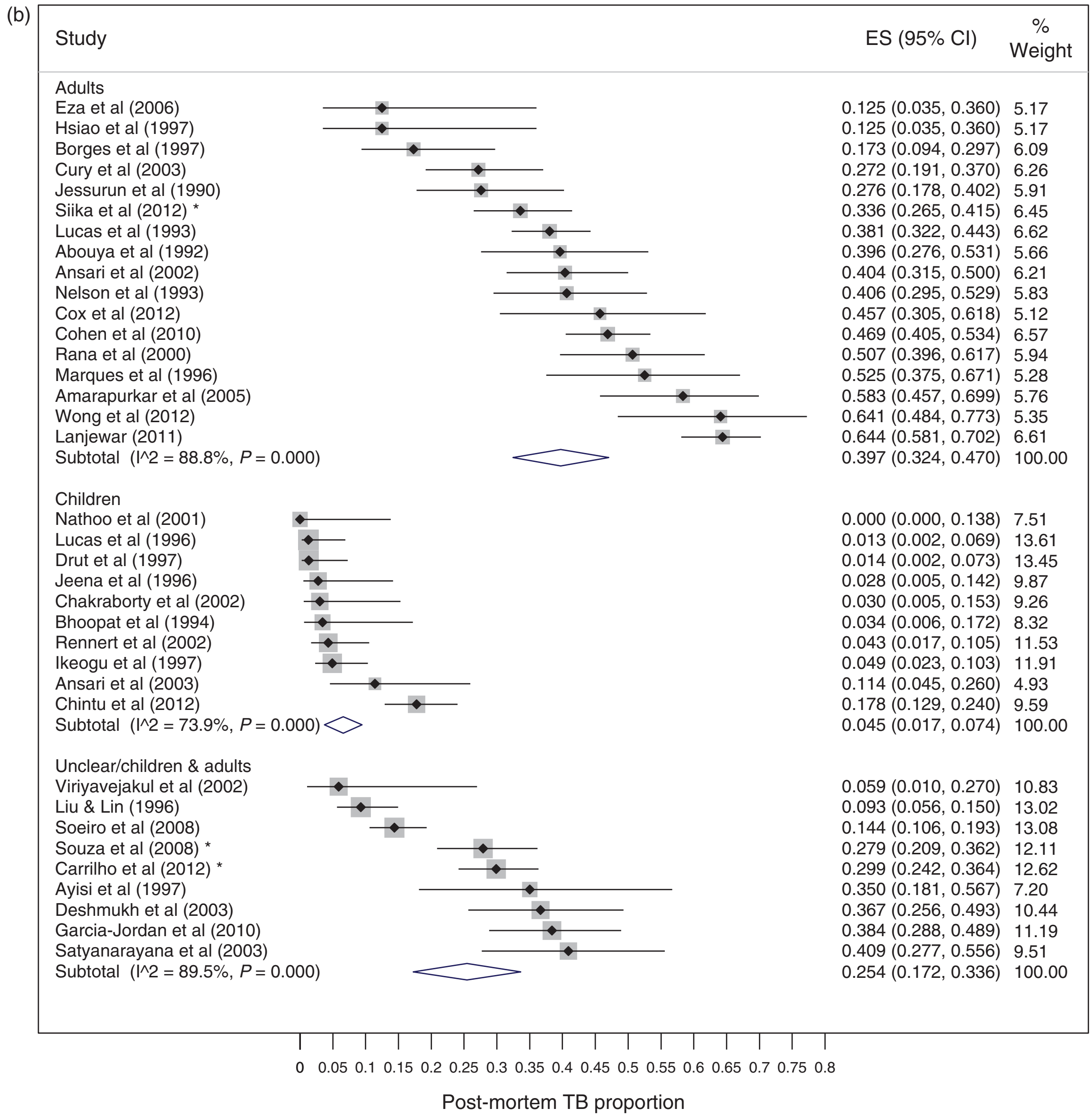

Fig. 2b. (*Continued*).

Discussion

This is the first systematic literature review and meta-analysis of the burden of TB diagnosed by autopsy studies of HIV-infected adults and children in resource-limited settings worldwide. The overall prevalence of TB in adults and children was huge and accounted for almost 40% of HIV-related facility-based deaths in adults. This is greater than the WHO/UNAIDS estimate that overall TB accounts for approximately 25% of HIV/AIDS-related deaths worldwide. In the present review, TB was regarded as the primary cause of death in 91.4% (85.8–97.0%) of cadavers in which it was present. Thus, consistent with other data [48], these autopsy studies strongly indicate that TB was directly contributing to mortality in HIV-infected patients, rather than simply being present as a marker of advanced immunodeficiency, like oral candidiasis. The prevalence among adults was particularly high in South Asia and Africa, where approximately 63 and 43% of adults had evidence of TB at autopsy, respectively. A pooled proportion of 45.8% (32.6–59.1%) of confirmed TB cases identified at autopsy remained undiagnosed at the time of death. These findings highlight the critical need for improvements in the prevention, diagnosis and management of HIV-associated TB.

Our findings were drawn from a large number of studies from around the world, contributing data on a total of 3237 autopsies of adults and children. Although TB prevalence at autopsy varied substantially between the 36 studies, we showed that age group (adults versus children)

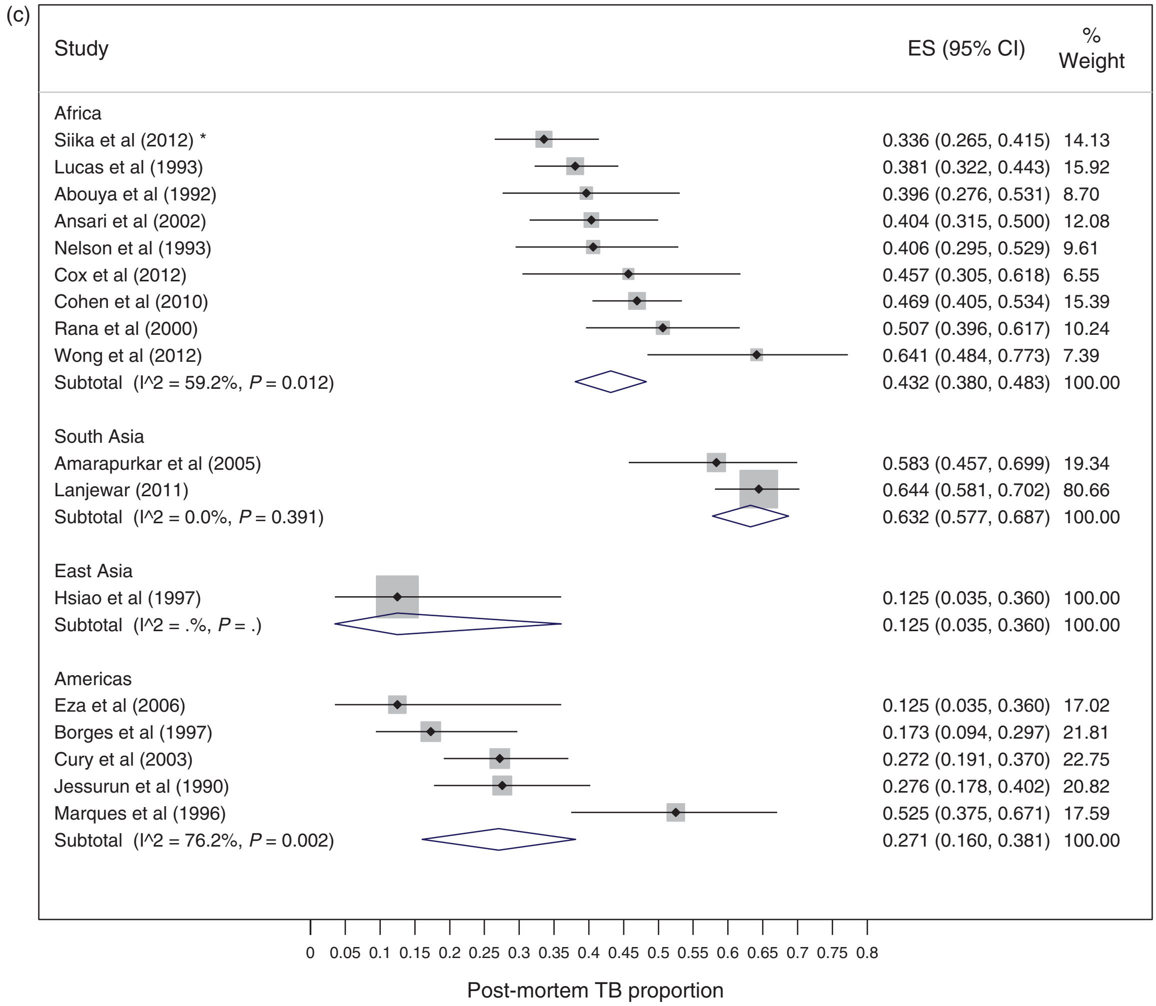

Fig. 2c. (*Continued*).

and geographic region were strongly associated factors. Other sources of heterogeneity potentially include the variable size of the studies, with the number of autopsies done ranging between 16 and 250. Different methods and case definitions were used to diagnose TB. In addition, although the vast majority of autopsy studies done were of hospital in-patients, a minority were of community-based deaths. Although the prevalence of TB among adult deaths in South Asia was extremely high, there were only two studies from this region and both were from the city of Mumbai, and therefore may not be representative of the rest of the Indian sub-continent. In contrast, far more data were available for sub-Saharan Africa, with multiple studies from countries located across west, east and southern Africa.

In only a minority of the 36 studies was it explicitly clear that consecutive, unselected HIV-infected in-patient deaths were studied. Moreover, in some studies, the autopsy rate was low. Thus, it is unclear to what extent the data included are truly representative of deaths in HIV-infected adults and children. Patient selection for autopsy might potentially enrich the proportion with TB in those studied. However, in a sensitivity analysis of studies ($n = 4$) conducted in Africa in which recruitment was considered to be at very low risk of selection bias, the pooled TB prevalence was actually higher (48.1%, [95% CI 39.1–57.1%) than that of all studies from the region. Thus, we found no evidence that might suggest that prevalence rates were high due to selection bias. Since embarking on this review and meta-analysis, one further post-mortem study from a tertiary referral hospital in Zambia has been published [49]. The data in this additional study are entirely consistent with the findings of this systematic review, and its inclusion would not have altered any of the summary estimates in our meta-analysis.

In the vast majority of HIV-TB cases in adults [pooled summary estimate 87.9% (82.2–93.7%) of TB cases), disease was disseminated, with the lungs, spleen, liver and lymph nodes being the most commonly involved organs at autopsy. This highlights the widespread extent of TB disease in patients with advanced HIV-related immuno-deficiency and suggests that microbiological diagnosis

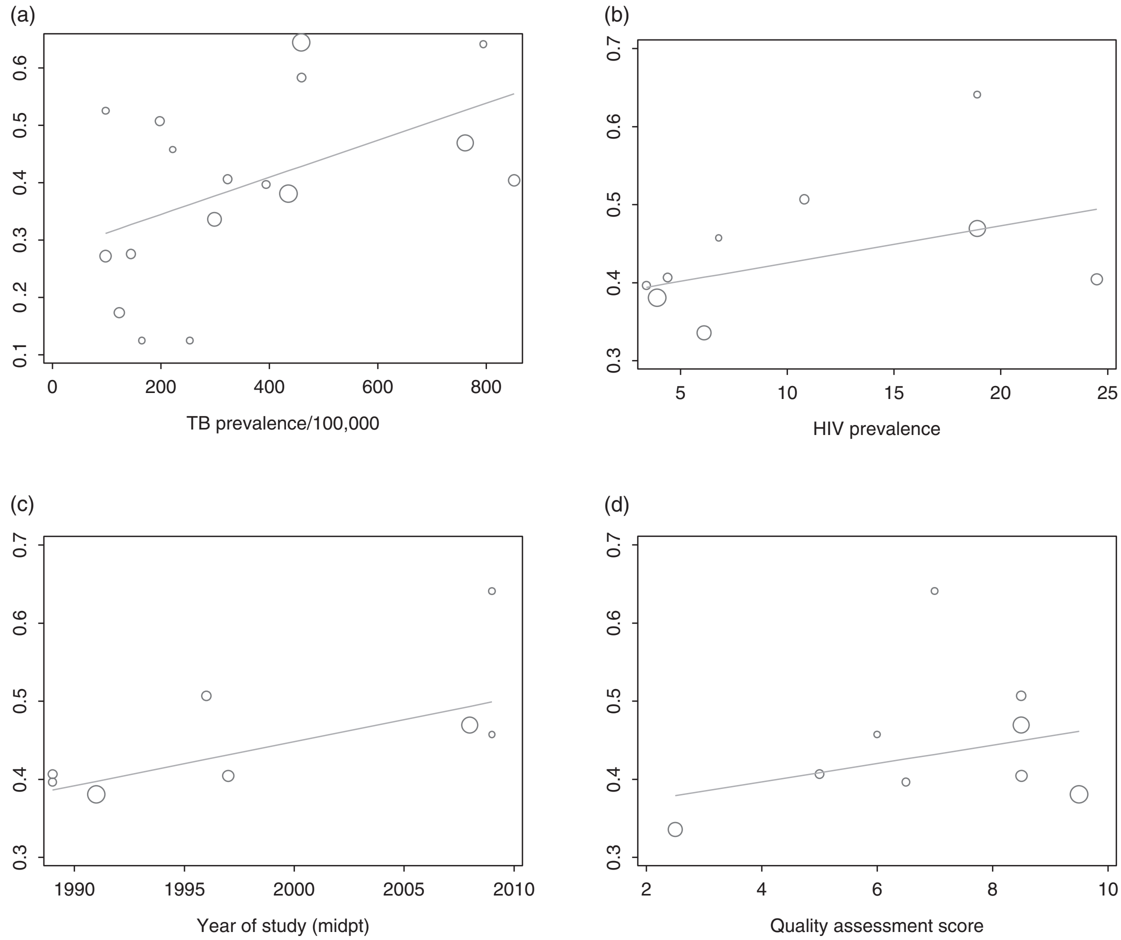

Fig. 3. Meta-regression analyses showing graphs of post-mortem prevalence of tuberculosis (Y-axis) plotted against the following. (a) The study mid-point national population tuberculosis prevalence estimate (X-axis) in autopsy studies of adults only ($n = 17$); and (b) the study mid-point national HIV prevalence; (c) year of the study mid-point (X-axis) for studies of adults in sub-Saharan Africa ($n = 9$); (d) quality assessment score (X-axis) for studies of adults in sub-Saharan Africa ($n = 9$).

need not rest solely on examination of respiratory samples. Almost one half [pooled proportion 45.8% (32.6−59.1%)] of confirmed TB cases identified at autopsy remained undiagnosed at the time of death, highlighting current critical limitations in approaches to TB diagnosis. The presentation of HIV-associated TB is often atypical or it may remain sub-clinical. This is compounded by the fact that sputum-based diagnosis is less sensitive in patients with HIV co-infection. This has lead to the development of management algorithms for suspected smear-negative TB [50] and research exploring strategies of systematically starting empirical TB treatment for those with advanced HIV who are at greatest risk of disease [51], such as the ACTG REMEMBER Trial (NCT01380080).

Much progress, however, has been made in recent years in the development of novel diagnostic tools for TB. The Xpert MTB/RIF assay (Cepheid, Sunnyvale, California, USA) is a semi-automated nucleic acid amplification test that can detect *Mycobacterium tuberculosis* and the presence of mutations conferring rifampicin resistance in less than 2 h [52]. It was endorsed by the WHO in 2010 as the initial diagnostic test for suspected HIV-associated pulmonary TB and for multidrug-resistant pulmonary TB in adults [53]. With a growing evidence base [54,55], this guidance has since been extended to include investigation of children and also the testing of non-respiratory samples to diagnose extra-pulmonary forms of TB [56]. The Xpert MTB/RIF assay provides a substantially higher sensitivity than sputum smear microscopy for TB diagnosis during active screening of patients with advanced HIV-associated immunodeficiency [57] and can also be used to screen non-respiratory samples, such as urine, from these patients [58].

Lipoarabinomannan (LAM) is a mycobacterial cell wall antigen for which a low-cost, point-of-care, lateral-flow assay has been developed (Determine TB-LAM Ag; Alere Inc. Waltham, Massachusetts, USA), allowing rapid TB diagnosis to be made from urine samples [59]. Although limited, sensitivity is highest in those with the most

Table 2. Prevalence and characteristics of post-mortem tuberculosis cases in included studies.

Authors	Autopsies	TB	Disseminated	Organs involved in TB cases	TB cases undiagnosed ante mortem	TB cases where TB regarded cause of death
Studies in adults						
Abouya *et al.* (1992) [22]	53	21 (39.6%)	19/21 (90%)			21/21 (100%)
Amarapurkar *et al.* (2005) [23]	60	35 (58.3%)	18/35 (51%)		23/35 (66%)	35/35 (100%)
Ansari *et al.* (2002) [24]	104	42 (40.4%)	37/42 (88%)	Lungs 41/42 (98%); spleen 35/42 (83%); liver 34/42 (81%); lymph nodes 34/42 (81%); kidney 22/42 (52%); gastrointestinal 18/42 (43%); bone marrow 10/42 (24%); central nervous system 4/42 (10%)	5/37 (14%)	38/42 (90%)
Borges *et al.* (1997) [25]	52	9 (17.3%)			6/9 (67%)	
Cohen *et al.* (2010) [16]	226	106 (46.9%)			46/110 (42%)[a]	
Cox *et al.* (2012) [15]	35	16 (45.7%)	16/16 (100%)	Spleen 13/16 (81%); liver 11/16 (69%); lymph nodes 11/16 (69%); lungs 9/16 (56%)	5/16 (31%)	13/16 (81%)
Cury *et al.* (2003) [26]	92	25 (27.2%)	17/25 (68%)			
Eza *et al.* (2006) [27]	16	2 (12.5%)	2/2 (100%)	Liver 2/2 (100%); oesophagus 2/2 (100%); lymph nodes 2/2 (100%); lungs 2/2 (100%); kidney 1/2 (50%); spleen 1/2 (50%); adrenal 1/2 (50%); thyroid 1/2 (50%); genitourinary 1/2 (50%)	1/2 (50%)	2/2 (100%)
Hsiao *et al.* (1997) [28]	16	2 (12.5%)			2/2 (100%)	1/2 (50%)
Jessurun *et al.* (1990) [29]	58	16 (27.6%)				
Lanjewar (2011) [31]	236	152 (64.4%)	143/152 (94%)	Lymph nodes 131/152 (86%); spleen 127/152 (84%); liver 118/152 (78%); kidney 87/152 (57%); central nervous system 29/152 (19%)		149/152 (98%)
Lucas *et al.* (1993) [20]	247	94 (38.1%)	84/94 (89%)	Lungs 88/94 (94%); central nervous system 19/94 (20%); gastrointestinal19/94 (20%)		80/94 (85%)
Marques *et al.* (1996) [11]	40	21 (52.5%)	16/21 (76%)	Kidney 11/21 (52%); lymph nodes 3/25 (12%)		
Nelson *et al.* (1993) [32]	64	26 (40.6%)	26/26 (100%)		13/26 (50%)	
Rana *et al.* (2000) [21]	75	38 (50.7%)	31/38 (82%)	Spleen 31/38 (82%); liver 30/38 (79%); kidney 16/38 (42%); gastrointestinal 11/38 (29%); central nervous system 9/38 (24%)	17/37 (46%)	35/38 (92%)
Siika *et al.* (2012) [17]	149	50 (33.6%)[a]				
Wong *et al.* (2012) [14]	39	25 (64.1%)	24/25 (96%)	Liver 22/25 (88%); spleen 21/25 (84%); lungs 19/25 (76%); lymph nodes 14/25 (56%); central nervous system 5/25 (25%); renal 11/25 (44%); bone marrow 16/25 (64%); pleura 3/25 (12%)	8/25 (32%)	14/25 (56%)
Studies in children						
Ansari *et al.* (2003) [19]	35	4 (11.4%)	4/4 (100%)	Lymph nodes 3/4 (75%); spleen 3/4 (75%); genitourinary 2/4 (50%), gastrointestinal 1/4 (25%)		4/4 (100%)
Bhoopat *et al.* (1994) [33]	29	1 (3.4%)	0/1 (0%)			
Chakraborty *et al.* (2002) [13]	33	1 (3.0%)	1/1 (100%)		0/1 (0%)	1/1 (100%)
Chintu *et al.* (2012) [18]	180	32 (17.8%)	10/54 (19%)			
Drut *et al.* (1997) [34]	74	1 (1.4%)				

Ikeogu *et al.* (1997) [12]	122	6 (4.9%)	4/6 (67%)		
Jeena *et al.* (1996) [35]	36	1 (2.8%)	0/1 (0%)		
Lucas *et al.* (1996) [36]	78	1 (1.3%)	1/1 (100%)		0/1 (0%)
Nathoo *et al.* (2001) [37]	24	0 (0%)			
Rennert *et al.* (2002) [38]	93	4 (4.3%)	2/4 (50%)		2/4 (50%)
Studies in adults and children or with unclear age range					
Ayisi *et al.* (1997) [39]	20	7 (35.0%)	7/7 (100%)	Gastrointestinal 1/7 (14%); central nervous system 1/7 (14%)	
Carrilho *et al.* (2012) [40][b]	214	64 (30.0%)[a]	51/64 (80%)		
Deshmukh *et al.* (2003) [41]	60	22 (36.7%)	14/22 (64%)	Lungs 18/22 (82%)	
Garcia-Jordan *et al.* (2010) [42]	86	33 (38.4%)	15/33 (45%)	Meningitis 3/33 (9%); pericarditis 1/33 (3%); abdominal 1/33 (33%); tuberculoma 1/33 (33%)	
Liu and Lin (1996) [43]	151	14 (9.3%)	NS	Lungs 10/14 (71%); lymph nodes 8/14 (57%)	
Satyanarayana *et al.* (2003) [44]	44	18 (40.9%)	18/18 (100%)		
Soeiro *et al.* (2008) [45]	250	36 (14.4%)	19/36 (53%)		
Souza *et al.* (2008) [46][b]	129	36 (28.0%)			
Viriyavejakul *et al.* (2002) [47]	17	1 (5.9%)	1/1 (100%)	Liver, spleen, kidneys, lymph nodes 1/1 (100%)	1/1 (100%)

TB, tuberculosis.
[a]Includes four HIV-negative TB cases.
[b]Reported number of cases with TB as cause of death only.

advanced HIV-associated immunodeficiency [59] and worst prognostic characteristics [60]. Thus, the assay has potential to be used as a screening tool for the large burden of undiagnosed disseminated TB among HIV-infected medical in-patients [61]. WHO is to review the growing evidence base for the assay in 2015. Urine can also be tested using the Xpert MTB/RIF assay, providing a useful diagnostic yield among patients with advanced immunodeficiency [58,62]. Intervention trials of urine-based screening among HIV-infected in-patients in hospitals in southern Africa are ongoing, including the LAMRCT (NCT01770730) and STAMP (ISRCTN71603869) trials.

The global scale-up of ART had provided treatment for an estimated 12.9 million people by 2013. However, this represented just 38% of those eligible for ART under WHO guidelines [63]. Despite ART scale-up, the prevalence of TB at autopsy in HIV-infected adults has remained high, with prevalence estimates of 34–64% in the four studies which have been done in Africa during the ART era [14–17]. Thus, we observed no reduction over time in the prevalence of TB found in autopsy studies done in sub-Saharan Africa between 1992 and 2012. Although ART reduces TB risk among patients across all $CD4^+$ strata [64], therapy is all too often started too late [65]. Patients continue to present to the healthcare service with advanced immunodeficiency and high risk of TB and death. Further scale-up of ART through expanded HIV testing and timely ART initiation at higher $CD4^+$ cell count thresholds are vital for more effective prevention of HIV-TB and associated deaths. Other effective interventions for prevention of HIV-associated TB, such as provision of isoniazid preventive therapy, also require further scale-up [2,66].

We found that the prevalence of TB at autopsy was much lower in HIV-infected children than in adults, and exceeded 10% in just two studies of children in southern Africa [18,19]. There are no global estimates available for TB incidence and mortality in HIV-infected children [1]. There were an estimated 550 000 new paediatric TB cases worldwide in 2013, and cohort studies in high TB burden countries have found a prevalence of HIV of 16–56% among such cases [1,67]. While the burden of disease found in HIV-infected children is much less than that in adults, additional work is needed to establish the true burden of disease at a global level.

Strengths of this study include the fact that it is the first systematic review and meta-analysis to be done of autopsy studies in HIV-infected patients in resource-limited settings at a global level and the fact that both adults and children were included. This is also the first review to evaluate site of TB disease among HIV-infected cadavers across studies. Limitations include the fact that few studies had been conducted in some global regions, such as south and south-east Asia.

In conclusion, this study has quantified the huge burden of TB found at autopsy of HIV-infected adults in resource-limited settings, illustrating that TB remains the most important opportunistic infection in people living with HIV. In addition, almost half of this disease remained undiagnosed at the time of death, and the prevalence of TB in autopsy studies of HIV-infected adults in studies done in Africa has tended to increase rather than decrease over a 20-year period, highlighting the ongoing failure of current prevention, case detection and treatment strategies. Further scale-up and timely initiation of ART is key in preventing HIV-associated TB. Development of screening algorithms and effective implementation of novel diagnostic tools is required to allow early case detection of HIV-TB and reduce mortality through early treatment initiation, when prevention fails.

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Authors' contributions: S.D.L. initiated and led the study and planned the analyses. R.K.G. did the literature searches and extracted the data. Data extraction was checked by S.D.L. and S.B.L. R.K.G. created the forest plots and tables. All authors interpreted the data. K.L.F. did the meta-analysis and meta-regression analysis. R.K.G. wrote the first draft of the paper with S.D.L. All authors provided input to subsequent drafts of the paper and all approved the final version.

Conflicts of interest

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The authors have no conflicts of interest to declare.

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