Deaths due to respiratory tract infections in Africa: a review of autopsy studies

Matthew Bates[a,b], *Victor Mudenda*[b,c], *Peter Mwaba*[a,d], *and Alimuddin Zumla*[a,b]

Purpose of review
According to the WHO, lower respiratory tract infections are one of the most prevalent causes of death in Africa. Estimates based on verbal autopsies are inaccurate compared with the gold standard for determining cause of death, the anatomical postmortem. Here, we review all respiratory postmortem data available from Africa and assess disease prevalence by HIV status in both adults and children.

Recent findings
Pulmonary and extrapulmonary tuberculosis was detected in over 50% of HIV-infected adults, four to five-fold more prevalent than in HIV-uninfected cases. Overall tuberculosis was less prevalent in children, but was more prevalent in HIV-uninfected compared with HIV-infected children. Bacterial pneumonia was more prevalent in children than adults and was relatively unaffected by HIV status. *Pneumocystis jirovecci* and human cytomegalovirus pneumonia were detected almost exclusively in HIV-infected mortalities, twice as prevalent in children as in adults. Coinfections were common and correlation with premortem clinical diagnoses was low.

Summary
Respiratory tract infections are important causes of mortality in Africa. Of the 21 reviewed studies, only four studies (all adults) were undertaken in the last decade. There is hence an urgent need for new postmortem studies to monitor cause of death in new and emerging patient groups, such as those on antiretroviral therapy and HIV exposed uninfected children.

Keywords
autopsy, HIV, lung disease, pneumonia, postmortem, respiratory tract infections, tuberculosis

INTRODUCTION

In Africa, according to the WHO, tuberculosis (TB) and other lower respiratory tract infections (LRTIs) are the most prevalent infectious causes of death, accounting for roughly 1.5 million deaths in 2008 [1]. This figure does not include 1.3 million deaths recorded as 'due to HIV/AIDS', where the specific cause of death is not reported [1] (Fig. 1). Together, TB, LRTIs and HIV/AIDS are thought to be responsible for over half of all infectious disease deaths in Africa. Despite significant successes with the rollout of antiretroviral therapy (ART) across the continent over the past decade [2,3], there were still 1.2 million AIDS-related deaths across Africa in 2010 and infectious diseases of the lung were reported as one of the major causes [4].

WHO cause-specific mortality estimates are based on data from national governments and international aid programmes [1], but population-wide monitoring of the pathogen-specific cause of death in many African countries is limited. The data that are collected come from a range of sources, mainly from clinical records and verbal autopsy studies, which are inaccurate. The gold standard for determining cause of death is through anatomical postmortem examination, observing gross disease, and if facilities are available, histopathological and microbiological investigation [5].

[a]University of Zambia and University College London Medical School (UNZA-UCLMS) Research and Training Programme, University Teaching Hospital, Lusaka, Zambia, [b]Department of Infection, Division of Infection and Immunity, University College London, London, UK, [c]Department of Pathology and Microbiology, University Teaching Hospital and [d]Ministry of Health, Lusaka, Zambia

Correspondence to Dr Matthew Bates, Department of Pathology and Microbiology, University Teaching Hospital, Nationalist Road, Lusaka RW1X, Zambia. Tel: +2 609 7404 4708; e-mail: matthew.bates@ucl.ac.uk

Curr Opin Pulm Med 2013, 19:229–237
DOI:10.1097/MCP.0b013e32835f4fe4

KEY POINTS

- Pulmonary infections are the most common cause of death seen at autopsy in Africa.
- Pulmonary and extrapulmonary TB are seen in up to 69% of HIV-associated adult deaths.
- Coinfections with multiple pathogens were seen in up to 66% of HIV-associated childhood deaths.
- Correlation between clinical-determined and postmortem-determined cause of death is low.
- There is a great need for more investment into rapid and accurate diagnostics for respiratory tract infections, especially in HIV-infected children and adults.

Postmortem studies give an indication of how accurate (or inaccurate) the premortem clinical diagnosis was, and the information obtained can have a significant impact on clinical management guidelines and local policy to improve clinical practice [5]. Postmortem studies are particularly useful for distinguishing between infections with similar clinical presentation and can identify other coinfections where multiple pathogens may have contributed to disease, or infectious comorbidity with AIDS-related malignancies and other noncommunicable diseases [6]. Conducting postmortem studies in some African cultural contexts is challenging [7,8], and so the number and heterogeneity of such studies is limited, making population-based estimates of cause-specific mortality difficult.

Here, we review the findings of all African published postmortem studies conducted to date. We present pooled data on the overall prevalence of different lung diseases, stratified by age and HIV status, and highlight levels of coinfection and correlation with clinical diagnosis.

SEARCH METHODOLOGY

The Pubmed database was searched using the term 'post mortem' OR 'Autopsy' AND 'Africa' AND 'HIV', which returned 148 articles. Twenty-one original postmortem studies were identified, in which the results of either complete (trunk organs and brain) or partial postmortems (typically restricted to the chest cavity) are reported. Thirty-seven articles were verbal autopsy studies or reviews on verbal autopsy methodologies. Verbal autopsy studies were not the focus of this review as they cannot differentiate between the specific pathogens responsible for causing LRTIs, and so were excluded [9]. The remaining 90 articles were also excluded: one article did not delineate postmortem findings between adults and children, 64 did not report any cause-specific mortality data relating to HIV-associated lung disease in Africa, nine were reviews, eight articles presented case studies, seven contained duplicate data or substudies, which overlapped with the selected studies (typically such articles focussed on a

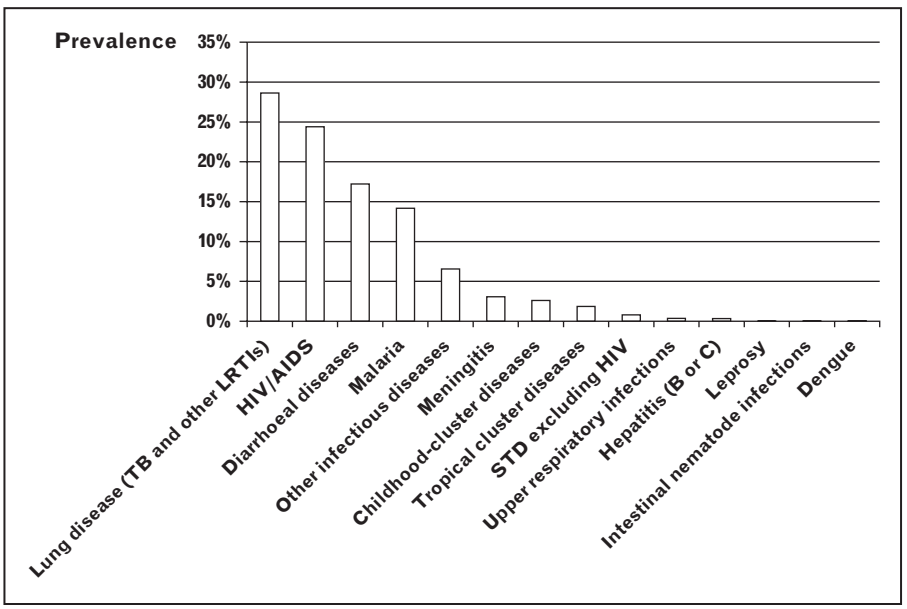

FIGURE 1. Constructed from WHO Global Health Statistics [1], cause-specific mortality estimates for the contribution of different infectious disease to communicable disease mortality in 2008. Data source did not specify error. LRTIs, lower respiratory tract infections; STD, sexually transmitted disease; TB, tuberculosis.

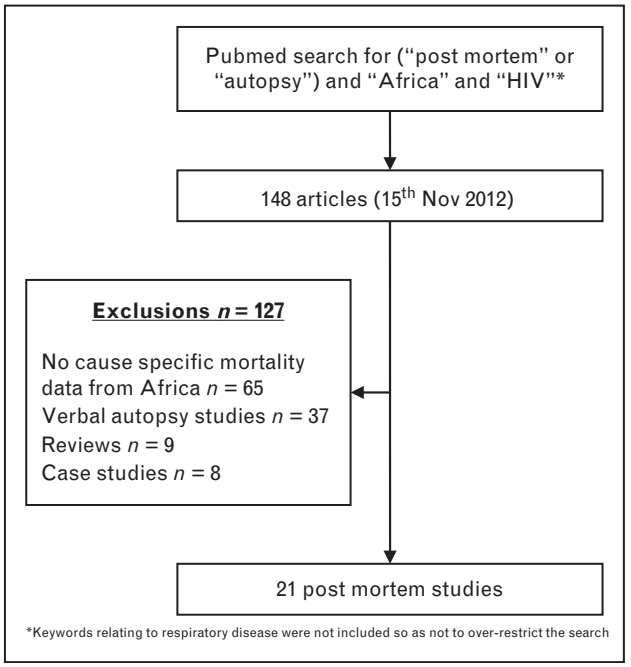

FIGURE 2. Literature search flow diagram.

specific pathogen), and one article was in French (Fig. 2).

POSTMORTEM STUDY RECRUITMENT AND DESCRIPTIVES

This review presents the results of 21 studies, 12 in adults and nine in children. Table 1 summarizes the recruitment characteristics for both adult and childhood studies, and illustrates clearly the heterogeneous nature of the studies undertaken [10–14,15▪▪,16–20,21▪,22–29]. All studies focused on inpatient deaths, but one included community mortalities brought in for forensic examination [13]. Four studies (all paediatric) selected patients specifically because they died with respiratory infections [6,25,26,28], or even more specifically, because they had a premortem diagnosis of TB [19]. Studies took place over a 20-year period, from 1992 to 2012, across 11 different African countries. Studies from West Africa included patients with HIV-2 as well as HIV-1 infection [10,11,20,22]. Three South African studies were from mining communities where lung disease would be expected to be more prevalent [18,19,30▪]. Paediatric studies tended to focus on young infants under 12 months of age.

All but four of the studies included in this review required relatives of the deceased to consent. Pooling the recruitment rates across those consenting studies for which the data are available suggests that in both adult and childhood studies, recruitment of HIV-associated deaths may be slightly easier than non-HIV associated deaths (Table 1). AIDS patients and their families may have spent more time in the health system and might be more sensitized to the rationale of research studies. Only one of the four nonconsenting studies had a recruitment rate of 100%, highlighting that it is not only the requirement for consent that impairs postmortem study recruitment rates, but sufficient trained pathologists and support personnel, and morgue and laboratory facilities are also required to undertake a representative number of postmortems in the given time frame. Ten out of 12 adult and six out of nine childhood studies declare an open bias towards either HIV or respiratory infections, and so these studies present an excellent opportunity to review cause-specific mortality in HIV-associated respiratory deaths across Africa.

ADULT POSTMORTEM STUDY FINDINGS

From a total of 12 adult studies [10–14,15▪▪,16–20,21▪], the results of 1273 postmortem examinations are reported. The HIV status is presented for 99% (1260/1273) of cases, with the majority (80.3%, 1012/1260) being HIV-positive mortalities. All of the studies were undertaken at secondary or tertiary referral centres where up to 70% of patients admitted may be HIV positive, with 60–66% of mortalities being among HIV-infected patients [10,31]. One study also included community deaths [10]. Reviewing the 12 studies, we extracted six key respiratory disease groups stated as either the primary or contributory cause of death: pulmonary TB, extrapulmonary or disseminated TB infection, bacterial pneumonia, *Pneumocystis jirovecci* pneumonia (PCP), human cytomegalovirus (HCMV) pneumonia and interstitial pneumonia. Pooling the data from all studies we assessed the prevalence of each disease group within the total number of autopsies undertaken, stratifying by HIV status. Among HIV-infected mortalities, pulmonary TB was the most prominent cause of death, with prevalence being 4.2-fold higher than among HIV-uninfected mortalities [35% (335/902) vs. 8.8% (20/226); $P < 0.001$]. Similarly, extrapulmonary or disseminated TB infections were 5.2-fold more prevalent in HIV-infected vs. HIV-uninfected mortalities [20.8% (188/902) vs. 4% (9/226); $P < 0.001$]. The prevalence of bacterial pneumonia did not differ by HIV status [27.7% (250/902) vs. 29.2% (66/226); $P = 0.656$]. PCP and HCMV pneumonia were detected in 5.3 and 7.5% of HIV-infected patients only, and were not detected at all in HIV-uninfected mortalities. Interstitial pneumonia was detected in 5% of cases or less, with no significant difference observed between HIV-infected and HIV-uninfected mortalities (Fig. 3).

Table 1. Adult and childhood study recruitment and descriptives

		Total			HIV infected			HIV uninfected				
	Country	Deaths	Postmortem	Recruitment rate	Deaths	Postmortem	Recruitment rate	Deaths	Postmortem	Recruitment rate	Postmortem type	Notes on study group
Adult studies ($n=12$)												
Nonconsenting studies												
Lucas *et al.* [10]	Cote D'Ivoire	1538	289	18.8%	1020	247	24.2%	518	42	8.1%	Full PM	Hospital admission and community deaths
Abouya *et al.* [11]	Cote D'Ivoire	100	78	78.0%	71	53	74.6%	29	25	86.2%	Partial PM	Pulmonary ward, lungs only
Consenting studies in which total number of deaths are not recorded												
Nelson *et al.* [12]	Democratic Republic of Congo	NA	63	NA	NA	63	NA	0	0	NA	Partial PM	AIDS death unknown cause, exclude brain
Kibayashi *et al.* [13]	Tanzania	NA	10	NA	NA	10	NA	0	0	NA	Partial PM	Neuropath focus, but also heart, lungs liver and kidneys
Menendez *et al.* [14]	Mozambique	NA	197	NA	179	139	77.7%	NA	58	NA	Full PM	Deaths during pregnancy or within 42 days thereafter
Wong *et al.* [15▪▪]	South Africa	NA	39	NA	NA	39	NA	0	0	NA	Full PM (Needle)	HIV and only medical admissions
Consenting studies in which total number of deaths are recorded												
Rana *et al.* [16]	Kenya	296	122	41.2%	155	75	48.4%	141	47	33.3%	Full PM	Medical admissions
Ansari *et al.* [17]	Botswana	945	128	13.5%	565	104	18.4%	380	24	6.3%	Full PM	Mainly pulmonary, medical admissions, >13 years
Murray *et al.* [18]	South Africa	357	104	29.1%	242	66	27.3%	115	38	33.0%	Partial PM	Prospective cohort of miners, heart and lungs only
Martinson *et al.* [19]	South Africa	1000	50	5.0%	NA	47	NA	NA	3	NA	Full PM	TB patients only
Agyei [20]	Ghana	224	134	59.8%	224	134	59.8%	0	0	NA	Partial PM	HIV and only medical admissions
Cox *et al.* [21▪]	Uganda	158	59	37.3%	NA	35	NA	NA	11	NA	Full PM	Infectious disease/gastroenterology ward
Pooled		2980	597	20.0%	1186	379	32.0%	636	109	17.1%		
Childhood studies ($n=9$)												
Nonconsenting studies												
Lucas *et al.* [22]	Cote D'Ivoire	408	155	38.0%	80	78	97.5%	328	77	23.5%	Full PM	Hospital admission and community deaths
Chakraborty *et al.* [23]	Kenya	33	33	100.0%	33	33	100.0%	0	0	NA	Full PM	Consecutive deaths at an orphanage
Consenting studies in which total number of deaths are not recorded												
Jeena *et al.* [24]	South Africa	NA	65	NA	43	31	72.1%	NA	34	NA	Partial PM	ICU, lung and liver
Chintu *et al.* [6]	Zambia	NA	348	NA	1603	264	16.5%	NA	84	NA	Partial PM	Respiratory patients only, lung only
Rennert *et al.* [25]	South Africa	NA	93	NA	NA	93	NA	NA	NA	NA	Partial PM	Respiratory patients only, lung and liver
Consenting studies in which total number of deaths are recorded												
Nathoo *et al.* [26]	Zimbabwe	618	24	3.9%	618	24	3.9%	NA	NA	NA	Partial PM	Pneumonia patients only
Ikeogu *et al.* [27]	Zimbabwe	334	184	55.1%	NA	122	NA	NA	62	NA	Partial PM	Admission and community deaths, lung only
Ruffini and Madhi [28]	South Africa	29	18	62.1%	29	18	62.1%	0	0	NA	Partial PM	HIV-positive or suspected pneumonia <2 years, lung only
Ansari *et al.* [29]	Botswana	250	47	18.8%	126	35	27.8%	124	12	9.7%	Full PM	Medical admissions
Pooled		1231	273	22.2%	2419	369	15.3%	124	12	9.7%		

NA, not availabe; PM, postmortem. Adapted from [5].

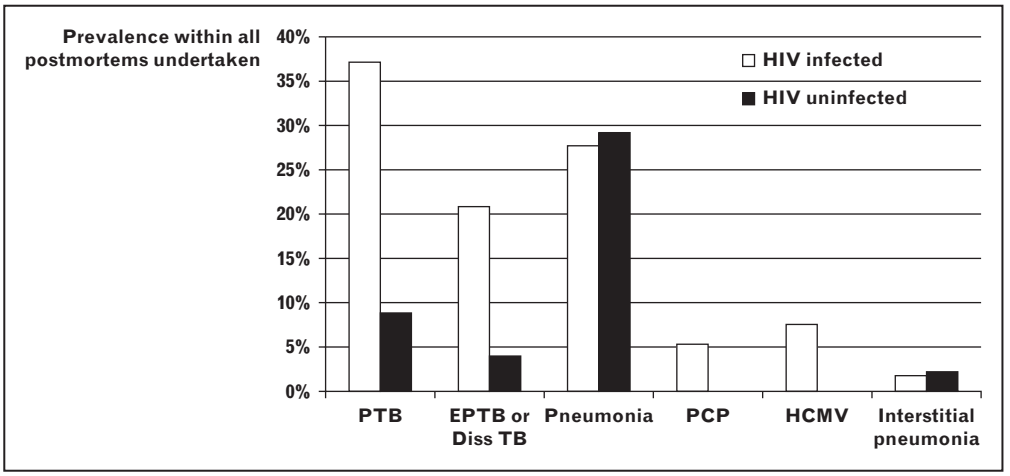

FIGURE 3. Relative prevalence of respiratory infections in adults at death, through postmortem examination stratified by HIV status. EPTB, extrapulmonary tuberculosis; HCMV, human cytomegalovirus; PCP, *Pneumocystis jirovecci* pneumonia; PTB, pulmonary tuberculosis; TB, tuberculosis.

CHILDHOOD POSTMORTEM STUDY FINDINGS

We extracted data from nine paediatric postmortem studies undertaken in Africa between 1996 and 2003 [6,22–29]. From a total of 832 postmortems, 72.7% (605/832) were in HIV-infected children. The most prevalent contributory cause of death identified in all childhood studies was bacterial pneumonia, with significantly higher prevalence in HIV-uninfected vs. HIV-infected children [56.4% (128/227) vs. 43.5% (263/605), $P < 0.001$] (Fig. 4). Conversely, PCP and HCMV pneumonia were both 10-fold more prevalent in HIV-infected vs. HIV-uninfected children [PCP: 23.6% (143/605) vs. 2.6% (6/227), $P < 0.001$; HCMV: 22.6% (137/605) vs. 3.5% (8/227), $P < 0.001$]. Prevalence of PCP and HCMV in HIV-infected children did not differ significantly, and together, they were the second most common contributory causes of death. The third most common finding was interstitial pneumonia of unknown origin, including lymphoid interstitial pneumonia, seen in 16% (133/862) of cases overall and not differing by HIV status. Around 8.5% (71/862) of all cases had pulmonary TB, which was significantly more prevalent in HIV-uninfected cases [11.9% (27/227) vs. 7.3% (44/605), $P = 0.034$]. This effect was driven solely by one study [6], with the baseline prevalence of pulmonary TB being roughly 2% in both HIV-infected and uninfected children if this study is excluded. Only seven cases of

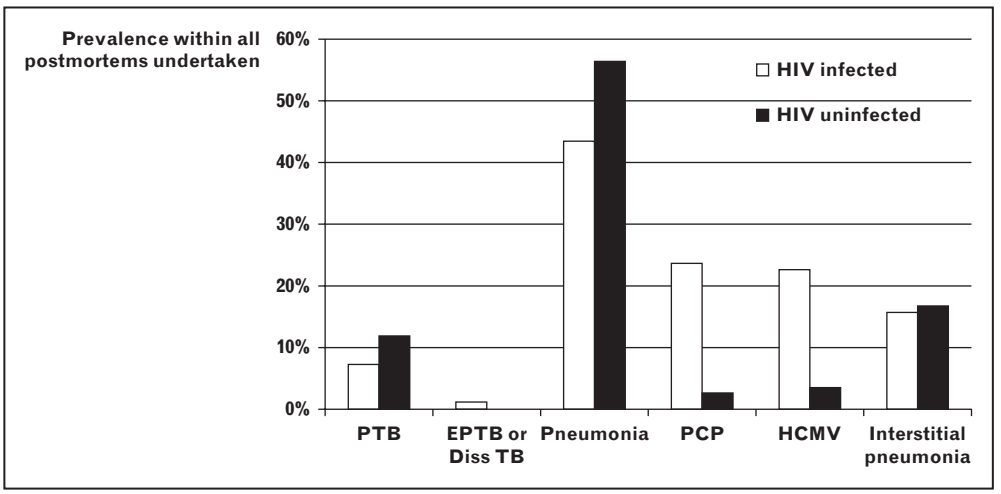

FIGURE 4. Relative prevalence of respiratory infections in children at death, through postmortem examination stratified by HIV status. EPTB, extrapulmonary tuberculosis; HCMV, human cytomegalovirus; PCP, *Pneumocystis jirovecci* pneumonia; PTB, pulmonary tuberculosis; TB, tuberculosis.

extrapulmonary or disseminated TB were documented, and all of these were in HIV-infected children.

COINFECTION WITH MULTIPLE PATHOGENS

Two adult [17,19] and four paediatric studies [6,25,27,29] explicitly state the prevalence of cases with multiple pathogens, with coinfection rates between 34 and 47% in adult mortalities, and between 46 and 66% in children (data not shown).

CORRELATION WITH CLINICAL DIAGNOSIS

Of the 21 studies analysed in this review, just seven provide a comparison of clinical vs. pathological diagnoses. Raw data for TB were presented in five studies [16,18–20,32]. Pooling of the results from these studies, and combing both HIV-infected and uninfected cases, shows that clinical diagnosis for TB has an overall sensitivity of 67.3% [95% confidence interval (CI) 60.3–73.7] and a specificity of 89.1% (95% CI 85.1–92.1) (Table 2).

DISCUSSION

Respiratory tract infections and HIV/AIDS are important causes of death in Africa. They are caused by an array of bacterial, mycobacterial, fungal and viral pathogens. As rapid, cheap and accurate diagnostic technologies are not widely available, many patients are treated empirically on the basis of clinical suspicion. Postmortem studies are the gold standard for determining both primary and secondary causes of death, and the results of such studies can be used to evaluate the accuracy of clinical diagnoses and to uncover missed causes of death and complex coinfections [5,33]. Current opinion on postmortem data from respiratory mortalities in HIV/AIDS in Africa is based on the relatively small number of postmortem studies that have been conducted over the last two decades.

The 21 postmortem studies presented in this review show pooled data for pulmonary TB, extrapulmonary or disseminated TB, bacterial pneumonia, PCP, HCMV pneumonia and interstitial pneumonia in adults and children, stratified by HIV status. For HIV-infected adults, TB (both pulmonary and extrapulmonary or disseminated infections) was the most common finding at postmortem, being detected in up to 69% of HIV-associated deaths [15▪▪], with a three to four-fold increase in prevalence among HIV-infected vs. HIV-uninfected cases. Although widespread roll-out of

Table 2. Sensitivity of clinical diagnosis of pulmonary tuberculosis compared with histological postmortem findings as a gold standard

	n	True positive	True negative	False positive	False negative	Sensitivity	Specificity	PPV	NPV
Ordi *et al.* [32]	139	0	137	0	2	0.0% (0–80.2%)	100.0% (96.7–100%)	NA	98.6% (98.6–99.8%)
Murray *et al.* [18]	104	9	66	18	11	45.0% (23.8–68.0%)	78.6% (68.0–86.5%)	33.3% (17.2–54.0%)	85.7% (75.5–92.3%)
Rana *et al.* [16]	75	20	28	10	17	54.1% (37.1–70.2%)	73.7% (56.6–86.0%)	66.7% (47.1–82.1%)	62.2% (46.5–75.8%)
Martinson *et al.* [19]	47	32	2	8	5	86.5% (71.1–93.3%)	20.0% (3.5–55.8%)	80.0% (63.9–90.4%)	28.6% (5.1–69.7%)
Agyei [20]	164	73	61	0	30	70.9% (61.0–79.2%)	100.0% (92.6–100%)	100% (93.8–100%)	67.0% (56.3–76.3%)
Overall	529	134	294	36	65	67.3% (60.3–73.7%)	89.1% (85.1–92.1%)	78.8% (71.8–84.6%)	81.9% (77.4–85.7%)

NA, not available; NPV, negative predictive value; PPV, positive predictive value.

ART services across the continent over the past decade has resulted in overall decreases in all-cause mortality [34], some centres have documented that the prevalence of TB as a primary cause of death is actually increasing, possibly due to a shift in focus from TB to ART services, and likely also due to population level demographic changes over time [30▪]. In HIV-uninfected adults, we identified pneumonia as the most common finding at postmortem.

All but four of the reviewed postmortem studies required the consent of the deceased's relatives. Pooled recruitment rates across all studies, which provided the raw data, suggest that up to 20% of those families who are approached give consent, with rates being slightly higher for HIV-infected cases. Although some studies have documented reasons for refusal to take part in postmortem studies [7], it is difficult to interpret this with respect to how the recruited postmortem study group may or may not be representative of the wider population. It is possible that deaths which were sudden and unexplained, or for which the relatives are not completely satisfied with the explanation given by the attending physician, might be more likely to be recruited. This might favour atypical clinical presentations, possibly caused by coinfection with multiple pathogens.

Some of the studies reviewed illustrate a high prevalence of coinfections with multiple pathogens in HIV/AIDS mortalities: 34–47% in adults [17,19], and 46–66% in children [6,25,27,29]. These studies almost exclusively recruited cases from inpatient deaths, but it has been estimated that up to half of all AIDS patients die at home [16]. It is not known whether causes of death differ between hospitalized and community deaths. Home deaths might plausibly be more likely to be late-stage mortalities, with patients maybe previously admitted, going home for palliative care. Conversely, earlier mortalities, such as those linked with ART initiation, might be more likely to occur in hospitalized patients. The majority of adult studies and all childhood studies present data from postmortems undertaken prior to ART roll-out, and so just the most recent postmortem study reported cause-specific mortality results by ART treatment status: they found TB in 87% of early ART deaths, compared with 57% in pre-ART and 60% in late-stage deaths, respectively [15▪▪].

From the nine childhood postmortem studies, bacterial pneumonia was the most prevalent cause of death, being significantly more prevalent in HIV-uninfected than in HIV-infected children. This differential was compensated by a 10-fold higher prevalence of both PCP and HCMV pneumonia in HIV-infected children. We show here that both PCP and HCMV are important causes of mortality in HIV-infected children, particularly those younger than 1 year of age [6,27]. PCP is now treated empirically with cotrimoxazole in all HIV-infected children, but for HCMV neither diagnostics nor treatment (intravenous ganciclovir) is generally available outside of certain referral centres in South Africa, where pilot data suggest that ganciclovir can dramatically reduce mortality in antibiotic-unresponsive HIV-associated severe pneumonia [35,36]. Pulmonary TB was much less prevalent in children than in adults, but still accounted for roughly 10% of deaths, and was slightly more prevalent in HIV-uninfected children. Children typically contract pulmonary TB from an adult relative, and it was interesting to note that HIV-uninfected children were at a similar risk for TB infection as HIV-infected children. Maternal HIV status was not recorded and it is likely that a significant proportion of childhood TB deaths, certainly in young infants, were in children who were maternally exposed to HIV, which has been shown to be linked with increased morbidity and mortality [37–39]. Most of the childhood postmortems in which pulmonary TB was identified as a primary cause of death came from one study, which highlights a broader point that there have been too few studies performed to properly assess both historical trends and geographical variation in the mortality contribution of different infections across Africa. The most recent childhood postmortem study was from 2003, and there is an urgent need for recent cause of death data from both HIV-infected children on ART and maternally exposed children from across the continent.

Lay interpretation of publications, which present disparity between clinical and pathological diagnoses, may be politically sensitive, and expose hospital authorities to either justified or unjustified criticism. It is maybe for this reason that only five of the 21 postmortem studies reviewed present raw data on correlation with clinical diagnosis. We present the pooled performance of clinical diagnosis for TB compared with postmortem findings from these five studies [16,18–20,32], demonstrating an overall sensitivity of just 67.3%. All five studies were undertaken relatively recently (four within the last 5 years) and at tertiary hospitals where laboratory results such as smear microscopy and mycobacterial culture would have been available and informed on clinical diagnosis premortem. In a recent record review study, TB was missed premortem in 23 of 44 (52%) cases, and wrongly attributed as the cause of death in 16% (18/110) of cases [40]. This occurred at a well-funded private hospital in South Africa, but most HIV-associated respiratory deaths in Africa occur at poorly resourced health centres where laboratory facilities are limited.

CONCLUSION

WHO estimates state that infectious diseases remain the primary cause of death in Africa, accounting for 65% of all deaths. Noncommunicable disease account for 28% of all deaths, and although the prevalence of diseases such as diabetes, cancer and stroke are rising [41], infectious diseases, and in particular, respiratory infections, will likely remain a priority for the foreseeable future [42]. Much of the HIV respiratory mortality data reviewed here comes from postmortem examinations conducted on ART-naive mortalities. With the steady expansion of ART treatment services across Africa [43], there is a great need for new postmortem data, ideally from large unified multisite studies with a simple methodology that is easily replicated [21▪]. Due to the sensitive nature of postmortem studies, and cultural differences between heterogeneous African societies, new techniques such as fine-needle biopsy could be employed to make studies less traumatic and more culturally acceptable [33]. Current priorities include children and adults on ART [15▪▪], HIV-infected and/or maternally exposed children, and maternal deaths which have been broadly neglected [14,32,44]. The high death rate in Africa due to LRTIs illustrates that there is an urgent need for new, rapid and accurate diagnostic tools for a range of respiratory pathogens, to help clinicians interpret complex and overlapping clinical symptoms, and to get more patients onto appropriate pathogen-targeted therapy.

Acknowledgements

This work was supported by the UBS Optimus Foundation, EDCTP and European Commission.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 322).

1. Global Health Observatory Data Repository: cause-specific mortality 2008 [database on the Internet]. WHO; 2008. http://apps.who.int/ghodata/?vid=720. [Accessed 16th November 2012]
2. Brinkhof MW, Boulle A, Weigel R, *et al.* Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-unrelated mortality. PLoS Med 2009; 6:e1000066.
3. Reniers G, Araya T, Davey G, *et al.* Steep declines in population-level AIDS mortality following the introduction of antiretroviral therapy in Addis Ababa Ethiopia. AIDS 2009; 23:511–518.
4. WHO. Global HIV/AIDS response: epidemic update and health sector progress towards universal access: progress report 2011. Geneva: WHO press; 2011.
5. Cox JA, Lukande RL, Lucas S, *et al.* Autopsy causes of death in HIV-positive individuals in sub-Saharan Africa and correlation with clinical diagnoses. AIDS Rev 2010; 12:183–194.
6. Chintu C, Mudenda V, Lucas S, *et al.* Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study. Lancet 2002; 360:985–990.
7. Lishimpi K, Chintu C, Lucas S, *et al.* Necropsies in African children: consent dilemmas for parents and guardians. Arch Dis Child 2001; 84:463–467.
8. Oluwasola OA, Fawole OI, Otegbayo AJ, *et al.* The autopsy: knowledge, attitude, and perceptions of doctors and relatives of the deceased. Arch Pathol Lab Med 2009; 133:78–82.
9. Snow RW, Armstrong JR, Forster D, *et al.* Childhood deaths in Africa: uses and limitations of verbal autopsies. Lancet 1992; 340:351–355.
10. Lucas SB, Hounnou A, Peacock C, *et al.* The mortality and pathology of HIV infection in a west African city. AIDS 1993; 7:1569–1579.
11. Abouya YL, Beaumel A, Lucas S, *et al.* Pneumocystis carinii pneumonia. An uncommon cause of death in African patients with acquired immunodeficiency syndrome. Am Rev Respir Dis 1992; 145:617–620.
12. Nelson AM, Perriens JH, Kapita B, *et al.* A clinical and pathological comparison of the WHO and CDC case definitions for AIDS in Kinshasa, Zaire: is passive surveillance valid? AIDS 1993; 7:1241–1245.
13. Kibayashi K, Ng'walali PM, Mbonde MP, *et al.* Neuropathology of human immunodeficiency virus 1 infection. Significance of studying in forensic autopsy cases at Dar es Salaam, Tanzania. Arch Pathol Lab Med 1999; 123:519–523.
14. Menendez C, Romagosa C, Ismail MR, *et al.* An autopsy study of maternal mortality in Mozambique: the contribution of infectious diseases. PLoS Med 2008; 5:e44.
15. ▪▪ Wong EB, Omar T, Setlhako GJ, *et al.* Causes of death on antiretroviral therapy: a postmortem study from South Africa. PLoS One 2012; 7:e47542.
This recent study from South Africa clearly stratifies by ART treatment status and identifies TB in 87% of early ART deaths.
16. Rana FS, Hawken MP, Mwachari C, *et al.* Autopsy study of HIV-1-positive and HIV-1-negative adult medical patients in Nairobi, Kenya. J Acquir Immune Defic Syndr 2000; 24:23–29.
17. Ansari NA, Kombe AH, Kenyon TA, *et al.* Pathology and causes of death in a group of 128 predominantly HIV-positive patients in Botswana. Int J Tuberc Lung Dis 2002; 6:55–63.
18. Murray J, Sonnenberg P, Nelson G, *et al.* Cause of death and presence of respiratory disease at autopsy in an HIV-1 seroconversion cohort of southern African gold miners. AIDS 2007; 6:S97–S104.
19. Martinson NA, Karstaedt A, Venter WD, *et al.* Causes of death in hospitalized adults with a premortem diagnosis of tuberculosis: an autopsy study. AIDS 2007; 21:2043–2050.
20. Agyei ALM, editor. Spectrum of opportunistic infections causing death in patients with AIDS in Ghana: correlation of clinical diagnosis with autopsy results. In: 11th Conference on Retroviruses and Opportunistic Infections; 8–11 February 2004; San Francisco, CA.
21. ▪ Cox JA, Lukande RL, Nelson AM, *et al.* An autopsy study describing causes of death and comparing clinico-pathological findings among hospitalized patients in Kampala, Uganda. PLoS One 2012; 7:e33685.
Although the number of postmortems undertaken in this study was quite low, the clear and rational methodology is an excellent model for future studies.
22. Lucas SB, Peacock CS, Hounnou A, *et al.* Disease in children infected with HIV in Abidjan. Cote d'Ivoire BMJ 1996; 312:335–338.
23. Chakraborty R, Pulver A, Pulver LS, *et al.* The postmortem pathology of HIV-1-infected African children. Ann Trop Paediatr 2002; 22:125–131.
24. Jeena PM, Coovadia HM, Chrystal V. Pneumocystis carinii and cytomegalovirus infections in severely ill, HIV-infected African infants. Ann Trop Paediatr 1996; 16:361–368.
25. Rennert WP, Kilner D, Hale M, *et al.* Tuberculosis in children dying with HIV-related lung disease: clinical-pathological correlations. Int J Tuberc Lung Dis 2002; 6:806–813.
26. Nathoo KJ, Gondo M, Gwanzura L, *et al.* Fatal Pneumocystis carinii pneumonia in HIV-seropositive infants in Harare, Zimbabwe. Trans R Soc Trop Med Hyg 2001; 95:37–39.
27. Ikeogu MO, Wolf B, Mathe S. Pulmonary manifestations in HIV seropositivity and malnutrition in Zimbabwe. Arch Dis Child 1997; 76:124–128.
28. Ruffini DD, Madhi SA. The high burden of Pneumocystis carinii pneumonia in African HIV-1-infected children hospitalized for severe pneumonia. AIDS 2002; 16:105–112.
29. Ansari NA, Kombe AH, Kenyon TA, *et al.* Pathology and causes of death in a series of human immunodeficiency virus-positive and -negative pediatric referral hospital admissions in Botswana. Pediatr Infect Dis J 2003; 22:43–47.
30. ▪ Lim MS, Dowdeswell RJ, Murray J, *et al.* The impact of HIV, an antiretroviral programme and tuberculosis on mortality in South African platinum miners, 1992–2010. PLoS One 2012; 7:e38598.
Although postmortem data are only provided for a subset of cases, this study is an excellent example of how good data recording from both postmortem and clinical records can faciliate changes in trends in cause-specific mortality over time.
31. Mudenda V, Lucas S, Shibemba A, *et al.* Tuberculosis and tuberculosis/HIV/AIDS-associated mortality in Africa: the urgent need to expand and invest in routine and research autopsies. J Infect Dis 2012; 205 (Suppl 2):S340–S346.

32. Ordi J, Ismail MR, Carrilho C, *et al.* Clinico-pathological discrepancies in the diagnosis of causes of maternal death in sub-Saharan Africa: retrospective analysis. PLoS Med 2009; 6:e1000036.

33. Turner GD, Bunthi C, Wonodi CB, *et al.* The role of postmortem studies in pneumonia etiology research. Clin Infect Dis 2012; 54 (Suppl 2):S165–S171.

34. Floyd S, Marston M, Baisley K, *et al.* The effect of antiretroviral therapy provision on all-cause, AIDS and non-AIDS mortality at the population level: a comparative analysis of data from four settings in Southern and East Africa. Trop Med Int Health 2012; 17:e84–e93.

35. Goussard P, Kling S, Gie RP, *et al.* CMV pneumonia in HIV-infected ventilated infants. Pediatr Pulmonol 2010; 45:650–655.

36. Zampoli M, Morrow B, Hsiao NY, *et al.* Prevalence and outcome of cytomegalovirus-associated pneumonia in relation to human immunodeficiency virus infection. Pediatr Infect Dis J 2010; 30:413–417.

37. Makasa M, Kasonka L, Chisenga M, *et al.* Early growth of infants of HIV-infected and uninfected Zambian women. Trop Med Int Health 2007; 12:594–602.

38. Marinda E, Humphrey JH, Iliff PJ, *et al.* Child mortality according to maternal and infant HIV status in Zimbabwe. Pediatr Infect Dis J 2007; 26:519–526.

39. Otieno RO, Ouma C, Ong'echa JM, *et al.* Increased severe anemia in HIV-1-exposed and HIV-1-positive infants and children during acute malaria. AIDS 2006; 20:275–280.

40. Field N, Murray J, Wong ML, *et al.* Missed opportunities in TB diagnosis: a TB process-based performance review tool to evaluate and improve clinical care. BMC Public Health 2011; 11:127.

41. Holmes MD, Dalal S, Volmink J, *et al.* Noncommunicable diseases in sub-Saharan Africa: the case for cohort studies. PLoS Med 2010; 7:e1000244.

42. Chihana M, Floyd S, Molesworth A, *et al.* Adult mortality and probable cause of death in rural northern Malawi in the era of HIV treatment. Trop Med Int Health 2012; 17:e74–e83.

43. Granich R, Williams B, Montaner J. Fifteen million people on antiretroviral treatment by 2015: treatment as prevention. Curr Opin HIV AIDS 2013; 8:41–49.

44. Lucas S. Maternal death, autopsy studies, and lessons from pathology. PLoS Med 2008; 5:e48.