@ Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study

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Summary

Background Accurate information about specific causes of death in African children dying of respiratory illnesses is scarce, and can only be obtained by autopsy. We undertook a study of children who died from respiratory diseases at University Teaching Hospital, Lusaka, Zambia.

Methods 137 boys (93 HIV-1-positive, 44 HIV-1-negative], and 127 girls (87 HIV-1-positive, 40 HIV-1-negative) aged between 1 month and younger than 16 years underwent autopsy restricted to the chest cavity. Outcome measures were specific lung diseases, stratified by age and HIV-1 status.

Findings The presence of multiple diseases was common. Acute pyogenic pneumonia (population-adjusted prevalence 39·1%, 116/264), *Pneumocystis carinii* pneumonia (27·5%, 58/264), tuberculosis (18·8%, 54/264), and cytomegalovirus infection (CMV, 20·2%, 43/264) were the four most common findings overall. The three most frequent findings in the HIV-1-negative group were acute pyogenic pneumonia (50%), tuberculosis (26%), and interstitial pneumonitis (18%); and in the HIV-1-positive group were acute pyogenic pneumonia (41%), *P carinii* pneumonia (29%), and CMV (22%). HIV-1-positive children more frequently had *P carinii* pneumonia (odds ratio 5·28, 95% CI 2·12–15·68, p=0·0001), CMV (7·71, 2·33–40·0, p=0·0002), and shock lung (4·15, 1·20–22·10, p=0·03) than did HIV-1-negative children. 51/58 (88%) cases of *P carinii* pneumonia were in children younger than 12 months, and five in children aged over 24 months. Tuberculosis was common in all age groups, irrespective of HIV-1 status.

Interpretation Most children dying from respiratory diseases have preventable or treatable infectious illnesses. The presence of multiple diseases might make diagnosis difficult. WHO recommendations should therefore be updated with mention of HIV-1-positive children. Improved diagnostic tests for bacterial pathogens, tuberculosis, and *P carinii* pneumonia are urgently needed.

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Introduction

Respiratory diseases are a leading cause of hospital admissions in both HIV-1-positive and HIV-1-negative children worldwide. In Europe and the USA, prevention and treatment of infections and increase in use of antiretroviral therapy has led to a fall in morbidity and mortality in HIV-1-infected children.[1] By contrast, the frequency of HIV-1 in children has risen in most developing countries; of an estimated 700 000 new infections in children reported in 2001, over 95% were in developing countries.[2] Children in these countries do not have access to the effective preventive and therapeutic treatments available in the west. Perinatally infected HIV-1-positive children rapidly progress to disease and death—in one study from central Africa[3] 89% of such children died by age 3 years.

In sub-Saharan Africa, results of several sentinel studies[4–8] have shown that pulmonary diseases are responsible for a large proportion of paediatric clinic attendances and hospital admissions. Reports from Malawi and South Africa show that these findings are uniform across sub-Saharan Africa.[9–12] Clinical features of tuberculosis, bacterial sepsis, and *Pneumocystis carinii* pneumonia in children overlap, and thus misdiagnosis is common. Guidelines[13] for management of respiratory illnesses in children do not refer specifically to HIV-1-positive children. Because of difficulties in accurate diagnosis, poor health-service resources, and shortage of expertise, much clinical paediatric practice in sub-Saharan Africa is based on empirical treatment, dependent on local impressions of common illnesses.

Accurate information on specific diseases in African children dying from respiratory illnesses is scarce. There is a need to obtain such data to place into perspective the relative importance of specific diseases as causes of mortality in African children. Knowledge of the causes of childhood lung diseases in a community is important in development of practical diagnostic, therapeutic, and prophylaxis protocols, and for epidemiological surveillance and control. Empiric management can be effective only if data about disease frequency, morbidity, and mortality are available. Since autopsies are the only way to obtain information on the actual causes of death, we undertook a large necropsy study to define the range of fatal pulmonary diseases in Zambian children in hospital, and to assess relations between these diseases, HIV-1 status, and age.

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Methods

Study design

We did a descriptive necropsy study of Zambian children who had died from respiratory disease and were inpatients at the University Teaching Hospital, Lusaka, Zambia. This hospital is the largest government hospital in Lusaka and the only one there providing inpatient care for children. Children who are ill enough to warrant admission are referred to the department of paediatrics and child health from all peripheral clinics serving the city population. About two-thirds of all childhood deaths in Lusaka take place in hospital.

Children who were dying from respiratory disease and were aged between 1 month and younger than 16 years (upper limit 16th birthday), were eligible for recruitment. The study was done between Sept 15, 1997, and June 15, 2000. Outcome measures were prevalence of specific lung pathology, stratified by age and HIV-1 status.

Consent

We designed study-specific enrolment forms to obtain consent for necropsy. The parents or guardians of all children who had died from respiratory disease who were available for interview during daylight working hours in the wards were approached by the study recruitment clinical officer and the study paediatrician in charge of the patient. All communication was in the language of the parent or guardian, through our multilingual recruitment officer. We explained details of the study to the parent or guardian, gave them written information about the study in the appropriate language, and allowed them time to consult any relatives present and come back with questions. When the parent or guardian refused permission for necropsy, we recorded the main reason given[14] and noted the age and sex of the child. To reduce anxieties about mutilation and avoid the time delay associated with complete examination, we requested consent for a necropsy examination limited to the organs of the chest. Before consent was obtained parents were counselled about HIV-1 tests, and we offered further counselling before and after the test to parents who wanted to know the results of the child's test and to be tested themselves.

The study was approved by the University of Zambia Research and Ethics Committee.

Necropsy and tissue samples

The recruitment officer liaised closely with the consultant pathologist so that the autopsy was done within 6 h after approval was obtained. A limited necropsy (restricted to the chest) was done with sterile techniques. We took, from both chest cavities, a section from every lobe of the lungs, one from the left and right main bronchus and trachea, the hilar and mediastinal lymph nodes, and a serum sample from the cardiac chamber (which was stored at −70°C). Fresh gloves and blades were used for every organ sampled.

HIV-1 testing

We tested for HIV-1 by two methods: first, a double ELISA test (Welcozyme, Wellcome Diagnostics, Oxford, UK) and antiglobulin recombinant ELISA (duPont de Nemours, Wilmington, DE, USA), and second, PCR analysis (Amplicor HIV-1, Roche Diagnostics Systems, New Jersey, USA) to amplify a sequence on a highly conserved region of the *gag* gene that identifies local African HIV-1 clades.

Histopathology

Histopathologists who were unaware of the patients' clinical diagnoses, age, and HIV-1 status processed the necropsy lung samples. Initial staining was with haematoxylin and eosin; silver methenamine and Ziehl-Neelsen tests for fungi and acid-fast bacilli were used as appropriate. We recorded diseases identified on examination of lung tissues. Respiratory-tract lesions with giant cells or viral inclusions were assessed by immunocytochemistry for specific virus infections: measles, adenovirus, herpes simplex types 1 and 2, CMV, and respiratory syncitial virus.

Data management and statistical analysis

We did univariate analyses with Epi Info (WHO, version 6.04c). Odds ratio with 95% CI were calculated with Cornfield methods,[15] and exact limits were calculated with Mehta and colleagues' method.[16] We established prevalence of specific lung diseases overall and by age and HIV-1 status. Stata version 6 was used to adjust these calculations to take into account the age and sex of the total population of paediatric respiratory deaths (including children who did not undergo autopsy).

Role of the funding source

The sponsors of the study had no involvement in the study design, collection, analysis, and interpretation of data, writing of manuscript, or decision to submit the report.

Results

1603 children were admitted with respiratory illness and died during the study period in the department of paediatrics. Of the parents or guardians of 1181 of these children who we approached to request consent to do a limited post-mortem examination, 891 (75%) refused to give permission and 290 (25%) consented.[14] Grounds for refusal varied: 383 (43%) thought autopsy was a waste of time since it would not benefit them; 236 (26%) had already organised transport for funeral arrangements and the death certificate had been issued; 77 (9%) stated traditional beliefs that ancestral spirits prohibit necropsy examination; 54 (6%) could not consent since the child was not their own and they wanted to consult relatives; 38 (4%) were of the opinion that the cause of illness should have been investigated before the death of the child, rather than after; 31 (3%) had limitation on burial time for religious reasons; 30 (3%) were not convinced of the rationale for necropsy; 13 (1%) thought the child was too young for necropsy; nine (1%) were anxious that the organs would be sold for transplantation; six (1%) said that they already knew that the child had HIV/AIDS.

There were small differences in age and sex between children who underwent autopsy and those whose parents or guardians refused to consent to this procedure; thus, 99 (37·5%) and 359 (40·3%), respectively, were aged younger than 6 months; 73 (27·7%) and 269 (30·2%), respectively, were aged 18 months or older; the proportions of boys in the two groups were 51·9% (137) and 53·4% (476), respectively.

We did necropsies on 264 children, of whom 137 (52%) were boys (93 HIV-1-positive and 44 HIV-1-negative) and 127 (48%) were girls (87 HIV-1-positive and 40 HIV-1-negative). Overall, 180 (68%) of these 264 children were HIV-1-positive and 84 (32%) were HIV-1-negative. HIV-1-positive children were aged between 1 and 168 months (median 8) and HIV-1-negative children were aged between 1 and 120 months (11·5). HIV-1 rates were 76 of 99 (77%) for children aged 0–5 months; 32 of 51 (63%) for 6–11 months; 22 of 41 (54%) for 12–17 months, and 50 of 73 (68%) for 18 months to younger than 16 years.

	Total*	Adjusted % (SE)†	HIV-positive (n=180)	HIV-negative (n=84)	Odds ratio (95%CI)	p
Diagnosis						
Acute pyogenic pneumonia	116 (44%)	39·1% (3·2)	74 (41%)	42 (50%)	0·70 (0·40–1·21)	0·22
PCP	58 (22%)	27·5 % (3·1)	52 (29%)	6 (7%)	5·28 (2·12–15·68)	0·0001
Tuberculosis	54 (20%)	18·8% (2·5)	32 (18%)	22 (26%)	0·61 (0·31–1·18)	0·16
CMV	43 (16%)	20·2% (2·8)	40 (22%)	3 (4%)	7·71 (2·33–40·0)	0·0002
Interstitial pneumonitis	30 (11%)	11·8% (2·1)	15 (8%)	15 (18%)	0·42 (0·18–0·96)	0·04
Shock lung	27 (10%)	11·5% (2·2)	24 (13%)	3 (4%)	4·15 (1·20–22·10)	0·03
Pulmonary oedema	19 (7%)	6·4% (1·6)	10 (6%)	9 (11%)	0·49 (0·18–1·38)	0·21
Lymphocytic interstitial pneumonitis	10 (4%)	3·8% (1·2)	9 (5%)	1 (1%)	4·37 (0·59–193·7)	0·21

PCP=*Pneumocystis carinii* pneumonia. *Fewer than ten cases were noted of: measles (five HIV-1-positive, two HIV-1-negative), pleurisy (five HIV-1-positive), pulmonary embolism (one HIV-1-negative), respiratory syncytial virus pneumonia (one HIV-1-positive, one HIV-1-negative), herpes simplex virus pneumonia (one HIV-1-positive), lipoidal pneumonia (one HIV-1-positive), malaria (two HIV-1-negative), normal lung (one HIV-1-positive, two HIV-1-negative), Kaposi's sarcoma (two HIV-1-positive), bronchiolitis (three HIV-1-positive). †Percentages and standard errors adjusted to show age/sex structure of all deaths from respiratory disease during the study period.

Table 1: **Lung diseases identified at necropsy, by HIV-1 status**

Table 1 shows the frequency and range of lung diseases overall and by HIV-1 status. Causes of lung disease were diverse, and multiple pathological findings were common in HIV-1-positive and in HIV-1-negative children. The most frequent major diseases diagnosed were acute pyogenic pneumonia (including bronchopneumonia, lobar pneumonia, and abscess), *P carinii* pneumonia, and tuberculosis (typical necrosis with acid-fast bacilli present). The next most common diseases were interstitial pneumonitis (non-specific and non-lymphocytic interstitial pneumonitis), shock lung (hyaline membrane disease), pulmonary oedema, and lymphocytic interstitial pneumonitis. Specific viral pneumonias (measles, adenovirus, respiratory syncytial virus, herpes simplex virus) were seen infrequently. CMV was the most commonly noted infection and most of these cases were mild; severe CMV necrotising pneumonia was recorded in only three cases. 39 (91%) of the 43 cases of CMV were children younger than 1 year. There were seven cases of measles. Kaposi's sarcoma was noted in two HIV-1-positive children, who were aged 35 months and 13 years. In three cases the lung was normal, which indicated extra-pulmonary cause of death.

We noted two distinct patterns of disease frequency when HIV-1 status was taken into account (table 1). *P carinii* pneumonia, CMV, shock lung, and LIP occurred more frequently in HIV-1-positive children than in those who were HIV-1-negative, whereas interstitial pneumonitis, acute pyogenic pneumonia, tuberculosis, and pulmonary oedema were more frequently noted in HIV-1-negative children.

Table 2 shows the three most common necropsy lung findings by age and HIV-1 status. In children aged 18 months and older, acute pyogenic pneumonia and tuberculosis were the two most frequent findings. In HIV-1-positive children overall, acute pyogenic pneumonia, *P carinii* pneumonia, and CMV were the first, second, and third most common findings, respectively, whereas in the HIV-1-negative group the three most common diseases were acute pyogenic pneumonia, tuberculosis, and interstitial pneumonia, respectively. In children younger than 6 months, *P carinii* pneumonia, CMV, and acute pyogenic pneumonia were the three most common findings in the HIV-1-positive group.

Table 3 shows the frequency of selected pathological findings by age and HIV-1 status. Of 58 children with *P carinii* pneumonia, 45 (78%) were less than 6 months of age, six were HIV-1-negative, five were over 18 months of age, three were 24 months old, and the other two were aged 27 months and 12 years. Tuberculosis was the third most frequently noted disease; it presented as pulmonary disease in 44 children and as miliary disease in ten. Tuberculosis was recorded in all age groups and we did not see a systematic difference in rate between HIV-1-positive and HIV-1-negative children.

More than one disease was identified in 114 of 264 necropsies—in 86 (48%) of 180 HIV-1-infected children and 28 (33%) of 84 HIV-1-negative children (p=0·03). A wide range of combinations of diseases was associated with all the major diseases detected. Acute pyogenic pneumonia occurred alone in 74 (64%) cases. The commonest association of acute pyogenic pneumonia was with tuberculosis (12 cases), pulmonary oedema (six

	HIV status	Number	First most common diagnosis	Second most common diagnosis	Third most common diagnosis
Age group					
0–5 months	Positive	76	PCP (51·3%, 39·6–63·0)	CMV (42·1%,30·9–54·0)	Acute pyogenic pneumonia (23·7%, 14·7–34·8)
	Negative	23	Acute pyogenic pneumonia (34·8%, 16·4–57·3)	Interstitial pneumonia (30·4%, 13·2–52·9)	PCP (26·1%, 10·2–48·4)
6–11 months	Positive	32	Acute pyogenic pneumonia (62·5%, 43·7–78·9)	PCP (18·8%, 7·2–36·4)	CMV (15·6%, 5·3–32·8)
	Negative	19	Acute pyogenic pneumonia (78·9%, 54·4–93·9)	Pulmonary oedema (15·8%, 3·4–39·6)	Tuberculosis (15·8%, 3·4–39·6)
12–17 months	Positive	22	Acute pyogenic pneumonia (45·5%, 24·4–67·8)	Tuberculosis (31·8%,13·9–54·9)	Interstitial pneumonia, pulmonary oedema, and shock lung (13·6%, 2·9–34·9)
	Negative	19	Acute pyogenic pneumonia (57·9%, 33·5–79·7)	Tuberculosis (36·8%,16·3–61·6)	Pulmonary oedema (10·5%, 1·3–33·1)
18 months–<16 years	Positive	50	Acute pyogenic pneumonia (52·0%, 37·4–66·3)	Tuberculosis (20·0%,10·0–33·7)	Shock lung (14·0%, 5·8–26·7)
	Negative	23	Tuberculosis (39·1%, 19·7–61·5)	Acute pyogenic pneumonia (34·8%, 16·4–57·3)	Interstitial pneumonia (21·7%, 7·5–43·7)
All patients	Positive	180	Acute pyogenic pneumonia (41·1%, 33·8–48·7)	PCP (28·9%, 22·4–36·1)	CMV (22·2%, 16·4–29·0)
	Negative	84	Acute pyogenic pneumonia (50·0%, 38·9–61·1)	Tuberculosis (26·2%, 17·2–36·9)	Interstitial pneumonia (17·9%, 10·4–27·7)

PCP=*Pneumocystis carinii* pneumonia. Data are percentages (95% CI). n=180 HIV-1-positive and n=84 HIV-1-negative.

Table 2: **Three most common lung diseases found at necropsy, by HIV status and age**

	Age group								Total
	HIV-1-positive				HIV-1-negative				
	0–5 months	6–11 months	12–17 months	18 months–<16 years	0–5 months	6–11 months	12–17 months	18 months–<16 years	
Pathological finding									
Acute pyogenic pneumonia	18	20	10	26	8	15	11	8	116
Pneumocystis carinii pneumonia	39	6	2	5	6	0	0	0	58
Tuberculosis	11	4	7	10	3	3	7	9	54
CMV	32	5	2	1	2	0	0	1	43
Interstitial pneumonia	5	3	3	4	7	2	1	5	30
Shock lung	11	3	3	7	1	0	0	2	27
Pulmonary oedema	4	2	3	1	2	3	2	2	19
Lymphocytic interstitial pneumonitis	2	0	2	5	0	0	0	1	10
Measles	1	1	1	2	0	2	0	0	7

Table 3: **Selected pathological findings by age and HIV status**

cases) and CMV (five cases). *P carinii* pneumonia as the sole finding was present in only 15 (26%) of 58 cases. With CMV it was common and was present in 25 patients three of whom also had tuberculosis. *P carinii* pneumonia and shock lung occurred in ten cases. Shock lung was always associated with another major primary disease. Tuberculosis alone was present in 25 cases.

Discussion

Our findings draw attention to several important points in the dialogue on management of respiratory diseases, in an era when epidemiology of paediatric lung disease is changing. First, most children in the study died from preventable or treatable infectious diseases. Second, despite the limitations, necropsy proved the best way to obtain accurate information about actual rates of specific diseases at death. Therefore, attempts should be made to bring back routine autopsy within health services for surveillance of killer diseases. Third, acute pyogenic pneumonia is the most important cause of death from pulmonary disease in children, whether HIV-1-positive or not. Fourth, we showed that *P carinii* pneumonia was an important cause of death in young African children, and since older children also die from this infection, UNAIDS recommendations for use of co-trimoxazole prophylaxis in HIV-1-positive children need to be revisited. Fifth, tuberculosis was the third commonest cause of death in Zambian children, and affected children from all age groups irrespective of HIV-1 status. This finding contrasts with previous autopsy data from Africa suggesting that tuberculosis was not a major cause of death in children.[14,15] Tuberculosis in children has been a neglected issue and now requires serious attention. Sixth, many children with respiratory illnesses presented with multiple infections, which could complicate the clinical picture and lead to misdiagnosis and inadequate treatment.

Last, the ethical, economical, and moral issues surrounding policy recommendations for management of respiratory infections in HIV-1-positive children in developing countries warrants serious debate. In a setting of few resources and little expertise, carefully designed guidelines are needed. Several diseases have overlapping clinical presentations, and with the gradual deterioration of health and diagnostic services, clinicians are increasingly faced with diagnostic dilemmas. Clinical paediatric practice is based on probabilities rather than on agent-specific diagnosis. To facilitate pathogen-specific treatment, further cheap, rapid, practical, sensitive, and specific tests should be developed for the identification of specific pathogens, especially bacterial pathogens, *Mycobacterium tuberculosis* and *P carinii*.

Rates of necropsy have fallen progressively throughout the world.[14] The reasons for this decline are many, varied, and complex. Autopsy studies may be biased because of study design and patient selection, and findings of hospital-based studies might not apply to rural areas. Limited necropsy might not identify important diseases in other organs. However, much useful data can be obtained from this procedure. Two necropsy studies of HIV-1-positive African children have been done; one in the Ivory Coast,[17] and one in Zimbabwe.[18] Two smaller necropsy studies have been reported from Botswana[19] and South Africa.[20] All these studies were very different in design and in population studied, and, like our investigation, had inherent weaknesses. Although we achieved very good autopsy rates compared with other studies, 75% of our requests for post-mortem examination were refused, and this high proportion could have been a source of bias in selection of patients. Although the sample population who underwent autopsy were fairly representative, with respect to age and sex of the total population of children who died from respiratory illness in the hospital, we have no information on HIV-1 status of those whose parents refused.

All African autopsy studies of children[17–20] have shown that pyogenic pneumonia and *P carinii* pneumonia were common. The results of the Ivory Coast[17] and Zimbabwe[18] studies showed that tuberculosis in HIV-1-positive and HIV-1-negative children was rare. These observations were initially supported by Vetter and colleagues'[7] clinical data, but findings of others on childhood tuberculosis and HIV-1 from west and central Africa indicate that tuberculosis is an important problem in children.[4–6,8,21] Our results accord with these observations. A brief report from Botswana showed that tuberculosis was present in 12·5% of 32 HIV-1-positive children.[19] With the rise in childhood HIV-1-infection in Africa, the range of pulmonary diseases is expanding, and continuous surveillance of fatal diseases through autopsies is required.

Acute pyogenic pneumonia was our most common finding in children of all ages, irrespective of HIV-1 status. These results are consistent with data from other clinical[4,9,22,23] and pathological studies.[17–19] Because suitable clinical samples are hard to obtain from children, studies of the microbial cause of pneumonia are difficult. Bacteriology data from autopsy studies are not accurate, since samples contain many contaminants and distinction between pathogens, opportunistic bacteria, and commensals becomes troublesome. Workers have previously used lung aspirates or blood cultures. In a study of 244 children who were admitted with pneumonia in Cape Town, South Africa, Zar and colleagues[10] detected bacteraemia in 35 of 244 (14%) blood cultures,

with equal frequency in HIV-1-positive and HIV-1-negative children. *Streptococcus pneumoniae* and *Staphylococcus aureus* were the most common isolates; others included *Pseudomonas aeruginosa*, *Escherichia coli*, *Haemophilus influenzae*, *Salmonella typhi*, *Campylobacter jejuni*, *Enterococcus faecalis*, *Klebsiella oxytoca*, *K pneumoniae*, and *Serratia marcescens*. A similar range of bacterial pathogens has been shown by others.[22]

High mortality due to pyogenic pneumonia in children is unacceptable since these bacterial infections are treatable with appropriate antibiotics.[23] Use of co-trimoxazole for *P carinii* pneumonia prophylaxis might provide cross-protection against bacterial infections. However, co-trimoxazole resistance may already be widespread in Africa. The antibiotic resistance patterns of common bacterial infections should be defined regionally, to provide some evidence base for rational empiric therapy.

P carinii pneumonia is strongly associated with immunosuppression. A decade ago, this infection was thought to be a rare manifestation of AIDS in Africa.[24,25] Lucas and colleagues[17] were the first to show, by an autopsy study in the Ivory Coast, the importance of *P carinii* pneumonia as a cause of death in HIV-1-positive children. Their findings were restricted to those aged younger than 15 months. Since then, results of clinical and pathological studies have shown that this disease is widespread and occurs in children in several African countries.[12,18,23,26-28] Our findings are further evidence that *P carinii* pneumonia has become a common and important cause of death in African children. Two findings of interest from our study differed from those of other autopsy studies from Africa:[17,19,21] first, we showed that this organism can occur in older children—in view of this information, the recommended period of co-trimoxazole prophylaxis in current guidelines might have to be extended; second, in no previous autopsy investigations from Africa was *P carinii* pneumonia identified in HIV-1-negative children, whereas we found this infection in six of our HIV-1-negative patients, all of whom were less than 6 months of age. *P carinii* pneumonia in infants without HIV-1 infection has been reported in the USA, and others have noted the disease in malnourished African children before the HIV-1 pandemic.[29]

P carinii pneumonia in children is associated with a very poor prognosis, even under conditions of intensive treatment and the therapeutic options as delivered in western countries.[10,26] Thus, we should focus attention on prevention rather than on diagnosis and treatment of this infection at a late stage. The joint United Nations programme on AIDS/HIV-1 (UNAIDS)[2,30] has recommended that co-trimoxazole be offered to all infants born to mothers with HIV-1 infection from 6 weeks to 6 months of age. However, large scale HIV-1-testing of mothers and mass prophylaxis for millions of young children poses practical problems in African countries.

Results of several clinical studies have shown that tuberculosis and the HIV-1 epidemic have an effect on childhood morbidity and mortality[4–6,13,19,21,31] but paediatric tuberculosis was not viewed by WHO as an important public-health problem, because risk to the community was perceived to be low. We showed that tuberculosis is now an important cause of childhood illness and can infect at any age irrespective of HIV-1 status. The high rate of childhood tuberculosis at autopsy indicates that the tuberculosis epidemic in the region is severe. Previous beliefs that tuberculosis did not arise in children younger than 2 years because of the short duration of exposure[17] are not borne out by our findings.

The differences in frequency of tuberculosis-related deaths between our results and those of others[17,18] could be attributed to several factors: (a) amplified rate of tuberculosis in the adult population leading to increased transmission to children; (b) raised frequency of HIV-1 in children and hence increased susceptibility to tuberculosis; (c) geographical differences in rates of HIV-1 and tuberculosis, and (d) host and pathogen factors. Because tuberculosis has many features in common with other respiratory illnesses, some children who do not have tuberculosis will meet the clinical criteria for diagnosis of tuberculosis, and receive a full course of antituberculosis treatment. However, others who have tuberculosis with concomitant bacterial infections or *P carinii* pneumonia will receive inadequate treatment, and therefore will die. We need new accurate, practical, and rapid diagnostic tests for tuberculosis.

CMV has similar clinical significance to *P carinii*, since both organisms cause opportunistic infection in the immunocompromised patient and can lead to fatal pulmonary diseases. Like *P carinii* pneumonia, CMV also causes pneumonia in immunocompetent infants. Our data suggest that CMV infection is common in HIV-1-positive infants and frequently exists concurrently with other lung infections; thus management is complicated. In most cases CMV infection was mild, and was probably clinically insignificant. We showed that only three children, all HIV-1-positive, died of necrotising CMV pneumonia. Treatment and prophylaxis for CMV pneumonia is expensive and potentially toxic, and management costs are beyond the means of health services of most African countries. Importantly, we identified measles pneumonia in seven children. This finding indicates that the measles immunisation programme is not wholly effective.

Clarity and consensus are needed in guidelines for the management of childhood respiratory diseases in developing countries. These guidelines should include specific advice for management of HIV-1-positive children. We urgently need widespread consultation of scientific evidence, followed by development of practical algorithms for management of respiratory infection in both HIV-1-positive and HIV-1-negative children.[32] Every effort must be made to integrate such procedures with the WHO integrated management of childhood infections technical and training guidelines.[13] Research should focus on development of cheap, practical, sensitive, and specific tests to identify specific pathogens.

Contributors

A Zumla, C Chintu, and S Lucas developed the study concept and design. A Zumla wrote the grant application and obtained funding for the study. C Chintu, A Zumla, and S Lucas were principal study supervisors. V Mudenda, D Maswahu, and S Lucas did the autopsies and histopathological examinations. C Chintu, K Lishimpi, G Bhat, and P Mwaba provided clinical care and counselling, and recruited patients. A Nunn provided statistical expertise and data management. F Kasolo and H Terenuma did laboratory work. A Zumla and A Nunn wrote the manuscript with contributions from C Chintu, S Lucas, V Mudenda, and P Mwaba.

Conflict of interest statement

None declared.

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