An epidemiological study of lower respiratory tract infections in Harare, Zimbabwe.

Student: Prichard Tawanda Mapondera

Internal Supervisor: Professor Andrew C. Whitelaw

External Supervisor: Dr Puja R. Myles (University of Nottingham, United Kingdom)

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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification. I confirm and declare that all authors have seen and approved the content and have contributed significantly to the work.

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Running title: LRTIs in Harare, Zimbabwe

Prichard T. Mapondera, Puja R. Myles, Andrew C. Whitelaw

[a] Division of Community Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.
[b] Division of Epidemiology and Public Health, University of Nottingham, United Kingdom.
[c] Division of Medical Microbiology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa and National Health Laboratory Service, Tygerberg Hospital, Cape Town, South Africa.

*__Corresponding author:__ Prichard T. Mapondera, Division of Community Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.
Email: *prichardmapondera@gmail.com*
Telephone: +263784453987

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ABSTRACT

Background

Lower respiratory tract infections (LRTI) are a leading cause of mortality and morbidity in all age-groups. In Zimbabwe, few epidemiological studies have mapped the aetiology and distribution of LRTIs as well as risk factors for LRTI-related mortality. Understanding the epidemiological profile of LRTIs is important in many ways. The aim of this study was to describe the aetiology and clinical aspects of LRTIs in patients reporting to a referral hospital in Harare, Zimbabwe.

Methods

The study was a cross-sectional survey of 103 patients who had microbiology reports associated with a clinical diagnosis of LRTI at the Harare Central Hospital during 2014. The records showed bacterial cultures were done on the majority of adult samples while most children samples were sent for viral testing. The record books had a lot of missing data.

Results

Enterobacteriaceae were the most frequently isolated organisms in the laboratory (11.7%). Pneumonia (45.6%) and influenza (44%) were the most prevalent acute respiratory illnesses in the study. HIV infection and underlying cardiovascular disease were significant risk factors for mortality with odds ratio of 4.78, p= 0.016 and 4.42, p= 0.0028 respectively.

Conclusion

Enterobacteriaceae were the most common isolates from patients with LRTI; with respiratory syncytial virus associated LRTIs being most common among children under 5. Being HIV positive and having cardiovascular disease is a strong predictor of death in patients with LRTIs. The amount of missing data also emphasised the importance of robust data management systems in hospitals to better inform epidemiological studies.

Keywords: lower respiratory tract infections, epidemiological profile, aetiology, Zimbabwe

INTRODUCTION

Lower respiratory tract infections (LRTI) are regarded as one of the leading causes of morbidity and mortality for all age-groups globally with an estimated 2.7 million deaths attributable to them in 2013 (1). The global incidence ranges from 40 to 50 per 1000 (2, 3) and infections of the respiratory tract are responsible for 4.4% of hospital admissions and 6.6% of primary care consultations (3). In Sub-Saharan Africa, the incidence is 44 episodes per 100 child years with 7 to 13% of the episodes warranting hospitalisation (4). The aetiology and symptomatology of respiratory diseases varies with age, gender, season, the type of population at risk and other factors. (5).

Aetiological agents implicated in the pathogenesis of LRTIs include viruses like respiratory syncytial virus, adenoviruses, influenza virus, human metapneumovirus and para-influenza virus (6) and bacteria such as *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis, Escherichia coli, Salmonella* species *Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae* (7). The HIV epidemic has led to the emergence of other aetiological agents which were previously not considered pathogenic like *Pneumocystis jirovecii,* while there is lack of data on the role other atypical pathogens like Mycoplasma and Legionella in LRTI in Africa, mainly due to difficulties in confirming the diagnosis. In immunocompromised patients and especially in children, these pathogens have been found in polymicrobial pneumonia (8). Furthermore the role of tuberculosis as an aetiological agent of LRTI in HIV-infected patients should be emphasised as *Mycobacterium tuberculosis* infection induces the activation of immune system cells which favour viral replication which may lead to development of opportunistic infection including LRTIs (9).

Therapy for LRTIs in the community is usually empirical; however there is growing concern about antimicrobial resistance that has complicated the selection of suitable antibiotics (10). Pneumococcal resistance to penicillin has been widely documented in Africa and the rest of the world (3, 11). Resistance to co-trimoxazole and chloramphenicol has also been described (3). According to the local guidelines using the Essential Drug List of Zimbabwe 2011 (EDLIZ), the choice of therapy is influenced by HIV status. However if tuberculosis and *P. jirovecii* pneumonia has been ruled out then amoxylin is the first drug of choice but in the case allergy to penicillin then

erythromycin can be given to patients with pneumonia and severe LRTIs. However the aetiological agent of pneumonia influence the drug of choice (12). An understanding of antimicrobial resistance patterns would better inform clinical decisions around antibiotic treatment.

In Zimbabwe and other developing countries where lower respiratory tract infections are one of the leading causes of morbidity and mortality, clinical management is often more difficult. There is a lack of technical expertise and resources required for etiological identification and antibiotic susceptibility testing to enable appropriate antibiotic therapy. In addition, little is known about the etiological distribution of pathogens causing LRTIs in Zimbabwe with the last study done in children more than 2 decades ago by Nathoo et.al (1993) (13). This study documented clinical and socio-demographic features and also identified risk factors for mortality in children hospitalized with acute lower respiratory tract infection. Malnutrition, severe LRTI, age of 1 to 6 months, concurrent diarrhoea, duration of cough greater than or equal to 14 days and previous history of admission for LRTI were significant risk factors for mortality in LRTI. The impact of HIV infection on mortality in children with LRTIs was found to be of major concern in Zimbabwe. The Zimbabwe Global Burden of Disease Study in 2010 showed that LRTIs cause 11.7% of premature deaths, and are second to HIV (29%) in terms of the number of years of life lost (YLLs) due to premature death in Zimbabwe (14).

The aim of the current study was to first, describe the aetiology and clinical aspects of acute respiratory illnesses, and second, investigate the risk factors for LRTI-related mortality in patients reporting to a referral hospital in Harare, Zimbabwe.

METHODS

Study design, setting and population

A cross-sectional survey using routinely collected patient data was conducted at Harare Central Hospital, which is the second largest tertiary care hospital in Harare, the capital city of Zimbabwe. Harare Central Hospital covers over half of Harare's population and patients presenting to the hospital could thus be considered representative of the general population of Harare. The satellite

clinics mostly refers patients to the Harare Central Hospital due to their close proximity to majority of high density suburbs as well as availability of laboratory facilities which are affordable. The patient population consisted of patients of all ages who had a respiratory tract sample submitted to the microbiology laboratory and who had signs and symptoms of LRTI from 1 January to 31 December 2014.

Study procedure

Laboratory methods and data

PTM, [Principal Investigator (PI)] used data recorded in the microbiology laboratory record books to identify patients who had the following specimens submitted: bronchial lavage, nasopharyngeal aspirate and sputum. A unique study identification number was assigned to each participant for anonymity and to ensure patient data confidentiality. Data were extracted from the laboratory record books on age, gender, clinical diagnosis prior to microbiology, test date, type of specimen collected, bacteriology and/or virology results, and antibiotic sensitivity results. According to the laboratory protocol, all respiratory samples were examined by Gram staining (for bacteria and yeasts) and KOH preparation or Periodic acid-Schiff-stained smears for fungal element detection and cultured for common bacterial respiratory pathogens on 5% human blood agar, MacConkey agar (for isolation and differentiation of gram negative bacilli), and chocolate agar (for *Haemophilus* and *Neisseria* species). Samples were also sent for virological testing if clinically requested and the laboratories used polymerase chain reaction (PCR) for identification. For tuberculosis detection, Ziehl-Neelsen stain was used first followed by a confirmation with Lowestein-Jensen culture medium. The records did not indicate if any adult samples were referred for viral detection.

Clinical data

The unique hospital number assigned to the patient on initial admission was used to link the medical records of the patients. Data were obtained only from clinical management records of patients of all ages who had reported with some but not limited to all clinical signs and symptoms of lower respiratory tract illness which include cough, dyspnoea, tachypnoea, chest pain, fever, wheezing and abnormalities on auscultation suggesting an LRTI and diagnosed by

the physician with an LRTI during the study period. The following data was retrieved from the medical records: route of referral, probable diagnosis, date of onset of clinical symptoms/illness and chest X-ray results. Information, if available, on comorbidities such human immunodeficiency virus (HIV) infection, laboratory confirmed tuberculosis (TB) (current or previously diagnosed), asthma, chronic obstructive pulmonary disease, diabetes, underlying malignancy and pregnancy was also collected. Furthermore, data on treatment and management of the acute respiratory tract illness such as antibiotics prescribed (by self or clinician), antivirals (peramivir, oseltamivir) prescribed (by self or clinician), inhaled corticosteroids, intravenous corticosteroids and hospitalisation, were extracted. Patient outcomes were recorded in terms of length of stay in hospital and whether the patient was discharged or deceased. Ambiguous or unclear records were clarified by the PI with the practitioner who recorded the details, or another experienced practitioner. For data entry validation, the PI and another independent assessor rechecked a ten percent sample of the data following completion of data entry to identify any data entry errors.

Data Management and Statistical Analysis

Data were entered into a Microsoft excel spreadsheet and stored in a password protected folder. All statistical analyses were carried out using Stata version 13 (Stata Corp, College Station, Texas, United States of America). Characteristics of the study sample were analysed using descriptive statistics with results expressed as numbers and percentages. The aetiology of LRTIs was described for the overall sample using percentages and distribution by age-group and gender was assessed. Differences in distribution of organisms by gender and age group were assessed using Fisher's exact test. Logistic regression was used to identify predictors of LRTI-related mortality. A sensitivity analysis of predictors of LRTI-related mortality was also conducted after the unadjusted logistic regression to evaluate if there was any impact caused by the missing values and in this case all the missing values were recoded as 'no'. However in every other analysis done all missing data was coded as missing and reported.

Ethical approval

Ethical approval and waiver of informed consent was obtained from the Human Health Research Ethics Committee of the University of Stellenbosch (S15/07/148) and Harare Central Hospital Ethics committee (HCHEC 160715/54). The methods followed in obtaining data were in accordance with the ethical standards of the committees that gave ethical clearance, and the Helsinki Declaration.

RESULTS

The analysis included 103 patients of whom 53% were male. Twenty children below the age of 15 were included in the study with 14 being under the age of 2 and of those 6 being neonates. The median age was 31.5 years with the age ranging from 0 years to 86 years. The mean age was 21.7 years (Standard Deviation, (SD) 14.1). 76.7% of patients were hospitalised and the mean length of stay in hospital was 4.7 days (interquartile range 2-6 days). Approximately 65% of hospitalised patients were discharged alive while 13.6% died in hospital and in 21.4 % the outcome was unknown. Table 1 summarises the study sample characteristics.

Table 1: Characteristics of the study sample (n=103)

Characteristic	Number (%)
Sex	
Male	46 (44.7)
Female	55 (53.4)
Missing	2 (1.9)
Referral	
Clinician	62 (60.2)
Self-referral	37 (35.9)
Other	4 (3.9)
Specimen	

Throat swab	1 (1.0)
Bronchial lavage	32 (31.1)
Nasopharyngeal aspirate	31 (30.1)
Sputum	39 (37.8)
Chest X-ray done	
No	37 (35.9)
Yes	61 (59.2)
Unknown	5 (4.9)
Chest X-ray Results	
Normal	11 (18.0)
Abnormal	46 (75.4)
CXR done but report not known	4 (6.6)
HIV	
No	63 (61.2)
Yes	24 (23.3)
Unknown/missing	16 (15.5)
TB (laboratory confirmed)	
No	68 (66.0)
Yes	15 (14.6)
Unknown/missing	20 (19.4)

Asthma	
No	70 (68.0)
Yes	7 (6.8)
Unknown/missing	26 (25.2)
COPD	
No	63 (61.2)
Yes	3 (2.9)
Unknown/missing	37 (35.9)
Heart disease	
No	57 (55.3)
Yes	28 (27.2)
Unknown/missing	18 (17.5)
Diabetes	
No	74 (71.8)
Yes	12 (11.7)
Unknown/missing	17 (16.5)
Cancer	
No	17 (69.5)
Yes	13 (12.8)
Unknown/missing	18 (17.7)
Pregnancy	
No	92 (89.3)

Yes	4 (3.9)
Unknown/missing	7 (6.8)
Hospitalisation in the last 12 months	
No	21 (20.4)
Yes	79 (76.7)
Unknown/missing	3 (2.9)
Discharged	
Discharged alive	51 (64.1)
Died in hospital	11 (13.6)
Unknown/missing/not applicable	17 (22.3)

Pathogen Spectrum

Potential pathogens were only isolated in 31/103 samples (30.1%); the remainder of the specimens were reported as either normal flora or no growth. A small proportion of samples were reported as Streptococcus viridans (6, 5.9 %) and Candida species (3, 0.97%); since these organisms are not generally regarded as likely causes of LRTI, they were also classified as normal flora. No patients had more than one organism isolated according to the records.The spectrum of pathogens isolated is shown in Fig 1. The most commonly isolated organisms were lactose fermenting Enterobacteriaceae (11.7%). Standard practice in the local microbiology laboratory is not to identify these organisms further, due to resource constraints. *Streptococcus pneumoniae*, *Staphylococcus aureus* and Group D Streptococcus were also isolated (Fig.1). Fifteen out of 20 children samples were sent for virology with 8 being found positive for RSV. Table 2 shows the distribution of the isolates relating to the sample processed.

Fig.1 Organisms Isolated (y axis is expressed as a % of all samples)

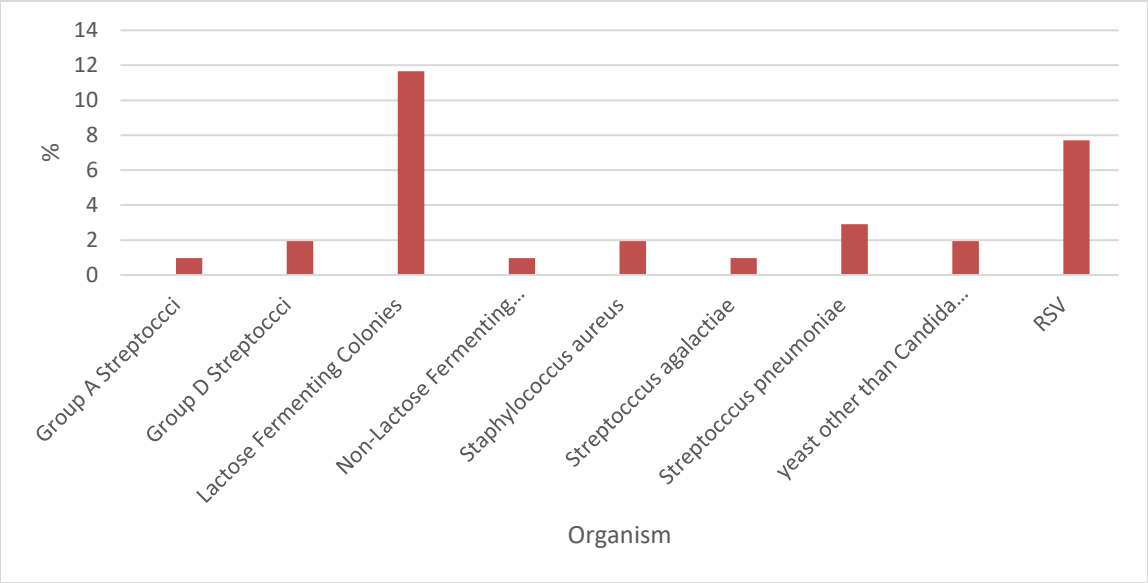

Table 2. Distribution of the isolates relating to the sample processed

	Group A Streptococcus	Group D Streptococcus	LFC	NLF	Staphylococcus aureus	Streptococcus agalactiae	Streptococcus pneumonia	Yeast other than candida
Specimen								
Throat swab	0	0	1	0	0	0	0	0
Bronchial Lavage	1	2	4	0	0	0	1	0
Nasopharyngeal aspirate	0	0	3	0	1	0	0	0
Sputum	0	0	4	1	1	1	2	2

LFC – Lactose Fermenting Colonies

NLF - Non Lactose Fermenting Colonies

Distribution of microorganisms by age and gender

There was no statistically significant difference in isolation rates by gender and age after conducting the Fisher's exact test ($p = 0.25$ and $p = 0.33$ respectively). If RSV is included, most organisms were isolated in children under 15 years, especially in the age group 6 to 15 years. The 8.7% period prevalence of RSV was all in children under 5 years of age.

Clinical Diagnoses associated with LRTI symptoms

The three most prevalent lower respiratory tract infections listed as probable diagnoses were pneumonia (45.9%), influenza (44%) and pulmonary tuberculosis (32%). (**Table 3**).

Table 3. Clinical Diagnoses associated with LRTI symptoms

Clinical Diagnoses	Number (%)
CCF	1 (1.0)
Influenza	43 (43.9)
Bronchitis	5 (5.1)
Pneumonia	45 (45.9)
Pleural effusion	17 (17.3)
Lung cancer	3 (3.1)
Pulmonary tuberculosis	31 (31.6)
RSV	8 (8.2)

Antimicrobial Susceptibility Profile

Antibiotic resistance patterns could not be analysed due to the fact that antibiotic susceptibility tests were only conducted on 28 isolates out of the 31 potential pathogens isolated, and there was a marked lack of consistency in the panels of antibiotics tested. No antimicrobial susceptibility tests were conducted for yeasts that were isolated.

Prescribing practices for LRTI

Antibiotics were prescribed to most patients and 92.2% of all participants had either self-prescribed an antibiotic or antibiotics were prescribed by the clinician. However, details about which specific agents were self-prescribed were not available in most of the record books. Intravenous corticosteroids were prescribed to 35.9% of hospitalised patients. Antivirals (peramivir, oseltamivir) were prescribed in 36.9% patients (Table 4).

Table 4. Drugs prescribed for patients with LRTI

	Yes (%)	No (%)	Unknown
Antibiotics	95 (92.2)	3 (2.9)	5 (4.9)
Antivirals	38 (36.9)	60 (58.2)	5 (4.9)
Inhaled steroids	25 (24.3)	72 (69.9)	6 (5.8)
Intravenous steroids	37 (35.9)	61 (59.2)	5 (4.9)

Predictors of LRTI-related Mortality

Univariate logistic regression analysis was conducted and the results are shown in Table 5. A significant association was found between being HIV positive and mortality [crude odds ratio (OR): 4.78 (95% CI: (1.34-16.98), p= 0.016] and heart disease was also a significant predictor of mortality [crude OR 4.42, (95% CI: (1.17–16.67) p= 0.0028]. No significant relationship was found between laboratory-confirmed TB and death (Table 4). Use of antiviral agents and intravenous steroids was significantly associated with mortality, [crude OR 7.74, (95% CI: (1.99-30.05) p=0.003] and (crude OR 3.6, (95% CI: (1.10- 11.76) p=0.034] respectively. It was not possible to conduct a multivariable analysis because of the small sample size.

Table 5: Predictors of mortality (unadjusted logistic regression results)

Independent predictor variable	Non-survivors Number (%)	Survivors Number (%)	Unadjusted OR (95% CI)	P value
Patient medical history (comorbidities)				
HIV				
No	58 (65.2)	5 (35.7)	1 (reference group)	
Yes	17 (19.1)	7 (50.0)	4.78 (1.34-16.98)	0.016
Missing	14 (15.7)	2 (14.3)	-	
TB				
No	59 (66.3)	9 (66.0)	1 (reference group)	
Yes	12 (13.5)	3 (21.4)	1.64 (0.39 -6.96)	0.503
Missing	18 (20.22)	2 (14.29)		
Heart disease				
No	53 (59.4)	4 (28.6)	1 (reference group)	
Yes	21 (23.6)	7 (50.0)	4.42 (1.17–16.67)	0.028
Missing	15 (16.9)	3 (21.4)		
Patient treatment characteristics				
Antivirals				
No	57 (64.0)	3 (21.4)	1 (reference group)	
Yes	27 (30.3)	11 (78.6)	7.74 (1.99-30.05)	0.003
Missing	5 (5.6)	0 (0.0)	-	
IV steroids				

No	56 (62.9)	5 (35.7)	1 (reference group)	
Yes	28 (31.5)	9 (64.3)	3.6 (1.10- 11.76)	0.034
Missing	5 (5.62)	0 (0.0)	-	
Inhaled steroids				
No	64 (71.9)	8 (57.1)	1 (reference group)	0.267
Yes	20 (22.5)	5 (35.7)	2 (0.59-6.81)	
Missing	5 (5.6)	1 (7.1)	-	
Antibiotics				
No	0 (0.0)	3 (3.37)	-*	
Yes	14 (100.0)	81 (91.0)		
Missing	0 (0.0)	5 (5.62)		

∗*Unable to calculate OR due to insufficient data*

OR= odds ratio; CI= confidence interval

The results of sensitivity analysis of predictors of LRTI-related mortality were almost similar to those of the unadjusted logistic regression with the exception of TB where the p value was now statistically significant. **(Appendix 1)**

DISCUSSION

This study provides an insight into the epidemiology of lower respiratory tract infections in Harare, Zimbabwe, despite the small sample size.

Pathogen Spectrum

The commonly isolated bacteria were lactose fermenting coliforms at 11.7%. Where bacteria could be differentiated, they mainly comprised *Escherichia coli* and Klebsiella. However, in this study they were put under one umbrella because most of the bacteria could not be differentiated to species level due to shortage of reagents at the laboratory. Nevertheless, this finding was

consistent with a study in Nigeria where *Klebsiella pneumoniae* was the most common cause of LRTIs (38%) (3). Conversely, *S. pneumoniae* and *Pseudomonas aeruginosa* were the most frequently isolated pathogens from respiratory samples in a study in Nepal (2). Gram positive bacteria were also isolated in this study though in small numbers, similar to the findings from Nigeria and Nepal (2, 3). All the respiratory syncytial viruses were detected in children and this is a common causative pathogen of LRTIs in children as shown in various studies (2, 15, 16).However this finding may have been affected by the circumstances that no adult samples were sent for virological tests. No testing was performed for atypical pathogens like Mycoplasma and Legionella as well as *Pneumocystis jirovecii* and we do not know how common these organisms may have been. This is in line with other studies which attribute this to either appropriate tests not being done or the organisms being totally missed (17). Furthermore many studies have shown some LRTIs being caused by more than 1 isolate but which was a different case in our study. (18, 19). This probably more of a reflection on the quality of the laboratory and the tests available than necessarily a true reflection of the incidence of combined infection.

Prevalence of LRTIs

Of all patients included in the study, pneumonia was the most common LRTI diagnosed in patients with a prevalence of 45.9% and this was consistent with a study involving autopsies from all over Africa (20). RSV associated LRTI was found only in children under 5, which is in keeping with a systematic review of RSV which showed that RSV was mainly found in children (16). This was different from a study done in Kenya where influenza was the most common LRTI in children (15). Most of the influenza was diagnosed during the winter season in Zimbabwe, which is a common seasonal pattern due to the cold. However the influenza was clinically diagnosed because of absence of formal testing in the study setting; hence, the difference in the two studies.

Predictors of Mortality

HIV positive status was a strong predictor of mortality [crude odds ratio (OR) 4.78, p 0.016)] and has been reported in earlier studies (21, 22). Another comorbidity, heart disease was as also a strong predictor of mortality in LRTI; and the literature suggests that underlying illnesses in general are strong predictors of death (23). No significant relationship was found between a diagnosis of TB and LRTI-related death in this study, but this may have been affected by the way

TB was diagnosed in the setting. Most TB is diagnosed by smear microscopy which has low sensitivity and therefore might miss some cases. However, the GeneXpert MTB/Rif (Cepheid) has been introduced to the country and is being rolled out; this may improve the laboratory diagnosis of TB. Although Isonaziad Preventive Therapy (IPT) with antitetroviral treatment has been widely documented to be very effective in reducing the risk of tuberculosis in HIV patient, but the data could not be collected in this study.

Limitations

The study took place at one referral hospital in Harare province, which is an urban area, and therefore the findings may not be generalizable to other provinces, especially rural areas in which the environment and other risk factors may be vastly different. The data used were from record books and data recording was prone to transcription errors. The major limitation was missing data which may have affected the mapping of the respiratory illness and led to under- or overestimation of results. The issue of sparse data regarding respiratory illnesses and other diseases in general is common in the Sub Saharan Africa despite recognition of respiratory illnesses being regarded as one of the leading causes of death in that region (24). Data were considered for a single year so it might not be a true reflection of the status quo and consequently, a 5 or 10 year analysis would better capture the actual epidemiological trends; nevertheless, this study provides an important preliminary analysis that could be used as a trigger to strengthen data recording and plan future epidemiological studies. This study used microbiological reports from the lab and clinical records from the wards to identify patients with LRTIs; however, a cross-sectional study involving recruitment of patients may be more informative than a retrospective record review. Antimicrobial susceptibility trends could not be established due to missing data and lack of required resources for these tests in the laboratory; this is a major setback in establishing drug resistance patterns. Unavailability of reagents and skilled labour led to the isolated organisms not being differentiated to species level and this limited the amount of information available. Furthermore, atypical pathogens like Mycoplsama, and Legionella as well as other pathogens like *Pneumocystis jirovecii* could not be isolated due to these constraints leading to a huge gap in the epidemiology of the pathogen spectrum causing lower respiratory tract infections. Records for most patients who reported to the hospital but were not admitted are not kept by the hospital, therefore contributing to missing data and leading to the small sample size in this study.

Recommendations

The hospital information management systems need a major overhaul as there was a significant amount of missing data. If possible, the hospital should consider moving to a computer-aided electronic data recording system that can easily link all patient records. There is also a need to educate staff on the importance of record keeping and maintenance. Provision of reagents and skilled labour is of paramount importance to improve isolation of pathogens, to enable the identification of bacteria to species level, and to perform consistent antibiotic susceptibility testing. Resources should be allocated to detecting viruses causing LRTIs as most of the specimens were being sent for microbiology and with only a few samples from children being sent to virology. Although setting up a virology laboratory is expensive but this can be a long term goal for the hospitals as virology is an important aspect of pathogen detection. With this data, hospitals can establish specific treatment regimens, based on prevalence, pathogen continuum and antibiotic susceptibility patterns over time.

Conclusion

Enterobacteriaceae are the most commonly isolated organisms from patients with lower respiratory tract infection, and respiratory syncytial virus associated LRTIs was most common among children under 5. Being HIV positive is a strong predictor of death in patients with LRTIs. Improved data management, including the systematic collection, consolidation and evaluation of morbidity and mortality reports and other relevant data, is needed in hospitals to enable a better understanding of the epidemiology of LRTIs and other diseases.

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Appendix 1: Sensitivity analysis results of LRTI-related mortality

Independent predictor variable	**Non-survivors Number (%)**	**Survivors Number (%)**	**Unadjusted OR (95% CI)**	**P value**
Patient medical history (comorbidities)				
HIV				
No	72 (80.9)	7 (50.0)	1 (reference group)	
Yes	17 (19.1)	7 (50.0)	4.2 (1.31 -13.70)	0.018
TB				
No	77 (86.5)	11(80.6)	1 (reference group)	
Yes	12 (13.5)	3 (19.4)	1.75 (0.43-7.19)	0.45
Heart disease				
No	68 (76.4)	4 (50.0)	1 (reference group)	
Yes	21 (23.6)	7 (50.0)	3.0 (0.96-9.65)	0.06
Patient treatment characteristics				
Antivirals				
No	62 (69.7)	3 (21.4)	1 (reference group)	
Yes	27 (30.3)	11 (78.6)	8.4 (2.17-32.6)	0.006
IV steroids				
No	61 (68.5)	5 (35.7)	1 (reference group)	
Yes	28 (31.5)	9 (64.3)	3.9 (1.2- 12.7)	0.02
Inhaled steroids	69 (77.5)	10 (64.3)	1 (reference group)	
No	20 (22.5)	5 (35.7)	1.9 (0.58 – 6.37)	0.3

Yes			
Antibiotics			
No	0 (0.0)	3 (3.37)	-*
Yes	14 (100.0)	81 (91.0)	
Missing	0 (0.0)	5 (5.62)	

**Unable to calculate OR due to insufficient data*

OR= odds ratio; CI= confidence interval