Prevalence of bacterial pneumonia among HIV-Seropositive patients in East Africa: Review

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Bacterial pneumonia is a significant cause of morbidity and mortality among the HIV-seropositive patients still in the era of combination Antiretroviral Therapy. The actual burden of bacterial pneumonia in HIV-seropositive patients is not well documented in East Africa. The purpose of this study is to evaluate the prevalence of pneumonia infection in HIV-seropositive patients in the region. Different electronic databases from PubMed, Google scholars, Scopus, Science direct and Web of Science were searched for articles published from 1994 to 2020 that assessed the prevalence of bacterial pneumonia in HIV-seropositive patients in East Africa. Data on the prevalence of bacterial pneumonia in HIV-seropositive patients in East Africa counties are limited. Therefore, only 13 articles about the prevalence of bacterial pneumonia in HIV-seropositive patients in East Africa were reviewed. Tanzania exhibited the highest level of bacterial pneumonia in HIV-seropositive patients at 59.76%, while Rwanda had the lowest level at 5.6%. The different risk factors identified, such as intravenous drugs, cigarette smoke and unvaccinated were associated with the development of bacterial pneumonia in HIV-seropositive patients. Bacterial pneumonia is a major public health problem and it is the leading cause of morbidity and mortality in HIV-seropositive patients in East Africa. This review will provide information to the scientific community, policymakers and program officers to design pneumonia preventive interventions in HIV-seropositive patients. The author recommended that further studies need to be conducted on the magnitude of bacterial pneumonia in HIV-seropositive patients in the region.

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Kindu Alem has completed his first degree in Applied Biology from Addis Ababa University, and his Master's degree in Applied Microbiology from Bahir Dar University, Ethiopia. He had been a high school and teachers' education college teacher for the last 11 years. Furthermore, he has been teaching undergraduate programs at Woldia University for the last 4 years. He has published four articles in the areas of COVID-19, solid waste management, food quality, and water quality in international journals. He is currently a lecturer in the Biology department of Woldia University.

PUBLIC INTEREST STATEMENT

Pneumonia is one of the leading causes of death and public health problem. It is an opportunistic infection and it is more common and severe because of in immune-suppression in HIV positive individuals, and it is also the major clinical manifestation of HIV patients. Pneumonia has a significant impact on the life, health-care costs, and survival of HIV patients. To understand the burden and delivery of health services of the disease in the region, the researcher conducted this systematic review to evaluate the prevalence of pneumonia infection in HIV-seropositive patients. There is a great research gap concerning the prevalence of bacterial pneumonia in HIV-seropositive patients in East Africa. This gap might be due to lack of equipped laboratory facilities in the region. Therefore, this gap will give information to the scientific community who would like to do research in the region.
1. Introduction

Bacterial pneumonia is one of the common infections among HIV-seropositive patients in Sub-Saharan African countries and it is a major public health problem (Simonetti et al., 2014; Solomon et al., 2018). It is a significant cause of morbidity and mortality among the HIV positive individuals still in the era of combination Antiretroviral Therapy (cART) (Harboe et al., 2014). The infection rate of this infection ranged from 3.9 to 20 cases per 100 persons per year in HIV-seropositive patients. The spectrum of HIV-associated opportunistic pneumonias is broad and includes bacterial, mycobacterial, fungal, viral, and parasitic pneumonias. In immunosuppressed patients, especially those who are human immunodeficiency virus (HIV) positive, pneumonia is a common opportunistic infection (Jolobe, 2018). The predominant bacterial opportunistic pathogens in the development of bacterial pneumonia were Streptococcus pneumoniae (S. pneumoniae), Haemophilus influenzae (H. influenzae), Staphylococcus aureus (S. aureus), and Mycobacterium tuberculosis (M. tuberculosis) (Clark, 2020; Marangu & Zar, 2019).

Streptococcus pneumoniae is one of the most important causative agent of pneumonia of respiratory tract infection and their co-existence in immunocompromised patients; especially those who are HIV positive have been documented. More than 60% bacterial pneumonia in adults is accounted by S. pneumoniae who require hospitalization. It is a gram-positive diplococcus with thick capsule, which is responsible for the organism’s virulence. In human immunodeficiency virus infected individuals, S. pneumoniae infections have emerged as an important cause of morbidity and mortality (Feldman & Anderson, 2016; Staiteh & Guidot, 2014). The incidence of HIV-associated pneumonias has decreased following the introduction of antiretroviral treatment (ART) but, in HIV-infected individuals, bacterial pneumonia became the most frequent infection (Conklin et al., 2015). Transmission is common from person-to-person through respiratory secretions, particularly within families and other groups in which people are in close contact (Yoshimine et al., 2001).

A study done in the United States demonstrated that bacterial pneumonia is more frequent in HIV-infected persons than HIV-uninfected persons, and the risk is higher among those with CD4 lymphocyte counts less than 200 cells/µl (Gingo & Morris, 2013). Pneumonia has been a major comorbidity in HIV infected individuals since the beginning of the HIV epidemic (Aston, 2017). The typical symptoms pneumonia includes fever, cough, sputum production and chest pain. Alcoholism, smoking, chronic disease of the lung or heart, immunosuppression and influenza are the predisposing factors for the development of pneumonia (Koss et al., 2015). In human immunodeficiency virus (HIV) infected persons, the respiratory tract is the most frequently infected sites. From the respiratory tract the lung has been the most frequently infected, ranging from 100% in the early period of the HIV epidemic to 70% in the era of highly active antiretroviral treatment (HAART) (Iwai et al., 2014). Thus, pulmonary complications are a major cause of morbidity and mortality among HIV-infected patients worldwide (Madeddu et al., 2013). It accounted for 72% of AIDS deaths globally (Aderaye, 1994). A study has reported that 34% prevalence of bacterial pneumonia in East Africa (Adhanom et al., 2019) but, there was no comprehensive data about the prevalence of HIV-seropositive patients associated with bacterial pneumonia.

Different studies that have been done in East Africa indicated the burden of bacterial pneumonia (Maitland et al., 2017; Umuhiza et al., 2021). However, these studies did not show consistencies and no review has been conducted to report the prevalence of bacterial pneumonia in HIV-seropositive patients. Therefore, the purpose of this paper is to review the current prevalence of bacterial pneumonia in HIV-seropositive patients and future research interventions to address in East Africa.
2. Methods

2.1. Search strategy
The review of the prevalence of pneumonia among HIV-seropositive patients literatures (years 1994 to 2020) was performed using electronic databases such as PubMed, Google scholars, Scopus, Science direct and Web of Science. The researcher conducted a comprehensive review published in English related to the topic. The author used the following core search terms or phrases: “prevalence”, “epidemiology”, “magnitude”, “bacterial pneumonia”, “HIV-seropositive patients” and “East Africa”. East Africa countries such as 5 Ethiopia (Aderaye, 1994; Aderaye et al., 2007; Adhanom et al., 2019; Genetu & Zenebe, 2020; Wachamo & Bonja, 2020), 2 in Kenya (Chakaya et al., 2003; Conklin et al., 2015), 1 in Rwanda (Batungwanayo et al., 1994), 3 in Tanzania (Daley et al., 1996; Morolahun et al., 2020; Mwita et al., 2012) and, 2 in Uganda (Rubaihayo et al., 2016; Yoo & Worodria, 2010) were included in this study as indicated in Table 1.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria
Research articles reporting only the prevalence of bacterial pneumonia in HIV-seropositive patients and published in English language done in East Africa countries were considered.

2.2.2. Exclusion criteria
All articles published in languages other than English, done outside East Africa, duplicated articles, researches which did not report the results of the researcher’s interest, and unpublished peer-reviewed journals were excluded.

3. Discussion

3.1. Prevalence of pneumonia
Recurrent bacterial pneumonia and Pneumocystis pneumonia (PCP) are two of the most frequent AIDS-defining diseases in the United States (Buchacz et al., 2016). Moreover, PCP has been increasingly reported in areas of the world such as sub-Saharan Africa, where it had previously been thought to be a rare pathogen. Furthermore, studies have done in Europe, USA and in sub-Saharan Africa confirmed that bacteria are the causative agents of bacterial pneumonia in around 40–75% of HIV-seropositive patients (Aston & Rylande, 2016; Huang & Crothers, 2009). In HIV-seropositive patients, S. pneumoniae is the most common bacteria cause a community-acquired pneumonia, implicated in approximately 20% of all bacterial pneumonias (Lu et al., 2008). The highest prevalence of pneumonia (59.76%) in HIV-seropositive patients in the study region is observed in Tanzania (Morolahun et al., 2020). Whereas, the lowest prevalence of pneumonia infection (5.6%) in HIV-seropositive patients is reported in Rwanda (Batungwanayo et al., 1994). The reason for this inconsistence result of the prevalence of bacterial pneumonia in HIV seropositive individuals in East Africa countries might to be due to lack of laboratory facilities in limited resource health centers in the region.

4. Bacterial pneumonia
Pneumonia is still one of the most common opportunistic infection in HIV patients, including in developed countries like United States, Canada, and Europe. The occurrence of pneumonia increased rapidly during the 1980s, occurring in 75% of individuals with AIDS, resulting in death rate up to 40%. Furthermore, the disease became one of the major AIDS-defining illnesses (Salzer et al., 2018). Even if the occurrence of the infection decreases, it is still a serious health concern for individuals living with HIV/AIDS (Djawe et al., 2015). Previous studies showed that bacterial pneumonia is the most common infection in HIV-seropositive patients, in whom the frequency of the infection is increased by >10 times higher than in healthy individuals (Miguez-Burbano et al., 2005; Segal et al., 2011). Streptococcus pneumoniae is the most common bacterial pathogen that causes pneumonia among HIV-infected individuals, implicated around 20% of all bacterial pneumonias. H. influenza accounts for 10–15% of cases of bacterial pneumonia in HIV patients.
| No. | References                          | Study Area | Study Period | No. of pneumonia infected people | No. of HIV-seropositive patients | Prevalence of pneumonia (%) |
|-----|------------------------------------|------------|--------------|----------------------------------|----------------------------------|-------------------------------|
| 1.  | Aderaye, 1994                      | Ethiopia   | 1994         | 3                                | 9                                | 33.3                          |
| 2.  | (Aderaye et al., 2007)             | Ethiopia   | 2007         | 39                               | 131                              | 29.8                          |
| 3.  | (Adhanom et al., 2019)             | Ethiopia   | 2019         | 110                              | 252                              | 43.7                          |
| 4.  | (Genetu & Zenebe, 2020)            | Ethiopia   | 2019         | 68                               | 163                              | 41.7                          |
| 5.  | (Wachamo & Bonja, 2020)            | Ethiopia   | 2020         | 90                               | 420                              | 21.4                          |
| 6.  | (Chakaya et al., 2003)             | Kenya      | 2003         | 19                                | 52                               | 36.5                          |
| 7.  | (Conkin et al., 2015)              | Kenya      | 2016         | 237                              | 549                              | 43.2                          |
| 8.  | (Batungwanayo et al., 1994)        | Rwanda     | 1994         | 5                                | 111                              | 4.5                           |
| 9.  | (Daley et al., 1996)               | Tanzania   | 1996         | 18                               | 127                              | 14.2                          |
| 10. | (Mwita et al., 2012)               | Tanzania   | 2012         | 13                               | 125                              | 10.4                          |
| 11. | (Morolahun et al., 2020)           | Tanzania   | 2020         | 98                               | 164                              | 59.8                          |
| 12. | (Yoo & Worodria, 2010)             | Uganda     | 2010         | 23                               | 62                               | 37.1                          |
| 13. | (Rubaihayo et al., 2016)           | Uganda     | 2016         | 12,165                           | 108,619                          | 11.2                          |
A similar study reported that *Pseudomonas aeruginosa* (*P. aeruginosa*) and *S. aureus* were bacterial pathogens that cause bacterial pneumonia and frequently increased in persons with HIV infection (Adhanom et al., 2019; O’Brien et al., 2019).

The incidence of bacterial pneumonia among individuals with HIV infection is greater than that among individuals without HIV. Currently, in HIV-infected patients, bacterial pneumonia is the most frequent infection as well as the most common admission diagnosis (Madeddu et al., 2013). Several studies have confirmed a clear correlation of an increased rate of pneumonia with decreasing CD4 cell counts (Gordin et al., 2008; Moir & Fauci, 2009; Woodhead et al., 2011). HIV infection is associated with a > 10-fold increased incidence of bacterial pneumonia (Buchacz et al., 2010). Lower respiratory tract infections (LRTIs) due to bacteria are the most common respiratory diseases among HIV-infected patients and are regularly the first clinical manifestations of the HIV infections (López-Palomo et al., 2004). In HIV-seropositive patients, bacterial pneumonia is regularly persistent, and persistent pneumonia is an AIDS-defining condition (O’Brien et al., 2019). However, the advent of antiretroviral therapy (ART), the incidence and mortality rate of AIDS-defining infections like pneumonia have dramatically decreased at an alarmingly rate since the late 90’s (Baral et al., 2013).

The common pathogens that cause bacterial pneumonia in HIV-infected patients include *S. pneumoniae*, *H. influenzae*, *Klebsiella pneumoniae* (*K. pneumoniae*), *P. aeruginosa*, *Escherichia coli* (*E. coli*), and *S. aureus* (Lee et al., 2019; Ramesh Kumar & Arunagirinathan, 2018). However, *S. pneumoniae* is the most common cause of pneumonia in HIV infected individuals which accounts for 40% of all bacterial pneumonia (Seidenberg et al., 2021). Community-acquired bacterial pneumonia caused by *S. pneumoniae* and *Haemophilus* species are also common in individuals without HIV infection (Muthumbi et al., 2017). In contrast, *P. aeruginosa* and *S. aureus* are both more commonly reported as community-acquired causes of pneumonia in individuals with HIV infection (Deen et al., 2012).

5. **Risk factors for the development of bacterial pneumonia**

Several of the the risk factors for pneumonia development are common in both developed and developing countries (Curran et al., 2008). Bacterial pneumonia can occur throughout the entire course of HIV infection, but the incidence increases as CD4 cell numbers decrease (Harboe et al., 2014). Intravenous drugs and smoking are risk factors for the development of bacterial pneumonia in this group of patients (Herrero & Olivas, 2012). Smoking cigarettes are associated with a two- to fivefold increase in the risk, particularly among patients with low CD4 + T cell counts (Barska et al., 2017). Other risk factors include age, gender, detectable HIV load and previous recurrent pneumonia (Samperiz et al., 2014). The incidence of pneumococcal disease is up to 50 times higher in children <2 years of age and in adults >65 years of age, than in adolescents. A male: female ratio of 1.5:2.1 is seen in most 80% of cases of bacterial pneumonia occur with a CD4 count, 400 cells per mm³, and recurrent pneumonia with a CD4 count, and 300 cells per mm³ (Meiring et al., 2016; Polle, 2016). The Centers for Disease Control (CDC) added recurrent bacterial pneumonia as an AIDS-defining condition in 1992 (Schneider et al., 2008). Moreover, use of wood as a fuel source, cook food in living room and being unvaccinated were others risk factors for the development of bacterial pneumonia (Adhanom et al., 2019). Another study done in East Africa revealed smoke of fuel wood, cooking food in living room, and being unvaccinated were the highest risk factors significantly associated with development of pneumonia (Gothankar et al., 2018). A similar study showed that cigarette smoking habit, intravenous drug use, measurable virus load, older age, and early iterative pneumonia are the major risk factors for the development of bacterial pneumonia in HIV-seropositive patients (Muthumbi et al., 2017; Navin et al., 2000). Several studies reported that *S. pneumoniae*, *H. influenza*, *S. aureus*, *P. aeruginosa*, *M. tuberculosis* were the most common bacterial pathogens that cause bacterial pneumonia in HIV-seropositive patients in East Africa (Adhanom et al., 2019; Kariuki & Dougan, 2014).
6. Diagnosis
Sputum microscopy (Gram stained sputum smears were examined microscopically for the detection of the bacteria) and sputum culture (sputum sample was inoculated on a Chocolate agar and MacConkey agar) were the most important diagnostic methods (Vechi et al., 2018). Polymerase chain reaction (PCR) is an important diagnostic method of bacterial pneumonia compared to microscopy and culturing methods. Serum (1, 3)-β-D-glucan is a highly sensitive diagnostic method of pneumonia (Karageorgopoulos et al., 2013). The main diagnostic methods of bacterial pneumonia in East Africa are clinical observation, culturing, chest radiography, and ultrasound radiography (Aston, 2017; De Benedictis et al., 2020). However, use of a combination of different diagnostic tests such as microscopy (immunofluorescence and conventional staining), chest radiography, ultrasound radiography, PCR, and (1, 3)-β-D-glucan is recommended (Aston, 2017; Karageorgopoulos et al., 2013; Salzer et al., 2018).

7. Treatment
Treatment of pneumonia by commonly used drugs has been complicated the selection of medication due to rapid development of drug resistance (Salzer et al., 2018). The principle of bacterial pneumonia treatment in HIV positive individuals is similar to that in individuals without HIV infection (Sisay et al., 2018). Different researchers in the previous time indicated that penicillin is cost-effective in the treatment of pneumonia before the outbreak of HIV infection in Africa (Bhutta et al., 2013; Enarson et al., 2014). A study done in India also showed that penicillin is the cost effective antibiotic to treat pneumonia in developing countries. For more than half a century, penicillin has been used as the standard drug for treating pneumonia infection (Harboe et al., 2014). WHO recommended that cotrimoxazole is a prophylactic agent against opportunistic infections among HIV/AIDS infected patients (Sisay et al., 2018). However, a study done in Ethiopia reported that 70.8% of bacterial isolates were resistant to cotrimoxazole (Genetu & Zenebe, 2020). A respiratory fluoroquinolone is an alternative to the beta-lactam in individuals who are allergic to penicillin and doxycycline is an alternative to the macrolide (Kaysin & Viera, 2016). However, the clinical effectiveness of short-term parenteral therapy against bacterial pneumonia in HIV-infected and HIV-uninfected patients with HIV-endemic, in developing countries is not well documented (Jones & Berkley, 2014).

8. Prevention
Prevention and control strategies should be implemented to address the consequence of pneumonia. Early diagnosis, proper ventilation, separate living rooms with kitchen, and health education are the major preventive strategies of pneumonia (Gedefaw & Berhe, 2015; Ranathunga et al., 2019). According to recent US Guidelines, individuals with HIV infection who have a CD4 cell count greater than 200 cells/μl should be given the 23-valent polysaccharide pneumococcal vaccine (D'Egidio et al., 2007). Since the time duration of the protective effect of vaccination is unknown, revaccination every 5 years should be considered (Pozniak et al., 2011). The vaccine is recommended for individuals who have a CD4 cell count less than 200 cells/μl (Grohskopf et al., 2018). If individuals with an advanced immunosuppressed plan to initiate antiretroviral therapy, the vaccine can be given after the CD4 cell count rises above 200 cells/μl (Yang et al., 2014). All individuals with HIV infections should be given the inactivated influenza vaccines annually earlier in influenza season (Grohskopf et al., 2019). The frequency of bacterial pneumonia could be reduced by daily administering of trimethoprim-sulfamethoxazole. However, given the specter of drug resistance, none of these medications should be prescribed solely for the prevention of bacterial infection (Bebell & Muiru, 2014). In conclusion, bacterial pneumonia is significantly increased among HIV-infected individuals who currently smoke cigarette, recommending that efforts to improve smoking termination could lead to considerable reduces in bacterial pneumonia.

9. Conclusion and recommendation
In individuals with HIV infection, bacterial pneumonia are the major causes of morbidity and mortality and are common reasons for referral to pulmonary and respiratory specialists for
diagnostic evaluation and treatment. The spectrum of HIV-associated bacterial pneumonias is broad and includes bacterial, mycobacterial, fungal, viral, and parasitic pneumonias. Therefore, determination of the prevalence of bacterial pneumonia in HIV-seropositive patients should be identified and documented; hence, the finding of this review helps to connect the knowledge gap about the occurrence of bacterial pneumonia in HIV-seropositive patients in East Africa. Precise early diagnosis, proper treatment and prevention of HIV-associated bacterial pneumonias are significant strategies for reducing the morbidity and mortality associated with HIV/AIDS.

10. Limitations
This review has been summarized the results of 13 articles about the prevalence of bacterial pneumonia in HIV-seropositive patients in East Africa. However, in Sudan, South Sudan, Burundi, Somalia and Eritrea no studies have ever been conducted to investigate the prevalence of bacterial pneumonia in HIV-seropositive patients. Furthermore, there were no recent articles regarding the prevalence of bacterial pneumonia in HIV-seropositive patients in East Africa. Therefore, this has led to a major variation in knowledge about the prevalence of bacterial pneumonia in HIV-seropositive patients in the region.

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Data availability
All data underlying the results are available as part of the article and no additional source data are required.

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