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BURDEN OF LOWER RESPIRATORY TRACT BACTERIAL INFECTION: A REVIEW

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ABSTRACT
Taking into account the burden of Lower Respiratory Tract Infection (LRTIs) , the findings from this systematic review found out that, the burden of lower respiratory tract infection is higher in developing countries and the major cause of lower respiratory tract infection are Streptococcus pneumoniae, Escherichia coli and Klebsiella pneumoniae. The frequency of lower respiratory tract infection is more common in children less than five years and older age group (age greater than 65). It was also found out that Gram negative rods such as Escherichia coli and Klebsiella pneumoniae demonstrated high resistance to most antibiotics such as cephalosporins while resistance was also documented by Streptococcus pneumoniae to some Beta-lactam antibiotic such as oxacillin. This type of review will be useful for health stakeholders and will provide information that can lead to efficient strategies for controlling the burden of LRTIs. As all settings in Africa are not able to diagnose bacterial aetiologies in people with LRTI, knowledge of major respiratory bacterial infections can help in this case to orientate the first-line treatment.
Keywords: Lower respiratory tract, Pathogens, Frequency, Susceptible, Resistance

INTRODUCTION

Lower respiratory tract infections (LRTIs) occur below the level of the larynx, i.e. in the trachea, the bronchi, or in the lung tissue. They include conditions such as tracheitis, bronchitis, bronchiectasis, lung abscess, tuberculosis, pneumonia (Kalgo *et al.*, 2016). Lower respiratory tract infection (LRTI) is considered as one of the major public health problems and a leading cause of morbidity and mortality in many developing countries (Rakshya *et al.*, 2018; GBD 2016; Lower Respiratory Infections Collaborators*, 2018*). There were approximate 11.9 million episodes of severe acute lower respiratory infections (ALRI) resulted in hospital admissions in young children worldwide (Nair *et al.*, 2013).

The etiology of LRTIs is diverse and complicated. Bacteria such as *Streptococcus pneumonia* (*S. pneumoniae*), *Haemophilus influenzae* (*H. influenzae*), *Staphylococcus aureus* (*S. aureus*), *Moraxella catarrhalis* (*M. catarrhalis*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and other Gram-negative bacilli are widely considered the major pathogens responsible for LRTIs (Musher and Thorner, 2014). Viruses also play an important role in LRTIs, especially in infants younger than 2 years (Juvén *et al.*, 2000). The common viral pathogens include respiratory syncytial virus (RSV), human metapneumovirus (hMPV), influenza virus (FLU) A and B, parainfluenza virus (PIV) 1 to 3 and adenovirus (ADV). The atypical bacterial pathogens that are recognized as childhood respiratory pathogens include *Mycoplasma pneumoniae* (MP), *Chlamydia pneumoniae*, and *Chlamydia trachomatis* (CT) (Pientong *et al.*, 2011). Previous studies conducted in different parts of the world indicated that the leading bacterial causative agents of community acquired pneumonia (CAP) are *Streptococcus pneumoniae* and *Haemophilus influenzae* followed by *Staphylococcus aureus.* (Shibl *et al.*, 2010; Egbe *et al.*, 2011; Müller *et al.*, 2007)

LRTI is also a leading cause of hospitalization in US children aged < 5 years (US Department of Health, 2011). Pneumonia and bronchiolitis are the most common causes of LRTI associated hospitalizations in US children aged <5 years (Singleton *et al.*, 2012). The first South African National Burden of Disease (SANBD-1) study ranked LRIs as the sixth leading cause of premature mortality in South Africa contributing to 3.8% of the years of life lost (YLLs) in the country in 2000 (Bradshaw *et al.*, 2003). WHO recognized respiratory diseases as the second most important cause of death for children under five years in 2010 (WHO, 2013). WHO states that pneumonia is one of the main three causes for newborn infant deaths (WHO, 2012). Pneumonia was diagnosed in approximately 156 million children in 2008 (151 million in developing countries and 5 million in developed countries) and led to 1.4 million deaths (28-34%

of all deaths in those younger than five years of age).

WHO reports in developing countries (e.g. Nigeria, Gambia, Senegal, Chad, Cameroon, Burkinofaso and Mali) demonstrate acute respiratory infection (ARI) incidence rate of 15-21% in children younger than five years old (WHO, 2013). Hospitalization rates of pneumonia (all causes) among children younger than two years in the United States have decreased (from 12 to 14 per 1000 population to 8 to 10 per 1000 population) after considering the pneumococcal conjugate vaccine as the routine childhood immunization plan since twelve years ago. Meta-analysis study reveals that 1.9 million children died from ARI in 2000 all over the world, two third of them in Southeast Asia and Africa. Approximately one in five child deaths (18 percent) worldwide occurred (WHO, 2009)

The incidence and associated mortality due to LRTI can be influenced by several factors including characteristics of the population at risk, standard of the health-care facilities available, immunosuppressive drugs, inappropriate antibiotic therapy, distribution of causative agents and prevalence of antimicrobial resistance. Highly resistant strains of Gram-negative bacilli (GNB) continue to spread in hospitals causing therapeutic problems in many parts of the world, particularly in developing countries and where isolation facilities for patients with resistant organisms are often inadequate (Navaneeth and Belwadi, 2002). The risk factors include: age, sex, socio-economic status, overcrowding, indoor air pollution, passive smoking, absence of ventilation, defects in immune system, lack of basic health services, lack of awareness and overuse and misuse of antibiotics. Some of these factors predisposing to ARIs are more prevalent in the rural communities with limited access to health care for their children and more exposure to indoor air pollution. In the rural communities, women use fire wood and kerosene stove for cooking mostly (Dongre *et al*., 2010; Ajaero and Onokala, 2013).

In aging adults, the burden of community acquired pneumonia (CAP) is of even greater concern when considering that the number of persons aged >60 years globally is projected to triple, from 673 million in 2005 to 2 billion by 2050. This will be most apparent in developing regions of the world, where this age group is projected to increase from 64% (2005) to 80% (2050) of the total population. The 50 least developed countries will record a more than 200% increase in their populations, from 0.8 billion in 2007 to 1.7 billion by 2050, compared with developed regions, which are projected to remain stable at a population of 1.2 billion (Kalgo *et al*., 2016). In Africa, lower respiratory tract infection and tuberculosis are ranked second and eighth leading cause of mortality rate respectively where as in Nigeria, lower respiratory tract infections constituted the second leading cause of mortality rate in all age brackets in 2002, a year in which tuberculosis was the seventh leading cause of death, accounting for 4% of all deaths (Umoh *et al.,* 2013).

In African countries, the situation is more complicated and management is often difficult due to the problem associated with the identification of the etiological agents and administration of appropriate treatment in cases requiring antibiotic therapy (Alter *et al.,* 2011). Current knowledge on bacterial etiology and antimicrobial susceptibility pattern would help reduce the indiscriminate antibiotic use and result in better therapeutic outcome and decrease in development of resistance. Evidence showed that bacteriological more effective antibiotics can reduce overall management costs, particularly with respect to consequential morbidity and hospital admission. To the best of my knowledge, no systematic reviews have been conducted to determine the prevalence, incidence, case fatality, duration or severity of LRIs and Antimicrobial resistance across the globe.

In order to present evidence on epidemiological parameters relating to LRI and pneumonia around the world, this systematic literature review was conducted to identify published studies that report the prevalence, incidence, case fatality, duration or severity of LRI and pneumonia. The findings from this review will also be used to estimate the morbidity burden due to LRI and pneumonia, bacterial etiology and current antimicrobial susceptibility pattern with the aim to provide accurate data for designing cost-effective interventions to curb the burden of respiratory infections and to guide future research.

Information sources and search strategy

The information used in this review included population-based surveys, cross-sectional studies, prospective or retrospective cohort studies, case–control studies. Studies across the world were reviewed and all English studies published from January 2000 to 2019 were included while all published studies before 2000 were excluded from this study

Burden of Lower Respiratory Tract Infection

Respiratory tract infection is caused by both viral and bacterial organisms. It has been known

that, viral infections are the main cause of mild to moderate pneumonia (especially in the first years of life) while bacterial infections are the leading cause of severe pneumonia. Many studies have observed that the majority of the respiratory bacterial pathogens are Gram negative (Navaneeth *et al*., 2002; Okesola *et al*., 2008; Mishra *et al*., 2012). The aetiological agents of LRTIs and their antibiotic susceptibility profile vary from area to area. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas* species, *Acinetobacter* species and other non-fermentative Gram-negative Bacilli (NFGNB) have often been recovered from LRTIs (Ozyilmaz *et al*., 2005). The most common bacterial pathogens isolated from LRTIs in some studies were *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (Okesola *et al*., 2008).

According to Japanese statistics, the current most common causes of death are malignant neoplasm, heart disease, pneumonia, and cerebrovascular disease, with pneumonia surpassing cerebrovascular disease in 2011 in Japan (Ministry of Health Japan, 2011). In 2015, 120,953 people died of pneumonia, accounting for 9.4% of total deaths in Japan. Of those deaths from pneumonia, 96% were among those aged 65 years or older (Ministry of Health in Japan, 2015). It is presumed that the main explanation for the increasing number of deaths from pneumonia in Japan is the aging of the population. In addition, the death rate due to senescence has increased markedly in recent years and it seems that there is a close correlation between senility and pneumonia. For example, aspiration resulting in pneumonia may be more likely to occur as a result of senescence. Conversely, repeated bouts of pneumonia contribute to progressive senescence. In this way, even though pneumonia may not be the direct cause of death in elderly patients, previous episodes of pneumonia may have contributed to their physical decline and subsequent death (Naoya and Yasuhiro, 2018). ARIs-related pneumonia was one of the leading cause of death that due to infectious disease in China (> 30,000 deaths annually) as well as globally (935,000 in 2013) (Liu *et al*., 2000; Rudan *et al*., 2010). WHO estimated burden of respiratory tract infections in 2010, estimates four and half million deaths due to respiratory tract infections among children every year. In India, 1.2 million deaths have been reported among children due to RTI among 5.9 million deaths globally and India has the highest number of deaths among children < 5 years of age and most of them are due to respiratory tract infections (WHO, 2012).

In Sub-Saharan Africa, LRTIs rank third after HIV/AIDS and malaria in terms of causes of mortality. LRTIs are the leading cause of death in nine African countries (GBD, 2013; Mortality and Causes of Death Collaborators, 2013). A systematic analysis in 2015 found that LRTIs caused 2.74 million deaths and 103 million disability-adjusted life years (DALYs) worldwide, making them the fifth leading cause of death overall and the second leading cause of DALYs (GBD, 2015; LRI Collaborators, 2015). Nearly 2·38 million deaths resulted from lower respiratory infections in 2016, making lower respiratory infections the sixth leading cause of mortality for all ages and the leading cause of death among children younger than 5 years (GBD, 2016; Lower Respiratory Infections Collaborators*, 2018)*. The burden of these infections is higher in Sub-Saharan Africa and Asia, where the highest mortality was among children under 5 years. For instance, 546.8 and 511.3 deaths per 10,000 were reported in Somalia and Chad, respectively meanwhile, the lowest reported mortality was in Finland in Western Europe, with 0.65 deaths per 100 000 (GBD, 2015; LRI Collaborators, 2015).

Prevalent Bacterial Pathogens of Lower Respiratory Tract Infection

The aetiology of ALRI, and pneumonia in particular, is difficult to establish (Mulholland 2007; Rudan 2005). Collecting body fluid specimens for microbiologic diagnosis from the site of infection can only be done in a small proportion of cases. Aetiology studies are therefore based on either insensitive or non-specific indirect methods such as blood culture, serology and microbiologic assessments of the upper airway. Based on some studies, about one fourth to one half of childhood pneumonia cases appear to have a primarily viral aetiologic agent, including human respiratory syncytial virus (RSV), parainfluenza and influenza viruses (Simoes 2006; Scott *et al*., 2008). Half or more are due to bacteria, with some presenting as a secondary infection of an acute viral process, including measles, influenza, or RSV (Rudan *et al*., 2008). Pertussis may also predispose to bacterial super-infections. HIV infection increases the risk of both *Streptococcus pneumoniae* and *Haemophilus influenzae* type b, together responsible for about half of pneumonia deaths, by 7-40 fold (O'Brien *et al*., 2009; Whatt *et al*., 2009). Though evidence is incomplete, bacterial episodes of pneumonia are believed to feature a higher severity and case-fatality ratio (CFR) than viral episodes (Simoes, 2006), hence the emphasis on antibiotic treatment of children with pneumonia.

Among children under 2 years, *S. pneumoniae* and *H. influenzae* type b (Hib) are estimated to cause 36% and 22% of radiological pneumonia cases respectively (O'Brien *et al*., 2009; Whatt *et al*., 2009), but other pathogens, including *Staphylococcus aureus*, *Mycobacterium tuberculosis* and non-typeable *H. influenzae*, play a substantial though poorly understood role (Simoes 2006; Scott, *et al*., 2008 and Rudan *et al*., 2008). The 2009 H1N1 influenza pandemic may alter the above patterns substantially, although historical and more contemporary evidence points to the importance of *S. pneumoniae* as a risk factor in fatal influenza cases (Klugman *et al*., 2009).

In a survey of the causal bacteria responsible for pneumonia in elderly Japanese patients, (Fukuyama *et al*., 2013; Ishida *et al*., 2012; Karino *et al*., 2013) the most frequently detected organisms were *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa*, normal oral flora, and *Klebsiella*. In any study in Japan, *S pneumoniae* has been the most frequently detected pathogenic species. Oral bacteria and anaerobic bacteria have been detected at a rate of 10% or more, suggesting that pneumonia caused by bacteria from the oral cavity is common (Yamasaki *et al*., 2013). According to a meta-analysis of research in Japan, the most common organisms causing CAP are *S pneumoniae* (18.8%), followed by *H influenzae* (7.6%) and *Staphylococcus aureus* (4.2%).

However, bacteria responsible for HAP and NHCAP tend to include more antibiotic-resistant strains than those seen in CAP (Naoya and Yasuhiro, 2018).

In Korea. Community-acquired pneumonia is caused by various bacteria. Similar distributions of these bacteria are seen between Korea and other countries. Bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae*, and *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Legionella pneumophila,* which are classified as causative bacteria of atypical pneumonia, and respiratory bacteria can cause pneumonia. However, it is difficult to differentiate between these causative bacteria in the early period after hospital admission. The most important causative bacteria of bacterial pneumonia are *S. pneumoniae*. They account for 27-69% of all causative bacteria of bacterial pneumonia (Chong *et al*., 2010; Jeon *et al*., 2011; Yoo *et al*., 2013; Jeong *et al*., 2013; Seong *et al*., 2014; Kim *et al*., 2014; Choi *et al*., 2015; Kang *et al*., 2017). *Haemophilus* or *Moraxella,* which are respiratory pathogens, commonly cause pneumonia in patients with a lung disease. The prevalence of these bacteria varies greatly in domestic data possibly because the separation and identification of these bacteria are difficult. *Staphylococcus aureus* are also relatively common causative bacteria. They commonly occur after an influenza epidemic.

Enteric gram negative bacilli or *Pseudomonas aeruginosa* pneumonia commonly occur in patients who have underlying lung diseases, who have alcohol addiction, or who have frequently undergone antibiotic treatment. The ratio of gram-negative bacteria including *Klebsiella pneumoniae* and *P. aeruginosa* to be relatively high. This may be because most studies have been conducted in tertiary university hospitals, and therefore, a large number of patients who are frequently admitted to a hospital for chronic respiratory diseases were included. Studies have reported mixed infections caused by two or more microorganisms to be relatively common. These infections include mixed infections caused by atypical causative bacteria of pneumonia. Distributions of causative bacteria may change depending on underlying diseases and risk factors. *M. pneumoniae, C. pneumoniae,* and *L. pneumophila* are the major causative bacteria of atypical pneumonia. Of the recently published studies on community-acquired pneumonia in Korea, very few have investigated the incidence of atypical pneumonia and its causative bacteria. A large number of published studies have been conducted at a single institution, or use a retrospective design. Therefore, the prevalence of atypical pneumonia in Korea and clinical significance can only be assessed with limited accuracy. In a domestic study on pneumonia, *Mycoplasma, C. pneumoniae,* and *Legionella* accounted for 6.3-9.2%, 7.1-13.2%, and 0.5-3% of all cases of pneumonia (Sohn *et al*., 2006; Song *et al*., 2008).

Table 1. The distribution of the major causative bacteria of community-acquired pneumonia in Korean adults

	Jeong *et al., 2013*	Seong *et al., 2014*	Chong *et al., 2010*	Choi *et al.,2010*	Yoo *et al., 2013*	Kim *et al., 2014*	Kang *et al., 2017*	Jeon *et al., 2011*
Gram-positive bacteria								
Streptococcus pneumoniae	59 (48.4)	44 (41.9)	52 (39.7)	276 (486)	51 (25.7)	88 (36.2)	43 (69.4)	21 (33.3)
Staphylococcus aureus	13 (10.7)	10 (9.5)	8 (6.1)	109 (19.2)	21 (11.0)	5 (2.0)	8 (12.9)	9 (14.3)
Streptococcus spp.	8 (6.6)	5 (4.8)	1 (0.8)	9 (1.6)	5 (2.6)	5 (2.0)	-	-
Gram-negative bacteria								
Klebsiella pneumoniae	14 (11.5)	6 (5.7)	26 (19.8)	105 (18.5)	17 (8.9)	7 (2.8)	3 (4.8)	13 (20.6)
Psedomonas aeruginosa	11 (9.0)	10 (9.5)	11 (8.4)	83 (14.6)	22 (11.5)	2 (0.8)	2 (3.2)	4 (6.3)
Haemophilus influenzae	7 (5.7)	1 (1.0)	1 (1.0)	105 (18.5)	10 (5.2)	5 (2.0)	7 (11.3)	7 (11.1)

Source: Mi *et al*., (2018)

There were associations of several viral agents with ARIs, such as: respiratory syncytial virus (RSV), human rhinovirus (HRV), human metapneumovirus (HMPV), influenza virus (IFV), parainfluenza virus (PIV), adenovirus (ADV) and human bocavirus (BoV), accounting for about 35–87% of children with ARI (Doan *et al*., 2014). Viral co-infections occurred in 4–33% of children hospitalized with ARIs, and may indicate an increasing risk for clinical outcome (Sung *et al*., 2009; Ruuskanen *et al*., 2013). Further, bacterial infections such as: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* were commonly observed in the later stage of diseases due to immune-compromised viral infections (Tregoning and Schwarze, 2010). Among several previous Chinese studies, it was found out that, *Streptococcus pneumonia*, *Haemophilus influenza, Hemophilus parainfluenzae and Escherichia coli* were the predominant pathogens (Qin *et al*., 2008); (Nanjing *et al*. 2011); (Zhang *et al*., 2015); (Peng *et al*., 2015).

An epidemiology of respiratory pathogens in children with lower respiratory tract infections in Shanghai, China, from 2013 to 2015 revealed that, of the 10,123 specimens obtained from the patients, 5,966 (58.7%) were positive for at least 1 pathogen. *Mycoplasma pneumoniae* (*M.pneumoniae*) was the most commonly detected pathogen (15.7%), followed by respiratory syncytial virus (RSV) (13.9%). Co-infections were found in 11.4% of patients. Of these coinfections, viral-bacterial co-infections were the most common. The detection rates for the respiratory pathogens varied considerably by age. RSV was the most common pathogen in children aged less than 24 months. Clear seasonal peaks were observed for RSV, *M. pneumoniae*, parainfluenza virus, human metapneumovirus, *Moraxella catarrhalis*, and *Haemophilus influenzae* infections. Study on prevalence of acute respiratory tract infections (ARI) in under five children in Lucknow District demonstrated that, the overall prevalence of ARI in children was approximately 23%. Prevalence was higher in boys (36%) than in girls (10%). Children old between 3-5 years less likely suffered from ARI (3%) than children from other age groups. In social class IV and class V, prevalence of ARI was more in rural area (31.4%, 37.1%) as compared to urban area (32%, 16%). A direct correlation was found between immunization status of children and occurrence of ARI along with a significant correlation between timely initiation of breast feeding and decreased occurrence of ARI (Abhishek *et al*. 2014). The Incidence of LRTI in the study carried out by Venkata *et al*. was 9.76% with male preponderance (65.33%) and most common among children in 1-4 years age group. Ratio of males to females was 1.9:1. 73.6% of cases were in low socio-economic group, 35.2% were found with PEM-I grade and 18.13% had no immunization coverage. Cough and breathlessness were the major symptoms and respiratory distress and clubbing were major signs in the study. Bronchopneumonia was the commonest cause (38.7%) followed by bronchiolitis and allergic bronchitis. 18.45 of cases had anemia and leucocytosis was also present.

Pulmonary infiltration was the major finding in the X-ray of chest. *Streptococcus pneumoniae* and *Klebsiella pneumoniae* were the common bacterial pathogens isolated (Venkata *et al*. 2017). An epidemiology and clinical characteristics of acute respiratory tract infections among hospitalized infants and young children in Chengdu, West China, 2009–2014 revealed that, Fifty-one percent of patients were identified with at least one respiratory pathogen. Human rhinovirus (HRV) (23%), Respiratory syncytial virus (RSV) (22.7%) was the most commonly identified viruses, with *Klebsiella pneumoniae* (11.5%) the most commonly identified bacterium in the study. The presences of more than one pathogen were found, and multiple viral, bacterial, viral/bacterial combinations were identified in 14.9, 3.3 and 13.9% of patients respectively. Respiratory viruses were identified throughout the year with a seasonal peak in December–February. Pathogens profiles and clinical associations were different between infants (< 1 year of age) and older children (> 1 year of age). Infants with ARIs were more likely to have one or more viruses than older children. Infants identified with multiple pathogens had significantly higher proportions of tachypnea than infants that were not (Jiayi *et al*., 2018).

In a study carried out at Medical College, Kolenchery, Kerala shows that, Out of the 54 samples processed, 31 yielded significant growth (57.4%). Only Gram-negative bacterial pathogens (37 isolates, 68.52%) were obtained during the study. The most common bacterial pathogen isolated was *Pseudomonas aeruginosa* (32.43%), *Klebsiella pneumoniae* (27.03%) ranking second (Thomos *et al*., 2016). Bacterial Etiologies of Acute Respiratory Infections Among Children Under 5 Years in Senegal are *Streptococcus pneumoniae* (17%; n = 29), *Moraxella catarrhalis* (15.43%; n = 25), and *Haemophilus influenzae* (8.02%; n = 13) were the most commonly isolated bacteria. (Dieng *et al*., 2018). Microbiological profile of lower respiratory tract infections in neurological intensive care unit of a tertiary care center from Central India find out that, out of the 230 LRT specimens evaluated, 198 (86.08%) were culture positive. A total of 254 pathogens were recovered with a predominance of Gram-negative isolates (*n* = 243; 96.05%). Pseudomonas aeruginosa was the most dominant pathogen followed by *Klebsiella pneumoniae* (Bajpai *et al*., 2013). A study conducted in Ethiopia at Addis Ababa's Black Lion Hospital, on adult patients with CAP revealed that *S. pneumoniae* (6%) and *S. aureus* (6%) were the most common pathogens followed by *Pseudomonas aeruginosa (P. aeruginosa)* (1%), and *Klebsiella pneumoniae* (1%). (Belayneh *et al*., 2015).

A study on bacterial pathogens of lower respiratory tract conducted at Aminu Kano Teaching Hospital Kano-Nigeria demonstrated that, Fourty three (43) bacterial isolates were isolated from two hundred (200) samples collected. *Streptococcus pneumoniae* (25.6%) has the highest percentage of occurrence, followed by *Klebsiella pneumoniae* (20.9%), *Escherichia coli* (20.9%) and *Staphylococcus aureus,* (16.3%) respectively. Others include *Proteus* species (4.7%), *Pseudomonas aeruginosa* (4.7%), *Haemophilus influenzae* (4.7%) and *Serratia* species (2.3%) as well. Age ranges 20 – 29 and 30 – 39 have the highest percentage of pathogens isolated (Taura *et al*., 2013). Isolation and identification of bacteria associated with Lower Respiratory Tract Infection among Patients Attending General Hospital Katsina, Nigeria revealed that, Out of the 85 patients screened, a total of 35 (41.18%) yielded clinically significant pathogens. *Klebsiella pneumoniae* (34.29%) was the predominant isolate detected, followed by *Staphylococcus aureus* (31.43%), *Pseudomonas aeruginosa* (25.71%) and *Escherichia coli* (8.57%). There was no *Streptococcus pneumoniae* isolated (Usman and Muhammad, 2017). Microbiology of Lower Respiratory Tract Infections in Benin City, Nigeria documented that, the prevalence of LRTIs increased significantly ($P < 0.001$) with age, with the age group of 71 years and older having the highest prevalence, 48.57% (Table 2). Generally, *Klebsiella pneumoniae* (30.16%) was the predominant isolate recovered, followed by *Haemophilus influenzae* (17.05%), *Staphylococcus aureus* (15.41%), and *Acinetobacter* species (0.66%) (Christopher *et al*., 2010). Epidemiology and Clinical Outcomes of Community Acquired Pneumococcal Infection in North-West Nigeria revealed that, out of 302 cases of bacteriologically proven community-acquired infections , 241 were pneumonia (Iliyasu *et al*., 2015).

Table 1 Distribution of pathogens identified from children with CAP within different global regions

	% of patients positive for pathogens in:				
Pathogen	United Kingdom	United State	Gambia	Nigeria	India
S. Pneumoniae	17.4	4.0	91.0	5.1	5.7
H. Influenzae	2.3	-	23.0	-	0.8
Group A Streptococci	10.5	1.0	-	-	-
S. aureus	2.3	1.0	6.0	37.3	0.8
M. Pneumoniae	9.9	8.0	-	-	4.3
Moraxella catarrhalis	2.3	-	-	-	-
Klebsiella pneumonia	0.8	-	-	15.3	0.2

Source: Rodrigues and Groves, (2018)

Risk Factors

The occurrence of ARI is determined by the exposure to various risk factors. Air pollution is a risk factor for both acute and chronic respiratory disease. One half of the world's population is exposed to high concentrations of solid fuel smoke that are produced by inefficient open fires, mainly in the rural areas of developing countries. Solid fuel smoke possesses the majority of the toxins found in tobacco smoke and has also been associated with a variety of diseases including ARI in children. Globally, indoor air pollution from solid fuel use is responsible for 1.6 million deaths due to pneumonia, chronic obstructive pulmonary disease and lung cancer. The highest exposures to second-hand smoke are found in Eastern Europe, the Western Pacific and South-East Asia, with more than 50% of some population groups exposed. Environmental factors such as overcrowding coupled with poor ventilation at homes and work places may make the health effects of indoor air pollution more pronounced. Exposure is particularly high among women and children, who spend most time near the domestic health (Ajobiewe *et al*., 2018).

Antimicrobial Resistance of the Bacterial Pathogens of LRTI

Antibiotic resistance is considered to be a worldwide problem, and unwise use of antibiotics has been recognized as a key contributor to the increasing rates of resistance (Ventola, 2015). Therefore, clinical practice typically uses empirical antibiotic selection to target the most likely pathogens based on antibiotic sensitivity data (Zhang *et al*., 2014). The antibiotic resistance associated with CA-LRTIs varies significantly depends on geographical locations and investigated populations (Felmingham, 2004; Ibrahim *et al*., 2014). Therefore, it is not adequate to simply copy the existing guidelines from other countries, which may be inappropriate and lead to serious problems in clinical practice. For example, the incidence of aminoglycosides and quinolones resistant-MRSA is relatively high in the USA (McDougal *et al*., 2010). Penicillin-resistant *S. pneumoniae* is also relatively high in USA (McDougal, 2008) and Southeast Asia (Felmingham, 2004). Moreover, most studies have described patterns in the resistance of bacterial pathogens among adults with respiratory tract infections, these patterns may occur differently in adults and children (Felmingham, 2004; Adam *et al*., 2013).

According to an analysis of HAP in Japan, methicillin resistant *S aureus* accounts for 17.5%, *P aeruginosa* 13.9%, and methicillin-sensitive *S aureus* 6.5%. A similar analysis of NHCAP reported *S pneumoniae* in 16.4% of cases, *Klebsiella* in 9.6%, and methicillin-resistant *S aureus* in 9.6%. However, it should be noted that in about half of cases, the bacteria responsible for aspiration pneumonia could not be identified (Naoya and Yasuhiro, 2018). The choice of antimicrobial therapy for bacterial LRTIs is relatively straight forward when the etiologic agents and their antibiotic susceptibility patterns are known. However, the clinical presentation is usually not specific enough to make a firm etiologic diagnosis whether in the community or hospital setting (Shah *et al*., 2010). In almost all cases, eradication of causative agents requires initiation of antimicrobial therapy before obtaining culture report; however, during the last few years, the increase in antibiotic resistance has compromised the selection of empirical treatment (Jonaidi, 2009) and how to choose an effective antimicrobial agent is a new challenge to the clinicians, as the composition and the resistance to antimicrobial agents of infection pathogens was changing frequently.

This trend is presumably due to the empirical administration of antibacterial therapy even before the availability of the culture results (Ahmed, 2013). Various other factors also contribute to the emergence of resistance such as irrational use of antibiotics, transmission of resistant bacteria from patient to patient and from healthcare practitioners to patients and vice versa (WHO, 2012; Mahmoud and Balkhy, 2012).

Nowadays, antibiotic resistance exerted by microorganisms against antibiotics is considered as a serious issue by global medicinal and research community (WHO, 2012; Mahmoud and Balkhy, 2012). Therefore, the clinicians and microbiologists worldwide are focusing on knowledge and strategies to limit the development of antimicrobial resistance. A study conducted at Kathmandu Model Hospital, Kathmandu, Nepal on Antibiotic Susceptibility Pattern of Gram-negative Isolates of Lower Respiratory Tract Infection revealed that Among 6 MDR isolates of *E. coli*, ESBL was detected in 4 (66.67%), among 15 MDR isolates of *K. pneumoniae*, ESBL was detected in 4 (26.66%) and of 9 MDR isolates of *Acinetobacter calcoaceticus baumannii* complex, ESBL was detected in 1(11.11%). All ESBL producing isolates are MDR. (Rakshya *et al*., 2018). Another study on antimicrobial resistance in bacterial pathogens among hospitalized children with community acquired lower respiratory tract infections in dongguan, china (2011– 2016) demonstrated that, *E. coli* exhibited high resistance to piperacillin and ampicillin, but relative low resistance to other antibiotics included ofloxacin, gentamicin and cephalosporins. Similarly, *E. coli* ESBLs had low resistance to ofloxacin and gentamicin, but only it had low resistance to ceftazidime and cefepime in the study. *K. pneumoniae* displayed low resistance to cephalosporins, but *K. Pneumoniae* ESBLs exhibited high resistance levels to cephalosporins except for cefepime (44.1%). *S. pneumoniae* isolates had a resistant rate of 29.0% to penicillin, and a high resistance level of macrolides, including erythromycin (96.7%) and clarithromycin (93.3%). However, the study indicated that *S. pneumonia*e isolates had a low resistance level to cephalosporins, such as ceftriaxone (7.1%), cefotaxime (10.0%) and cefepime (4.2%). The results also showed 21.7% of *P. aeruginosa* were resistant to piperacillin, and had low resistance levels of ceftazidime (13.6%) and cefepime (4.3%). The study also exhibited a low resistant rate to other antibiotics, including ofloxaxin (10.0%) and gentamicin (13.6%). Alarmingly high percentage of extended spectrum beta-lactamase and methicillin resistant *Staphylococcus aureus* isolates were detected.

The resistance to cephalosporins, aminoglycosides and carbapenem were remarkable from January 2010 to December 2012 in the Microbiology Department of a Teaching Tertiary Care Hospital, central India (Bajpai *et al*., 2013). Study of Gram Negative Bacterial Isolates from Lower Respiratory Tract Infections (LRTI) and their antibiogram pattern in a Tertiary Care Hospital in South India showed that, most of the gram negative bacterial isolates were resistance to commonly used cephalosporins. *Klebsiella* showed resistance to most of the drugs like Amoxyclav (87.8%), cefuroxime (83.3%), Ceftazidime (81.1%), ceftriaxone (70.5%). Pseudomonas showed relatively lesser resistance pattern , Amoxyclav (89%), Ceftazidime (37.5%) . *E. coli* showed resistance to most of the cephalosporins, flouroquinolones and Amoxyclav (63.5%). *Acinetobacter* showed sensitivity only to higher level antibiotics like Imipenam (4.8%) and Piperacillin/Tazobactam (16.7%) (Arthi *et al*., 2016).

Antimicrobial susceptibility pattern of bacterial isolates from community acquired pneumonia patients in Jimma University Specialized Hospital, Jimma, Ethiopia revealed that, Most *S. pneumoniae* isolates were resistant to oxacillin (55%). High resistance rates of *S. aureus* isolates were observed to tetracycline (100%), penicillin (81.3%), trimethoprim-sulfamethoxazole (81.3%), erythromycin (75%), and doxycycline (50%). Gram-negative bacteria isolates were resistant to tetracycline (66.7-100%), doxycycline (50-100%), trimethoprim-sulfamethoxazole (66.7-100%), and ampicillin (66.7-100%). Resistance to two or more drugs was also observed. Among 62.7% of bacterial isolates (Belayneh, *et al*., 2015). Current Trend of Antibiotic Resistance in Lower Respiratory Tract Infections (LRTIs): An Experience in a Teaching Hospital in Bangladesh demonstrated that, gram positive organisms showed maximum sensitivity to imipenem (94.6%), meropenem (97.3%) and cefotaxime (75%). The resistance pattern varied for different organisms. *Staphylococcus aureus* isolates were mostly resistant to amoxicillin and ceftazidime (89.2%), whereas, *Streptococcus pneumoniae* was to ceftazidime, amoxicillin and cotrimoxazole (81.2%). In case of gram negative isolates, *Klebsiella sp.* was mostly resistant to ceftriaxone, ceftazidime and amoxicillin (100%). *Escherichia coli* were resistant to amoxicillin, cotrimoxazole and vancomycin (100%). (Borkot *et al*., 2016). Antibiotic Susceptibility Pattern of Gram-negative

Isolates of Lower Respiratory Tract Infection at Nepal revealed that, High prevalence of multidrug-resistance and extended- spectrum beta- lactamase producers were observed in respiratory isolates (Rakshya *et al*., 2018).

Treatment of Lower Respiratory Tract Infection

According to the Infectious Diseases Society of America (IDSA)/American Thoracic Society Consensus guidelines, macrolides are the drug of choice (with strong recommendation; Level I evidence) for formerly healthy adult outpatients with CAP, with no risk factors for drug-resistant *S. pneumoniae* (DRSP) infection. In the presence of comorbidities or other risk factors for DRSP infection, either a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin) or combination of beta-lactam plus a macrolide or amoxicillin-clavulanate is preferred (Mandell *et al*., 2007). The IDSA/American Thoracic Society Consensus guidelines recommend the use of a macrolide (strong recommendation; Level I evidence) for the management of CAP in previously healthy adults, with no risk factors for DRSP infection. In patients with comorbidities or use of antimicrobials for the past 3 months or other risk factors for DRSP infection, combination of beta-lactam plus a macrolide is recommended (strong recommendation; Level I evidence) (Mandell *et al*., 2007).

According to the NICE guidelines (December 2014), (Clinical Guideline, 2014) amoxicillin is preferred over macrolide or tetracycline in low-severity CAP. The guideline suggests macrolide or tetracycline in case of allergy to penicillin. In patients with moderate-to-severe CAP, dual therapy with amoxicillin and macrolide is suggested. Similarly, in highly severe CAP, dual therapy with a beta-lactamases-table beta-lactam and macrolide is suggested.

According to the European Respiratory Society–The European Society for Clinical Microbiology and Infectious Diseases guideline, amoxicillin or tetracycline is recommended as the choice of antibiotic. Macrolide is recommended as an alternative in case of hypersensitivity to first-line agent (Woodhead *et al*., 2011).

Prevention and Control of Lower Respiratory Tract Infection

Preventing pneumonia in children is an essential component of a strategy to reduce child mortality. Immunization against Hib, pneumococcus, measles and whooping cough (pertussis) is the most effective way to prevent pneumonia. Adequate nutrition is key to improving children's natural defences, starting with exclusive breastfeeding for the first 6 months of life. In addition to being effective in preventing pneumonia, it also helps to reduce the length of the illness if a child does become ill. Addressing environmental factors such as indoor air pollution (by providing affordable clean indoor stoves, for example) and encouraging good hygiene in crowded homes also reduces the number of children who fall ill with pneumonia. In children infected with HIV, the antibiotic cotrimoxazole is given daily to decrease the risk of contracting pneumonia (WHO, 2019). The pneumococcal polysaccharide vaccine (PPV) is for people over 65 and anyone over the age of two who's in a high-risk group. Most adults will only need to have this vaccination once in their life. The pneumococcal conjugate vaccine (PCV) is given to infants by the NHS. Babies get their first dose when they're two months old (British Lung Foundation, 2019).

CONCLUSION

In conclusion, the burden of Lower Respiratory Tract Infection is higher in children below the age 5 and elderly persons in developing countries while in older aged group in developed countries. It was also revealed from this review that, most cases of Lower Respiratory Tract Infections are treated based on presumptive diagnosis in most developing countries which in turns attributed to the development of resistance to commonly used antibiotics. Therefore it is recommended that, a definitive diagnosis as well as the antimicrobial susceptibility should be carried out before the use of antibiotics is initiated to reduce the burden LRTI and resistance in developing regions.

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