International Research Journal of Medical Sciences _____ ISSN 2320 – 7353
Vol. **8(1),** 10-20, February **(2020)** *Int. Res. J. Medical Sci.*

Review Paper

Childhood pneumonia in the developing countries: Causative agents, diagnosis and management strategies emphasizing the current status

Saddam Hossain[1], Md. Reaz Morshed[2], Sanjay Saha Sonet[3], Rashedul Islam[4], Atkeeya Tasneem[3] and Mohammad Mahbub Kabir[3*]

[1]Industrial Microbiological Research Division, BCSIR Laboratories, Chittagong, Bangladesh
[2]Department of Biochemistry and Molecular Biology, Noakhali Science and Technology University, Noakhali-3814, Bangladesh
[3]Department of Environmental Science and Disaster Management, Noakhali Science and Technology University, Noakhali-3814, Bangladesh
[4]Quality Assurance Department, Essential Drugs Company Limited (EDCL), Bangladesh
mahbubkabir556@gmail.com

Available online at: www.isca.in
Received 19th November 2019, revised 18th January 2020, accepted 20th February 2020

Abstract

Pneumonia, a lower respiratory infection is regarded as the number one cause of death of children over the world. There were 5.9 million deaths of children aged less than 5 in 2015, more than half of that deaths were occurred by means of infections which create infectious diseases such as pneumonia, tetanus, meningitis, malaria, diarrhea, measles, sepsis and AIDS. Among them pneumonia was responsible for 16% of deaths. Nearly *72% of child deaths caused by pneumonia occur in only 15 countries although they are home to only 55% of the world's population aged less than 5. These are India, Nigeria, Pakistan, Democratic Republic of Congo (DRC), Angola, Ethiopia, Indonesia, Chad, Afghanistan, Niger, China, Sudan, Bangladesh, Somalia, and United Republic of Tanzania. The significant risk factors which are responsible for childhood pneumonia are lack of immunization, lack of exclusively breastfeeding, insufficient nutrition, indoor air pollution, low birth weight, and crowding. Along with these causes, Streptococcus pneumoniae, Haemophilus influenzae and human respiratory syncytial virus are the key causative agents associated with childhood pneumonia. Although pneumonia disease has remarkably decreased due to interventions in health care facilities and improving awareness, but the scenario is still acute in developing countries due to improper diagnosis and inadequate treatment, particularly the children and aged people are more vulnerable. Therefore, it is utmost necessary to conduct extensive research to investigate constrains of pneumonia diagnosis, improvement of treatment facilities including vaccines and antibiotics and adoption of proper management systems so that child survival and burden of pneumonia can be reduced.*

Keywords: Pediatric pneumonia, ALRI, child mortality, aetiology, prevention strategies, management.

Introduction

Pneumonia is one of the one of the acute respiratory tract infections (ARTI) mainly caused by any of virus, fungi and bacteria that has the potential to infect the lungs. In the developing countries, pneumonia substantially attacks the children whose age is under 5 years and the leading pathogenic agents are *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenza* type b (Hib), and human respiratory syncytial (HRS) virus[1]. Throughout the world, it is a most public pestiferous lung disease that creates inflammation resulting in reduction of oxygenation, inadequacy of breath, and eventually demise. Every year, about 1.189 million children aged under 5 years die of pneumonia. It is reported that when one child die of pneumonia in a developed country, mean while 2000 children die of pneumonia in developing countries[2]. In developing countries, there are limitations in proper antimicrobial therapy, regular vaccination, enhanced nourishment, and improved oxygen therapy which are responsible for higher death due to pneumonia. From the last two decades, many significant improvements have been made in syndromes of pneumonia, its etiology, and proper therapy[3]. In 1980, the World Health Organization (WHO) developed a standard management strategy to decrease the pneumonia induced morbidity and mortality in children younger than 5 years in developing countries through early diagnosis and empirical antibacterial therapy of pneumonia[4]. The epidemiology of morbidity and mortality and the comprehension of the main etiological agents of pneumonia as well as causes, diagnosis, treatment and prevention of pneumonia with children aged less than 5 years will be reviewed in this paper.

Epidemiological status of Pneumonia in the developing countries

Worldwide 1.5 million children aged under 5 years died of pneumonia which is 18% of overall 8.8 million childhood deaths in every year[5]. In South-Asia and sub-Saharan Africa, it was estimated over 90% of deaths whereas only <1% of these

deaths occurred in developed countries[6]. Even though there is a similarity in the incidence of ARI in both developed and developing countries, morbidity and mortality is 10-15 times higher in developing countries due to ARI[7]. The yearly occurrence of childhood pneumonia in developing countries is not only more common: 7-40 versus 2-4 cases/100 children in turn, but also is more severe than that of developed countries[8-10]. There are a number of ways by which pathogens of pneumonia can spread and dispatched through direct proximity with nasal secretions, inhabit respiratory tube and may then happen blood-borne diseases. HIV-infected children are more likely to get pneumonia or who transplant organ and are receiving the rapy that reduce their immune responses to infections. The correlation between pneumonia and fatality was investigated data from 44 countries in children extensively[11].

According to that investigation, the estimated pneumonia-ascribable death is ranged from 8% to 36% and it also displayed a log-linear interaction that made a mortality estimation in children aged less than 5 years of average 1.9 million deaths caused by pneumonia when indexed to the global population in 2000. This estimate has been further authorized by recent studies based on current data and has further more exhibited a decline in pneumonia-ascribable deaths[12]. It has been estimated that the worldwide occurrence of clinical pneumonia cases is around 0.30 incidents for each child in each year. Relatively it is equivalent to 15.0 crore new events in every year[13]. It is represented that the new pneumonia episodes occur about 73.89 percent in mostly fifteen countries and more than half in only six countries: Indonesia, Bangladesh, Pakistan, India, Nigeria and China. The maximum incidence of clinical pneumonia was estimated in Eastern-Mediterranean (0.28), Africa (0.33), and then South-East-Asia (0.33). A substantial ratio of pneumonia episodes of 7-13% of cases of severe pneumonia requiring hospitalization[14].

Severe respiratory infection in children may also interlinked with the development of life-long respiratory morbidity and sickness[15]. ALRI is responsible for 25% deaths among children (<5 years old) and accounts for 40% of all infantile deaths in Bangladesh[16]. The most common causative agent of pneumonia and other respiratory diseases (both bacterial and viral) were identified in 30% cases and the case fatality rates were 14% in bacterial pneumonia and 3% in viral pneumonia[17].

The United Nation Inter-agency Group for Child Mortality Estimation (UNIGME) database provides about 17000 data points for mortality of children aged under 5 years for one hundred ninety five countries that includes vital systems of registration, population poll, domestic inspection, and sample registration methods. Five projections based on scenario for the period of 2016 to 2030 for fatality is created that estimate national, regional, and global mortality of children older than 5 years up to 2030 for each scenario owing to providing for insights into the death toll of children under-5 associated with post-2015 targets[18].

Current status of childhood pneumonia in the developing countries

The most significant efforts in the twenty-one century is to improve the perception of the etiology and epidemiology of childhood pneumonia done by Child Health Epidemiology Reference Group (CHERG). It was suggested by the analysis in developing countries childhood pneumonia under 5 years old throughout the world is most incident which is near to 0.30 incidences per child/year acquired through the main approach. The number of incidence of new pneumonia is 151.78 million per year, and average 13.1 million (10.6–19.6 million) or 8.7% (7–13%) of whole number is severe enough to have need of hospitalization[13]. In 2004, UNICEF also revealed the incidence of pneumonia and pneumonia deaths of children aged less than 5 years throughout the world regions where the incidence of pneumonia in children aged less than 5 years in developing countries was about to 0.30 incidences per child/year.

In 2013, World health Organization (WHO) has divided 192 countries into six major regions such as the region of Western pacific, Africa, America, Europe, Eastern-Mediterranean, and South–East Asia - and further subdivided by the level of development into “A”, “B”, “C”, “D” and “E”[13]. The objective of that classification was to carry out the estimate of mortality, causative pathogens, incidence, morbidity, and underlying risk factors for 192 countries[13]. From the population division of United Nation (UN) an estimation of the children under-5 was found in 2010[19]. The frequency of new incidence of community acquired pneumonia (CAP) for 2010 was determined in children aged less than 5 in some developing countries along with South-Asian countries from 192 countries (Table-1).

Table-1: The frequency of new incidence of CAP for children aged less than 5 in 2010 in some developing countries along with South-Asian countries[19].

Country	New episodes (Incidence) All ALRI
Malaysia	2828151
Nigeria	7339761
Indonesia	21578876
Turkey	6412702
Egypt	9008118
Iran (Isl. Rep.)	6149331
Bangladesh	14707333
Pakistan	21418111
India	127960004
Sri Lanka	1892699
Nepal	3506023
Bhutan	70891
Afghanistan	5545968
Maldieves	25984

The prevalence of new episodes of pneumonia was mentionable in only six countries including Nigeria, Pakistan, China, India, Russian Federation and USA among six major regions-AFRO, EMRO, WPRO, EURO, AMRO, and SEARO[19].

The Figure-1 states that India was reported with the highest pneumonia cases than other prevalent countries in 2010.

As the new incidence of pneumonia for 192 countries in 2010 is available, it will act as a powerful tool for estimation of current episodes of pneumonia in the developing countries. Though a significant achievement has been observed, more than nineteen thousands children still die every day. Most of them are due to preventable and treatable infectious diseases. According to WHO and UNICEF 2010, nearly 80% of deaths of children aged less than 5 come about in South Asia and sub-Saharan Africa, and about half of the deaths, in one of five countries: Democratic Republic of the Congo (DR Congo), Nigeria, India, Pakistan and China. More than 33% of global child deaths take place in India and Nigeria alone. Mostly the region of Africa has the uppermost load of worldwide child mortality[14]. Although the population of children under 5 years old of the world consists of 20%, it has about 45% global deaths of children aged less than 5 and 50% of universal deaths from pneumonia.

But the deaths of European region and American region constitute less than 2% and 3% respectively. On the other hand, pneumonia only causes over 88% of all demises happened in children aged less than 5 in 40 countries. The most significant fact is that 75% of all these demises are predominant in just 10 countries namely Nigeria (204000), India (408000), Ethiopia (112000), DR Congo (126000), Pakistan (91000), Afghanistan (87000), China (74000), Bangladesh (50000)), Angola (47000) and Niger (46000) in accordance with the basis of supervisory estimates of World Health organization (WHO) for 2000[14]. According to annual progress report by UNICEF in 2015 revealed that 16,000 children die in 2015. The highest mortality of children under-5 were in the India and Angola. Together with these**,** the highest national mortality of children aged less than 5 were found in sub Saharan Africa. The ten top countries with the highest mortality and the highest frequency of demise of children aged under 5 are shown in Table-2[15].

During the past 25 years, there has been substantial advancement in endurance of children in the world. The under-5 mortality around the world has shown a downward trend from 89.9 deaths/1000 live births in 1990 to 43.0 in 2015. On the other hand, globally the mortality of under-5 reduced gradually from 12.56 million to 5·95 million yearly. The Millennium Development Goal (MDG) 4 was not achieved though the mortality rate of children aged less than 5 lowered by 53% in that period. All MDG regions have more than 50% of mortality rate children aged under-5 except Oceania at the regional whereas North Africa, North America, East Asia and West Indies have lowered the mortality of children aged under-5 by 75% or more since 1990. MDG 4 was accomplished by two regions especially East Asia and North America in accordance with that point estimates[17]. The achievement of MDG 4 set in 2000 was also gained by about sixty two countries all over the world by reducing their mortality rate of children aged under-5 by 75% or more.

They were twelve low-income countries including-Liberia, Tanzania, Nepal, Mozambique, Uganda, Malawi, Madagascar, Niger, Rwanda, Ethiopia, Cambodia and Eritrea and also twelve lower-middle income countries-Bangladesh, Armenia, Bhutan, Indonesia, Georgia, Kirghizia, Egypt, Bolivia, EI Salvador, Nicaragua, East-Timor and Yaman. The mortality of children aged under-5 were significantly reduced by at least 50% and 30% percent by an additional 74 countries as well as another 41 countries respectively. If the mortality remains stable in each country according to 2015, around 94·5 million children may be dead prior to the age of 5 years in the period of 2016 to 2030. Although each country continues in reduction of its mortality increasingly which was counted from 2000 to 2015, around 69.0 million would die. Around 56·0 million deaths will be projected by 2030, if each country accomplishes MDG 4 of mortality of children aged under-5 at the rate of 25 deaths or fewer/1000 live births by 2030. Almost all sub-Saharan African countries require to speed up the prosperity to gain this target[18].

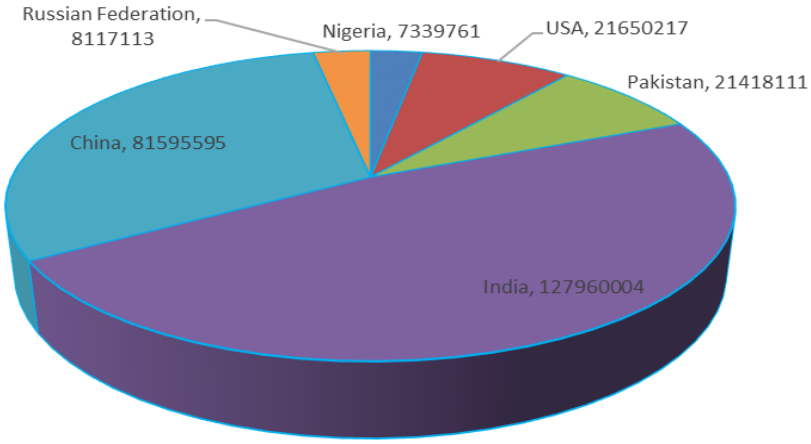

Figure-1: Highest pneumonia cases in 6 countries in 2010

Table-2: Top ten countries with highest mortality rate and highest number of death of children aged under 5 in 2015[14].

Country	Mortality of children aged less than 5 (Deaths per 1,000 live births)	Country	Death of children aged less than under 5 (Deaths per 1,000 live births)
Angola	157	India	1201
Chad	139	Nigeria	750
Central African Republic	130	Pakistan	432
Somalia	137	China	182
Mali	115	Ethiopia	184
Sierra Leone	120	DR Congo	305
Benin	100	Angolia	169
Nigeria	109	Indonesia	147
Niger	96	Bangladesh	119
DR Congo	98	Tanzania	98

Etiological factors of childhood pneumonia

Pneumonia is occurred due to a mixture of numerous factors including pathogenic agents, milieu, hygiene, and health-seeking behaviors. But, clinical pneumonia in children is known to be caused by frequent exposure to risk factors having close association with the vector, the ambience and infection. It is mainly occurred by bacteria and viruses. The number one causative factor of pneumonia in developing countries is bacteria. *Streptococcus pneumonia* was identified in 30-50% of pneumonia incidents among these bacteria[20,21]. Other bacteria are also involved in childhood pneumonia including *Staphylococcus aureus*, *Haemophilus influenza* type b (Hib) and *Klebsiella pneumoni*. According to a multi-centered study performed in 7 countries, the second commonest causative agent in highly severe pneumonia was *Staphylococcus aureus*[22]. Human metapneumo virus, Adenovirus, Human respiratory syncytial (HRS) virus, Influenza virus, and Para-influenza virus are most commonly known among the viruses responsible for childhood pnuemonia[24]. In developing countries, virus testing studies revealed that RSV was found in around 14-39% of hospitalized children for pneumonia or bronchiolitis[23]. Moreover, the appearance of elevated levels of other viruses namely boca virus, the newly revealed HKU-1 virus and rhino virus associated with pneumonia in children has also been confirmed by PCR technique[24].

It is evident that the coupled infection by virus and bacteria may be involved in pneumonia incidents of developed world. In 30-40% of CAP, the coupled infection of virus and bacteria may be responsible[17]. Initial infection by RSV increases the risk of bacteria-infected pneumonia leading to the deaths in pneumonia[25]. In Pakistan, it was found that more than 25% patients with RSV was exposed to the infection of bacteria with *H. influenzae* or *S. pneumoniae*[26]. The secondary infection of measles can cause pneumonia although measles pneumonia is uncommon[27]. *Pneumocystis jirovecii,* formally known as *P. Carinii* is etiological agent for pneumo cystis pneumonia (PCP) which is observed among HIV-infected children that cause pneumonia with increased mortality. The children aged under-6 months carrying HIV-infection are very susceptible to this bacteria whereas infants aged from 6 weeks to 6 months are at highest risk for the infection[28]. The young HIV-exposed uninfected infants and mal nourished children is also infected by PCP. Jeena *et al.*, identified the presence of *Mycobacterium tuberculosis* among eight percent of HIV-infected and HIV-uninfected children to be admitted to a hospital for acute pneumonia[29]. Together with these causative agents, some ancillary pathogens are also responsible for CAP in child of various age groups and with severe acute malnutrition. *Mycoplasma pneumoniae* (greater than 5 years), *Chlamydia pneumoniae, Chlamydia trachomatis* (3-19 weeks), *Moraxella catarrhals*, *Klebsiella pneumoniae, Escherichia coli,* Coronavirus, Enterovirus, CMV, *Listeria monocytogenes*, *Ureaplasma urealyticum, Acinetobacter species, Bordetella pertussis,* andmethicillin-resistant *Staphylococcus aureus* (MRSA) are well understood among them[30].

Diagnosis of Childhood Pneumonia

Pneumonia is diagnosed by various ways including observing the signs and symptoms, a physical examination, health care providers, and diagnostics. Cell cultures and chest X-rays followed by antigen test of blood or urine are usually used to detect pathogens from the infected part of the body of the pneumonia patients. The radiological and laboratory findings

should be ensured to diagnose it accurately. Particularly, the degree and site of the infection of pathogens for pneumonia can be confirmed by Chest X-rays and laboratory tests. But, suspected incidence of pneumonia in resource-poor settings are diagnosed by observing their clinical signs and symptoms without using these technologies[31]. Fever, inadequacy of breathing, cough, headache, decreased appetite and wheezing are most ordinary symptoms of childhood pneumonia. Children aged under-5 with severe incidence of pneumonia may have a complication of breathing problem, i.e., their chests moving in or retracting lower chest wall in drawing during inhalation. In case of young infants with pneumonia other problems such as convulsions, hypothermia, insensibility, languor, and feeding complications may be observed. Study reveals that children are supposed to be experienced with pneumonia if they have cough and breathing complications[31].

The localization of infiltrates should not be used as a distinctive criterion although it is significant for differential diagnosis. The differential diagnosis includes primary tuberculosis with other pathogens. Diffuse infiltration can be observed in PCP and occasionally also occurred by chlamydia in the case of upper lobe infiltrate. Caregivers can play a vital role in identifying the signs and symptoms of pneumonia in children by using a stethoscope and/or observing the respiratory rate and any breathing complications of children for diagnosis. The WHO identifies pneumonia as a severe occurrence of cough or fast breathing known as tachypnea. Pneumonia having a breathing rate of ≥ 50 breaths per minute in a child aged under-12 month and ≥40 breaths per minute in aged 12-60 months is designated as simple (non-severe). Patients are categorized as severe pneumonia who have pneumonia with chest wall in drawing. But, it is regarded as very severe pneumonia having signs such as inability to drink, excessive sleepiness, central cyanosis, convulsion, extreme malnutrition or persistent vomiting. The cut-off values for diagnosing pneumonia is ≥60 breath per minute due to the increased risk of mortality in infants aged under-2 months. This is characterized as severe pneumonia needing instant referral for in-patient care[32,33]. The category of severe pneumonia is highly precise for lower respiratory infections that are deeply associated with disease severity and age. Moreover, the WHO did define tachypnea had the highest sensitivity and specificity with radio- logically confirmed pneumonia according to several studies in children of <5 years[34,35].

The aetiology of pneumonia cannot be clearly defined by the clinical and radiographic feature in case of community acquired pneumonia. During examining the aetiology, the following points should be measured[36]. i. Pneumonia caused by bacteria and virus may not be distinguished by acute phase reactants, C-reactive protein (CRP), white blood cell count, procalciton in general test and neutrophil count[37,38]. ii. Identification of bacterial infectious agent and their antibiotic sensitivity by blood culture may be useful. But test result for HIV-uninfected children with CAP shows only 5% positive of blood cultures. In case of HIV-infected children, the test result shows around 18% positive of blood cultures[39]. iii. White Blood Cell (WBC) and neutrophil count (PMN) leukocytosis shows bacterial pneumonia and lymphocytic leukopenia shows viral pneumonia[40]. iv. If specific infectious agents are present, pleural fluid should be aspirated and examined. v. When TB is supposed, Mantoux test or Mendel (tuberculin skin test), sputum induction and gastric lavage or gastric irritation are designated[41].

Molecular techniques have been used by some investigators to sputum or nasopharyngeal specimens due to the shortage of blood samples in order to direct determination of pathogens[42,43]. Besides adopting specific detection of bacterial infectious agent, advanced molecular techniques such as PCR are capable of identifying the role of viruses in childhood pneumonia[44-46]. It is helpful in accurate detection of viruses such as boca-virus, rhino-virus, and the newly exposed HKU1 virus[24].

Management of childhood pneumonia in the developing

The basis of WHO/IMCI/ARI case-management guidelines is the early diagnosis and rapid institution of empiric antibiotic therapy to decrease the mortality related to pneumonia in developing countries. Any severe or very severe cases of pneumonia require hospital admittance for parenteral medications. But, simple pneumonia (only in case of tachypnea) could be medicable at home through an oral first–line antibacterial agent according to protocol. All infants aged under-2 months suffered from pneumonia should be treated with parenteral antibiotics at the time of hospitalization in a severe case[24,32,33]. The first-line antibacterial agents should be active, dependable, widely accessible and reasonably priced in resource-poor countries[47].

Pneumonia related child mortality can be reduced by active case management[48]. Exact empirical treatment with antibiotic should result in reduction of breathing rates and improvement within 48 hours of therapy in cases of simple pneumonia generally[49]. When the patient's general conditions do worsen within 72 hours of therapy and persistent tachypnea is yet observed (breathing rate is not decreased by ≥ 5 breaths/minute) before referral or changing antibacterial agent, an ordered short-term assessment by the primary health care provider is requisite in order to measuring possible reasons of non-responsiveness to treatment. If the first-line antibacterial agent is not worked properly, and HIV and TB are present, a second-line antibacterial agent is highly required. High dose amoxicillin (amx) (80 to 100mg/kg/day) with clavulanate (co-amoxiclav) for 5 days, or an azalide/macrolide supplementary to the amx if patient with age of 3 years or more can use then. If the primary therapy was co-trimoxazole, the standard dose of amx should be changed[50]. Therefore, the WHO has come up with the guidelines to effectively manage the pneumonia recently[32] (Table-3).

Oxygen therapy is required as the signs and symptoms in the case management instructions do not detect hypoxia. Although having high sensitivity to recognize severe disease[52]. The oxygen-delivery systems and routine therapy of hypoxia by pulse oximetry result in a major decrease in mortality[53,54]. It is possible to identify the children those require hospitalization by observing signs and symptoms at beginning and after 12 hours together with pulse oximetry. The consideration of alternative therapy is also greatly possible then[51].

Existing treatment facilities for the management of pediatric pneumonia

Supportive management besides antibiotic therapy is necessary for children with CAP. The adequate nutrition (calorie requirements), fluid therapy, oxygen therapy, micronutrient supplementation, the use of antipyretics and analgestics are the supportive treatment for reducing child mortality. The hand washing practice, controlling air pollution, screening of blood during transfusion and patient education also the key measures to control the childhood pneumonia (Table-4).

Table-3: Current antibiotic guidelines for CAP in children according to updated WHO and IMCI recommendations[51].

Severity of pneumonia	Drugs	Routes	Doses	Frequencies	Durations
Pneumonia	Amoxicillin	Oral	15 mg/kg or	3 times daily	5 days
			30 mg/kg	2 times daily	3 days
	Trimethoprim-sulfamethoxazole (TMP/SMX)	Oral	4 mg/kg	2 times daily	3 or 5 3 or 5 days
Severe pneumonia	β-lactam antibiotics	Intravenous	-	-	5 days
	Penicillin G		50 mg/ kg	4 times daily	
	Ampicillin		25 mg/kg	3 times daily	
Very severe pneumonia	β-lactam antibiotics	Intravenous	50 mg/kg	4 times daily	10 days
	Penicillin G or Ampicillin		25 mg/kg	2 times	10 days
	Gentamicin		7.5 mg/ kg	1 daily	10 days

Table-4 Caring treatment in the management of pneumonia in the developing countries.

Calorie requirements[17]		Fluid therapy[17]	Micronutrient supplementation	Oxygen therapy[51]
Brest-fed children	Non-Brest fed children			
50-60 kcal/kg/day	80-100 kcal/kg/day	Appropriate rehydration	20 mg of zinc for hospitalized children with CAP[56].	Hypoxia should be treated by using oxygen therapy.
Sufficient carbohydrate intake as well as a large proportion of lipids.		50 ml/kg/day intravenously	Vitamin A Children with measles-related acute pneumonia should not take vitamin A. Vitamin A set containing 200,000 IU on two days for measles significantly reduced overall and Pneumonia-specific mortality[57].	Antipyretics and analgesics[51] Paracetamol: 15mg/kg/doseis given for 4 to 6 or 8 hours but latter is very effective. Paracetamol and codeine (0.5mg/kg/dose): Adequate analgesia
Blood transfusions[54] Children only used to blood transfusion in the event of tissue hypoxia or cardiovascular compromise.		Hand ablution Washing hand with soap can decrease the risk of respiratory infections and diarrhea[55].	Indoor air pollution Reduction of pneumonia incidence is possible by 22-46% with the help of cleaner gaseous fuels in the household and well-maintained stoves.[58].	Patient education Patient's education is to search for signs and symptoms of pneumonia.

Specific preventive strategies to reduce childhood pneumonia

Some specific strategies are referred including immunization, antibiotic therapy, and HAAR therapy for HIV-infected children early to tackle childhood pneumonia[51].

Immunization: Vaccines such as Measles, BCG, pertussis and influenza vaccines etc. should be given as routine immunization to all children. While vaccination it should be kept in mind that the mode of immune suppression regulates the protection and efficiency in children with HIV infection. Symptomatically children with HIV infection should not take BCG[36]. Several vaccines including pertussis, measles, influenza, and pneumococcal vaccines are accessible and suggested for worldwide adoption for the prevention of pneumonia[59]. Recently, there has been notable progress in the institution of these life-saving vaccines mostly in low-income countries. Hib vaccine required almost 20 years to be introduced in 70% of low-income countries since its first introduction in any country whereas 15 and 11 years are to be needed in case of PCV and rotavirus vaccines.

Other vaccines in immunization

Influenza vaccine: Vaccination has been found to be active in moderately immune suppressed (CD4 counts between 200 and 500cells/µl) HIV-infected adults[60]. Influenza vaccine is safe to use in HIV-infected children according to current evidence. Therefore, children with HIV infection should take influenza vaccine yearly[36].

Varicella vaccine: Varicella vaccine may be given to asymptomatic or mildly immune suppressed children with HIV infection at 12-15 months. This is not required for symptomatic immune suppressed HIV infected children for potential risk of dissemination of the disease[36].

Prophylaxis to prevent childhood pneumonia: Prophylaxis against Pneumocystis Jirovecii Pneumonia (PCP): Primary and secondary infection by Pneumocystis jirovecii in children with HIV infection can be stopped perfectly by prophylaxis with oral TMP/SMX. It requires authentic determination of suspected patient and mother of patient with HIV[61].

A noteworthy reduction in PCP has been ensued in countries of routine prophylaxis. It was found that mortality and hospitalization of patient was reduced around 42% and 24% respectively by prophylaxis in control trail of PCP[62]. WHO recommended the use of TMP/SMX therapy for HIV exposed or infected children with age between four to six weeks.

Mycobacterial diseases prevention: Isoniazid (INH) has been used effectively as a protective agent in children who are prone to TB disease[63]. Every children aged under-5who are expounded to a homey TB contact daily for six months should take prophylaxis (10mg/kg). But, prophylaxis should be offered for six months regardless of their age to children with HIV infection who are unprotected to a household contact. Furthermore, the HIV-infected tuberculin skin test-positive children should also be provided with prophylaxis when there is no a known household contact[36]. The prophylaxis cuts the risk of TB disease by 36% in patients with HIV infection with a tuberculin skin test.

An INX/placebo prophylaxis conducted in South Africa on children with HIV infection showed a reduction of TB incidence and mortality by 71.876% and 53.897% respectively[64].

Human respiratory syncytial virus (HRSV) prevention: The humanized moAb (monoclonal antibody) for the stopping of HRSV infection is applicable for children in developing countries without any benefit costs analysis. The children aged under 6 months are at high risk for severe RSV infection, i.e. premature babies (<37 weeks of gestation) do not get benefit from the antibody. Usually, children aged 12 months or more with immedicable lung diseases or connate heart diseases due to HRSV infection are most likely to be benefitted[65].

Highly active anti-retroviral (HAAR) therapy: The HAAR therapy is very fruitful approach to alter immunity in the course of decreasing pneumonia incidents and opportunity of infections in children with HIV. According to national guidelines of South Asian Thoracic society, all HIV-infected children having immunological, medical, and social criteria for HAAR therapy at the suitable stage of the disease should be given highly active antiretroviral therapy[36].

Overall key protection against and prevention of childhood pneumonia[66]: i. 15-23% reduction in childhood pneumonia could be accomplished by exclusively breastfeeding for the first6 months of early life. ii. The use of antibiotics could be considered as an effective and inexpensive way to treat childhood pneumonia. iii. Vaccinations lead to 49% reduction of pneumonia infections. iv. Use of a clean cook stove also leads to 50% reduction in contracting pneumonia.

Conclusion

Pneumonia is the number one reason of the death of children that killed an estimated 9, 35,000 children aged under-5 in 2015 throughout the world. In developing countries, the main factors which are responsible for pneumonia in children are pneumococcus, Hib, and RSV, but approximations of their comparative position differ in various settings. In developing countries, it has an excessive problem of morbidity and mortality that create economic crisis and health burden on families as well as the whole country. So, prevention of pneumonia is a burning question for saving the lives of children, respecting economic costs as well as relief from illness. In addition, an integrated care management system could have mentionable reduction of mortality due to pneumonia by 16.5%

with taking vaccines against Hib and pneumococcus. Entirely, mortality of children could be decreased by breast feeding promotion and zinc supplementation. A rigorous effort to further comprehend the disease is essential to alleviate morbidity and mortality of children through a combined action of preclusion and treatment interventions over vaccines and antibiotics. Moreover, interventions required for the improvement of preventive strategies in HIV prevalence areas especially where children are highly HIV infected. Concrete efforts must make the deaths of children avoidable in the upcoming years and increase their longevity to lead a healthy and sustainable livelihood by reducing morbidity and mortality. It is imperative to take urgent actions in the territories and countries with rampant mortality of children aged less than 5, mainly in South Asia and sub-Saharan Africa. This will lead to significant improvement in the health of children overall and hopefully the successful accomplishment of MDG 4 is possible in high-burden territories and countries in the next few years.

References

1. Cashat-Cruz M., Morales-Aguirre J.J. and Mendoza-Azpiri M. (2005). Respiratory tract infections in children in developing countries. 16(2), 84-92. *Seminars in pediatric infectious diseases,* 16(2), 84-92.

2. De Onis M., Onyango A.W., Borghi E., Garza C. and Yang H. (2006). Comparison of the World Health Organization (WHO) Child Growth Standards and the National Center for Health Statistics/WHO international growth reference: implications for child health programmes. *Public health nutrition,* 9(7), 942-947.

3. Izadnegahdar R., Cohen A.L., Klugman K.P. and Qazi S.A. (2013). Childhood pneumonia in developing countries. *The Lancet respiratory medicine*, 1(7), 574-584. https://doi.org/10.1016/S2213-2600(13)70075-4

4. Rodríguez L., Cervantes E. and Ortiz R. (2011). Malnutrition and Gastrointestinal and Respiratory Infections in Children: A Public Health Problem. *Environmental research and public health,* 8(4), 1174-1205.

5. Black R.E., Cousens S., Johnson H.L., Lawn J.E., Igor Rudan I., Bassani D.G., Jha P., Campbell H., Walker C.F., Cibulskis R., Eisele T., Liu L. and Mathers C. (2010). Global, regional, and national causes of child mortality in 2008: a systematic analysis. *The Lancet,* 375(9730), 1969-1987. https://doi.org/10.1016/S0140-6736(10)60549-1

6. Rajaratnam J.K., Marcus J.R., Flaxman A.D., Wang H., Levin-Rector A., Dwyer L., Costa M., Lopez A.D. and Murray C.J. (2010). Neonatal, postneonatal, childhood, and under-5 mortality for 187 countries, 1970-2010: a systematic analysis of progress towards Millennium Development Goal 4. *The lancet,* 375(9730), 1988-2008.

7. Pavia A.T. (2011). Viral infections of the lower respiratory tract: old viruses, new viruses, and the role of diagnosis. *Clinical infectious diseases,* 52(suppl. 4), S284-S289.

8. Selwyn B. (1990). The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries. *Review of infectious diseases* 12(Suppl. 8), S870-S888.

9. Pio A. (2003). Standard case management of pneumonia in children in developing countries: the cornerstone of the acute respiratory infection programme. *Bulletin of the world health organization*, 81(4), 298-300.

10. Singh V. (2005). The burden of pneumonia in children: an Asian perspective. *Paediatric respiratory reviews,* 6(2), 88-93.

11. Williams B.G., Gouws E., Boschi-Pinto C., Bryce J. and Dye C. (2002). Estimates of world-wide distribution of child deaths from acute respiratory infections. *The Lancet infectious diseases*, 2(1), 25-32.

12. Liu L., Johnson H.L., Cousens S., Perin J., Scott S., Lawn J. E. and Mathers C. (2012). Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *The Lancet*, 379(9832), 2151-2161.

13. Rudan I., Tomaskovic L., Boschi-Pinto C. and Campbell H. (2004). Global estimate of the incidence of clinical pneumonia among children under five years of age. *Bulletin of the World Health Organisation,* 82(12), 895-903.

14. Rudan I., Boschi-Pinto C., Biloglav Z., Mulholland K. and Campbell H. (2008). Epidemiology and etiology of childhood pneumonia. *Bulletin of the World Health Organization,* 86(5), 408-416B.

15. Puchalski Ritchie L.M., Howie S.R.C., Arenovich T., Cheung Y.B., Weber M., Moore S. and Adegbola R.A. (2009). Long-Term Morbidity from Severe Pneumonia in Early Childhood in the Gambia West Africa. A Follow-Up Study. *International journal of tuberculosis and lung disease*, 13(4), 527-532.

16. Baqui A.H., Black R.E., Arifeen S.E., Hill K., Mitra S.N. and Al Sabir A. (1998). Causes of childhood deaths in Bangladesh: results of a nationwide verbal autopsy study. *Bulletin of the World Health Organization,* 76(2), 161.

17. Ashraf H., Jobayer M. and Alam N. (2010). Treatment of childhood pneumonia in developing countries. *Health management*, Sciyo, 59-88. ISBN: 978-953-307-120-6

18. You D., Hug L., Ejdemyr S., Idele P., Hogan D., Mathers C. and Alkema L. (2015). Global, regional, and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Inter-agency Group for Child Mortality Estimation. *The Lancet*, 386(10010), 2275-2286.

19. Rudan I., O'Brien K.L., Nair H., Liu L., Theodoratou E., Qazi S., Lukšić I., Fischer Walker C.L., Black R.E. and Campbell H. (2013). Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. *Journal of global health*, 3(1), 010401.

20. Shann F. (1986). Etiology of severe pneumonia in children in developing countries. *The Pediatric infectious disease journal,* 5(2), 247-252.

21. Berman S. (1991). Epidemiology of acute respiratory infections in children of developing countries. *Review of infectious diseases*, 13(Suppl. 6), S454-S462.

22. Asghar R., Banajeh S., Egas J., Hibberd P., Iqbal I., Katep-Bwalya M. and Mino G. (2008). Chloramphenicol versus ampicillin plus gentamicin for community acquired very severe pneumonia among children aged 2-59 months in low resource settings: multicentre randomised controlled trial (SPEAR study). *Bmj*, 336(7635), 80-84.

23. Weber M.W., Mulholland E.K. and Greenwood B.M. (1998). Respiratory syncytial virus infection in tropical and developing countries. *Tropical medicine & international health*, 3(4), 268-280.

24. Nichols W.G., Campbell A.J.P. and Boeckh M. (2008). Respiratory viruses other than influenza virus: impact and therapeutic advances. *Clinical microbiology reviews*, 21(2), 274-290.

25. Bustamante-Calvillo M.E., Velázquez F.R., Cabrera-Munõz L., Torres J., Gómez-Delgado A., Moreno J.A. and Muñoz-Hernández O. (2001). Molecular detection of respiratory syncytial virus in postmortem lung tissue samples from Mexican children deceased with pneumonia. *The Pediatric infectious disease journal,* 20(5), 495-501.

26. Ghafoor A., Nomani N.K., Ishaq Z., Zaidi S.Z., Anwar F., Burney M., Quresbi A.W. and Ahmad S.A. (1990). Diagnoses of acute lower respiratory lhlct infections in children in rawalpindi and islamabad, pakistan. *Reviews of infectious diseases*, 12(Suppl. 8), S907–S914.

27. Tupasi T.E., Lucero M.G., Magdangal D.M., Mangubat N. V., Sunico M.E.S., Torres C.U., de Leon L.E., Paladin J.F., Oaes L. and Javato M.C. (1990). Etiology of acute lower respiratory lhlct infection in children from alabang, metro manila. *Reviews of infectious diseases*, 12(Suppl. 8), S929–S939.

28. Chintu C., Mudenda V., Lucas S., Nunn A., Lishimpi K., Maswahu D., Kasolo F., Mwaba P., Bhat G., Terunuma H. and Zumla A. (2002). Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study. *The Lancet,* 360(9338), 985-990.

29. Jeena P., Pillay P., Pillay T. and Coovadia H. (2002). Impact of HIV-1 co-infection on presentation and hospital-related mortality in children with culture proven pulmonary tuberculosis in Durban, South Africa. *The international journal of tuberculosis and lung disease*, 6(8), 672-678.

30. Chisti M.J., Tebruegge M., La Vincente S., Graham S.M. and Duke T. (2009). Pneumonia in severely malnourished children in developing countries – mortality risk, aetiology and validity of WHO clinical signs: a systematic review. *Tropical medicine and international health*, 14(10), 1173-1189.

31. World Health Organization. Department of Child, Adolescent Health, World Health Organization, & UNICEF. (2005). Handbook IMCI: Integrated management of childhood illness. World Health Organization.

32. Shann F., Hart K. and Thomas D. (1984). Acute lower respiratory tract infections in children: possible criteria for selection of patients for antibiotic therapy and hospital admission. *Bulletin of the World Health Organization,* 62(5), 749-753.

33. Mulholland E.K., Simoes E.A.F., Costales M.O.D., McGrath E.J., Manalac E.M. and Gove S. (1992). Standardized diagnosis of pneumonia in developing countries. *Pediatric Infectious Disease Journal*, 11(2), 77-81.

34. Kundra S., Singh T. and Chhatwal J. (2008). Utility of Indian adaptation of Integrated Management of Childhood Illness (IMCI) algorithm. *The Indian journal of pediatrics,* 75(8), 781-785.

35. Mittal K., Gupta V., Khanna P., Kaushik J.S. and Sharma A. (2014). Evaluation of Integrated Management of Neonatal and Childhood Illness (IMNCI) algorithm for diagnosis and referral in under-five children. *The Indian journal of pediatrics*, 81(8), 797-799.

36. Zar H., Jeena P., Argent A.C., Gie R. and AMadhi S. (2009). Diagnosis and management of community—acquired pneumonia in childhood—South African Thoracic Society guidelines. *Southern African journal of epidemiology and infection,* 24(1), 25-36.

37. Toikka P., Irjala K., Juvén T., Virkki R., Mertsola J., Leinonen M. and Ruuskanen O. (2000). Serum procalcitonin, C-reactive protein and interleukin-6 for distinguishing bacterial and viral pneumonia in children. *The Pediatric infectious disease journal,* 19(7), 598-602.

38. Korppi M., Remes S. and Heiskanen-Kosma T. (2003). Serum procalcitonin concentrations in bacterial pneumonia in children: a negative result in primary healthcare settings. *Pediatric pulmonology,* 35(1), 56-61.

39. Madhi S.A., Kuwanda L., Cutland C. and Klugman K.P. (2005). The impact of a 9-valent pneumococcal conjugate vaccine on the public health burden of pneumonia in HIV-infected and uninfected children. *Clinical infectious diseases,* 40(10), 1511-1518.

40. Austrian R. and Gold J. (1964). Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. *Annals of internal medicine,* 60(5), 759-776.

41. Zar H., Hanslo D., Apolles P., Swingler G. and Hussey G. (2005). Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *The Lancet,* 365(9454), 130-134.

42. Klugman K.P., Madhi S.A. and Albrich W.C. (2008). Novel approaches to the identification of Streptococcus pneumoniae as the cause of community-acquired pneumonia. *Clinical infectious diseases*, 47(Suppl. 3), S202-S206.

43. Mehr S. and Wood N. (2012). Streptococcus pneumoniae–a review of carriage, infection, serotype replacement and vaccination. *Paediatric respiratory reviews,* 13(4), 258-264.

44. Tsolia M.N., Psarras S., Bossios A., Audi H., Paldanius M., Gourgiotis D., Kallergi K., Kafetzis D.A., Constantopoulos A. and Papadopoulos N.G. (2004). Etiology of community-acquired pneumonia in hospitalized school-age children: evidence for high prevalence of viral infections. *Clinical infectious diseases,* 39(5), 681-686.

45. Lee J.H., Chun J.K., Kim D.S., Park Y., Choi J.R. and Kim H.S. (2010). Identification of adenovirus, influenza virus, parainfluenza virus, and respiratory syncytial virus by two kinds of multiplex polymerase chain reaction (PCR) and a shell vial culture in pediatric patients with viral pneumonia. *Yonsei medical journal,* 51(5), 761-767.

46. O'Callaghan-Gordo C., Bassat Q., Morais L., Díez-Padrisa N., Machevo S., Nhampossa T., Nhalungo D., Sanz S., Quintó L., Alonso P.L. and Roca A. (2011). Etiology and epidemiology of viral pneumonia among hospitalized children in rural Mozambique: a malaria endemic area with high prevalence of human immunodeficiency virus. *The Pediatric infectious disease journal,* 30(1), 39-44.

47. Saffar M.J. and Rezai M.S. (2014). Management of Lower Respiratory Tract Illnesses in Developing Countries: A Narrative Review. *Journal of pediatrics review,* 2(2), 47-56.

48. Sazawal S. and Black R.E. (2003). Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. *The Lancet infectious diseases,* 3(9), 547-556.

49. Grant G.B., Campbell H., Dowell S.F., Graham S.M., Klugman K.P., Mulholland E.K. and Qazi S. (2009). Recommendations for treatment of childhood non-severe pneumonia. *The Lancet infectious diseases*, 9(3), 185-196.

50. Ayieko P. and English M. (2007). Case management of childhood pneumonia in developing countries. *The Pediatric infectious disease journal,* 26(5), 432.

51. Gray D. and Zar H. (2010). Childhood pneumonia in low and middle income countries: Burden, prevention and management. *The Open infectious diseases journal,* 4, 74-84.

52. Usen S. and Weber M. (2001). Clinical signs of hypoxaemia in children with acute lower respiratory infection: indicators of oxygen therapy [Oxygen Therapy in Children]. *The international journal of tuberculosis and lung Disease,* 5(6), 505-510.

53. Duke T., Wandi F., Jonathan M., Matai S., Kaupa M., Saavu M., Subhi R. and Peel D. (2008). Improved oxygen systems for childhood pneumonia: a multihospital effectiveness study in Papua New Guinea. *The Lancet*, 372(9646), 1328-1333.

54. Matai S., Peel D.E., Wandi F., Jonathan M., Subhi R. and Duke T. (2008). Implementing an oxygen programme in hospitals in Papua New Guinea. *Annals of tropical paediatrics,* 28(1), 71-78.

55. Luby S.P. and Halder A.K. (2008). Associations among handwashing indicators, wealth, and symptoms of childhood respiratory illness in urban Bangladesh. *Tropical medicine & international health*, 13(6), 835-844.

56. Brown N. and Roberts C. (2004). Vitamin A for acute respiratory infection in developing countries: a meta-analysis. *Actapaediatrica,* 93(11), 1437-1442.

57. D'Souza R.M. and D'Souza R. (2002). Vitamin A for the treatment of children with measles—a systematic review. *Journal of tropical pediatrics*, 48(6), 323-327.

58. Niessen L., Hove A.t., Hilderink H., Weber M., Mulholland K. and Ezzati M. (2009). Comparative impact assessment of child pneumonia interventions. *Bulletin of the World Health Organization*, 87(6), 472-480.

59. Munos M.K., Walker C.L. and Black R.E. (2010). The effect of rotavirus vaccine on diarrhoea mortality. *International journal of epidemiology*, 39(suppl. 1), i56-i62.

60. Tasker S.A., Treanor J.J., Paxton W.B. and Wallace M.R. (1999). Efficacy of influenza vaccination in HIV-infected persons: a randomized, double-blind, placebo-controlled trial. *Annals of internal medicine*, 131(6), 430-433.

61. Zar H. (2003). Prevention of HIV-associated respiratory illness in children in developing countries: potential benefits. *The international journal of tuberculosis and lung disease,* 7(9), 820-827.

62. Chintu C., Bhat G., Walker A.S., Mulenga V., Sinyinza F., Lishimpi K., Farrelly L., Kaganson N., Zumla A., Gillespie S.H., Nunn A.J. and Gibb D.M. (2004). Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. *The Lancet,* 364(9448), 1865-1871.

63. Cobelens F.G., Egwaga S.M., Ginkel T.V., Muwinge H., Matee M.I. and Borgdorff M.W. (2006). Tuberculin Skin Testing in Patients with HIV Infection: Limited Benefit of Reduced Cutoff Values. *Clinical infectious diseases,* 43(5), 634-639.

64. Zar H.J., Cotton M.F., Strauss S., Karpakis J., Hussey G., Schaaf H.S., Rabie H. and Lombard C.J. (2007). Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. *Bmj,* 334(7585), 136.

65. Samson L. (2009). Prevention of respiratory syncytial virus infection. *Paediatrics& child health,* 14(8), 521-526.

66. UNICEF and WHO (2009). Global action plan for prevention and control of pneumonia (GAPP). *Geneva, Switzerland*, 1-24. Available online at: https://apps.who.int/iris/bitstream/handle/10665/70101/WHO_FCH_CAH_NCH_09.04_eng.pdf?sequence=1(Accessed on 15/11/2019)