ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Review Article

Impact of Hib and Pneumococcal Conjugate Vaccines on the Epidemiology of Childhood Pneumonia in Sub-Saharan Africa: Analysis of WHO/UNICEF Data

Ng'weina Francis Magitta*

Department of Biochemistry and Department of Clinical Pharmacology, Mbeya College of Health and Allied Sciences, University of Dar es Salaam, Mbeya, Tanzania

***Corresponding Author**: Ng'weina Francis Magitta, Department of Biochemistry and Department of Clinical Pharmacology, Mbeya College of Health and Allied Sciences, University of Dar es Salaam, Mbeya, Tanzania.

Received: March 27, 2018; **Published:** May 02, 2018

Abstract

Pneumonia contributes to a substantial burden of disease among children in developing countries. This reality is partly attributed to the presence of high level of risk factors for acquisition and progression of pneumonia. Specifically, until the recent past, sub-Saharan Africa (SSA) did not have access to the otherwise available effective vaccines for control of two major causative pathogens of pneumonia in children. The recent introduction of these vaccines in the routine immunization programs together with increased scale up of control programs against other childhood infections such as TB, pertussis, and HIV in the context of the raising trend in the living conditions of people in SSA could result in the reduction of the incidence of childhood pneumonia. This review attempts to analyze and examine the available WHO and UNICEF resources and repositories of data on estimates from SSA between 1999 and 2016 on the burden of childhood pneumonia prior and after introduction of Hib and pneumococcal conjugate vaccines. Further to that, collateral dataset on other pneumonia-relevant interventions are closely examined. This analysis provides a bird's eye view on the potential areas for investment towards accelerating the achievement of national, regional and global targets through scaling up of effective interventions.

Keywords: *Pneumonia, Hib; Pneumococci; Conjugate Vaccines; Children; Africa*

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome; BCG: Bacillus Calmette-Guérin; CTX: Co-trimoxazole; DPT: Diphtheria, Pertussis, Tetanus; EPI: Expanded Programme for Immunization; GAPPD: Global Action Plan for Pneumonia and Diarrhea; GAVI: Global Alliance for Vaccine and Immunization; GBD: Global Burden of Disease; HAART: Highly Active Antiretroviral Therapy; HIB: *Haemophilus influenzae*; HIV: Human Immunodeficiency Virus; IgA: Immunoglobulin A; LRT: Lower Respiratory Tract; LRTI: Lower Respiratory Tract Infection; MCV: Measles Containing Virus; PCV: Pneumococcal Conjugate Vaccine; PMTCT: Prevention of Mother-to-Child Transmission; ROS: Reactive Oxygen Species; SDGs: Sustainable Development Goals; SSA: sub-Saharan Africa; TB: Tuberculosis; UNICEF: United Nations International Children's Emergency Fund; WHO: World Health Organization

Background

The current Global Burden of Disease (GBD) study and UNICEF report on child survival shows a steady decline in under-five child mortality [1,2]. However, overall child mortality remains substantially high in low income countries particularly those in the sub-Saharan Africa (SSA). It is estimated that about 50% of under-five deaths are known to occur in this region [1,2]. In children aged above one year, pneumonia, diarrhoea and malaria are the leading causes of deaths; typically, deaths occur in those who are already weakened by malnutrition and HIV/AIDS. Following multiple interventions, malaria-attributable deaths have drastically declined. *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* are the major cause of pneumonia, meningitis and sepsis in children globally [3]. Likewise, few studies conducted in Africa, have reported a similar pattern of pathogens [4-7]. However, with the advent of effective pneumococcal

and Hib conjugate vaccines, the pattern of pathogens will likely change to the predominance of viral and atypical pathogens [8]. Lack or low coverage of immunization is the single most important risk factor for childhood death from vaccine-preventable causes in Africa. This is compounded by lack of well-equipped laboratories, shortage of skilled healthcare workforce and inadequate supply of affordable medicines and services. Improvement in the global initiatives for child survival through Expanded Programme for Immunization (EPI), in partnership with Global Alliance for Vaccines and Immunization (GAVI) and Global Action Plan for Pneumonia and Diarrhoea (GAPPD) are the most cost-effective approaches for reducing these vaccine-preventable deaths [2]. Effective strategies for prevention of pneumonia-related mortality are critical for achieving Sustainable Development Goals (SDGs).

Epidemiology of pneumonia

Risk factors for pneumonia in Africa

The major bacterial isolates from children with pneumonia are *S. pneumoniae* and Hib which are collectively responsible for over 60% of cases [3]. In addition to causing pneumonia, both pathogens cause invasive diseases such as septicemia and meningitis in young children [9,10].

Typically, both *S. pneumoniae* and Hib respectively express polyribosyl ribitol phosphate and polysaccharide capsular antigens which resist phagocytosis [7,11,12]. Other pathogenic mechanisms include direct invasion of blood vessels through penetration of the nasopharyngeal epithelium, production of immunoglobulin A (IgA) protease which facilitates attachment to mucosal surfaces and inhibition of secretory IgA which normally binds bacteria to mucin to facilitate their clearance from the respiratory tract as well as production of pneumolysin which perforates and destroy ciliated epithelial cells thereby impairing the normal protection against bacterial invasion [13]. Besides pneumococci and Hib, a range of pathogens such as other uncommon bacteria, viral and atypical organisms, may be responsible for causing pneumonia in specific hosts and settings. The invasive infection triggers sustained inflammatory perturbation characterized by heightened generation of detrimental cytokines, free radicals and reactive oxygen species (ROS) which perpetuates pathogenicity and tissue damage. The combination of all these pathogenic mechanisms in the lower respiratory tract (LRT), results in a protracted acute inflammatory response that lead to the infiltration and consolidation of the lung parenchyma which eventually causes impairment of gaseous exchange and hypoxaemia.

A range of host and environmental factors are known to contribute to the increased risk of developing pneumonia. Children with general poor health especially in the context of severe under-nutrition and deficiency of critical micronutrients such as vitamin A and zinc are at greater risk of developing pneumonia. Furthermore, HIV infection and associated immunodeficiency increases the susceptibility to pneumonia. Thus, in this HIV-infected pediatric population, poor coverage of highly active antiretroviral therapy (HAART) as well as lack of prophylaxis against *Pneumocystis jiroveci* with cotrimoxazole (CTX) can potentially increase risk of developing pneumonia [14,15]. Inadvertently, there are increased odds for developing pneumonia in children from low socio-economic status and poor living conditions characterized by lack of exclusive breast-feeding during early infancy, poor sanitation, lack of access to quality healthcare, as well as poor housing with inadequate ventilation and exposure to environmental and indoor pollution. Similarly, it is well founded that the risk factors for childhood pneumonia may be tracked back during pregnancy and early childhood. Thus, factors which have a negative impact on developmental trajectory of the respiratory system, and those associated with prematurity and low birth weight together with exposure to early childhood respiratory infections can all have a common final pathway on the increased risk of pneumonia [16].

Burden of pneumonia in Africa

World Health Organization (WHO) estimated pneumonia as the number cause of death in children, accounting for 16% of all deaths under five years old, killing 920 136 children in 2015 [17]. Over the recent decades, there has been a steady global decline in the majority of cause-specific mortality rates in children. However, the decline of pneumonia-attributable mortality has remained slow from 1.7 million in the year 2000 to the 920 000 in 2015; a significantly slower rate compared to malaria, diarrhea, measles and HIV. The more recent UNICEF report, estimates pneumonia to account for 18% of deaths among under-fives, killing about 880 000 children in 2016 [18]. Consistently, pneumonia has remained the leading cause of death, with the highest toll in SSA. Likewise, the large proportion of victims has remained those aged less than 2 years [18]. The current data indicates diarrhea as the second important cause of mortality in children in SSA, indicating that integrated interventions targeting risk factors for both pneumonia and diarrhea could potentially serve lives. The healthcare cost for antibiotic treatment of children with pneumonia is enormous and the majority of countries in SSA do not have adequate capacity and resources.

Global and regional interventions against pneumonia

Of recent past, through global campaigns, Africa has undertaken multiple intervention programs for improving child survival. These interventions either directly or indirectly contribute to the control strategies for childhood pneumonia. These interventional programs include introduction of Hib and pneumococcal conjugate vaccines; increased coverage of BCG for tuberculosis (TB), DPT for pertussis (and diphtheria, and tetanus) and measles; increased coverage of prevention of mother-to-child transmission (PMTCT) of HIV and wide coverage of pediatric HAART and care. On the other hand, campaigns for prevention of malnutrition and supplementation for micronutrient as well as strategies for poverty alleviation, all have indirect improvement of child survival.

It has been clearly demonstrated that the introduction of specific vaccines against S. pneumonia and Hib in high-income countries has substantially reduced the attributed mortality. The vaccination against these important pathogens has been demonstrated to protect against colonization, invasion and subsequent LRT infection. For instance, in the UK, the introduction of Hib vaccine in infants reduced the risk of serious infection from 1:600 to 1: 30,000 by 5 years of age [19]. Thus, introduction of routine Hib and pneumococcal conjugate vaccines in Africa is likely to result in a direct reduction of the burden of pneumonia in children [20]. Globally, by 2016, pneumococcal vaccine was available in 134 countries with the total vaccine coverage estimated at 70%, albeit with great regional variations [21].

Similarly, indirect benefit can be achieved by vaccinations against systemic debilitating diseases or specific respiratory diseases contributing to the impairment of the immunological defense of the respiratory tract. The latter include pulmonary TB, measles, and pertussis. For instance, increased coverage of the immunization against TB, measles and pertussis improves the overall health and immune status of children and their ability to resist LRTI. In addition, HIV infection, through weakening of the immune system, increases the vulnerability of children to other infections including TB, pneumonia and diarrhea [14,15]. Thus, strategies geared to increase PMTCT and HAART coverage have spin-off effects on the pneumonia-related morbidity and mortality in children [14]. Likewise, strategies that aim to improve the quality obstetric care which targets to prevent low birth weight and prematurity provides newborns with adequate lung maturity and greater immunological 'prosperity' during infancy and childhood. Moreover, indirectly, diarrheal diseases have substantial impact on overall child health and survival. Thus, introduction of RotaC vaccine together with supplementation with vitamin A and micronutrients such as zinc have been shown to reduce severity and episodes of diarrhea, and the risk of malnutrition in children [22].

Methods

This study was a cross-sectional retrospective survey on the trend of childhood pneumonia in SSA using online resources. The data included country and regional estimates over the period ranging from 1999 to 2016, purposely selected to include the period prior and after introduction of key pneumonia-preventive vaccines in Africa.

Data on country-specific and regional estimates on childhood pneumonia were accessed from WHO and UNICEF online repository and resources [18]. Data included, cause-specific country, regional and global estimates on the burden of pneumonia as well as the immunization coverage, paying particular attention on the initial introduction and coverage of Hib and pneumococcal conjugate vaccines. In addition, other vaccines with indirect protection against pneumonia were also accessed and included in the study. All countries within WHO Africa region were included in the study. The data were collected and analyzed using standard excel spread sheet.

Results

As highlighted in figure 1, BCG has the highest coverage in Africa, with a plateau at about 80% over the last 10 years. This is followed by measles and DPT vaccines which have also remained at coverage of slightly less than 70% over the last 10 years. It is also highlighted that Hib which was initially introduced in Africa in 1999, remained with poor coverage only until 2009, where the coverage increased to about 70% ever since. The most recent, pneumococcal vaccine, initially introduced in Africa in 2009, has steadily increased to the coverage of about 60% in 2016.

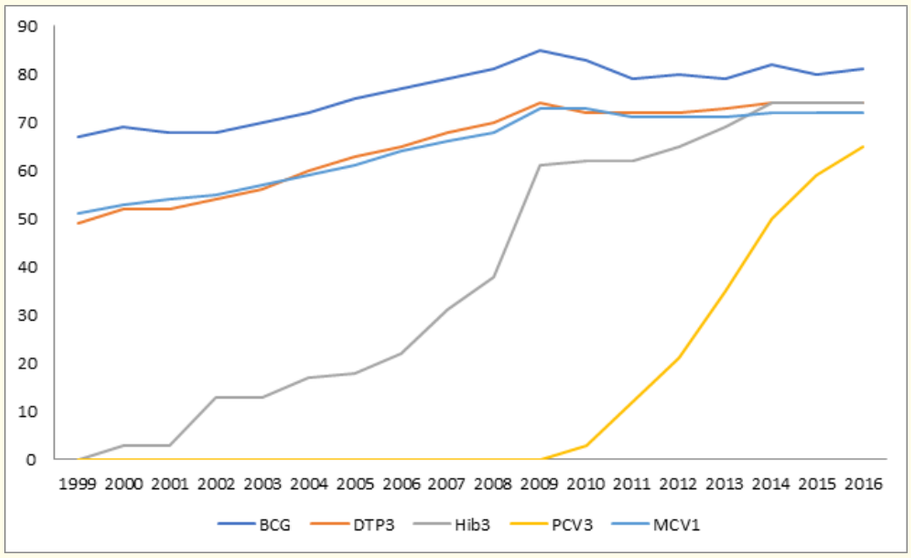

Figure 1: *Trend of immunization coverage for BCG, MCV1, DPT3, Hib3, and PCV3 vaccine in WHO Africa region between 1999 and 2016.*

Country-specific coverage of Hib and pneumococcal conjugate vaccines are highlighted in figure 2. Overall, all countries in WHO Africa region administers vaccinations against Hib albeit with significant variations. Top five countries with the highest Hib and pneumococcal conjugate vaccines coverage – for over 90% - include Rwanda, Tanzania, Sao Tome and Principe, Eritrea and Botswana. Moreover, nine countries - Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Guinea, Seychelles, Somalia and South Sudan – had not started pneumococcal conjugate vaccination by 2016.

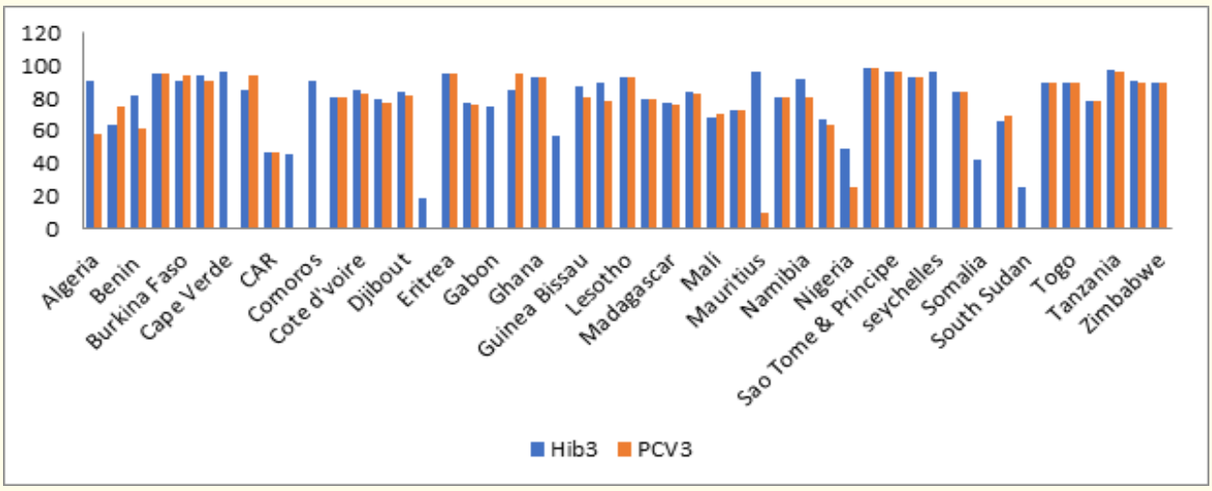

Figure 2: *Country-specific coverage of Hib3 and PCV3 vaccines in WHO Africa region.*

Global and WHO Africa regional mortality trends due to acute respiratory infection (ARI) between 2000 and 2016 are highlighted in figure 3. There is a steady decline globally, but the rate of decline is significantly lower in WHO Africa region.

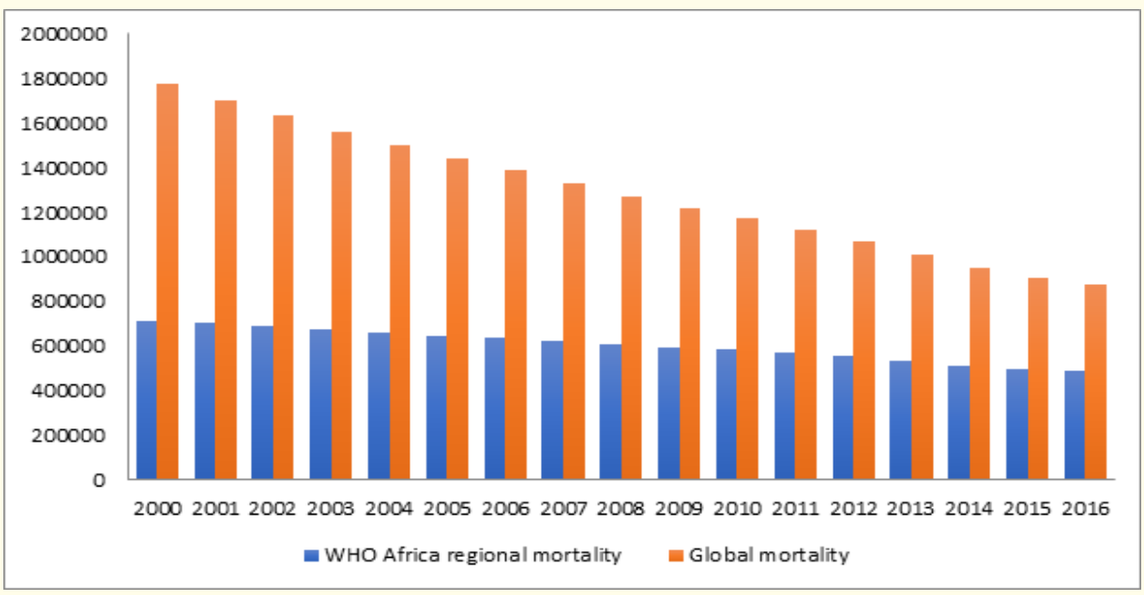

Figure 3: *Global and regional estimates of trends of under-five mortality due to ARI between 2000 and 2016.*

A steady decline of pneumonia-specific mortality in under-five children over the last 16 years is highlighted in figure 4. It is evident that there is a decline in overall mortality among under-five and those aged less than one year. The mortality rate has remained constant or very slowly declining for children aged less than one month.

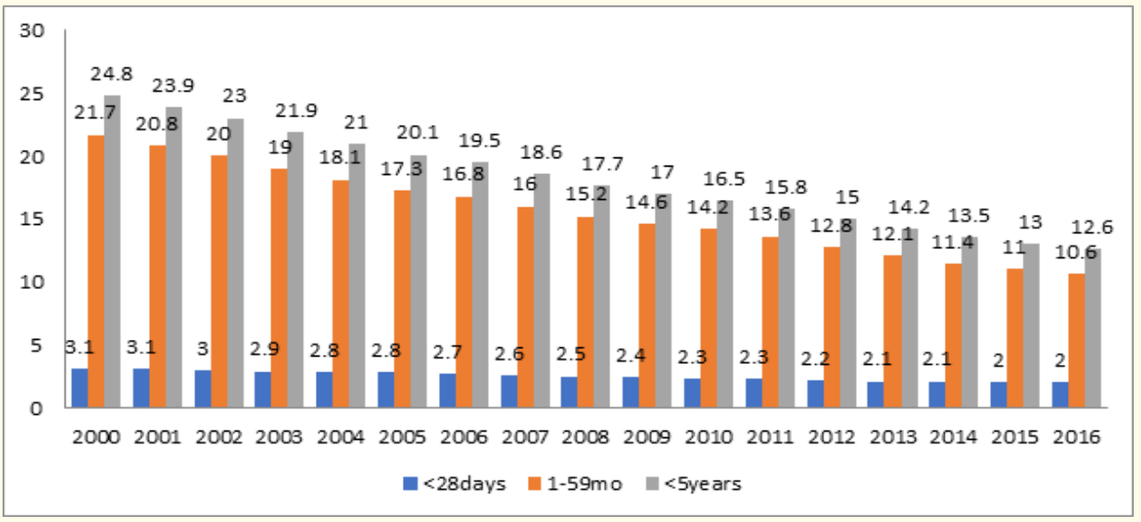

Figure 4: *Trend of estimates of acute LRTI-attributed death rates per 1000 live births among neonates, infants and overall under-five children in WHO Africa region.*

Discussion

Over the last two decades, great strides have been made globally on the protection, prevention and treatment of children with pneumonia. Nevertheless, the burden of childhood pneumonia in SSA has remained enormous. The burden of pneumonia is particularly high among those aged less than one month indicating either the presence of poorly-defined host factors or unaddressed environmental factors including altered patterns in pneumonia-causing pathogens.

The slow rate of decline in the burden of pneumonia in SSA is largely attributed to the persistence of the specific risk factors associated with the likelihood of contracting and developing pneumonia. The most important reason is the late introduction and slow pace of coverage of Hib and pneumococcal conjugate vaccines in the routine immunization programs in Africa. These vaccines provide the most cost-effective approach for protection and prevention of severe forms of pneumonia particularly in the context where healthcare disparity and inequality are prevalent. Thus, the impact of the recently introduced Hib and pneumococcal conjugate vaccines is likely to manifest over the next few years. This projection is well observed in developed countries, such as the UK, where, for instance, the introduction of Hib vaccine in infants reduced the risk of serious infection from 1:600 to 1: 30,000 by 5 years of age [19].

The observed significant decline in global burden of pneumonia is additionally attributed to the indirect interventions. In order for Africa to realize the full impact of protection and prevention of pneumonia, these indirect interventions are critical in providing additional benefit bearing in mind that there are causative pathogens other than Hib and pneumococci. The first category of indirect interventions includes scale up of other indirectly protective vaccination programs such as those against TB, measles and pertussis. All these vaccinations are never beyond 80% - too low threshold for adequate to provision of relevant protective herd immunity. Rotavirus is an important cause of diarrheal diseases in children in Africa and thus, can have profound impact on the dynamics of childhood pneumonia. Thus, the recent introduction of RotaC vaccine is expected to have positive impact on the reduction of the burden of pneumonia, as projected under GPPD action plan [17]. The uncontrolled migration and forced mobility of populations across geopolitical systems compounded with myths and misconceptions regarding vaccination greatly hamper coordinated strategies for achieving immunization targets in Africa.

The second category of interventions having indirect impact on the burden of pneumonia in SSA includes those targeting HIV infection and care [23]. Africa has the largest proportion of pediatric HIV/AIDS population amid low level of PMTCT services and HAART coverage [24]. Thus, in order for African countries to speed up the rate of decline of pneumonia, a purposeful focus should be placed on improving the coverage of PMTCT services and HAART alongside the improvement of general pediatric HIV care including prophylaxis against *Pneumocystis jirovecii* using CTX and adequate nutritional support [14,15].

The third category of indirect intervention against pneumonia includes strategies for improvement of the overall child health, nutritional support, micronutrient and vitamin A supplementation, clean water supply and sanitation together with improvement in housing for reduction of indoor pollution [17,22,25]. Women and young children often spend long hours in the poorly ventilated houses during preparation of food for the family. Thus, reduction in the exposure to indoor pollution through provision of alternative, clean energy for cooking and lighting at homes could provide additional protection and prevention against childhood pneumonia [25].

Conclusions

The burden of childhood pneumonia is declining at slower rates in Africa compared to other regions. The highest burden is recorded among the infants indicating that specific drivers could be operative in this age category. Specific studies are therefore required to elucidate the pathogenic mechanisms and drivers in this age group and suggest better preventive strategies. In order to tackle the burden and achieve global target of childhood pneumonia, Africa needs to develop, adopt, scale up and accelerate the purposeful programs aiming to increase coverage of relevant, proven integrated interventions. The strategies should include the expansion of immunization programs, improvement of living standards and provision of affordable healthcare. Of particular relevance to African setting, the socio-cultural dimension centered on health-seeking behavior deserves a special attention.

Bibliography

1. GBD. "Global, Regional, and National under-5 Mortality, Adult Mortality, Age-Specific Mortality, and Life Expectancy, 1970–2016: A Systematic Analysis for the Global Burden of Disease Study 2016". *Lancet* 388.10053 (2016): 1459-1544.

2. UNICEF. Levels and Trends in Child Mortality Report (2017).

3. DeAntonio R., *et al*. "Epidemiology of Community-Acquired Pneumonia and Implications for Vaccination of Children Living in Developing and Newly Industrialized Countries: A Systematic Literature Review". *Human Vaccines and Immunotherapeutics* 12.9 (2016): 2422-2440.

4. Benet T., *et al.* "Etiology and Factors Associated with Pneumonia in Children under 5 Years of Age in Mali: A Prospective Case-Control Study". *PLOS One* 10.12 (2015): e0145447.

5. Enwere G., *et al.* "Epidemiology and Clinical Features of Pneumonia According to Radiographic Findings in Gambian Children". *Tropical Medicine and International Health* 12.11 (2007): 1377-1385.

6. Roca A., *et al.* "Invasive Pneumococcal Disease in Children<5 Years of Age in Rural Mozambique". *Tropical Medicine and International Health* 11.9 (2006): 1422-1431.

7. Usen S., *et al.* "Epidemiology of Invasive Pneumococcal Disease in the Western Region, the Gambia". *Pediatric Pediatric Infectious Disease Journal* 17.1 (1998): 23-28.

8. David M., *et al.* "Community-Acquired Pneumonia in Children a Changing Spectrum of Disease". *Pediatric Radiology* 47.11 (2017): 1392-1398.

9. Campbell J D., *et al.* "Invasive Pneumococcal Infections among Hospitalized Children in Bamako, Mali". *Pediatric Infectious Disease Journal* 23.7 (2004): 642-649.

10. Campbell JD. "The Causes of Hospital Admission and Death among Children in Bamako, Mali". *Journal of Tropical Pediatrics* 50.3 (2004): 158-163.

11. McCullers JAand EI Tuomanen. "Molecular Pathogenesis of Pneumococcal Pneumonia". *Frontiers in Bioscience* 6 (2001): D877-D889.

12. van der Poll T and SM Opal. "Pathogenesis, Treatment, and Prevention of Pneumococcal Pneumonia". Lancet 374.9700 (2009): 1543-1556.

13. Cockeran R., *et al*. "Pneumolysin as a Vaccine and Drug Target in the Prevention and Treatment of Invasive Pneumococcal Disease". *Archivum Immunologiae et Therapiae Experimentalis (Warsz)* 53.3 (2005): 189-198.

14. Gray DM. "Community-Acquired Pneumonia in Hiv-Infected Children: A Global Perspective". *Current opinion* 16.3 (2010): 208-216.

15. Madeddu G., *et al*. "Bacterial Community-Acquired Pneumonia in Hiv-Infected Patients". *Current Opinion in Pulmonary Medicine* 16.3 (2010): 201-207.

16. Larson CP. "Poverty During Pregnancy: Its Effects on Child Health Outcomes". *Paediatrics and Child Health* 12.8 (2007): 673-677.

17. UNCEF. "Pneumonia and Diarrhoea; Tackling the Deadliest Diseases for the World's Poorest Children". (2012).

18. UNICEF. "Estimates of Child Cause of Death, Acute Respiratory Infection (2018).

19. Heath PT and J Mc Vernon. "The Uk Hib Vaccine Experience". *Archives of Disease in Childhood* 86.6 (2002): 396-399.

20. Roca A., *et al* "Estimating the Vaccine-Preventable Burden of Hospitalized Pneumonia among Young Mozambican Children". *Vaccine* 28.30 (2010): 4851-4857.

21. WHO/UNICEF. Estimated Coverage by Country, Year and Vaccine (2016).

22. Chen H., *et al.* "Vitamin a for Preventing Acute Lower Respiratory Tract Infections in Children up to Seven Years of Age." *Cochrane Database Systematic Reviews* 1 (2008): CD006090.

23. Tornheim JA., *et al*. "The Epidemiology of Hospitalized Pneumonia in Rural Kenya: The Potential of Surveillance Data in Setting Public Health Priorities". *International Journal of Infectious Diseases* 11.6 (2007): 536-543.

24. Slogrove AL. "Maternal Hiv and Paediatric Lung Health". *Paediatric Respiratory Reviews* 21 (2017): 47-53.

25. Smith KR., *et al.* "Indoor Air Pollution in Developing Countries and Acute Lower Respiratory Infections in Children". *Thorax* 55.6 (2000): 518-532.

Volume 7 Issue 5 May 2018