Immunological Responses to Pneumococcal Conjugate Vaccine and Intestinal Nematodes Infestation in Children

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**Authors’ contributions**

This work was carried out in collaboration between all authors. Author LAA wrote the 1st draft of the review paper manuscript, developed a research proposal out of this concept and is currently undertaking the research study. Authors FNM and DSY managed the literature searches and made corrections on the 1st and 2nd drafts. All authors read and approved the final manuscript.

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**ABSTRACT**

Pneumonia is among the leading killer diseases of children under five years in Kenya. The most common bacteriological cause of severe and fatal pneumonia is *Streptococcus pneumoniae* (*S. pneumoniae*). *S. pneumoniae* is usually carried in the nasopharynx of healthy people, but occasionally leads to invasive pneumococcal diseases (IPDs), such as meningitis, pneumonia, otitis, sinusitis and bacteremia. Annually, World Health Organization (WHO) estimates the occurrence of one and a half million of deaths in children under five years, mainly in poor countries. In Kenya, A 10-valent Pneumococcal Conjugate Vaccine (PCV10) introduction into routine immunization schedule has resulted in reduction of the incidence of Invasive Pneumococcal diseases (IPD). However, there is a need to systematically evaluate the confounding factors that...
limit vaccine efficacy. A common although often overlooked confounding factor in the PCV10 vaccination efficacy is the presence of gastrointestinal nematode parasites in humans, particularly in children living in slums. Here the intestinal nematodes are prevalent and their effects result in an immuno-compromised state. We review the possibility of concurrent intestinal nematode infestation altering PCV10-induced responses in children and the need to devise efficacious treatment strategies.

**Keywords: Intestinal nematodes; child health; pneumonia; vaccines; immune responses; infectious diseases.**

1. INTRODUCTION

The rapid expansion of populations in the tropics has increased the risk of transferring both respiratory pathogens and heminthic infections. A combination of poverty and overpopulation stimulates the spread of severe respiratory infections. The occurrence of pneumococcal infection varies with locality due to host, pathogen and ecological dynamics [1]. Bacterial pneumonia is principally common and frequently fatal in children living in the tropics. *Streptococcus pneumoniae* a common bacteriological source of severe and lethal pneumonia is a natural colonizer of the nasopharynx. The World Health Organization (WHO) recommends that developing countries by having high childhood mortality ought to introduce Pneumococcal Conjugate Vaccines (PCV; Table 2) into their routine vaccination timetables [2]. Pneumococcal Conjugate Vaccine defensive ability which is built on the environmental frequency of pneumococcal serotypes has been incorporated into a number of nationwide vaccination programmes for hindrance of severe pneumococcal diseases in young children.

From 2011, 37 GAVI qualified countries have been permitted to introduce PCV for immunization to avoid pneumococcal diseases [3]. Introduction of PCV 10 into routine vaccination program in Kenya has led to noticeable decrease of the occurrence of Invasive Pneumococcal diseases (IPD) in infants and young children [3]. There is indication that co-infection of disease causing pathogens and pneumococcal bacteria can end in compromised immune systems [4]. Subsequently, since co-infection with other pathogens is possible to distress the immune reaction following vaccination, the confounding factors that might possibly limit vaccine effectiveness need to be measured in designed more effective protective and/or treatment regimens. One common, although unnoticed effect, is the existence of gastrointestinal nematode parasites in susceptible human inhabitants particularly children. This is predominantly significant in regions where nematode infections are dominant, such as informal settlements as a result of the poor hygiene and frequency of nematode invasion [5]. The occurrence of intestinal nematodes and the associated immune inadequacy involves cautious analysis. Probably, treatment plans with this concern would be more effective. The immune reaction of a host to any vaccine would be ideal in the absence of other infections.

Evaluation of immunological reactions in nematode and pneumonia infections in diverse organisms demonstrates that T helper (Th) cells create signature cytokine arrays. These Th reactions are prompted mainly by intracellular versus extracellular pathogens that make available the cellular and molecular foundation for counter regulatory expression of defensive immunity throughout simultaneous infections [6]. Intestinal nematode infections prompt Th2 immune reactions with increased levels of interleukin (IL)-4, IL-5 and IL-10 at much higher than levels of IFN-g and IL-2 [7]. On the other hand, the exposure to bacterial pathogens is responsible for Th1- derived protection with production of higher levels of IFN-g and IL-2 [8] which inhibits development of Th2 cells expressing IL-4 dependent immunity to extracellular intestinal nematodes [9]. Cytokines derived from Th1 and Th2 immune responses cross-regulate one another, the consequences of this condition are still poorly understood. However, an evaluation of the immunological profiles together with intestinal nematode infection could probably give new information which can aid in designing intervention and new treatment protocols in the affected children.

2. *Streptococcus pneumoniae* PREVALENCE AND SYMPTOMS

*Streptococcus pneumoniae* causes 14.5 million incidences of severe illness in children less than
5 years old globally and 826,000 deaths yearly [10]. More than half of these deaths occur in African children. In 2008 for example, approximately 8.8 million deaths occurred globally in children less than five years and pneumococcal disease resulted in a predictable 521,000 of these deaths [11]. In the developed world, Invasive Pneumonia Disease (IPD) is infrequent in neonates but peaks in the subsequent year of life [12]. Pneumonia is one of the primary killers of children [13] claiming about 30,000 lives every year in Kenya. This is a large fraction of the 124,000 under-five child deaths in a year [13,14].

*Streptococcus pneumonia* is a natural invader of the nasopharynx. Nevertheless, certain aspects such as age and alterations in immune status can result in the bacteria spreading to the brain, causing meningitis; the middle ear, resulting in otitis media; the lungs, causing pneumonia and, even into the bloodstream, giving rise to septicemia (Fig. 1). Pneumonia is thus a significant infectious disease marked by the mortality and morbidity rates, and this expound why it is imperative to constantly explore the efficacy of newly advanced control mechanisms in order to develop new strategies that could curb its effects especially in children.

In Kenya, Pneumonia results in one in every five deaths in children 5 years and below, as a result the preparation to introduce PCV10 started in 2010, and in 2011 the vaccine was introduced to the Kenya population [16].

### 3. PNEUMOCOCCAL CONJUGATE VACCINE (PCV)

The pneumonia vaccine is an inactivated bacteria which allow the immune system to identify and fight the active bacteria, *S. pneumoniae*, and inhibit individuals from being sick with pneumonia [3,17]. The pneumococcal vaccine prevents illnesses produced by *S. pneumoniae* in children over 2 years of age and adults at risk. The vaccine is administered by injection [3]. A single dose of the pneumococcal vaccine is usually adequate for most individuals. Though, for individuals 65 years and above, who received their first dose before age 65, a second dose is recommended. Side effects linked with the pneumococcal vaccine are typically minor. The most commonly reported side effects include pain and redness at the injection site or fever.

Introduction of pneumococcal conjugate vaccine into the routine vaccination schedule of established countries over the past 13 years has caused a dramatic decline in the occurrence of invasive pneumococcal disease [18]. Moreover, immunized individuals are less likely to be carriers of vaccine-serotype pneumococci, and are therefore less likely to transfer the infection, than non-immunized individuals. Successful vaccination protocols in Sub-Saharan Africa would boost the success of health service delivery efforts in limited resource settings.

<table>
<thead>
<tr>
<th>Location of S. pneumoniae</th>
<th>Nasopharynx</th>
<th>Sinusitis</th>
<th>Otitis media</th>
<th>Bacteremia</th>
<th>Pneumonia</th>
<th>Meningitis</th>
<th>Pneumonia</th>
<th>Osteomyelitis, Septic arthritis</th>
</tr>
</thead>
</table>

*Fig. 1. Common forms of pneumonia*

*Adapted from WHO 2013, Different forms of invasive and non-invasive pneumonia diseases*
At a population level, immunization results in a reduction in the prevalence of the serotypes of pneumococci carried in vaccine, both in vaccinated and unvaccinated individuals. It also leads to a reduction in the incidence of invasive pneumococcal disease caused by the vaccine-serotype pneumococci in the whole population. Within four years after the introduction of PCV into the childhood inoculation program in the USA, the occurrence of invasive pneumococcal diseases caused by the serotypes present in the vaccine decreased by 62% in people aged 5 years or older [19]. The study [17] indicated that indirect defense provided by PCV was greater than its direct protection, and this aspect had an intense effect on estimates of the cost-effectiveness of the vaccine. Co-infection with other pathogenic organisms would likely limit the benefits of the variety of vaccines in use in Sub-Saharan Africa.

In 2011, Kenya became one of the first countries in Africa to introduce PCV and the first country to use the PCV10, a 10-valent PCV conjugated to non-typeable Haemophilus influenzae protein-D ([20]; Table 1). Because PCV10 uses protein-D from non-typeable H. influenzae as its carrier protein, it might prompt defense against infections caused by non-typeable H. influenza. The PCV10 vaccine was introduced into the routine infant vaccination programme concurrent with a catch-up campaign for infants. PCV10 is administered simultaneously with pentavalent vaccine (diphtheria, whole cell pertussis, tetanus, hepatitis B, and H. influenzae type b combined vaccine) at age 6, 10, and 14 weeks. In 2011, all infants were encouraged to present for a three-dose catch-up schedule 4 weeks apart [17].

4. EFFECTIVENESS OF PNEUMOCOCCAL CONJUGATE VACCINES

Studies carried out on 7-valent pneumococcal conjugate vaccine (PCV7), which was licensed by the United States Food and Drug Administration (FDA) in late 2000, indicated the vaccine to be greatly effective in inhibiting invasive pneumococcal diseases (IPD) in young children. The 13-valent pneumococcal conjugate vaccine, also known as Prevnar 13® or PCV13, licensed by FDA in February 2010, offers defense against infections caused by a greater variety of pneumococcal serotypes (“strains”). PCV13 is similar to PCV7 but includes 6 additional serotypes (Table 2). This means that it offers defense against infections produced by a greater variety of pneumococcal serotypes. Studies have shown that PCV13 causes the immune system to create protective antibodies, which recognize the pneumococcal bacteria, similar to PCV7 and PCV10 [21]. Since routine vaccine introduction, rates of invasive pneumococcal disease caused by the serotypes included in the vaccine have declined. Rates of invasive pneumococcal disease caused by some serotypes not in the vaccine have increased. However, these increases have been small compared to the decreases in vaccine type serotypes.

Pneumonia vaccines have been shown to be about 60-70% effective in preventing IPD such as meningitis and bacteremia [1,17]. Other factors can also lower vaccine efficacy within the host. Infection with intestinal nematodes is one likely confounder. The health impacts of intestinal nematodes depends on a number of factors which include nutritional status of the host, species of the parasite, mixture of species, duration of infection and number of parasites. This indicates a high possibility of an immune-compromised state in children harboring these nematodes.

5. PREVALENCE AND COMPLICATIONS OF INTESTINAL NEMATODES

Nematode worms are the most prevalent parasites globally infecting an estimated

<table>
<thead>
<tr>
<th>Age in weeks</th>
<th>Age in months</th>
<th>Age in years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>4 - 8</td>
<td>6 - 8</td>
</tr>
<tr>
<td>10 - 16</td>
<td>14 - 24</td>
<td>6 - 12</td>
</tr>
<tr>
<td>9 - 12</td>
<td>12 - 15</td>
<td>1 - 5</td>
</tr>
</tbody>
</table>


*Primary doses are given at least 4 weeks apart
*Adapted from [3,16]. Summary of vaccines given to children in Kenya
Table 2. Pneumococcal conjugate vaccine summary

<table>
<thead>
<tr>
<th>Target age group</th>
<th>Infants (under 12 months of age), Children 6 weeks to 5 years, Adults &gt;50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of administration</td>
<td>Intra muscular (IM) injection</td>
</tr>
<tr>
<td>Maximum and minimum interval between doses</td>
<td>4-8 weeks interval</td>
</tr>
<tr>
<td>Diseases prevented by the vaccine</td>
<td>Pneumococcal diseases, invasive (pneumonia, meningitis, other invasive diseases) and non-invasive (otitis media, sinusitis, bronchitis) caused by vaccine serotypes</td>
</tr>
<tr>
<td>Vaccine schedule</td>
<td>WHO recommends 3 primary doses (the 3p+0 schedule) starting as early as 6 weeks of age, or, as an alternative, 2 primary doses by the age of 6 months plus a booster dose at 9 - 15 months of age (the 2p + 1 schedule)</td>
</tr>
<tr>
<td>Likely duration of protection</td>
<td>Available data suggests that protection will last at least four to six years in healthy children. Children with HIV infection may require a booster dose to sustain protection.</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Known hypersensitivity to a prior dose. Infants with a moderate or severe illness (temperature ≥39°C) should not be vaccinated until their condition improves</td>
</tr>
<tr>
<td>Side effects</td>
<td>Local reactions (redness, pain and swelling) and fever.</td>
</tr>
</tbody>
</table>

**PCV types**

<table>
<thead>
<tr>
<th>Description</th>
<th>PCV 7 (Also known as Prevnar)</th>
<th>PCV10 (Also known as Synflorix)</th>
<th>PCV13 (Also known as Prevnar 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- The Heptavalent PCV produced from seven prevalent strains of <em>S. pneumoniae</em> bacteria</td>
<td>- Decavalent PCV Containing antigen from ten pneumococcal serotypes, - Additional serotypes are 1, 5, and 7F.</td>
<td>- Modified PCV10 and contains 13 serotypes - Additional serotypes are 3, 6A, 19A</td>
<td></td>
</tr>
<tr>
<td>- It is gradually being removed from the market due to reduced efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotypes</td>
<td>4, 6B, 9V, 14, 18C, 19F, 23F</td>
<td>1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F</td>
<td>1,3,4,5,6A,6B,7F,9V,14,18C,19A,19F,23F</td>
</tr>
</tbody>
</table>

*PCV =Pneumococcal Conjugate Vaccines - are Polysaccharide-protein conjugate vaccines with no live bacteria

*Adapted from WHO paper on Pneumococcal vaccines 2012, Comparative summary of characteristics of PCV7, PCV10 and PCV13

The symptoms indicating the presence of a GI parasite are commonly associated with the severity of infection. Consequently, a slight nematode infection is often asymptomatic while a mild to heavy infection can be linked with painful and severe symptoms. However, indirect damage can occur in the absence of any noticeable infection. For example, it has been observed that the burdens of nematode infection are greatly over-dispersed with a theoretical proportion of 80% of all worms in less than 20% of those infected [5,24].

6. IMPACT OF INTESTINAL NEMATODES ON CHILD HEALTH

The symptoms indicating the presence of a GI parasite are commonly associated with the severity of infection. Consequently, a slight nematode infection is often asymptomatic while a mild to heavy infection can be linked with painful and severe symptoms. However, indirect damage can occur in the absence of any noticeable infection. For example, it has been observed that...
insignificant levels of GI nematodes interfere with milk production in animals [8].

Summary outcomes of two major studies [23,21] found that in humans, the effects of GI parasites depend on the species, the mixture of species, the duration of infection and the number of worms. Moreover, the spread of worms among hosts is highly skewed such that minorities of individuals usually have moderate-to-heavy infections and are more likely to be clinically affected. The strength of infections depends on the size and nutritional status of the host although there is evidence that treating worms can lead to improvements in growth and nutritional status, but deworming alone does not treat any underlying nutritional shortfalls that have been initiated by infection.

The principal mechanisms by which GI parasites damage human hosts include diverse, yet additive physiological development. These take into account feeding on host tissues, including blood, leading to a loss of iron and protein (especially with hookworm), resulting in mal-digestion or mal-absorption of nutrients. This can result in stimulation of inflammatory responses that could affect appetite and food intake or change the metabolism and storage of key nutrients such as iron. This pathway causes typical responses to infection, such as fever and increased metabolic rate which end in immune responses to infection.

Table 1. Prevalent intestinal nematodes species in Sub-Sahara Africa (SSA)

<table>
<thead>
<tr>
<th></th>
<th>Hookworms</th>
<th>Ascaris lumbricoides</th>
<th>Trichuris trichiura</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated population infected in SSA</td>
<td>198 million</td>
<td>173 million</td>
<td>162 million</td>
</tr>
<tr>
<td>Estimated % disease burden in SSA</td>
<td>34%</td>
<td>21%</td>
<td>27%</td>
</tr>
<tr>
<td>Country with highest burden in SSA</td>
<td>Nigeria</td>
<td>Nigeria</td>
<td>Nigeria</td>
</tr>
<tr>
<td>Estimated %</td>
<td>38 million</td>
<td>55 million</td>
<td>34 million</td>
</tr>
</tbody>
</table>

*Adapted from [25-27], Comparative statistics of hookworms, A. lumbricoides and T. trichiuris in SSA (Sub-Sahara Africa)

Table 2. Symptoms and complications of the prevalent species of intestinal nematodes in humans

<table>
<thead>
<tr>
<th>Infection site</th>
<th>Symptoms</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hookworms Attach to intestinal walls and ingest blood</td>
<td>Colic</td>
<td>Anaemia</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>Ascites - severe protein loss with fluid build-up in the abdomen</td>
</tr>
<tr>
<td></td>
<td>Intestinal cramps</td>
<td>Child slow growth and mental development</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indigestion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood in stool</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Ascariasis Blood (larvae), Lungs (larvae), Small intestine</td>
<td>Coughing and gagging</td>
<td>Nutritional deficiencies</td>
</tr>
<tr>
<td></td>
<td>Vomiting round worms</td>
<td>Intestinal blockage and perforation</td>
</tr>
<tr>
<td></td>
<td>Wheezing and shortness of breath</td>
<td>Duct blockages – of liver, pancreas</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irregular stool</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td>Trichiuriasis Large intestine</td>
<td>Bloody diarrhea</td>
<td>Malnutrition</td>
</tr>
<tr>
<td></td>
<td>Painful frequent defecation</td>
<td>Iron deficiency anaemia</td>
</tr>
<tr>
<td></td>
<td>Fecal incontinence</td>
<td>Rectal prolapse</td>
</tr>
<tr>
<td></td>
<td>Abdominal pains</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flatulence</td>
<td></td>
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<tr>
<td></td>
<td>Weight loss</td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from [20,27,23,28], Comparative infection characteristics of Hookworm, Ascariasis and Trichiuriasis
Although it is possible that decreased child development operates through the mechanisms outlined above, the causal associations underlying underdeveloped physical and intellectual development are still not well established. Poly-parasitism or co-infection with either multiple gastro-intestinal nematodes and/or protozoa in the young is widespread [28]. Co-infection between the nematodes themselves or with protozoa and the impact of both on the health and nutritional status of the host is not well understood and is understudied [29]. Independently, it has been well documented that persistent infection with a particular nematode can impair physical and mental growth [26] and also affect the nutritional status and general development of children [25].

7. IMPORTANCE OF NEMATODES IN URBAN AREAS

There seems to be a transformation in the epidemiology of some of these parasites related to population growth and overcrowded living conditions in urban and slum environments [30,31]. This alteration causes more understanding to permit control efforts in urban settings. Several diseases, mainly nematode infections, have in history essentially affected countryside populations. Nevertheless, in several low and middle-income countries [25] town relocation has led to the formation of urban resident settlements with high rates of infection with many different parasites particularly with both protozoa and nematodes [22]. Studies on urban ecology point out common risk aspects for poly-parasitism in these locations [26]. These comprise households lacking cemented floors, absence of health and hygiene education, deficiency of uncontaminated channeled water, ill sustained latrines and children walking shoeless. Although urbanization can stimulate access to health facilities and public works, congestion and poor hygiene will prime higher contamination rates through faster closeness of the infested to larger susceptible inhabitants. Nematodes such as hookworms, *A. lumbricoides* and *T. trichiura* are regularly known to thrive in these urban settings [32].

8. STRATEGIES FOR TREATMENT AND CONTROL OF INTESTINAL NEMATODES

Slum settlement raises exposure of children to nematode invasion. This has caused fresh urban parasitology epidemiology besides, an upsurge in poly-parasitism. This consequently needs new approaches for the improvement and application of community control methods. Distinctively, public-health involvements are important to lasting control in a community. The collective involvements comprise but are not restricted to delivery of clean water, communal health training, diet cleanliness practices, and upkeep of operational sanitation structures. Conversely, the application and sustainability of such involvements is demanding. Epidemiological large scale studies using morbidity questionnaires are progressively used to direct spatially undisputable and beneficial sanitation [32]. Pharmaceutical involvements such as large scale Mass Drug Administration (MDA) grounded on indigenous appeals collected from parasitological reviews is similarly applied to the infected inhabitants as management and control measure [33,34]. Countrywide school-based MDA is economical and permits better numbers of the inhabitants to be treated [35,36]. Chemotherapy for nematode infection comprises a mixture of a benzimidazol (albendazol or mebendazol) [19].

Public contribution in disease control is significant. Because of the relationship between congested living and poly-parasitism, children continue to be the target of disease control interventions since they are affected more by the effects of gastro intestinal nematodes. Children are often the reservoir, contributing to continued maintenance of transmission.

9. HOST IMMUNOLOGIC RESPONSES TO INTESTINAL NEMATODES AND PNEUMONIA INFECTIONS

The immune system reacts to the infection with *S. pneumoniae* by producing neutrophils and macrophages to engulf the bacteria which infested the interstitium and alveoli [37], the middle ear or the meninges [38]. IL-6, TNF, and IL-1 are the key element mediators released during inflammatory process. Additional infection into the bloodstream leads to overwhelming systemic reactions or septic shock, severe interruption of normal tissue construction and cell counts, and can eventually result in death [37]. Cooperation between the two components of immunity, innate and adaptive, is crucial in the generation of protection against *S. pneumoniae* (Fig. 2).
Inborn protection is the type of the immune reaction occurring within hours of primary bacterial introduction, and is thus, non-specific. It involves cellular component, mechanical and chemical barriers, as well as physical barriers. Recognition of preserved pathogen-associated molecular patterns (PAMPs) on the pathogen by pattern recognition receptors (PRRs) found on cells such as macrophages and dendritic cells (DCs) leads in a series of signaling events, resulting in the manufacture of abundant cytokines and chemokines [37,39].

Neutrophils and macrophages are engaged and stimulated by chemical mediators to kill and phagocytose the bacteria. DCs, which have particular processing abilities, will drift from the border to secondary lymphoid organs and
mature, causing their ability to competently lead T cells for adaptive reactions. The collaboration between DCs and T cells starts the adaptive arm of the immune reaction, which happens in an antigen-specific method, and thus takes further time to advance [39].

The adaptive immune reaction begins when DCs present antigen in complex with MHC to naïve T cells. The activated T cells can then facilitate B cells to also identify the same antigen though linked recognition. This collaboration results in stimulation of B cells, and permits their multiplication and expansion into antibody-producing plasma cells [39]. Antibodies are critical in clearing extracellular pathogens such as *S. pneumoniae*.

Activated T cells can expedite B cells into becoming antibody-secreting plasma cells. It has since been observed that adaptive immune reaction is vital to the clearance of extracellular pathogens such as *S. pneumoniae* [39,40]. Antibodies can counteract the bacterium by stopping it from binding its cellular target or opsonize it, thus encouraging its uptake by phagocytes such as macrophages [22]. The binding of antibody to the bacterial exterior can trigger complement either via the classical or alternative pathways [39]. This stimulation is essential to accomplish effective clearance of the pathogenic organism [40].

Discrete immunoglobulin (Ig) isotypes retain coinciding and distinctive effector roles on the origin of the particular Fc region expressed. Therefore, the design of Ig isotypes produced through a bacterial infection, in addition to the epitope specificity and similarity of the Ig, may affect the level of defense given by such an antibody. IgG isotypes such as IgG3, IgG2b, and IgG2a, which are connected with Th1 (gamma interferon [IFN-γ]-dominant) immune reactions, are predominantly effective at facilitating complement fixation and both complement- and Fc-mediated bacterial opsono-phagocytosis [41]. In distinction, IgG1 provoked all through Th2 (interleukin-4 [IL-4]-dominant) immune reactions may have a role in countering pathogenic proteins without prompting complement activation and inflammation [42].

Gastrointestinal (GI) nematodes prompts a classical immediate-type hypersensitivity reaction win which IgE antibody, mucosal mast cells, and tissue and blood eosinophils are distinctly raised. An overall need for CD4+ T cells in encounter to GI nematodes has been detected in numerous rodent models of infection [6]. Nematodes encourage the increase of CD4+ Th2 cells that produce a cytokine array that consist of IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 [43].

Cytokines in the setting of a parasitic infection, initiate an indiscriminate type 2 response. Creation of IL-4 raises production of IgE and functions as a co-factor with IL-3 and IL-9 for enlargement of intestinal mucosal mast cells [6]; nematode-induced eosinophilia is reliant on the appearance of IL-5. Infective larvae fuel IL-5 and IL-9.

10. COUNTER-REGULATORY IMMUNOLOGIC RESPONSES IN COINFECTION

Even though it has remained known that adaptive immune reactions to extracellular bacteria is mainly deliberated by antibody, a report by Malley and others, offers confirmation for an antibody-independent machinery of defense from pneumococcal infection [7]. Their results propose that CD4+ T cells are adequate to prompt immune reactions.

A differentiated cytokine response would essentially down regulate the shared Th1/Th2 cytokine array [9,44]. Thus, the cytokine position of the host might impact the course of active vaccination or protection to an infection. Initiation of a solid Th1 response would probably restrict resistance to GI nematodes that are sensitive to Th2-dependent defensive mechanisms. Worm-induced division in the direction of type 2 reactions and down-regulation of Th1 protection may be important to both human and animal populations that have a tendency to obtain prolonged worm infections.

11. SUMMARY AND CONCLUSIONS

The evidence is mounting that there is an association of poverty and dynamic geographical characteristics in low income and low to middle income countries which includes a shift in the infection and co-infection of nematodes and pneumococcal disease causing pathogens. This parallels increases in communicable diseases including HIV and Tuberculosis. While the perceived benefits of population sub-group immunity may be addressed by specific vaccine conjugate selected for national programs, it is important to recognize variations due to local geographic factors and serotype prevalence before vaccination. Although the PCV10 has
been used successfully against pneumococcus in Kenyan children, there appears to be reduced efficacy by 2013 since when the vaccine was first introduced to 2011. It is therefore likely that there is an immunological factor at play: immunologically, the production of IL-12 and IFN-γ resulting from exposure to bacterial pathogens is responsible for Th1-derived protective responses that also can inhibit development of Th2-cells expressing IL-4-dependent immunity to extracellular intestinal nematodes and vice versa.

Nematodes, which are more prevalent in children than any other age-group, are known to be immunosuppressive, and as a result, they could be playing a part in reducing efficacy of the vaccine in the children harbouring the infection. Interpretation of immunological profiles in children with evidence of nematode infection and vaccinated with PCV10 compared with those vaccinated, but, without the infection could reveal whether or not nematode infection could be posing any challenge on the vaccine efficacy. This ideally would include evaluation of the immunological profile together with helminth infection status. Inclusion of such data in designing key interventions and treatment protocols for children would have significant and beneficial impact on public health particularly in migratory populations characteristic of urban slums in Sub Saharan Africa.

The authors declare that there is no conflict of interests regarding the publication of this paper.

**CONSENT**

It is not applicable.

**ETHICAL APPROVAL**

A research proposal titled “Assessment of Impact of Paediatric Intestinal Nematodes Infestation on Immunological Responses to Pneumococcal Conjugate Vaccine”, was developed from this review paper concept. Ethical approval was obtained from GLUK (Great Lakes University of Kisumu) Research Ethics Committee (GREC) Ref: No. GREC/204/14/2015.

**COMPETING INTERESTS**

Authors have declared that no competing interests exist.

**REFERENCES**


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