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Review Article

A Review of Pneumococcal Vaccines

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Abstract

Background: Pneumococcal vaccination is a key element to reduce the global burden of the disease in children and adult population. Vaccination against *S. pneumoniae* is implemented in many developed countries. The presently used vaccines are safe, well tolerated but relatively expensive and require modification due to the immunological changes of the epidemic strains.

Aim: In this review, we will look into the types and Contraindications of pneumococcal vaccines.

Methodology: The review is comprehensive research of PUBMED since the year 1993 to 2018.

Conclusion: Vaccination against *S. pneumoniae* is becoming a routine procedure in most developed countries. Increasing the rate of pneumococcal vaccination will help decrease the burden of disease in both healthy and immunocompromised patients.

Keywords: *Prevalence; Risk Factors; Human Papilloma Virus; ELISA; Kaduna State; Nigeria*

Introduction

Pneumococcal diseases (invasive diseases, pneumonia, otitis media, and sinusitis) are among the most frequent preventable infectious diseases carrying a very high morbidity and case fatality rate worldwide. With the current deficit of active antibiotics due to the spread of antibiotic resistances, vaccination against *S. pneumoniae* has become the primary option for controlling this pathogen [1].

Streptococcus pneumoniae, or "pneumococcus," causes pneumonia and infections of the brain and blood that is responsible for mortality in children under five years. Pneumococcal diseases are a major public health problem worldwide. *S. pneumoniae* is Gram-positive encapsulated cocci. Pneumococci are transmitted by direct contact with respiratory secretions from patients and healthy carriers. Al-

though transient nasopharyngeal colonization rather than disease is the normal outcome of exposure to pneumococci, bacterial spread to the sinuses or the middle ear, or bacteremia following penetration of the mucosal layer, may occur in persons susceptible to the involved serotype [2,3].

Pneumococcal vaccination is a key element to reduce the global burden of the disease in children and adult population [4]. Vaccination against *S. pneumoniae* is implemented in many developed countries. The presently used vaccines are safe, well tolerated but relatively expensive and require modification due to the immunological changes of the epidemic strains [5].

Worldwide, an estimated 541,000 deaths were attributed to pneumococcal disease in children < 5 years in 2008 and nearly all of them occurred in low-income countries. Among the wealthy population, nearly all deaths due to pneumococcal disease occur in the elderly, as children in these populations are routinely vaccinated against pneumococcal disease [6,7]. *S. pneumoniae* is responsible for 15 - 50% of all episodes of community-acquired pneumonia, 30 - 50% of all cases of acute otitis media and a significant proportion of bacterial meningitis and bacteremia [8].

There are 2 types of pneumococcal vaccines for adults in Canada-conjugate and polysaccharide. The conjugate vaccines-the 13-valent pneumococcal conjugate vaccine (Pneu-C-13) and the 10-valent adsorbed pneumococcal conjugate vaccine with non-typeable *Haemophilus influenzae* protein D, diphtheria, or tetanus toxoid-are delivered intramuscularly [9].

Contemporary vaccines against *S. pneumoniae* based on targeting the capsule polysaccharides saved millions of lives but have some limitations related to the heterogeneity of capsule polysaccharides of the epidemic *S. pneumoniae* strains and short T-independent immunological memory [1].

High-risk patients include those with either congenital or acquired immunosuppression (e.g. through organ transplantation, HIV infection, chemotherapy or radiation treatment, or immunosuppressant medications [e.g. high-dose steroids, antirejection drugs, biologic medications]). Patients at the highest risk (those with immunosuppression or who have chronic diseases) should receive the conjugate vaccine, followed by the polysaccharide vaccine 8 weeks later [10].

Pneumococcal capsular polysaccharide vaccine

Pneumococcal capsular polysaccharide vaccine can be divided into at least 90 serotypes according to the structure of the PS in the capsule surrounding the bacterium. The capsule seems to be the most important virulence factor; all strains isolated from infections are encapsulated. The capsule helps the bacterium escape the host defense mechanisms [11].

The first successful clinical trial of a vaccine with four serotypes was demonstrated by MacLeod among military recruits in 1945. This was followed by a trial of a hexavalent pneumococcal polysaccharide vaccine. Unfortunately, interest in further development waned with the advent of penicillin, which was thought to be the 'magic bullet' for the pneumococcus. Researches into the development of polyvalent pneumococcal polysaccharide vaccines were continued. A 14-valent polysaccharide vaccine was licensed in 1977. This was soon followed by the 23-valent vaccine, which was licensed internationally in 1981 [12].

A capsular PS vaccine containing 23 of the most common serotypes/groups has proven protective in immune competent adults and in some groups at risk; it has also been shown to have an impact on death rates due to pneumonia in Papua New Guinea [13].

The 23-valent capsular polysaccharide vaccine is not effective in children less than 2 years old, the most vulnerable age group for invasive pneumococcal disease. The reason for the vaccine's poor immunogenicity and its lack of efficacy in children is thought to be the nature of the PS antigen. PS antigens are type 2 T-cell independent (TI) antigens, which stimulate mature B cells without the help of T cells. In humans, the B cells of newborns do not respond to most of the PS antigens. Responsiveness develops only slowly during the first years of life. Furthermore, the TI antigens do not induce immunologic memory and the maturation of the immune response; anti-PS antibodies have low avidity and the switch from one isotype to another does not happen even after repeated immunizations [14].

The immune response can be enhanced by the coupling of the polysaccharide antigen to a protein carrier that can be processed and presented to T-cells bearing specific receptors for the protein complex. The T-cells exposed to the polysaccharide-protein conjugate are able to promote vigorous antigen-specific B-cell proliferation and memory maturation [15].

Pneumococcal conjugate vaccines

Another approach to solving the poor immunogenicity of the capsular PS antigens has already moved to the clinical phase-III trials. The development of a protein conjugate vaccine for the pneumococcus has involved the selection of a few prevalent serotypes, and these have been individually coupled to an immunogenic carrier protein [16]. Different proteins have been selected for conjugation, and these include diphtheria and tetanus toxoids, the meningococcal outer-membrane complex, and diphtheria protein CRM197. Several vaccine formulations incorporating between four and 11 pneumococcal capsular polysaccharide types have been subjected to safety and immunogenicity studies.

The PS antigen in a conjugate vaccine seems to benefit at least partly from the immunologic characters of the carrier protein. There are three types of PCV available on the global market, which go by the brand names: Prevnar, Synflorix and Prevnar 13.

Prevnar (PCV7) was a heptavalent vaccine, it contains the cell capsule sugars of seven serotypes of the bacteria *S. pneumoniae* (4, 6B, 9V, 14, 18C, 19F and 23F), conjugated with diphtheria proteins. It was approved for use in the United States in February 2000, and vaccination with Prevnar was recommended for all children younger than two years, and for unvaccinated children between 24 and 59 months old who were at high risk for pneumococcal infections [17].

Synflorix (PCV10) is produced by GlaxoSmithKline. It contains ten serotypes of pneumococcus (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) which are conjugated to a carrier protein. Synflorix received a positive opinion from the European Medicines Agency for use in the European Union in January 2009 and GSK received European Commission authorization to market Synflorix in March 2009 [18].

Prevnar 13 (PCV13) replaced Prevnar. It contains thirteen serotypes of pneumococcus (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) which are conjugated to diphtheria carrier protein. After waiting for the outcome of a trial underway in the Netherlands, the Centers for Disease Control and Prevention (CDC) recommended the vaccine for adults over age 65 in August 2014 [19]. In June 2012, the U.S. Food and Drug Administration approved PCV13 for all adults older than 50 years, for the prevention of pneumonia and invasive pneumococcal disease. Much of this recommendation was supported by evidence from immunogenicity trials in which more than 800 vaccine-naive subjects aged 60 to 64 years old were randomized to receive one dose of either PCV13 or PPSV23. In June 2012, PCV13 was recommended by the Advisory Committee on Immunization Practices (ACIP) for adults older than 18 years with immune-compromising conditions. This recommendation was based largely on a 2010 randomized controlled trial that studied the secondary prevention of invasive pneumococcal disease in nearly 500 subjects, most of whom had HIV. In this population, two doses of PCV7 resulted in a significant decrease in the rate of recurrent invasive pneumococcal disease over 5 years [20,21].

Since the development of protein conjugate vaccines, several studies have evaluated the safety of different formulations, including two-, five-, seven- and nine-valent formulations. Prior to licensure, over 22 000 children received the vaccines, and there have been no reports of severe systemic or life-threatening reactions attributable to the vaccine [22]. Although much work has been done on standardizing the laboratory technique for the determination of antibody concentration in serum, it is still not known what concentration of serotype-specific antibody confers protection. It also remains contentious whether a given concentration will confer protection against the different forms of non-invasive (mucosal) and invasive pneumococcal disease [23].

Duration of immunity

The duration of the raised antibody titres induced by the vaccine is still a matter of uncertainty. Pneumococci remain a part of the normal flora of the respiratory tract, so a state of peaceful coexistence may be maintained so long as the host has a competent immune system (including a functioning spleen). Hence the duration of immunity is hard to calculate and must be found by measuring antibodies and

observing the incidence of disease in those who have been vaccinated [24]. It is assumed that because the vaccine induces immunologic memory, immune protection is likely to last for a long time, possibly for life. However, this is not known for sure. It is, in fact, not clear at this stage if a fourth dose, as recommended by the current schedule in infancy, will be required in all settings [25].

Contraindications

Pneumococcal vaccines are contraindicated in patients with a history of anaphylaxis after vaccination, those with allergy to components of the vaccine (e.g. diphtheria carrier protein, Pneu-C-13, latex), or those who are diphtheria or tetanus toxoid carriers. Vaccines can be given during a minor illness, regardless of fever, but should be avoided in severe illness. A Pneu-C-13 dose should be administered at least 1 year after any previous dose of Pneu-P-23. A Pneu-P-23 dose can be given 8 weeks after Pneu-C-13. Both vaccines can be co-administered with the varicella-zoster and influenza vaccines [26].

Conclusion

Vaccination against *S. pneumoniae* is becoming a routine procedure in most developed countries. Increasing the rate of pneumococcal vaccination will help decrease the burden of disease in both healthy and immunocompromised patients.

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