

# Role of Vaccines



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## Introduction

Since the time of discovery of smallpox vaccination in 1796 by Edward Jenner, vaccinations have a major impact on global health. Immunization is a process of inducing immunity against a specific disease and it can be induced actively by administration of vaccine or toxoid to produce humoral or cell-mediated immune response.

Vaccines may contain live attenuated organisms, inactivated or killed organisms, toxoids or subunits of antigen. It may be derived from cell culture techniques.

Pneumococcal and Influenza vaccinations have played a positive role in preventing streptococcal and influenza infection, changing the outlook of lower respiratory tract infection.

## Streptococcal Infection

*Streptococcus pneumoniae* (SP) infections are one of the major causes of morbidity and mortality worldwide;<sup>1</sup> Pneumococcus is one of the principal etiological agents of community acquired pneumonia (CAP), bacterial meningitis, otitis media, and chronic obstructive pulmonary disease (COPD) exacerbations. All age ranges are involved, but it is the elderly and children who are particularly at high risk. Over hundred years ago Sir William Osler defined pneumonia "a special enemy of old age", "the natural end of elderly people". In children aged less than 2, in developed countries, the incidence of the invasive form of infection has been estimated as 150 cases per year every 100,000 people<sup>1</sup>. Every year, in the US alone, more than 40,000 deaths due to SP have been estimated, and this number could increase because of ageing population in developed countries and the emergence of antibiotic-resistant strains of SP.

An estimated 10.6 million children under five years of age die each year; 90% of these deaths occur in developing countries.<sup>2,3</sup> Acute respiratory infections, most notably pneumonia, are a leading cause of mortality among children in developing countries. In 2000-2003 pneumonia was the leading cause of death in the under-five age group.<sup>2</sup>

*S. pneumoniae* is a gram positive, encapsulated diplococcus that is part of the normal flora of the human nasopharynx.<sup>4</sup> Nasopharyngeal colonization is transient and typically asymptomatic. It is more common and prolonged among children than among adults. In some circumstances, pneumococci from the nasopharynx enter adjacent structures (e.g. paranasal sinuses and middle ear) and can be aspirated into the lungs or enter the blood stream resulting in disease. Infection of the blood stream and subsequent infection of secondary sites is referred to as invasive disease.

## Vaccine

Over the years, two kinds of vaccines have been developed: the 23-valent pneumococcal polysaccharide vaccine (PPV) and the heptavalent pneumococcal conjugate vaccine (PCV).<sup>5</sup> Both of

them exploit the polysaccharide antigens of the pneumococcal capsule and their ability to induce an antibody response by producing specific protective immunoglobulins.

Pneumococcal capsular polysaccharides, the outer coat that serves as the primary pneumococcal antigens eliciting a host immune response, induce a T-cell independent immune response which does not develop in children until around two years of age. In contrast, when polysaccharides are covalently coupled to immunogenic proteins such as the mutant diphtheria toxin CRM197 used in PCV7 and PCV9, a T cell-dependent response is elicited. This type of response is already present in infants, thus making PCV a good immunogen for infants and toddlers. Another characteristic of T-cell dependent responses is the induction of immunological memory characterized by affinity maturation and a booster response on subsequent exposure to the antigen. In addition to eliciting T-cell dependent immune responses, conjugate vaccines can confer both systemic and mucosal immunity. Serum immunoglobulin IgG and secretory IgA can be detected in the saliva of toddlers and infants after parenteral vaccination with PCV formulations.<sup>6,7</sup> The mucosal immune response contributes importantly to protection against respiratory tract colonization with serotypes included in the vaccine.

The 23-valent vaccine (PPV) includes 25 mg of all the 23 capsular polysaccharides isolated from 23 different pneumococcal strains, purified and treated with phenol. Since it is made up of polysaccharide and non-protein antigens, the PPV induces an antibody response independent from T lymphocytes; for this reason, it has a reduced immunogenicity compared to a hypothetical protein vaccine and it does not produce any immunological memory, therefore lack of booster effect when administering other doses after the first one.

The PPV is scarcely immunogenic in children below 2 years of age because of the immaturity of their immune system; for children in this age bracket, the conjugate polysaccharide vaccine is recommended. The conjugate vaccine employs a protein component as adjuvant, allowing to recruit T lymphocytes in the antibody response; in this way, its immunogenicity is increased, thus permitting to obtain immunological responses also in babies not weaned. Moreover, T-dependent response facilitates to obtain immunological memory.

The 23-valent vaccine includes serotypes 1,2, 3,4,5,6B, 7F,8,9N, 9V,10A,11A, 12F, 14, 15B, 17F, 18C, 19A,19F,20,22F,23F,33F; some of these serotypes have a fair cross-reactivity with serotypes which are not contained in the vaccine (namely 6B,6A,15B,15A), providing potential coverage of more than 23 serotypes. The choice of serotypes for inclusion in the vaccine is made so as to comprise the main serotypes that have developed antibiotic resistances and the most virulent serotypes responsible for invasive infections; about 90% of the invasive pneumococcal infections are caused by vaccine serotypes.<sup>8,9</sup>

The PPV has a good immunogenicity, with a percentage of antibody response of about 75–85% in adult healthy subjects. Responses equal to or slightly inferior to controls are reported in elderly, patients with immunodepressed nephropathy, COPD, splenectomized subjects, and in those affected by chronic organ pathologies.<sup>8,9</sup>

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The antibody response after a single dose of PPV begins 7–10 days after vaccination; IgM are the first ones to appear but they can be measured only for few months. IgG are characterized by slow growth, with a concentration peak even after 70–100 days, and are long lasting, thus providing long-term immunity. IgA response is observed after PPV vaccine, although it may be variable and transitory.

In healthy adults, the antibody level remains high for more than 5 years, and sometimes even for 10 years. A definitely lower duration, of three years or less, can be pointed out in elderly, immunodepressed, splenectomised and nephropathy patients.<sup>7</sup> In the light of the above discussion, vaccination is recommended in all subjects at risk. As patients at risk may remain so over considerable spans of years, it may be necessary to provide revaccination after several years. The term revaccination and not booster is used because the PPV does not involve T lymphocytes in the immunologic response and, therefore, it does not determine any immunologic memory.

In heptavalent conjugate vaccine, seven serotypes i.e. 4, 6B, 9V, 14, 18C, 19F, 23F are present. They represent the most frequently antibiotic-resistant serotypes and the most frequently involved in invasive infections in children. The polysaccharide conjugate vaccine provides an optimal level of protection against invasive disease, with percentages of efficacy of about 90%; however, as well as the 23-valent vaccine, it has a lower efficacy, with percentages ranging from 20% to 90%, against non-invasive pneumonia.<sup>10</sup>

#### Usefulness

Indirect protection of the unvaccinated population through reduced transmission of serotypes included in the vaccine (“indirect effects” or “herd immunity”) is likely to result in significant prevention of invasive disease in adults and young infants and Hospitalizations for viral-associated pneumonia may decrease due to prevention of viral-associated secondary pneumococcal infections.

#### Indications

PPV anti-pneumococcal vaccination is indicated to all aged above 65, high risk subjects ( 2 to 65 years ) affected by chronic degenerative organ pathologies, such as diabetes mellitus, chronic kidney insufficiency, nephrotic syndrome, advanced chronic hepatopathy, chronic pulmonary or cardiovascular pathologies, subjects affected by immunodepressive pathologies, splenectomized subjects or with functional asplenia, cerebrospinal fluid leaks, alcoholism, immunocompromised conditions / medications, long term health care facility subjects. It is also recommended for current smokers.<sup>11</sup>

Use of PPV23 after PCV is recommended for certain high risk groups (e.g. children with sickle cell disease, HIV, and other immune deficiencies) in industrialized countries and may be considered in some developing countries, depending on local conditions and resources. The EPI childhood schedule, followed by many developing and industrialized countries, recommends a 6, 10, 14 week schedule for the primary series of DTP, polio, hepatitis B and Hib vaccine.<sup>4</sup>

#### Efficacy of vaccine<sup>11,12,13,14,15</sup>

Parameters	Evidence based comments
Efficacy against IPD such as bacteremia and meningitis of PPSV23 and conjugated vaccines	Strong evidence ( Cochrane review)
Prevention of pneumonia in patients with asthma	Efficacy not well established

Parameters	Evidence based comments
Impact on morbidity and mortality in COPD patients	No evidence
Stroke reduction	No evidence
Reducing the risk of acute myocardial infarction	Conflicting data
efficacy against all-cause pneumonia	Inconclusive evidence (Cochrane review)
Reduction in all cause mortality	No reduction

#### Revaccination<sup>16,17</sup>

The Advisory Committee on Immunization Practices does not recommend routine revaccination of immunocompetent adults because data on the safety and effectiveness of additional doses are insufficient.

A single revaccination is recommended in adults  $\geq 65$  years of age if they were vaccinated more than five years previously at a time when they were less than 65 years of age, as well as in immunocompromised patients and individuals with functional or anatomic asplenia five years or more after the first dose.

## Influenza

Influenza or Orthomyxoviridae are single stranded RNA viruses and primarily affect birds and mammals. There are three types: A, B and C. and type A is further subdivided in to H and N subtype based on two surface glycoproteins Hemagglutinin (HA) and Neuraminidase (NA). Type A is most virulent human pathogen, also affects birds, horses and other mammals. Type B almost exclusively affects humans where as type C affects human, dogs and swine and generally causes mild disease.

Hemagglutinin (HA) and neuraminidase (NA) are the two large glycoproteins on the outside of the viral particles. HA is a lectin that mediates binding of the virus to target cells and entry of the viral genome into the target cell, while NA is involved in the release of progeny virus from infected cells, by cleaving sugars that bind the mature viral particles.<sup>18</sup> Thus, these proteins are targets for antiviral drugs. Furthermore, they are antigens to which antibodies can be raised. Influenza A viruses are classified into subtypes based on antibody responses to HA and NA. These different types of HA and NA form the basis of the H and N distinctions in, for example, H5N1. There are 16 H and 9 N subtypes known, but only H 1, 2 and 3, and N 1 and 2 are commonly found in humans.<sup>19</sup>

It was earlier believed that influenza mainly occurs in colder climates. However in tropical areas such as south China or Singapore, where there is constant warm climate with little annual temperature change, influenza can occur any time of the year. Influenza occurs somewhere in the world every month of the year. In India, Influenza outbreaks are observed during rainy season in July – August in Pune whereas in Delhi influenza is reported though out the year with highest incidence during winter months November to January.<sup>20</sup>

## Nomenclature

Nomenclature for the virus includes, virus type, place where virus was isolated, strain number, year of isolation and subtype according to haemagglutinin and neuraminidase.

## Antigenic drift

Antigenic drift is due to point mutation in Hemagglutinin and Neuraminidase genes. Minor changes in antigenic character over time seen mainly with type A and B. it is responsible for

minor outbreaks and rarely epidemics.

## Antigenic shift

Genetic reassortment between circulating human and animal strains is responsible for antigenic shifts and phylogenetic evolution that accounts for emergence of new strains of virus. It is only observed with type A virus as it is the only type known to infect variety of species. Such shift results in emergence of new subtype and results in pandemics.

Mutations resulting in small changes in HA and NA does not result in change of subtype. It occurs continuously and leads to emergence of new strain every year. To study these mutations in the year 1952, the network was established, WHO Influenza Global Surveillance Network. Currently it has 128 institutions from 99 countries as recognized national influenza centers. These centers serve as the global alert mechanisms for emergence of influenza virus with pandemic potentials and also recommend the content of influenza vaccines for the season.

### Types of influenza vaccines

1. Live attenuated influenza vaccine to be administered by intra nasal route.  
Or
2. Inactivated vaccines which may be whole virus vaccine, Split-virion Vaccine, Subunit vaccine, Adjuvanted vaccines, Virosomal vaccines or Cell culture derived vaccines. These are available for intramuscular or subcutaneous injections.

Vaccine type	Composition	Immunogenicity	Reactogenicity
Whole-virus (no longer used)	Whole virus	+++	+++
Split-virion	Surface proteins, nucleocapsid and matrix proteins	++	++
Subunit	Surface proteins	++	+
Virosomal	Surface proteins plus virosomes	++	+
Adjuvanted	Surface proteins plus adjuvant	+++	++
Intradermal (subunit)	Surface proteins	+++	++

Over view of differences between LAIV (live) and inactivated vaccines<sup>21</sup> :

Parameters	LAIV (Intranasal spray)	Inactivated influenza vaccine ( intra muscular injection)
<b>Type of Vaccine</b>	Live virus	Killed Virus Non-infectious virus
<b>Can be administered to person with medical risk factors for influenza-related complications</b> (- Chronic Pulmonary diseases - Chronic metabolic diseases Diabetes mellitus - Chronic Cardiovascular diseases - Chronic renal dysfunction	No	Yes

Parameters	LAIV (Intranasal spray)	Inactivated influenza vaccine ( intra muscular injection)
- Haemoglobinopathies - Immunosuppression - Preganacy)		
<b>Can be administered to family members or close contacts of immunosuppressed.</b>	No	Yes
<b>Route</b>	Intranasal spray	Inactivated influenza vaccine (intra muscular injection)
<b>Efficacy</b>	Less efficacious (++)	More efficacious(++++)
<b>Side effects</b>	Commonly seen : Runny nose, Headache muscle aches and fever	Well tolerated Sore arm ,injection site redness Guillian Barre Syndrome ( rare )
<b>Contraindicated</b>	Children younger than 2 years of age. ages 2-4 old with a history of recurrent wheezing or reactive airways disease, or older persons who have any medical condition that confers an increased risk of influenza-related complications	Can be given to younger children with asthma.
<b>Approval</b>	2 to 49 years Limited approval -USA and Russia	>6 months Approved in more than 100 countries

## Efficacy of the Vaccines

Vaccine effectiveness in preventing laboratory-confirmed influenza illness when the vaccine strains are well matched to circulating strains is 70-90% in randomized, placebo-controlled trials conducted among children and young healthy adults, but is lower among elderly or immunocompromised persons. In years with a suboptimal match, vaccine benefit is likely to be lower, although the vaccine can still provide substantial benefit, especially against more severe outcomes.<sup>21</sup>

The relative efficacy of LAIV and inactivated vaccines among young adults varies and depends on the specific population and the antigenic match between the vaccines and circulating strains.

Further research is required to compare LAIV and TIV in adults and would also be valuable in older children and adolescents. The role of pre-existing immunity as well as vaccine impact on influenza illness of varying severity also needs to be examined.

## Repeat Vaccination

Among HIV-infected patients, the rate of seroconversion after the first dose of an adjuvanted H1N1 influenza A vaccine was 68% and increased to 92% after a second doses.<sup>22</sup> In patients with solid organ transplants an overall lower response has been observed.<sup>23</sup>

## Current Strain

It is recommended that vaccines for use in the 2011-2012

influenza season contains the following:<sup>24</sup> (it is the same strain recommendation as previous year)

- A/California/7/2009 (H1N1)-like virus;
- A/Perth/16/2009 (H3N2)-like virus;
- B/Brisbane/60/2008-like virus.

7th April 2011 on World health day, WHO has launched a worldwide campaign to prevent antibiotics resistance and to ensure its usefulness for our future generation and theme of this campaign is “Antimicrobial resistance : no action today – no cure tomorrow”. Six point policy of the campaign puts a lot of stress on infection prevention and control. Rational use of vaccination would definitely help us achieve our goals.

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