

# Pneumococcal infections and immunization in diabetic patients

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## ABSTRACT

India is today facing a diabetes epidemic and has the maximum number of patients with diabetes in the world. People with diabetes are more prone to develop all types of infections. Pneumococcal infections are a common cause of morbidity and mortality, and people with diabetes are more prone to develop pneumococcal infections. With the availability of the pneumococcal vaccine, most international organizations now recommend that people with diabetes should be vaccinated against pneumococcal disease. This article tries to provide a balanced review of the place of pneumococcal vaccination in Indian diabetic patients.

**KEY WORDS:** Diabetes, immunization, pneumococcal vaccination

## Introduction

Diabetes is a chronic illness that requires lifelong medical care, both for control of metabolic derangements and prevention of infective and vascular complications. The two major types of diabetes are type-1 (insulin-dependent) diabetes mellitus, which is due to a T-cell driven autoimmune destruction of insulin producing cells in the pancreatic islets, and type-2 (noninsulin-dependent) diabetes mellitus, which is characterized by insulin resistance, often associated with other features such as obesity, hypertension, dyslipidemia, and accelerated arteriosclerosis.

The prevalence of type 2 diabetes is rapidly increasing in

direct proportion to urbanization, increasing obesity, physical inactivity and aging of the population. In India, 50.8 million people are already affected by diabetes and this is expected to increase to 87 million by 2030.<sup>[1]</sup>

## Why are Diabetic Patients at Risk for Infections?

Patients with diabetes have higher risk for bacterial and viral infections leading to complications and high morbidity and mortality. Clinically, the most important infections are preventable bacterial infections of the skin, the urinary tract, and the respiratory tract.<sup>[2]</sup> It has been assumed that specific aberrations in host defense mechanisms (antibody response, cell-mediated immunity, leukocyte function, and colonization rates) account for the increased case fatality rate which results from bacterial and viral infections such as influenza and pneumococcus.<sup>[3]</sup> Other factors associated with diabetes (age, renal disease, and cardiovascular disease) have been shown to be significant co-morbid factors that can increase the risk of sequel of certain infections.<sup>[3]</sup>

Diabetes mellitus has been identified as an independent risk factor for developing respiratory tract infections.<sup>[4]</sup> There are

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no data on the burden of lower respiratory infections in India. World Health Organization (WHO) data from low and middle income countries suggest that lower respiratory tract infections remain the third leading cause of death.<sup>[5]</sup> *Streptococcus pneumoniae* remains the major cause of pneumonia in spite of widespread vaccination.<sup>[6]</sup> Apart from pneumonia and its complications, viz., empyema and lung abscess, the pneumococcus also causes other clinical syndromes such as sinusitis, otitis media, tracheobronchitis, bacteremia, meningitis and peritonitis, some of which have high case fatality rates.<sup>[3,6]</sup> Diabetes is a well-known risk factor for pneumococcal infection and predisposes individuals to nasopharyngeal colonization with the pneumococcus which is associated with invasive infection.<sup>[7]</sup>

Pneumococcal pneumonia is the most common form of acute bacterial community acquired pneumonia.<sup>[8]</sup> Bacteremia is seen in nearly 30% (8–50%) of individuals with pneumococcal infections, and of these, 15–20% are fatal despite treatment with antibiotics.<sup>[7]</sup> Also, there are several studies which show that diabetes is one of the most common co-morbidities in patients with pneumococcal infection.<sup>[9-14]</sup>

### **Prevention of Pneumococcal Disease**

Assessment of the burden of disease due to vaccine-preventable disorders clearly shows that pneumococcal disease is the leading cause of death in all age groups.<sup>[15]</sup> The high case fatality rate from bacteremic pneumococcal disease demands effective preventive strategies including immuno-prophylactic measures. Diabetic patients have a normal response to pneumococcal vaccination, and vaccination is a cost-effective preventive strategy.<sup>[2,16]</sup> Immunization with Pneumococcal Polysaccharide Vaccine (PPV, which includes 23 purified capsular polysaccharide antigens representing 85–90% of the serotypes of *S. pneumoniae*) in diabetic patients significantly reduces morbidity and mortality related to pneumococcal disease.<sup>[17]</sup>

The 23 valent PPV (PPV23) can be given as a subcutaneous or intramuscular injection (preferably in the deltoid muscle or lateral mid thigh). The serotypes included in the vaccine are 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F. One dose (0.5 ml) of 23 valent vaccine contains 25 mcg of each polysaccharide antigen dissolved in isotonic solution with phenol (0.25%) or thiomersol (0.01%) added as preservative. The six serotypes that cause invasive drug resistant pneumococcal infections (6B, 9V, 14, 19A, 19F and 23F) are represented in the 23 valent vaccine.<sup>[18]</sup>

The antibody response after a single dose of PPV begins 7–10 days after vaccination; IgM antibodies are the first to appear but can be measured only for a few months. IgG antibodies develop slowly, with a concentration peak even after 70–100 days, and are long lasting, thereby providing long-term immunity.<sup>[19]</sup>

Pneumococcal capsular polysaccharide antigens induce type specific antibodies that enhance opsonization, phagocytosis and subsequent killing of pneumococcus by leukocytes and phagocytes. The antigen-specific antibody response is indicated by a twofold or

greater rise in serotype specific antibody developing in 2–3 weeks in greater than 80% of healthy young adults.<sup>[18]</sup> The levels of antibody that correlate with protection have not been defined.

In the recent wake of pandemic influenza A (H1N1) disease, Centers for Disease Control and Prevention (CDC) issued an interim guidance on use of 23 valent pneumococcal polysaccharide vaccine. During influenza outbreaks, pneumococcal vaccines may be useful in preventing secondary pneumococcal infections and reducing illness and death. CDC's Advisory Committee on Immunization Practices (ACIP) recommends a single dose of PPSV23 for all people 65 years and older and for persons 2–64 years of age with certain high-risk conditions.<sup>[20]</sup>

### **Efficacy of the Vaccine**

In a study by Butler *et al.*,<sup>[21]</sup> the efficacy of PPV23 (as a percentage of the reduction in the risk of infections from serotypes included in the vaccine among vaccinated individuals compared with unvaccinated individuals) was found to be 84% in diabetic patients. A recent nested case control study from India conducted among older adults at high risk of developing pneumococcal infection showed that PPV23 provides significant protection with odds ratios of 0.2, 0.25 and 0.33 against recurrent lower respiratory infections, exacerbations of chronic obstructive pulmonary disease (COPD) and hospitalizations, respectively.<sup>[22]</sup>

### **Safety of the Vaccine**

The vaccine is generally safe, but mild local side effects may be seen. Injection site reactions consisting of pain, soreness, erythema, warmth, local indurations occur.<sup>[18]</sup> Fever is the most common side effect. The clinical experience over three decades has shown that pneumococcal vaccine is generally safe. PPV23 is indicated for vaccination against pneumococcal disease caused by those pneumococcal types included in the vaccine.<sup>[18]</sup> The vaccine does not prevent development of disease by types of pneumococcus other than those found in the vaccine.

### **Contraindication to the Vaccine**

The vaccine is contraindicated in persons who are hypersensitive to any component of the vaccine.

### **Worldwide Recommendations on Use of Pneumococcal Vaccination**

Worldwide bodies like ACIP, American Diabetes Association (ADA), American College of Physicians, American Academy of Family Physicians, National Health and Medical Research Council (Australia), Canadian Medical Association, and Australia–New Zealand Society for Geriatric Medicine recommend at least one dose of pneumococcal vaccine for adults with diabetes in their lifetime.<sup>[23-27]</sup>

### **Indian Recommendations**

The Geriatric Society of India recommends the use of PPV for

- persons aged 50 years and above and
- persons aged 2 years or above with certain underlying medical conditions such as diabetes.<sup>[18]</sup>

### Revaccination

A one-time revaccination is recommended by the ADA and ACIP for individuals >64 years of age, previously immunized when they were <65 years of age, if the vaccine was administered > 5 years ago.<sup>[23,24]</sup>

### Should All Diabetic Patients Receive Pneumococcal Vaccination?

Diabetes is in itself a risk factor for invasive pneumococcal infection. In addition, there exist a substantial number of diabetic patients who have other co-morbidities like renal complications, coronary artery disease, COPD, chronic liver disease, malignancies, etc. For this subset of diabetic patients, pneumococcal vaccination should be recommended on priority by virtue of being at more risk than those with diabetes alone. The proceedings of a meeting of the status on Adult Immunization in India were recently published under the auspices of the Association of Physicians of India which includes a section on pneumococcal vaccinations in India.<sup>[7]</sup> The authors state that pneumococcal vaccine is not recommended at present in India and make some statements in support of their view.

It is, however, probably not fair to state that on account of absence of data on pneumococcal disease in India, vaccination is not recommended. A recent nested case control study from South India clearly showed more than 80% protection by PPV23 against lower respiratory tract infections in the elderly, including those with diabetes.<sup>[22]</sup>

### Recommendations

In the absence of substantial published data on pneumococcal disease in India, we would recommend the following guidelines regarding pneumococcal vaccination in people with diabetes in India.

- To collect as much data on the incidence of pneumococcal disease as possible from different parts of India, particularly in people with diabetes.
- Until these data become available, to inform all diabetic patients that pneumococcal vaccination is available and discuss the options of vaccination with them.
- To recommend pneumococcal vaccination at least for those diabetic patients at increased risk, e.g., older patients (>50 years of age), those with nephropathy or renal insufficiency or other co-morbidities, e.g., malignancy.
- To do studies in India on the effect of pneumococcal vaccination in those with diabetes.
- Assess cost-effectiveness of the vaccine in diabetes.

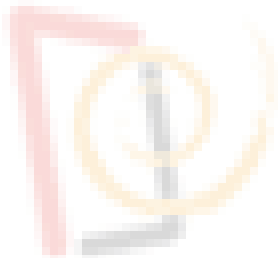
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#### Announcement

As part of an Indo-US Collaboration, the National Institutes of Health, USA has sponsored a series of workshops since 2006 on various aspects of clinical research (with an emphasis on clinical trials), including biostatistics, study design and randomization issues, data management, research ethics, and regulatory aspects. As a continuation of this series, a 3 day workshop on observational studies is planned for March 2011 (15-17) in Mumbai. The workshop will be held in collaboration with the Department of Clinical Pharmacology, Seth GS Medical College & KEM Hospital.

The workshop is aimed primarily at biomedical researchers. Investigators involved in clinical research, who are in a position to lead clinical research studies, should find this workshop useful. This email is to seek your help in dissemination of information about the workshop. I request you to kindly circulate this information in your institution, particularly among those who have appropriate expertise and experience to benefit from the workshop.

Only a limited number of applicants will be accepted. Applicants should email a short (less than one page; **please do not send a CV**) summary of their experience and expertise in clinical research including one or two key publications, **as an email attachment** (MS Word or PDF) to [njgogtay@hotmail.com](mailto:njgogtay@hotmail.com) by Jan 10, 2011. A selection committee will notify the successful applicants of acceptance by end Jan 2011. The decision of this committee will be final and binding.

A limited number of scholarships for travel and lodging will be available for qualified applicants whose institution cannot cover their expenses.