

Consensus Recommendation for India and Bangladesh for the Use of Pneumococcal Vaccine in Mass Gatherings with Special Reference to Hajj Pilgrims

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ABSTRACT

Respiratory tract infections are prevalent among Hajj pilgrims with pneumonia being a leading cause of hospitalization. *Streptococcus pneumoniae* is a common pathogen isolated from patients with pneumonia and respiratory tract infections during Hajj. There is a significant burden of pneumococcal disease in India, which can be prevented. Guidelines for preventive measures and adult immunization have been published in India, but the implementation of the guidelines is low. Data from Bangladesh are available about significant mortality due to respiratory infections; however, literature regarding guidelines for adult immunization is limited. There is a need for extensive awareness programs across India and Bangladesh. Hence, there was a general consensus about the necessity for a rapid and urgent implementation of measures to prevent respiratory infections in pilgrims traveling to Hajj. About ten countries have developed recommendations for pneumococcal vaccination in Hajj pilgrims: France, the USA, Kuwait, Qatar, Bahrain, the UAE (Dubai Health Authority), Singapore, Malaysia, Egypt, and Indonesia. At any given point whether it is Hajj or Umrah, more than a million people are present in the holy places of Mecca and Madina. Therefore, the preventive measures taken for Hajj apply for Umrah as well. This document puts forward the consensus recommendations by a group of twenty doctors following a closed-door discussion based on the scientific evidence available for India and Bangladesh regarding the prevention of respiratory tract infections in Hajj pilgrims.

Key words: Hajj, pneumococcal vaccination, pneumonia, prevention

INTRODUCTION

Around 10% of the world's Muslim population (176 million) reside in India. Annually, 3–5 million of Muslims (including 0.17 million from India) embark on Hajj pilgrimage to Mecca, Saudi Arabia. India has the second largest number of Hajj pilgrims each year, after Indonesia.

Seventy percent of the quota is government allotted, and 30% of pilgrims undertake private travel.^[1]

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Respiratory tract infections are common during Hajj.^[2] Of these, pneumonia is the most common cause of hospital admission, accounting for one-third of hospitalizations. In a retrospective review of 567 patients hospitalized with pneumonia in Saudi Arabia, the mean age was 43 years (SD 22 years).^[2] *Streptococcus pneumoniae* is a leading cause of pneumonia in Hajj pilgrims.^[2,3] There is a significant burden of community-acquired pneumonia (CAP) in India.^[4] Similarly, *S. pneumoniae* has been isolated as the most common etiological agent for CAP in Bangladesh.^[5] While the disease can be treated, prevention also has its own merits.

Guidelines for preventive measures and adult immunization have been published in India, but the implementation of the guidelines is low.^[6,7] Moreover, there is a need for extensive awareness programs across India, taking in account the size and diversity of the country. While there is limited literature available from Bangladesh regarding guidelines for adult immunization for the prevention of respiratory infections; there is evidence of significant mortality due to respiratory infections in Bangladesh.^[8,9] Given this national situation in India and Bangladesh, there has been a general consensus about the necessity for a rapid implementation of measures to prevent respiratory infections in pilgrims traveling to Hajj.^[7,10] These preventive measures cover general measures and specific measures: Vaccination against flu and pneumococci.

While previously, efforts had been made to increase the awareness and education of preventive measures such as vaccination for Hajj pilgrims, there are still challenges in ensuring the pilgrims complete the vaccination before they embark on their journey to Hajj. This document puts forward the consensus recommendations by a group of doctors following a closed-door discussion based on the scientific evidence available for India and Bangladesh regarding the prevention of respiratory tract infections in Hajj pilgrims [Table 1]. Clinical judgment in relation to individual subjects should be relied on before these recommendations are put into practice.

BACKGROUND OF HAJJ AND UMRAH

The World Health Organization (WHO) defines mass gatherings as “events attended by a sufficient number of people that strain the planning and response resources of a community, state, or nation.”^[11] The Centers for Disease Control and Prevention defines a mass gathering as “more than a specified number of people (which may be as few as 1000 although 25,000 is most commonly used), at a specific location, for a specific purpose, for a defined period of time.”^[12] The most common health problems

at mass gatherings are traumatic injuries, respiratory and cardiac issues, heat-related illness, alcohol or drug effects, and gastrointestinal illnesses.^[12]

Hajj is one of the largest annual mass gatherings in the world. All able-bodied adult Muslims, who can afford to do so, are required to do it once in a lifetime. Due to Muslim (lunar-based) calendar, Hajj shifts forward by approximately 10 days each successive year, leading to its coincidence with different seasons every few years. Men, women, and children of all ages attend Hajj.^[1] There is enormous diversity in terms of ethnic origin and socioeconomic status.^[2] Because of the sheer number and crowding of people, stampedes have been known to occur. And also, there is an opportunity for the spread of respiratory infections. Travel to Mecca and Madina outside of the Hajj season is referred to as Umrah. More than a million people are present in the holy places of Mecca and Madina at any given point of time, be it Hajj or Umrah. Thus, preventive measures taken for Hajj apply for Umrah as well.^[2]

HAJJ AND UMRAH: DESTINATION MAP

The rituals performed during Hajj are depicted in Figure 1.^[12,13] The Hajj formally begins on the 8th day of Dhul-Hijjah (Zul-Hijjah) - the 12th month of the Muslim lunar calendar.^[12,13] On this 1st day of the Hajj, the pilgrims walk a few miles to Mina and camp there overnight. It falls on a date about 11 days earlier each year. The pilgrims spend the “Day of Arafah” (9th day of Dhul-Hijjah) in Arafah, an empty plain. They commit the entire day to supplication and devotion. In the evening, they move to Muzdalifa. They camp there overnight and offer various prayers.^[12,13] On the 9th day of Dhul-Hijjah, they return to Mina and throw seven pebbles at a pillar that symbolizes Satan’s temptation of Abraham. (The Qur’an describes how Satan tried to persuade Abraham to not ritually murder his son Ishmael, as commanded by God). The pilgrims then sacrifice a sheep, recalling how Abraham sacrificed a sheep that God had provided in place of his son. The meat is distributed to friends, relative, and the poor. Afterward, they return to Mecca and perform a final tawaf and sa’i. They symbolize the completion of the Hajj by cutting their hair.^[14]

MASS GATHERINGS: IMPLICATIONS FOR INFECTIOUS DISEASES

The massive convergence of people from widely distributed geographical areas presents an opportunity for heavy transmission of pathogens between susceptible

Table 1: Consensus recommendations from India and Bangladesh: 10 key points

1. Respiratory tract infections are common during Hajj. Pneumonia is the most common cause of hospital admission during Hajj. Pneumonia accounts for one-third of hospitalizations in Saudi Arabia during Hajj. *Streptococcus pneumoniae* is a leading cause of pneumonia in Hajj pilgrims
2. There is a high burden of pneumococcal disease in India. Guidelines for preventive measures and adult immunization have been published in India, but the implementation of the guidelines is low. While in Bangladesh there is a significant mortality due to respiratory infections but data on guidelines for adult immunization are limited. These preventive measures against respiratory infection cover general measures and specific measures: Vaccination against flu and antipneumococcal
3. The sudden coalescence of people from widely distributed geographical areas presents an unparalleled opportunity for pathogens to infect susceptible individuals crowded together. At any given point whether it is Hajj or Umrah, more than a million people are present in the holy places of Mecca and Madina. Therefore, the preventive measures taken for Hajj apply for Umrah as well
4. For Hajj, the KSA requires three mandatory vaccines (meningococcal, poliomyelitis, and Yellow fever). Meningococcal quadrivalent is mandatory to all pilgrims, while polio and yellow fever from endemic areas only. The Saudi Ministry of health is assessing vaccines for the prevention of pneumococcal infections. The ministry is also in the process of defining the exact burden of pneumococcal sepsis (pneumonia, meningitis, or invasive disease) during Hajj
5. Each country needs to develop its local vaccine recommendation strategy including flu and pneumococcal vaccine recommendations, regardless the decision of the KSA or mass gathering Center of Medicine, which rely in addition to scientific evidence on other aspects of the World Health Organization recommendation and local Saudi consensus including political endorsement
6. Health professionals and other professionals involved in front-line health care are a priority group for vaccination because of the increased risk of contracting the illness and transmitting it to their families and their patients. Setting an example and the counseling about vaccination given by health-care professionals represent one of the principle success factors in keeping to vaccination targets
7. Antiflu vaccination-seasonal flu vaccination can be considered depending on the current season
8. There are currently two pneumococcal vaccines available PCV 13 and PPV 23. PCV13 is a conjugate vaccine, while PPV 23 is a polysaccharide vaccine. The pneumococcal conjugate vaccine differs from the pneumococcal polysaccharide vaccine in several ways. The PCV 13 is labeled for both pediatrics and adults. It induces immunological memory, offers prolonged protection, has a booster effect, does not induce hypo-responsiveness, is known to reduce nasopharyngeal carriage, and offers herd protection. On the other hand, there is demonstrated efficacy of PPV23 against IPD in adults, but inconsistent data regarding its effectiveness against CAP. The CAPiTA study demonstrated PCV13 efficacy in reducing pneumonia episodes in pneumococcal pneumonia caused by vaccine serotypes
9. ACIP voted to recommend the following
 - a. Adults of 65 years of age or older who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown should receive a dose of PCV13 first, followed by a dose of PPSV23
 - b. Adults of 65 years of age or older who have not previously received PCV13 and who have previously received one or more doses of PPSV23 should receive a dose of PCV13
10. The working group for the prevention of pneumococcal disease in Hajj pilgrims recommends that considering the economic situation of the patient PCV13 may be recommended 4 weeks before undertaking travel to Hajj in order to ensure protection against both invasive pneumococcal disease and pneumonia. PPV23 may be offered to these patients on return from their Hajj journey depending on their risk status

PCV13: 13-valent pneumococcal conjugate vaccine, PPV23: Pneumococcal polysaccharide vaccine 23, CAPiTA: Community Acquired Pneumonia Immunization Trial, IPD: Invasive pneumococcal disease, KSA: Kingdom of Saudi Arabia, CAP: Community acquired pneumonia, ACIP: Advisory Committee on Immunization Practices

individuals. Once the mass gathering ends, the returning infected individuals (including asymptomatic ones) can result in rapid dissemination of pathogens, which is exacerbated by air travel. Thus, pilgrims can be exposed to novel, emerging or re-emerging pathogens. Mass gatherings allow for the intermingling of different pathogens or the subtypes of the same pathogen. As the world's population increases, so will the size of mass gatherings. Limiting the effect of infectious disease at mass gatherings will require drawing upon past experiences^[15] and strict infection control measures should become the cornerstone for limiting the spread of infectious disease.

IMPLICATIONS ON MORBIDITY AND MORTALITY OF RESPIRATORY TRACT INFECTIONS DURING HAJJ

Lower respiratory tract infection is the most common source of infection leading to severe sepsis and septic shock (>50% of patients).^[3] Respiratory diseases are the most common cause of hospital admission during Hajj^[16,17] the Middle East respiratory syndrome (MERS) has a mortality rate exceeding 50%^[18] The etiology of respiratory infections during Hajj include: Viral (rhino, influenza, RSV, adeno,

hMPV, enterovirus, and corona [MERS-CoV]),^[3,13,19] bacterial (Pneumococci, *Haemophilus influenzae*, *Mycobacterium tuberculosis*, *Bordetella pertussis*, Streptococci, Chlamydia, *Mycoplasma*, *Legionella*, *Klebsiella*, *Pseudomonas*, *Staphylococcus aureus*, and Gram-negative bacteria),^[3,13,18] and other causes (Candida).

HEALTH AND SAFETY RISKS DURING HAJJ

Besides respiratory tract infections, trauma (e.g., stampede, motor vehicle accidents), heat stroke and heat exhaustion, sunburn, dehydration, and fire-related injuries are known to cause health and safety risks during Hajj. Less common infections causing hospitalization during Hajj include gastroenteritis, skin infection, and sepsis.^[20] Infectious diseases presenting a health risk to the pilgrims and local population at all stages of the Hajj include influenza viruses, coronaviruses, pneumococcal sepsis, tuberculosis, meningococcal sepsis, polio, yellow fever, gastrointestinal infections, acute gastroenteritis (e.g., *salmonella* species, *campylobacter* species), food poisoning (e.g., *bacillus cereus*), cholera, typhoid, and dysentery, viral diarrhea (e.g., rotavirus and norovirus), viral hepatitis B, C, D, and E, arboviral infections (e.g., hemorrhagic fevers and Alkhurma virus), parasitic (e.g., malaria, scabies, gut parasites, nematodes, trematodes, and cestodes), fungal (e.g., *tinea* species skin infections), and blood-borne

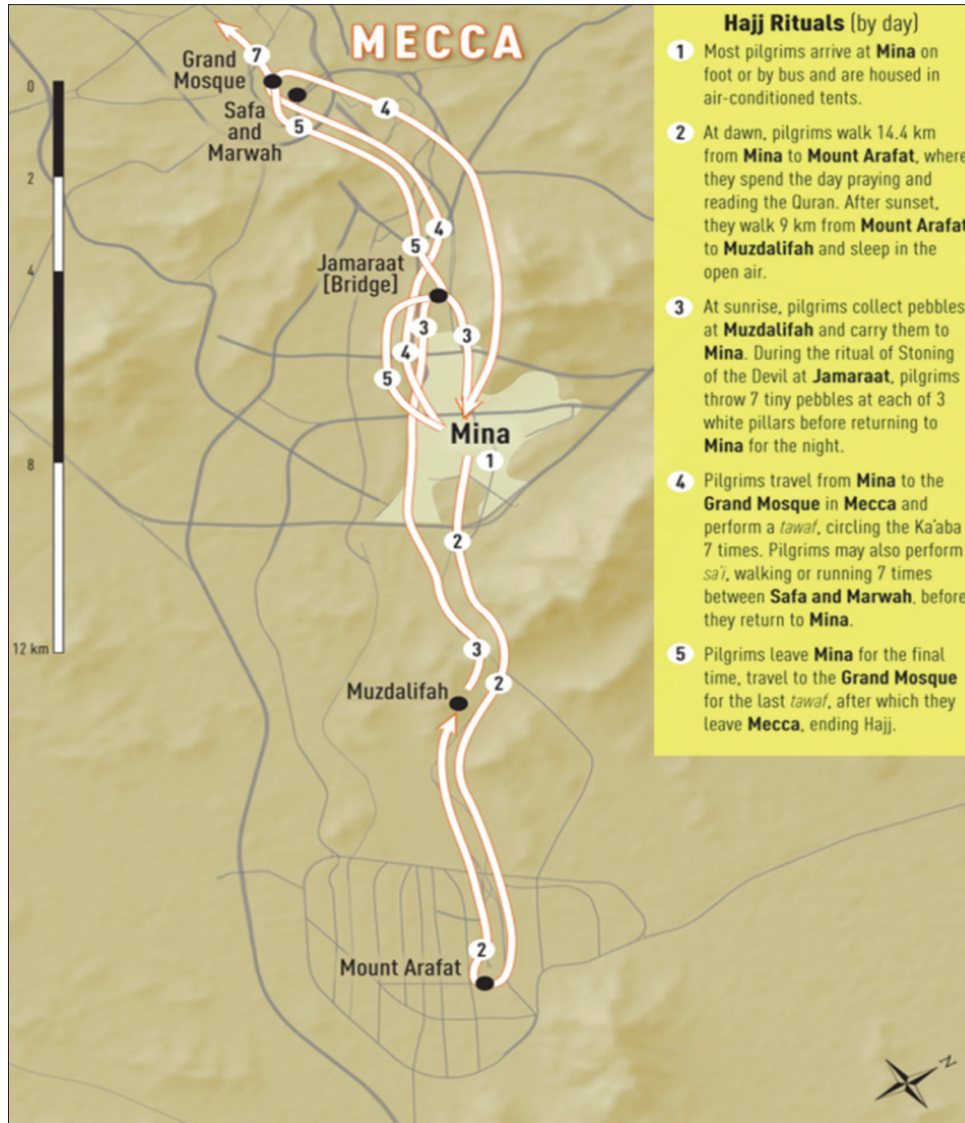


Figure 1: Hajj destination map

diseases; human immunodeficiency virus, zoonoses, brucellosis, and leishmaniasis.^[19]

This part of the document summarizes the general measures and the immunization measures to be undertaken for pilgrims traveling to Hajj and Umrah.

GENERAL MEASURES

General measures related to host defenses; the following^[21] are recommended to curb the spread of respiratory infections:

- Practice frequent hand washing with soap and water or with antiseptic substances (especially after coughing or sneezing)
- Use napkins while coughing or sneezing and dispose used napkins into waste baskets
- Try to avoid touching eyes, nose, and mouth
- Avoid direct contact with symptomatic individuals and do not share belongings with them
- Wear masks, especially in crowded places
- Maintain personal cleanliness
- Stay away from camels and avoid direct contact with them
- Do not consume raw camel milk or camel meat which is not cooked well
- Practice smoking cessation; avoid alcohol and unnecessary drug consumption
- Ensure control of chronic illnesses (diabetes mellitus, chronic obstructive lung disease [COPD], congestive heart failure, chronic renal failure, chronic liver disease, HIV/AIDS infection, etc.) by visiting health-care provider before embarking for Hajj
- Take healthy meals on a timely basis and adequate intake of water.

MEASURES FOR IMMUNIZATION

Current recommendations for Hajj and Umrah by the Kingdom of Saudi Arabia

For Hajj, the Kingdom of Saudi Arabia (KSA) requires three mandatory vaccines (meningococcal, poliomyelitis, and yellow fever). The quadrivalent meningococcal vaccine is mandatory for all pilgrims, while polio and yellow fever are for those from endemic areas only. The Saudi Ministry of Health is currently assessing the role of vaccines for the prevention of pneumococcal infections. The ministry is in the process of defining the exact burden of pneumococcal sepsis (pneumonia, meningitis, or invasive disease) during Hajj. It is recommended that pilgrims be up-to-date with the immunization schedule in their home country.^[22-26]

Each country needs to develop its local vaccine recommendation strategy (including flu and pneumococcal vaccine recommendations), regardless of the decisions of KSA or mass gathering center of medicine, which rely (in addition to scientific evidence) on other recommendations by WHO and on local Saudi consensus (including political endorsement).

Influenza vaccination - seasonal flu vaccination can be considered depending on the current season.

Pneumococcal vaccination - around ten countries are engaged in developing or have developed recommendations for pneumococcal vaccination for Hajj pilgrims: France, the USA, Kuwait, Qatar, Bahrain, the UAE (Dubai Health Authority, Health Authority of Abu Dhabi), Singapore, Malaysia, Egypt, and Indonesia. However, there is a lack of consensus as to whether pneumococcal vaccination should be recommended specifically for travelers to Hajj or for all adults. In most countries, the uptake is low.

Health professionals and other professionals involved in front-line health care are a priority group for vaccination because of the increased risk of contracting the illness and transmitting it to their families and their patients. Comprehensive counseling about vaccination by health-care professionals represents one of the principal success factors in achieving vaccination targets.

PNEUMOCOCCAL VACCINATION

Global epidemiology of pneumococcal disease in adults and Hajj pilgrims

S. pneumoniae is the most commonly identified causative pathogen in CAP in adults in most regions of the world.

The burden of pneumococcal disease in adults is high, with increasing age and presence of comorbidities having a significant impact on the risk of developing disease. The risk factors for the pneumococcal disease include smoking, age ≥ 50 years, asthma, diabetes, chronic obstructive lung disease (COPD), alcohol use, HIV, and other immunosuppressive conditions. Age is one of the key risk factors for pneumococcal disease. Comorbidities increase the risk of incidence and morbidity of pneumococcal disease.^[7,11,27,28] A recent study showed that the maximum number of pilgrims from India are elderly.^[29]

IMPACT OF HAJJ ON PNEUMOCOCCAL TRANSMISSION

Hajj attendance increases the risk of respiratory infections including pneumonia. *S. pneumoniae* is a frequently identified pathogen, found in about 10% of respiratory tract samples of symptomatic Hajj pilgrims; and at least 20% of these isolates are penicillin resistant.^[28] However, the burden of pneumococcal disease at Hajj is not precisely defined at the serotypic level and it is hypothesized that due to intense mixing of pilgrims, the distribution of pneumococcal serotypes at Hajj could be different from that met with in the pilgrims' country of origin.

As at least one-third of Hajj pilgrims are considered "at risk" of pneumococcal disease either by virtue of age or preexisting medical conditions. Thus, consideration should be given to vaccinating these high-risk pilgrims against pneumococcal disease. Other preventive measures such as smoking cessation, pollution reduction, and vaccinations against influenza and pertussis should also be considered. Precisely defining the epidemiology of pneumococcal disease to identify an optimum vaccination schedule for Hajj pilgrims is a current research priority.

In Saudi Arabia, the most prevalent pneumococcal serotypes are 23F, 6B, 19F, 18C, 4, 14, and 19A, and 90% of the serotypes are covered by pneumococcal vaccination.^[27] In the cross-sectional study in Hajj, serotype 3 was the most common serotype in Hajj, followed by 19F and 34.^[28] However, due to lack of Hajj-specific data, the Saudi Arabian Ministry of Health has not yet recommended pneumococcal vaccine for pilgrims.

PNEUMOCOCCAL INFECTIONS AT HAJJ: RESEARCH TRENDS

In a cross-sectional study performed in the KSA during the 2011–2012 Hajj seasons, nasopharyngeal swabs were taken from 3203 Hajj pilgrims (beginning of Hajj: 1,590;

end of Hajj: 1,613) from 18 countries. The overall carriage of *S. pneumoniae* was 6.0%, with the carriage at the beginning and end of Hajj being 4.4% and 7.5%, respectively. Isolates nonsusceptible (at the beginning and end of Hajj) to one antibiotic were 2.5% and 6.1%, respectively, and those nonsusceptible to three or more antibiotics were 0.6% and 2.2%, respectively. A total of 51 serotypes were isolated, with serotype 3 being the most common.^[29]

A study on French pilgrims during the 2012 Hajj ($n = 169$), nasal swabs were taken before departing from France and before departing from the KSA; additional swabs were taken from pilgrims who suffered a respiratory infection during the pilgrimage (41.4%). Before departing from France, 7.3% were positive for *S. pneumoniae*, while at the end of Hajj, 19.5% tested were positive. Of the 34 pilgrims testing positive for *S. pneumoniae* during their stay in the KSA, 32 (94.1%) had tested negative before departing from France.^[30]

During the 2013 Hajj, nasal and throat swab specimens were obtained from 129 pilgrims before they departed from France and before they left the KSA: Polymerase chain reaction testing of the samples was undertaken for respiratory pathogens. The proportion of specimens positive for *S. pneumoniae* pre-Hajj was 50.0% and post-Hajj was 62.0%. Of the eighty pilgrims testing positive for *S. pneumoniae* before leaving the KSA, 29 (36.3%) had tested negative before departing from France.^[31]

PNEUMOCOCCAL VACCINES CURRENTLY AVAILABLE IN INDIA AND BANGLADESH

Currently, two pneumococcal vaccines are available - pneumococcal conjugate vaccine 13 (PCV13) and pneumococcal polysaccharide vaccine 23 (PPV23). PCV13 is a conjugate vaccine while PPV23 is a polysaccharide

vaccine. The PCV differs from the PPV in several ways [Table 2]. The PCV13 is effective in infants^[32] and has also recently been approved for adults. It induces immunological memory,^[32] offers prolonged protection,^[32,33] has a booster effect,^[33] does not induce hyporesponsiveness,^[32] is known to reduce nasopharyngeal carriage,^[34] and offers herd protection.^[34] On the other hand, there is demonstrated efficacy of PPV23 against invasive pneumococcal disease (IPD) in adults, but inconsistent data regarding its effectiveness against CAP.^[35,36] In two large meta-analyses performed by Huss *et al.* and Moberley *et al.* in the year 2009 and 2008, respectively, when the randomized control trials were taken into account there was little evidence for vaccine protection.^[35,37] Besides, the phenomenon of hyporesponsiveness is seen with revaccination PPV23.^[37,38] PPV23 and PCV13 act differently. This could be an important consideration while making a recommendation for pneumococcal vaccination for Hajj pilgrims, particularly since some pilgrims travel to Hajj more than once in their lifetime. Another important consideration when making a pneumococcal vaccination recommendation is the fact that PCV13 can be safely coadministered with the influenza vaccine in a patient, though at a different site.^[39] PCV13 is currently approved in India for children <5 years of age and adults >50 years of age; in contrast, in Bangladesh, PCV13 is approved for all age groups.

REVIEW OF PNEUMOCOCCAL VACCINATION STRATEGIES FOR ADULTS

Advisory Committee on Immunization Practices recommendations for 13-valent pneumococcal conjugate vaccine

In August 2014, the Advisory Committee on Immunization Practice (ACIP) voted to recommend PCV13 for routine

Table 2: Differences between 13-valent pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccine 23

| Vaccine | Advantages | Disadvantages |
|--------------------|--|---|
| PPV23 ^o | <ul style="list-style-type: none"> Long experience (licensed in 1983) Not expensive At present, relatively high serotype coverage for IPD in elderly (60-70%) Considerable efficacy proven against IPD (50-70%) in immunocompetent elderly Cost-effective proven for elderly people even if it only prevents IPD | <ul style="list-style-type: none"> T-cell-independent immune response (IgM antibody produced, response declines in 3-5 years and no anamnestic response at revaccination) Decrease in memory B cell frequency after PPV23 Weak immunogenicity in some individuals Unclear (null to small) efficacy against nonbacteremic pneumococcal pneumonia. No effect on nasopharyngeal carriage No efficacy demonstrated in reducing nasopharyngeal carriage No impact proved in reducing overall pneumococcal disease burden |
| PCV13 ^o | <ul style="list-style-type: none"> T-cell-dependent immune response (larger duration and boosting effect at revaccination) High efficacy (80-90%) against vaccine type IPD proven in children Significant efficacy against pneumococcal pneumonia (CAPITA study) Potential efficacy in reducing nasopharyngeal carriage Considerable impact in reducing all pneumococcal disease burden shown by prior PCV7 | <ul style="list-style-type: none"> Short experience (approved in 2011) Expensive At present, relatively small serotype coverage for IPD in the elderly (30-40%) Future reduction of vaccination impact in adults/elderly (because of probable indirect effects from PCV13 pediatric use) |

PCV13: 13-valent pneumococcal conjugate vaccine, PPV23: Pneumococcal polysaccharide vaccine 23, CAPITA: Community Acquired Pneumonia Immunization Trial, IPD: Invasive pneumococcal disease, IgM: Immunoglobulin M

use to help protect adults aged 65 years and older against pneumococcal disease caused by the 13 type-specific serotypes included in the vaccine^[40] [Table 3].

Specifically, the ACIP voted to recommend the following:

- Adults of 65 years of age or older who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown should receive a dose of PCV13 first, followed by a dose of PPSV23 at least a month later
- Adults of 65 years of age or older who have not previously received PCV13 and who have previously received one or more doses of PPSV23 should receive a single dose of PCV13.

On December 30, 2011, the US-FDA approved PCV13 for prevention of pneumonia and IPD caused by PCV13 serotypes among adults aged 50 years and older. The US-FDA approved PCV13 for an adult indication under the accelerated approval pathway, which allows the agency to approve products for serious or life-threatening diseases. Approval of PCV13 for adults was based on immunogenicity studies that compared antibody responses to PCV13 with antibody responses to PPV23, a vaccine that is considered to provide protection against IPD but for which no consensus exists regarding protection against nonbacteremic pneumococcal pneumonia.^[40] The ACIP recommended PCV13 for routine use in healthy adults based on the following evidence. Pneumococcal pneumonia

is the most common type of community-acquired bacterial pneumonia in the US. About 900,000 Americans get pneumococcal pneumonia each year, nearly half of whom require hospitalization.^[41] Among adults of 50 years of age and older, there are approximately 440,000 cases of pneumococcal pneumonia each year in the US,^[42] with approximately 25,000 pneumococcal disease-related deaths annually.^[42] Estimates have placed the yearly direct and indirect costs of adult hospitalizations and outpatient cases due to pneumococcal pneumonia in the US at nearly \$5 billion.^[43]

In addition to this, the ACIP decision was also based on the positive results of the largest to date efficacy trial (community-acquired pneumonia immunization trial in adults [CAPiTA], CAP immunization trial) on PCV13.^[44] In this study, 84,496 subjects were vaccinated in a 1:1 ratio with a single dose of PCV13 or placebo.

Recently, the ACIP recommendation was amended for spacing between PCV13 and PPV23 in adults >65 years [Figure 2]. The old ACIP recommended that PPV23 can be given after 6–12 months after PCV13. The new recommendation states that the recommended interval for adults receiving PCV13 and PPV23 to be at least 1 year apart, regardless of sequence.

In summary, this means that PCV13 is given first followed by PPV23 with spacing at least 1 year. If the adult above 65 years received PPV23, then he will receive PCV13 after 1 year as the older recommendation. The ACIP Committee believe that this amendment will have a dual impact; first it will give a better immune response, and second will allow medicare and insurance companies to cover both vaccines since they would not be received in the same year and the spacing now is 1 year, whether started by PCV13 or by PPV23.

There were no clinical studies evaluating the efficacy of the two vaccines given in series available, resulting in the ACIP referencing immunogenicity studies. Data from 16 of these studies suggested that shorter intervals could be associated with greater local reactogenicity; longer intervals could lead to a superior immune response than a single dose of either vaccine. Other considerations included an increased risk window for infection, timing and reducing visits to vaccination providers and revised regulations that cover two pneumococcal vaccines given in series and administered 1-year apart.

Recommended intervals between PCV13 and PPSV23 delivery remain unchanged for persons aged 2 years or

Table 3: New Advisory Committee on Immunization Practices recommendations for the use of 13-valent pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccine 23

| Pneumococcal vaccination status | Schedule of vaccination |
|---|---|
| Pneumococcal vaccine-naïve persons Adults of aged ≥65 years who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown | One dose PCV13 followed by a dose of PPV23 PPV23 should be given 6-12 months after PCV13 If PPV23 cannot be given during this time window, the dose of PPV23 should be given during the next visit The two vaccines should not be coadministered, and the minimum acceptable interval between PCV13 and PPV23 is 8 weeks |
| Previous vaccination with PPV23 Adults of aged ≥65 years who have previously received ≥1 doses of PPV23 | Should receive a dose of PCV13 if they have not yet received it A dose of PCV13 should be given ≥ 1 year after PPV23 For those for whom an additional dose of PPV23 is indicated, it should be given 6-12 months after PCV13 and ≥ 5 years after the most recent dose of PPV23 |

PCV13: 13-valent pneumococcal conjugate vaccine, PPV23: Pneumococcal polysaccharide vaccine 23

older with medical indications, and PPV23 is to be given 8 weeks or more after PCV13 for those aged 19 years or older with certain underlying medical conditions.^[45]

COMMUNITY-ACQUIRED PNEUMONIA IMMUNIZATION TRIAL IN ADULTS

CAPiTA was a randomized, double-blind, placebo-controlled clinical trial of PCV13 versus placebo conducted in the Netherlands in 84,496 subjects aged 65 years or older. The primary outcome was to confirm the efficacy of PCV13 in preventing the first episode of confirmed vaccine-serotype (VT) pneumococcal CAP. The results from CAPiTA have been published in the *New England Journal of Medicine* [Table 4].^[44]

Primary efficacy endpoint

There were 139 first episodes of VT-CAP, which occurred in 49 subjects in the PCV13 group and ninety subjects in the

placebo group (vaccine efficacy [VE] were 45.6%; 95.2% confidence interval [CI] 21.8–62.5).

Secondary efficacy endpoints

Nonbacteremia and noninvasive CAP occurred in 33 subjects in the PCV13 group and sixty subjects in the placebo group (VE 45.0%; 95.2% CI, 14.2–65.3); VT-IPD occurred in seven subjects in the PCV13 group and 28 subjects in the placebo group (VE 75.0%; 95% CI, 41.4–90.8). The efficacy persisted throughout the duration of the trial, which had a mean follow-up of 3.97 years. The safety profile of PCV13 in this study was consistent with that observed in previous studies of PCV13 in adults.

USE OF PNEUMOCOCCAL VACCINATION DURING HAJJ

The WHO and other regulatory bodies from several countries have identified an unmet medical need for an effective vaccine to prevent pneumococcal pneumonia in adults.^[35] Ten countries have developed recommendations for pneumococcal vaccination in Hajj pilgrims; however, the implementation of recommendations is poor. A recent study pointed out that about two-third of the pilgrims have at least one risk factor warranting pneumococcal vaccination; pneumococcal vaccination is indicated for about one-third regardless of the Hajj status; only 7% of pilgrims in whom pneumococcal vaccine was indicated were advised the same by general practitioners, and the overall knowledge of the pilgrims about the severity of pneumonia and the existence of vaccine was low.^[46]

Table 4: Community-Acquired Pneumonia Immunization Trial results

| Efficacy endpoint | Vaccine group | | VE (%) | 95.2% CI | P* |
|--|-------------------------|---------------------|--------|--------------|--------|
| | Prevenar 13 (n=42, 240) | Placebo (n=42, 256) | | | |
| First episode of confirmed VT pneumococcal CAP | 49 | 90 | 45.56 | 21.82, 62.49 | 0.0006 |
| First episode of confirmed NB/NI VT pneumococcal CAP | 33 | 60 | 45.00 | 14.21, 65.31 | 0.0067 |
| First episode of VT-IPD | 7 | 28 | 75.00 | 41.43, 90.78 | 0.0005 |

*P value significant. VT-IPD: Vaccine-serotype invasive pneumococcal disease, VT: Vaccine-serotype, CAP: Community acquired pneumonia, NB/NI: Nonbacteremic/noninvasive, VE: Vaccine efficacy, CI: Confidence interval

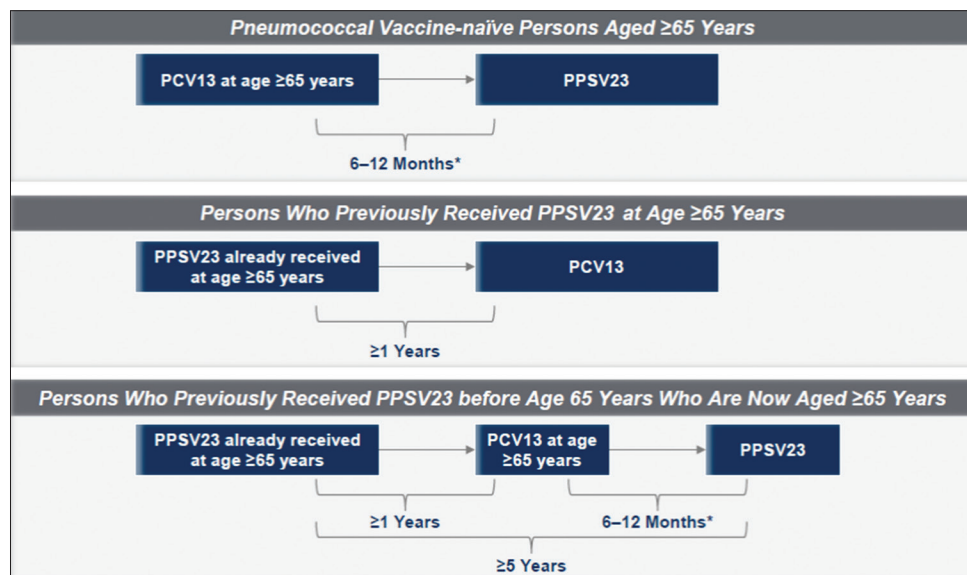


Figure 2: Chart of vaccination sequence as per ACIP

The working group for the prevention of pneumococcal disease in Hajj pilgrims recommends that after taking into account the economic situation of the patient, PCV13 may be recommended 4 weeks before travel to Hajj in order to ensure optimal protection against both IPD and pneumonia. PPV23 may be offered to these patients on return from their Hajj journey depending on their risk status. The vaccination sequence to be followed has been mentioned in Figure 2. This is in concurrence with the Indian recommendations for vaccination in older adults released by the Geriatric Society of India.^[7]

There is a substantial economic burden involved with travel to Hajj. Hajj travel packages typically include airfare, accommodation, meals, and internal bus trips.^[47] On an average, the cost is the US \$6000 for an individual to make the annual pilgrimage.^[48] Cheap packages of around the US \$2000 exist but require pilgrims to stay in same-sex dormitories with strangers.^[49] Other costs include telephone calls/postage; laundry; food, snacks and drinks, souvenirs, gifts, etc., To this, may be added healthcare-related costs of hospitalization, medications (cost of antibiotic use) and clinical emergencies. Hence, it is important that the most cost-effective and efficacious vaccine for the prevention of pneumonia should be recommended.^[50]

CONCLUSION

Respiratory infections during Hajj can result in an international health emergency situation or an epidemic outbreak. The Saudi Health Ministry requests the concerned countries to raise awareness among the pilgrims about contagious diseases, their symptoms, their modes of spread, complications, and preventive measures. Measures that prevent the spread of infections into Mecca and Madina ultimately prevent the pilgrims carrying infections back to their home countries. This document envisages itself as one such step contributing to the prevention of respiratory infections in Hajj pilgrims from India and Bangladesh.

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Conflicts of interest

There are no conflicts of interest.

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