Streptococcus pneumoniae (pneumococcus) is the leading cause of morbidity and mortality worldwide. The World Health Organization (WHO) estimates that pneumococcus is responsible for over a million deaths worldwide annually, the highest mortality from all vaccine-preventable infectious diseases. Vaccination against pneumococcal infections is currently recommended globally for all children <5 years old, adults >65 years old, and people >6 years old with certain risk factors for community-acquired pneumococcal pneumonia or invasive pneumococcal disease (IPD). These recommendations are based on age groups and other risk factors [Table 1]. The most recent population census in Saudi Arabia showed that a large majority of the population (89.5%) are <50 years of age, many of whom have risk factors for contracting pneumococcal infections.[5,6] There is a high prevalence in the younger age groups of diabetes, cardiovascular diseases, chronic renal, liver and lung diseases, and hemoglobinopathies in Saudi Arabia.[7-15] In addition, millions of pilgrims come to Saudi Arabia every year from all over the world for the Umrah and Hajj, and transmission of S. pneumoniae (including antibiotic resistant strains) between pilgrims is expected to occur. Vaccination against pneumococcus for pilgrims is not currently mandated for travelers to Saudi Arabia. Since the epidemiology of pneumococcal disease is constantly changing, including an increase in nonvaccine pneumococcal serotypes, vaccination policies on the effectiveness and usefulness of vaccines require regular revision. These findings may challenge the age limit of 65 years recommended by other guidelines for the routine administration of pneumococcal vaccine, and hence the age limit of 50 years is more appropriate in Saudi Arabia.[3] Therefore, the younger population, the prevalence of chronic

**Abstract:**

Streptococcus pneumoniae (pneumococcus) is the leading cause of morbidity and mortality worldwide. Saudi Arabia is a host to millions of pilgrims who travel annually from all over the world for Umrah and the Hajj pilgrimages and are at risk of developing pneumococcal pneumonia or invasive pneumococcal disease (IPD). There is also the risk of transmission of S. pneumoniae including antibiotic resistant strains between pilgrims and their potential global spread upon their return. The country also has unique challenges posed by susceptible population to IPD due to people with hemoglobinopathies, younger age groups with chronic conditions, and growing problem of antibiotic resistance. Since the epidemiology of pneumococcal disease is constantly changing, with an increase in nonvaccine pneumococcal serotypes, vaccination policies on the effectiveness and usefulness of vaccines require regular revision. As part of the Saudi Thoracic Society (STS) commitment to promote the best practices in the field of respiratory diseases, we conducted a review of S. pneumoniae infections and the best evidence base available in the literature. The aim of the present study is to develop the STS pneumococcal vaccination guidelines for healthcare workers in Saudi Arabia. We recommend vaccination against pneumococcal infections for all children <5 years old, adults ≥50 years old, and people ≥6 years old with certain risk factors. These recommendations are based on the presence of a large number of comorbidities in Saudi Arabia population <50 years of age, many of whom have risk factors for contracting pneumococcal infections. A section for pneumococcal vaccination before the Umrah and Hajj pilgrimages is included as well.

**Key words:**

Guidelines, Hajj, pneumococcus, vaccine

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pneumococcal vaccines by searching the terms “vaccines” or “prevention” for the period from March 01, 2000, to March 01, 2016. Substantive data from these agencies were also reviewed. We used the search terms “S. pneumoniae” or “pneumococcus” and combined them with the terms “vaccines” or “prevention” for the period from March 01, 2000, to March 01, 2016. Substantive reviews and guidelines identified on the subject have been referenced. Relevant data on international guidelines and the best practices were obtained and put into context for the Saudi Arabia health services.

Methods

We conducted a systematic review of the literature related to S. pneumoniae and pneumococcal vaccines by searching the PubMed, Embase, and Cochrane databases and websites and documents of the WHO, US Centers for Disease Control, UK Public Health England, the ECDC, and Kingdom of Saudi Arabia Ministry of Health. Updates and press statements from these agencies were also reviewed. We used the search terms “S. pneumoniae” or “pneumococcus” and combined them with the terms “vaccines” or “prevention” for the period from March 01, 2000, to March 01, 2016. Substantive reviews and guidelines identified on the subject have been referenced. Relevant data on international guidelines and the best practices were obtained and put into context for the Saudi Arabia health services. These data were reviewed by SCIPV, a group of Saudi experts in the field of respiratory and infectious diseases. Consensus among the SCIPV members was followed wherever there was a lack of evidence. We graded the evidence into four categories:

- Evidence Category A: Randomized controlled trials with substantial body of data
- Evidence Category B: Randomized controlled trials with limited body of data
- Evidence Category C: Nonrandomized trials and observational studies
- Evidence Category D: Consensus judgment by SCIPV

Each section was prepared by a member of the panel and then internally reviewed by other members. The panel conducted round-table discussions frequently and jointly. International experts helped in reviewing the guidelines.

Epidemiology

S. pneumoniae (pneumococcus) is global in distribution and affects all age groups. Those at highest risk of severe pneumococcal disease are very young children, the elderly (>65 years old), and those with risk predisposing factors, which are summarized in Table 1. All risk factors that included in Table 1 are applicable to Saudi Arabia population. Pneumococcal serotypes causing community-acquired pneumonia (CAP) and IPD differ between various geographical areas, and the distribution seems to be dependent on the period the studies were conducted and the use of pneumococcal vaccines in the geographical locations. To the panel knowledge, no large-scale controlled studies have been conducted in Saudi Arabia on the relative importance of pneumococcal infections and the true burden of pneumococcal infections is unknown. Several reports indicate that pneumococcal infections are common and impose an important burden on Saudi Arabia health services.

A retrospective analysis conducted in two regions between 1999 and 2003 before the introduction of PCV found that the average annual incidence of IPD in children aged ≤5 years was 17.4/100,000 population. The incidence during the 1st year of life was almost 4 times more than the average incidence in the following 4 years. IPD presented as meningitis and bacteremia in 23.2% and 76.7% of cases, respectively. Another study from three hospitals in Mecca city reported that S. pneumoniae was the main isolate from age groups <10 and ≥10 with an incidence rate of 56.8% and 57.9, respectively. In a report from a university hospital in Riyadh conducted between 2000 and 2004, 62% of pneumococcal isolates from all age groups and 83% of isolates from children aged <2 years were included in the PCV7. In a recent large prospective population-based study of CAP in hospitalized adults in the USA, a pathogen was identified in 38% of patients and S. pneumoniae was the responsible pathogen in 5% of them.

Pneumococci are becoming increasingly resistant to commonly used antibiotics worldwide, and management of pneumococcal diseases is becoming more difficult with the spread of multidrug resistant (MDR) strains. Since the identification...
of MDR *S. pneumoniae* (resistant to >3 different antimicrobial classes) in the 1970s, its prevalence has steadily increased in many countries. In 1988, a report from Saudi Arabia showed that all *S. pneumoniae* isolates were sensitive to penicillin and vancomycin, but 65% were resistant to trimethoprim-sulfamethoxazole. A newer study reporting childhood pneumococcal bacteremia in Riyadh showed that 20.4% of the isolates were penicillin-resistant and 22% were MDR. Worryingly, recent reports show that more than half of pneumococcal isolates are now resistant to penicillin. Many penicillin-resistant pneumococci in these studies were found to be resistant to other antimicrobial drugs, for example, macrolides, trimethoprim-sulfamethoxazole, and extended-spectrum cephalosporins. Other studies between 2005 and 2010 have reported IPD in children aged <5 years with 66% and 62% resistance to penicillin and erythromycin strains, respectively. Based on international experience, the introduction of pneumococcal vaccines has been shown to reduce the rate of the disease, especially those caused by drug-resistant strains due to the protective action of the vaccine against serotypes responsible for drug resistance.

**Bacteriology**

*S. pneumoniae* (pneumococcus) is a gram-positive lancet-shaped diplococcus. The pneumococcal cell wall surface is covered by a polysaccharide capsule which consists of teichoic acid and peptidoglycan. The capsule is an essential virulence factor and means of evading the immune system by resisting phagocyte killing. On the basis of differences in the composition of this capsule, over >90 distinct pneumococcal serotypes have been identified. In general, immunity following infection is serotype-specific, but cross-protection between related serotypes could occur. Antibodies directed to the capsule polysaccharide are highly protective and they play a central role in protection. They also form the basis for immunogenic and protective immune responses generated by current vaccines. Available pneumococcal vaccines contain capsular polysaccharides from common serotypes that are associated with severe invasive disease. It has been noted that the distribution of serotypes that cause pneumococcal diseases varies based on many factors that include age, disease type and severity, and geographic region.

**Clinical Manifestations**

The clinical manifestations of *S. pneumoniae* infection are wide ranging from asymptomatic carriage to rapidly fulminant disease. Direct extension from the nasopharynx through local invasion or inhalation of contaminated infected droplets can cause conjunctivitis, sinusitis, otitis media, pharyngitis, tonsillitis and pneumonia, and acute exacerbations of chronic obstructive pulmonary disease (COPD). Direct invasion can cause bacteremia and IPD occurs through hematogenous spread to all organs and tissues of the body. Common clinical presentations of IPD include septicaemia, bacterial meningitis, lobar pneumonia, endocarditis, osteomyelitis, septic arthritis, peritonitis, cellulitis, myositis, periportal cellulitis, and abscesses. IPD affects mainly extremes of ages: <12 months and ≥65 years. Other groups who are more likely to develop IPD are shown in Table 1. In a systemic review of literature from the Arabian Peninsula and Egypt that covered the period between 1990 and 2007, the incidence range of IPD in children aged ≥5 years was 3.4–53.5/100,000 population. IPD presented as bacteremia in 61–100% and meningitis in 3–25% for children aged <2 years. The case fatality and morbidity rates for pneumococcal meningitis were 0–22% and 10–62%, respectively.

**Transmission**

Transmission of pneumococci from person-to-person occurs by direct contact with respiratory secretions, such as saliva and mucus, or by droplets coughed up by an infected patient. Many people, especially children, have the pneumococci in their nostrils, pharynx, or throats without manifesting symptoms or signs of ill health. This is called asymptomatic carriage where *S. pneumoniae* colonize the upper respiratory tract in 5–10% of healthy adult and 20–40% of healthy children. Carriage usually requires frequent or prolonged close contact and overcrowdedness and is associated with young age, female gender, winter season, and exposure to antibiotics during the previous month. Susceptibility to infection occurs more in situations such as malnutrition, fatigue, or recurrent viral infection and seasonal variation with a tendency toward peaking in the winter. After colonization in the nasopharyngeal, infection of nearby sites may develop. Alternatively, infection might also be caused by direct aspiration into the bronchial tree causing pneumonia or by hematogenous invasion leading to bacteraemia, meningitis, or infection of other distant organs.

**Types of Pneumococcal Vaccines**

The development and introduction of pneumococcal vaccines represented a major advance for prevention of pneumococcal infections. The widespread use of vaccines in recent years has led to reductions in the incidence of pneumococcal disease in high-risk population. At population level, the decline is occurring for both those who are vaccinated and also among older, nonvaccinated children, and adults since the vaccine effectively eradicates nasal colonization as well. This phenomenon is called the “herd effect” that can result in a significant decline in pneumococcal disease due to serotypes contained in the vaccine in individuals who do not receive the vaccine.

Currently, there are two different types of pneumococcal vaccines recommended for use: (1) PPSV23 and (2) pneumococcal protein-conjugate vaccine. Both vaccines are inactivated vaccines and do not contain any live organisms. The efficacy of the vaccines is limited to the specific pneumococcal strains from which the capsular serotypes were used to make the vaccine and thus does not extended to other serotypes. The adult vaccine (PPSV23) protects against 23 strains, and in Saudi Arabia the childhood vaccine (PCV13) protects against 13 strains with overall protection around 50–70%. Due to the high burden of IPD caused by serotypes included in the two available vaccines, wider protection may be provided using both vaccines in certain situations. Both pneumococcal vaccines are available in Saudi Arabia.

**Pneumococcal polysaccharide vaccines**

PPSV23 contains purified capsular polysaccharide from each of the 23 capsular types of *S. pneumoniae* (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and...
PCV13 is available as a single dose of 0.5 mL. It’s storage conditions may lead to the separation of the vaccine into a white deposit and a clear supernatant; therefore, the vaccine should be shaken well to ensure a status of white homogeneous suspension. It should not be administered if there is residual particulate after shaking. The vaccine should be administered intramuscularly at any time of the year. Due to lack of safety and immunogenicity data, PCV13 cannot be recommended to be injected intradermally, subcutaneously, or intravenously.

**Recommendations for Pneumococcal Vaccination in Healthy Individuals**

Taking into account our literature review and deliberations of SCIPV committee, the STS SCIPV pneumococcal vaccination recommendations are summarized below and in Tables 2, 3 and Figure 1.

**Pneumococcal vaccination for healthy adults**

PCV13 is effective in preventing vaccine-type pneumococcal, bacteremic and nonbacteremic CAP, and vaccine-type IPD.

*Interestingly, it has been shown that the immune response to included serotypes is higher in the elderly who receive PCV followed by PPSV23.*

All vaccine-naïve adults age ≥50 years should receive one dose of PCV13 followed by PPSV23 after 1-year or more. Individual who received PPSV23 should receive PCV13 at least 1-year later from the last dose of PPSV23 [Evidence Category A].

**Routine vaccination for healthy children**

Four doses of heptavalent PCV13 in infants are highly effective in preventing IPD and results in significant immune response for all serotypes included in the vaccine.

All children (including children with high-risk conditions) are strongly recommended to receive 4 doses of PCV13 at the 1st year of life. As per the National Immunization Program, the vaccine should be received at age 2, 4, 6, and 12 months [Evidence Category A].

**Catch-up vaccination for healthy children**

In children <6 years, the incidence of the IPD, the immunological responses, and the safety results from various studies support the use for catch-up schedules utilizing PCV13. Table 2 illustrates the recommended PCV13 catch-up doses in children <6 years [Evidence Category A].

**Recommendations for Pneumococcal Vaccinations in High-risk Individuals**

Pneumococcal vaccines have been shown to reduce the risk of IPD and to induce a high immunological response to the vaccine-related serotypes in a high-risk group individual [Table 1] [Evidence Category A].

- Adult individuals ≥50 years with high-risk conditions: Similar to healthy adults, i.e., one dose of PCV13 followed by PPSV23 after 1-year or more
- Children ≥6 years and adults <50 years with high-risk conditions: To be vaccinated according to Table 3
Children 2–6 years with high-risk conditions: One dose of PPSV23 at least 8 weeks after the last PCV13 [Evidence Category B]

Children <2 years with high-risk conditions should receive routine and catch-up pneumococcal vaccination similar to healthy children [Evidence Category B].

Coadministration with Other Vaccines

Concomitant administration of PCV13 and trivalent inactivated influenza vaccine (TIV) has been shown to be immunogenic and safe. A randomized, double-blind study has reported a slightly lower pneumococcal serotype-specific antibody concentrations with PCV13 plus TIV compared with PCV13 alone or TIV alone among adults aged ≥65 years.[102] Currently, there are no data on the safety or efficacy of the coadministration of pneumococcal vaccine with other vaccines (tetanus, diphtheria, pertussis, or zoster vaccine) among adults.

Vaccination in Special Situation in Saudi Arabia

Pneumococcal vaccination for the Hajj and Umrah

The Hajj and Umrah are the largest recurrent mass gatherings in the world where Muslims from different countries travel to the holy places in Mecca and Madinah in Saudi Arabia.[103] A large number of pilgrims coming to the Hajj have many of the underlying risk factors listed in Table 1 for pneumococcal disease. Because of the limited space, close contact with other pilgrims, congested places, air pollution, shared accommodation, and extreme fatigue, the Hajj conditions expose pilgrims to high risk of infection with different pneumococcal serotypes and amplification of the pneumococcal carriage state. As an international gathering, the Hajj may also lead to globalization of the

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**Table 2: Catch-up program with 13-valent pneumococcal conjugate vaccine for children <6 years presents for pneumococcal vaccination for the 1st time**

| Age at first dose | Number of doses | Timing |
|-------------------|----------------|--------|
| 2-6 months        | 4 doses        | 3 doses in the 1st year 8 weeks apart and final 4th (booster) dose after the 1st birthday and 8 weeks away from the last dose |
| 7-11 months       | 3 doses        | 2 doses in the 1st year at least 4 weeks apart, and final 3rd dose (booster) after the 1st birthday 8 weeks away from the last dose |
| 12-23 months      | 2 doses        | 2 doses that are 8 weeks apart |
| >2 years and <6 years | 1 dose only | |

**Table 3: Recommended pneumococcal vaccination for high-risk individual aged >6 years and <50 years**

| Conditions                          | Not previously vaccinated | Already received PPSV23 only |
|-------------------------------------|----------------------------|------------------------------|
| High risk immunocompetent           | Administer one dose of PPSV23* | No need to repeat unless age is >50 years** |
| Immunocompromised                   | Give a single PCV13 dose first, followed by 8 weeks later by a dose of PPSV23 | Give single PCV13 dose first, followed by 8 weeks later by a dose of PPSV23 (at least 5 years form last PPSV23 dose) |
| Functional and anatomical asplenia  | Revaccination with PPSV23 every 5 years | Revaccination with PPSV23 every 5 years |

*In case of CSF leak and cochlear implant give PCV13 followed by one dose of PPSV23 8 weeks later, **In case of CSF leak and cochlear implant give a single dose of PCV13 first, followed by 8 weeks later by a dose of PPSV23.

CSF = Cerebrospinal fluid, PCV13 = 13-valent pneumococcal conjugate vaccine, PPSV23 = 23-valent pneumococcal polysaccharide vaccine
respiratory pathogens.\textsuperscript{104} Such a situation mandates the need for more preventive measures, such as vaccines and face mask.\textsuperscript{103,105}

During the 2011–2012 Hajj session, a survey of pneumococcal nasal colonization in adults was conducted at the beginning and the end of Hajj.\textsuperscript{106} By comparing the end of Hajj to pre-Hajj data, the overall carriage rate increased from 4.4% to 7.5%, the carriage of PCV23 serotypes from 2.3% to 4.1%, the carriage of PCV13 from 1.1% to 3.6%, antibiotic nonsusceptible isolates from 2.5% to 6.1%, and multiple nonsusceptible isolates from 0.6% to 2.2%. A similar report from France showed 2.7-fold increase in the nasal carriage rate of \textit{S. pneumoniae} in the pilgrims returning from the 2012 Hajj pilgrimage.\textsuperscript{107} Interestingly, only 7% of pilgrims received advice from their general practitioner about pneumococcal vaccination before the Hajj and the uptake of the vaccine among pilgrims was as low as 5%.\textsuperscript{107,108} Another report from Australia found that only 14.2–28.7% of all pilgrims received the pneumococcal vaccine and 29–45.3% of the high-risk group received it.\textsuperscript{109} Behavioral interventions are also recommended that includes good hand hygiene technique and cough etiquette, wearing a face mask, and contact avoidance can be effective to avoid acute respiratory illness among Hajj pilgrims.

SCIPV recommends the enforcement of the following recommendation before the Hajj season:

\begin{itemize}
  \item All persons at \( \geq \) 50 year are recommended to receive combined vaccination with PCV13 and PPSV23 before the Hajj. However, for those planning immediately before Hajj, it is recommended to administer one dose of PPSV23 [Evidence Category D]
  \item Immunocompetent persons \(<\) 50 years with risk factors are recommended to receive single dose PPSV23 at least 3 weeks before the Hajj [Evidence Category D]
  \item Because of lack of evidence, it is not recommended to provide a pneumococcal vaccine routinely to healthy persons aged \(<\) 50 years.\textsuperscript{110}
\end{itemize}

Pneumococcal vaccination for pregnant and lactating women

Pregnancy is not a risk factor for pneumococcal diseases. However, a pregnant woman who has another risk factor for pneumococcal diseases might receive the vaccine during the second or third trimesters as both PCV13 and PPSV23 are probably safe during this period [Evidence Category B].\textsuperscript{111,112} The safety of these vaccines has not been reported among newborns whose mothers were inadvertently vaccinated during pregnancy, it is advisable to delay the vaccination until the second trimester if indicated. Reduction of neonatal infections after vaccination has been documented.\textsuperscript{113}

Pneumococcal vaccination for individuals with sickle cell disease

Sickle cell disease (SCD) is an autosomal recessive disorder, results from the production of abnormal hemoglobin \( S \), and is associated with significant morbidity and mortality. The annual prevalence of SCD was found to be almost constant in Saudi Arabia with an average rate of 4.5%: 4.2% carriers and 0.3% diseased.\textsuperscript{114} This survey reported regional variability of SCD, with the highest prevalence (13.4%) in the eastern province.\textsuperscript{115}

\textit{S. pneumoniae} is known to be one of the major organisms that cause infection in patients with SCD.\textsuperscript{116} This is mainly related to the status of functional asplenia that presents in 80% of cases before the end of the 1st year of age. Asplenic status is a known risk factor for infection with encapsulated organisms (such as \textit{S. pneumoniae}).\textsuperscript{117} Such patients are usually 30–600 fold more susceptible to IPD than healthy person.\textsuperscript{117} Pneumococcal vaccines and penicillin prophylaxis have led to a significant decrease in the rate of IPD in those patients.\textsuperscript{117}

Since the introduction of PCV7, the incidence of IPD among persons with SCD in the USA decreased by 90.8% among children aged <2 years and by 93.4% among children aged <5 years.\textsuperscript{117} Another study revealed a drop in the incidence of IPD among African American <18 years with SCD by 53% in 2009 compared to 1988 era.\textsuperscript{118} Finally, both PCV7 and PPSV23 have shown an additive effect manifested by significantly higher antibody titer for children with SCD aged \( \geq \) 2 years receiving both vaccines compared to children received PPSV23 alone.\textsuperscript{119}

SCIPV recommendation for pneumococcal vaccination of SCD patients are as follows: [Evidence Category A]

\begin{itemize}
  \item For children with SCD aged <2 years, vaccination by PCV13 similar to healthy children by administration of 4 doses of PCV13 at age 2, 4, 6, and 12 months
  \item For children with SCD aged from 2 to <6 years, vaccination by PCV13 similar to healthy children catch-up program [Table 2]; however, they should receive an additional dose of PPSV23 at least 8 weeks after the last PCV13
  \item For individuals with SCD aged \( \geq \) 6 years: Vaccination as shown in Figure 1.
\end{itemize}

Pneumococcal vaccination for splenectomized persons

The common reasons for splenectomy in Saudi Arabia are posttrauma (mainly due to motor vehicle accidents), hematological reasons, and portal hypertension.\textsuperscript{120-122} In addition to clearing unopsonized bacteria, the spleen has a major role in humoral immunity by functioning as a reservoir of mononuclear cells and produces antibodies mainly IgM following exposure to various antigens.\textsuperscript{10,123} In splenectomized persons, loss of these functions predisposes to an increased incidence of overwhelming postsplenectomy infections.\textsuperscript{121} Splenectomy patients are exposed to an increased risk of specific infections caused by encapsulated bacteria including \textit{S. pneumoniae}, especially in the first 2 year post splenectomy.\textsuperscript{86,124}

SCIPV recommendations for splenectomized persons are as follows: [Evidence Category B].

For those undergoing elective splenectomy, it is recommended to administer pneumococcal vaccination at least 14 days before splenectomy or 14 days after splenectomy.\textsuperscript{122}

\begin{itemize}
  \item For children <24 month, it is recommended to administer PCV13
  \item For children \( \geq \) 24 months till 6 years, it is recommended to administer PPSV23
  \item For children \( \geq \) 6 years and adults individuals, the administration of PCV13 in addition to PPSV23 according to the following:
\end{itemize}
• For individuals who have not previously received either PCV13 or PPSV23, a single dose of PCV13 should be given, followed by a dose of PPSV23 at least 8 weeks later
• For individuals who have previously received one or more doses of PPSV23, a single dose of PCV13 should be given one or more years after the last PPSV23 dose was received
• For individuals who require additional doses of PPSV23, it should be given no sooner than 8 weeks after PCV13 and at least 5 years after the most recent dose of PPSV23.

Acknowledgments
We are grateful for the expert advice from Prof. Alimuddin Zumla and Prof. Peter Wilson, University College London and Dr. Ron Behrens, London School of Hygiene and Tropical Medicine, United Kingdom; and UCL Hospitals NHS Foundation Trust, United Kingdom; Prof. Daniel M. Mushan, Baylor College of Medicine, Houston, Texas, USA; and Prof. Antoni Torres, Hospital Clinic de Barcelona, Spain.

Financial support and sponsorship
The Saudi Thoracic Society provided kind support for the Scientific Committee for Influenza and Pneumococcal Vaccinations.

Conflicts of interest
There are no conflicts of interest.

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