ABSTRACT

Infection control in the setting of the office based clinic, involves the early detection of disease; disease prevention through vaccination as in influenza and pneumococcal vaccinations; and through screening for asymptomatic disease as in tuberculosis. Family physicians play an important role in these aspects within the community.

Although influenza vaccination is effective, the take up rate of vaccination locally is low. Annual vaccination with the current vaccines are strongly recommended in high risk populations such as the elderly, the immunocompromised and, those with co-morbidities. The inactivated trivalent vaccine is the most commonly used.

Latent Tuberculosis (TB) Infection is asymptomatic and often goes undetected. Prevention of progression to overt TB can be achieved by identifying high risk persons and the early detection by either the tuberculin skin test or interferon gamma release assays (IGRAs).

Invasive pneumococcal disease can lead to significant morbidity and mortality in the young and elderly. In the preventive control of this disease, there are two types of pneumococcal vaccines currently available – the polysaccharide vaccine and the conjugate vaccine. Recommendations for the two different vaccines are in accordance with different at risk populations.

Keywords: Influenza vaccination, Latent TB infection, Pneumococcal vaccination

INTRODUCTION

Infection control in the setting of the office based clinic, involves both the early detection of disease as well prevention through vaccination. This article will focus on three infections in the local context where family physicians (FPs) play an important role in the control of disease.

Although influenza is a very common illness in Singapore, vaccination is effective, the take up rate of vaccinations locally is low. The emphasis in this section on influenza will be on the effectiveness of vaccination in reduction of morbidity and mortality, particularly in high risk patient groups. Tuberculosis (TB) is still endemic in Singapore, and the value of screening for latent TB infection (LTBI) is often not recognised or done often enough. Thus this section looks at LTBI more closely and what can be done to enable early detection. Finally invasive pneumococcal disease can result in significant morbidity and mortality, especially in high risk persons. The key to control of this disease will again be prevention via vaccination and the section on pneumococcal disease serves as an update on the aspects of pneumococcal vaccination.

INFLUENZA

Influenza in Singapore

Influenza is an acute viral disease of the respiratory tract characterised by fever and symptoms such as sore throat, cough, coryza, headache and myalgia. It is spread from person to person mainly through infectious respiratory secretions released during coughing and sneezing.

The causative agent is the influenza virus and three types that infect humans are recognised – influenza A, B and C. The virus sub-types comprise various combinations of the haemagglutinin (H) and neuraminidase (N) antigens. Influenza A viruses are the most prevalent and important. They include the H1N1 and H3N3 sub-types that have been associated with pandemics and widespread epidemics. Influenza B is occasionally associated with regional epidemics, and influenza C is usually associated with sporadic cases and minor localised outbreaks.

In temperate and cold climates, the peak incidences of influenza occur twice a year – December to March in the northern hemisphere (NH) and June to September in the southern hemisphere (SH). In tropical and sub-tropical areas, the peaks can occur either twice a year or throughout the year. In Singapore, influenza viruses circulate all year round with a bimodal increase in incidence observed in April to July and November to January.

Using the month of December 2013 as a snap shot of the influenza pattern in Singapore, there were 2,458 attendances in the polyclinics for acute respiratory infections of which 1% were classified as influenza like illness (ILI). Of the ILI samples tested (n=172), the overall prevalence of test positive influenza cases was 62.8%. The viral isolates were influenza A (H3N2) 68.5%, influenza B 22.6% and influenza (H1N1) 8.2%.

From previous retrospective analysis, it is clear that influenza infections have been a significant burden to the local population. Even the inter pandemic seasons can contribute to excess mortality, although significantly less than the pandemic years (1918, 1957 and 1968).

Complications of Influenza and Populations at risk

The symptoms of uncomplicated influenza reflect both local symptoms (nasal congestion, cough, pharyngitis) as well as
systemic effects (headache, fever, chills, anorexia, myalgia) which cause more of a nuisance than any real morbidity. However, influenza can cause complications (Table 1), some of which are serious and can lead to mortality. Certain populations such as the elderly, the immunocompromised and those with co-morbidities, have increased risk of complications of both seasonal as well pandemic influenza (Table 2).

**TABLE 1. COMPLICATIONS OF INFLUENZA**

<table>
<thead>
<tr>
<th>Respiratory system</th>
<th>Central Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>Influenza associated acute encephalitis</td>
</tr>
<tr>
<td>Secondary bacterial infection</td>
<td>Post- influenza encephalitis</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>Cardiovascular System</td>
</tr>
<tr>
<td></td>
<td>Myocarditis</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Admission to hospital</td>
<td></td>
</tr>
<tr>
<td>Admission to ICU</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2. POPULATIONS AT RISK OF COMPLICATIONS OF SEASONAL INFLUENZA**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Populations at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>Age 2 – 5 years</td>
</tr>
<tr>
<td></td>
<td>Any co-morbid condition</td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td>Any cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td>Neurocognitive disease</td>
</tr>
<tr>
<td></td>
<td>Age &gt; 65</td>
</tr>
<tr>
<td></td>
<td>Any co-morbid condition</td>
</tr>
<tr>
<td></td>
<td>Any chronic lung disease</td>
</tr>
<tr>
<td>Admission to hospital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td>Chronic steroid use</td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td>Admission to ICU</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any co-morbid condition</td>
</tr>
<tr>
<td></td>
<td>Any chronic lung disease</td>
</tr>
<tr>
<td></td>
<td>Age &gt; 65</td>
</tr>
<tr>
<td></td>
<td>Any co-morbid condition</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Any cardiovascular disease</td>
</tr>
<tr>
<td>Death</td>
<td>Any neuromuscular disease</td>
</tr>
<tr>
<td></td>
<td>Immunocompromised</td>
</tr>
<tr>
<td></td>
<td>Any neuromuscular disease</td>
</tr>
<tr>
<td></td>
<td>Endocrinological disease</td>
</tr>
</tbody>
</table>

Source: Mertz D et al, 2013

**Influenza Vaccination**

**Vaccine composition**

Vaccination is an important form of prevention of influenza and its complications in high risk persons. However, the influenza virus remains highly unusual among infectious diseases in that it has a rapid evolutionary and high mutation rate. Influenza viruses exhibit an antigenic ‘drift’ resulting from the sequence variation in progeny viruses. In addition, there is exchange of genome segments between viruses when more than one virus infects the host cell. This is called ‘reassortment’ and can lead to the emergence of ‘novel’ virus sub-types, some of which have caused influenza pandemics. As a consequence, new vaccines are needed almost every year if an optimal match of the vaccines and the new viruses are to be achieved.

Both the World Health Organisation (WHO) and the United States Centre for Disease Control (CDC) maintain a global surveillance of the seasonal and pandemic influenza strains and make recommendations on the composition of the seasonal vaccines. The recommendations are based on the prevailing strains of the previous year for both the NH and SH. In Singapore, the Expert Committee on Immunisation (ECI) of the Ministry of Health makes the recommendations based on the WHO guidelines. In the local context, annual vaccination is generally sufficient to protect non-travelling individuals against the circulating influenza strains. Travellers receive the current NH or SH vaccines depending on the time of the year and region of travel. However, if there is a change in the latest vaccine composition, an earlier re-vaccination before the normal cycle is due, may be necessary for high risk individuals locally as well as travellers.

For the coming 2014-2015 NH season, the composition has remained unchanged from the 2013 – 2014 NH and 2014 SH vaccines. Therefore the ECI recommends no re-vaccination outside the normal annual cycle.

**Vaccine types**

Although the most common influenza vaccines used locally are the trivalent inactivated vaccines, there are several vaccine options available. The following information is based on the recommendations of the U.S. Advisory Committee on Immunisation Practices (ACIP):

- Vaccines can either be trivalent (two Influenza A and one influenza B viruses) or quadrivalent (two influenza A and B viruses each). The quadrivalent vaccines tend to be more expensive.
- The most common vaccines are inactivated vaccines (IV) which are administered as an intra-muscular injection.
- An intradermal injection is also available using a smaller needle, but this is approved only for ages 18 through 64 years.
- Different vaccines are approved for different ages. Most standard IVs are approved for 6 months of age and above.
- A live attenuated vaccine (LAV) is available. This is quadrivalent and comes in an intra-nasal spray formulation which is approved for ages 2 through 49 years. The ACIP recommends the LAV, if available and if there are no contraindications, preferentially for healthy children of 2 to 8 years.
An egg-free recombinant trivalent vaccine (RIV3) or a cell culture based (grown in animal cell culture) inactivated influenza vaccine (CCIV3) is available for those with serious egg allergy (see egg allergy). The RIV3 is approved for ages 18 through 49 years and the CCIV3 for 18 years and older.

Recommendations for vaccination

The recommendations by the Ministry of Health of Singapore (Table 3) are generally similar to the ones by both the WHO and the U.S. CDC. The focus is on the extremes of ages and high risk individuals. Those residing in institutions providing intermediate and long term care (ILTC) services are also at risk and should receive the vaccination. These institutions include community/chronic sick hospitals, nursing/welfare/sheltered homes, hospices and ex-psychiatric facilities. To prevent transmission to high risk groups, it is also important that health care workers, staff of the ILTC institutions as well as caregivers of those at risk receive the vaccination.

It should also be noted that since August 2012, the ECI recommends that pregnant women receive the vaccination at all stages of their pregnancy. Medisave use for the influenza vaccination in high risk groups has been allowed since January 2014.

Contra-indications to vaccination

The ACIP recommends that the following persons should not receive the IV:

- Children younger than 6 months.
- Those with a previous severe reaction to any component of the vaccine including egg protein (see egg allergy) such as anaphylaxis, angioedema and respiratory distress.
- Those with a past history of Guillain- Barré Syndrome within 6 weeks of receiving the vaccine.
- Moderate to severe illness with or without fever. The vaccine should be post-phoned.

In addition to the above contra-indications, the LAV should also not be given in the following persons:

- Pregnant women.
- Immunocompromised.
- Children 2 to 5 years with asthma or wheezing in the preceding 12 months.
- Those aged 5 years or older with asthma.
- Those who have taken anti-viral medication in the preceding 48 hours.
- Those with medical conditions which might predispose to higher risks of complications of influenza.
- Children and adolescents on concomitant use aspirin or aspirin containing medications.

Egg allergy

Most standard influenza vaccines are grown in embryonated chicken eggs. Persons with an egg allergy who have experienced only urticaria after exposure to eggs should proceed with the vaccination, with an observation period of 30 minutes to watch for reactions. The IV, RIV3 or CCIV3 vaccines should be used because there is limited data on the use the LAV in this setting. For those with serious egg allergy such as anaphylaxis, angioedema, light-headedness, recurrent emesis and respiratory distress, or those who have required adrenaline or emergency intervention in the past, the RIV3 or the CCIV3 may be used.

### TABLE 3. RECOMMENDATIONS FOR INFLUENZA VACCINATION BY THE MINISTRY OF HEALTH SINGAPORE

<table>
<thead>
<tr>
<th>Age Group</th>
<th>High Risk Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children and Teens</td>
<td>Aged between 6 months to 5 years</td>
</tr>
<tr>
<td>Adults</td>
<td>Aged between 6 months to 18 years on long term aspirin</td>
</tr>
<tr>
<td></td>
<td>(risk of Reye's Syndrome)</td>
</tr>
<tr>
<td></td>
<td>Women is all stages of pregnancy</td>
</tr>
<tr>
<td></td>
<td>Aged &gt; 65 years and above</td>
</tr>
<tr>
<td></td>
<td>Health care workers</td>
</tr>
<tr>
<td></td>
<td>Caregivers of those with high risk</td>
</tr>
<tr>
<td></td>
<td>Chronic lung disease including asthma</td>
</tr>
<tr>
<td></td>
<td>Chronic cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td>On long term follow-up and preceding hospitalisation</td>
</tr>
<tr>
<td></td>
<td>Chronic metabolic disease e.g., Diabetes</td>
</tr>
<tr>
<td></td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td></td>
<td>Neurological disorders</td>
</tr>
<tr>
<td>All</td>
<td>Hepatic disorders</td>
</tr>
<tr>
<td></td>
<td>Hematologic disorders e.g. Thalassaemia</td>
</tr>
<tr>
<td></td>
<td>Immunosuppression</td>
</tr>
<tr>
<td></td>
<td>Medications</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Receiving intermediate and long term care (ILTC) services</td>
</tr>
</tbody>
</table>

LATENT TUBERCULOSIS INFECTION

Disease Burden in Singapore

Tuberculosis (TB) is a major cause of death and disability in many parts of the world especially in developing countries. TB is also endemic in Singapore. In 2012 a total of 2,203 new cases of TB were notified among Singapore residents and long staying foreigners. The incidence rate of TB in Singapore’s total population was 41.4 per 100,000 persons in 2012. Smear positive and smear negative cases formed 30% and 50% of new cases respectively, while extra-pulmonary cases accounted for 14%.

Initial tuberculous infection is usually asymptomatic and goes unnoticed. This is referred to as latent TB infection (LTBI). About 10% of immune-competent adults with LTBI will eventually progress to active disease, and half of these will do so within the first 2 years of infection. The risk of progression is increased in immune-compromised persons and children under 5 years. Thus identification and treatment of individuals with LTBI is an important aspect in the overall management and control of TB.
Risk Factors for Infection and Progression

High risk persons for TB fall into 2 categories:

- Those at higher risk for TB exposure or infection / Increased risk of LTBI.
- Those at higher risk for TB disease once infected / Increased risk of progression from LTBI to active TB.

Increased risk of LTBI:

- Infants, children and adolescents who have close contact with high risk adults.
- Employees of long term care facilities, hospitals, clinics and medical laboratories.
- Foreign-born persons from countries with high prevalence of TB.
- High-risk racial and ethnic minorities, as defined locally.
- Close contacts of those suspected or known to have active TB.
- Residents and employees of congregate living facilities – prisons, nursing homes, hospitals and shelters.
- Birth in TB endemic area.
- Low socio-economic status.

Increased risk of progression from LTBI to active TB:

- Children < 4 years old.
- Infection with Mycobacterium tuberculosis within the last 2 years.
- Injection or use of illicit drugs or other locally high-risk substances.
- Tobacco and alcohol use.
- Untreated or inadequately treated TB including chest radiography findings of previous TB.
- Low BMI.
- Low Vitamin D.
- Iron overload.
- Gastrectomy or intestinal bypass.
- Silicosis.
- Chronic renal failure or end stage renal disease.
- Immuno-compromised conditions:
  - Long term use of cortico-steroids or other immuno-suppressants.
  - Human immunodeficiency virus infection.
  - Diabetes mellitus.
  - Malignancy.

Screening for LTBI

The aim of testing is to identify persons at high risk for TB who would benefit from treatment of LTBI. The decision to screen for TB is thus a decision to treat. LTBI screening is effective in 2 groups of persons – those at risk of contracting TB and those at risk of progressing from LTBI to active TB (reactivation). Routine screening outside these high-risk groups highlighted above leads to high false-positive test rates. The table below shows the criteria for screening:

There are 2 methods currently available for LTBI screening, the traditional tuberculin skin test (TST) or Mantoux test and the more recent interferon-gamma release assays (IGRAs). The TST consists of an intra-dermal injection of tuberculin material which causes an induration in 48-72 hours due to a delayed T-cell mediated hypersensitivity response. Although the test is not expensive, it is operator dependent and affected by previous Bacille Calmette-Guerin (BCG) vaccination.

The IGRAs are an important advance in the diagnosis of LTBI. They are in-vitro blood tests of cell-mediated immune response, which measure the T-cell release of interferon-gamma following stimulation by antigen unique to Mycobacterium tuberculosis. The IGRA that is available here is the QuantiFERON-TB Gold test. The main advantages of the IGRAs over the TST is that they are not affected by the BCG status and do not need a second visit to read the test. They have high specificity (>95%) and good sensitivity (>80%). However, they are very expensive.

Both the TST and the IGRAs are not able to distinguish latent infection from active TB and should not be used to diagnose active TB where they have low sensitivity and specificity.

Treatment of LTBI

All those at risk of LTBI and have tested positive by the TST or IGRA should have a chest x-ray to exclude active pulmonary TB as well as to serve as a baseline for future comparison should symptoms develop. All such persons with a negative chest x-ray should then be offered treatment with a single anti-tuberculous drug as prophylaxis against the development of overt clinical infection.

The regimen of choice is Isoniazid (INH) given daily for 6 to 9 months. INH is generally well tolerated and adverse reactions such as hepatitis, gastro-intestinal disturbances, peripheral neuropathy and rashes are rare. Rifampicin is the alternative of choice in those who are intolerant to INH.

PNEUMOCOCCAL DISEASE

Pneumococcal disease in Singapore

Invasive pneumococcal disease is an acute bacterial infection of the respiratory tract, brain or blood stream caused by Streptococcus pneumonia. It is an important source of morbidity and mortality in young children, older adults and persons with conditions that effect their immune response to bacteria. The mode of transmission is by droplets or close contact with the nasopharyngeal secretions of an infected person.

A total of 163 laboratory confirmed cases of invasive pneumococcal infection were reported in 2012, an increase of 12.2% compared to 2011. Pneumococcal bacteraemia has a mortality rate of 21.4%. In a national study among hospitalised patients between 1995 and 2004, 36% of the cases with pneumococcal disease were below the age of 15 years. While the overall mortality was 3.2%, the figure was much higher at...
8.4% for those above 75 years. Prevention of the disease is thus important in the young and elderly as well as certain high risk persons.

**Pneumococcal vaccination**

**Vaccine Types**

Vaccination aims for a reduction in both pneumococcal pneumonia as well as invasive pneumococcal disease. There are two types of vaccines:

- Pneumococcal polysaccharide vaccine (PPSV23).
- Pneumococcal conjugate vaccine (PCV13).

The PPSV23 consists of purified capsular polysaccharide proteins from 23 pneumococcal types which account for 60-70% of invasive disease in adults. It has been used for adults for some time:

- Reduces the risk of invasive disease as well as invasive and non-invasive pneumococcal pneumonia.
- Is poorly immunogenic in young children.
- Not shown a reduction in all cause pneumonia.

The PCV13 consists of capsular polysaccharide proteins from the 13 most common types that cause disease. PCV13 is covalently linked to a non-toxic protein that renders the polysaccharide more antigenic in infants and toddlers as well as the elderly. The PCV13 is thus recommended for:

- Infants.
- Children.
- The elderly and certain high risk adults.

Medisave use for the pneumococcal vaccination has been allowed since January 2014.

**Indications and vaccination schedules for adults**

Recommendations for the two different vaccines are in accordance with different at risk populations. For immuno-competent persons between 19 to 64 years with certain medical conditions and risk factors (Table 5), the ACIP advises the following:

- A single dose of PPSV23 alone.
- Routine re-vaccination of the PPSV23 is not recommended.
- The PCV13 is not recommended in this group without immune-compromised or specific high risk conditions.

For specific high risk individuals and immune-compromised persons (Table 5), the ACIP recommends sequential dual vaccination of the PPSV23 and the PCV13 according to the following schedule:

- For those that have not previously received either the PCV13 or the PPSV23 (vaccine naive), a single dose of PCV13 should be given, followed by a dose of PPSV23 at least 8 weeks later.
- For those that have previously received one or more doses of the PPSV23, a single dose of the PCV13 should be given one or more years after the last dose of the PPSV23.
- For those high risk patients < 65 years who have received the dual sequential vaccination, a single re-vaccination of the PPSV23 ≥ 5 years after the first dose should be given. In fact, some authorities recommend regular re-vaccination at 5 to 6 year intervals in asplenic patients at particularly high risk of overwhelming pneumococcal infection.
- For those that require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after the PCV13 and at least 5 years after the most recent dose of PPSV23.
For immune-competent adults ≥ 65 years, the previous recommendation was a single dose of PPSV23. However, the ACIP has just recently recommended that all those above 65 years, regardless of immune status, should also receive the dual sequential vaccination as follows:

- For those that have not previously received either the PCV13 or the PPSV23 (vaccine naive), or if the vaccination history is unknown, single dose of PCV13 should be given, followed by a dose of PPSV23 given 6 to 12 months later. The minimum acceptable interval is 8 weeks.
- For those that have previously received one or more doses of the PPSV23, a single dose of the PCV13 should be given one or more years after the last dose of the PPSV23.
- For those whom an additional dose of PPSV23 is indicated (specific high risk or immune-compromised), the subsequent PPSV23 dose should be given 6 to 12 months after the PCV13 and ≥ 5 years after the last dose of PPSV23.

Vaccination in children
For infants, young children and teens, the ACIP recommends the following:

- Between the ages of 2 months to 5 years with no specific high risk conditions, the PCV13 is recommended as part of the routine childhood vaccination. The doses vary according to the age.
- Additional PPSV23 vaccination is recommended in children between 2 months and 5 years with increased risk of pneumonia.
- Pneumococcal vaccination is generally not recommended in normal healthy children above 5 years.
- Vaccination is advised in those from 6 to 18 years with high risk conditions and immunocompromised states using both the PCV13 and PPSV23 very much in accordance to the adult guidelines for similar groups.

Vaccination in children is discussed further in Unit 3.

CONCLUSIONS
FPs are well placed to help in the control of infection in the primary care setting. To aid them in this task, this article has served to update FPs on the current recommendations for
the vaccinations of influenza and pneumococcal disease as well as the screening of LTBI. However, medical knowledge is rapidly evolving and guidelines change from time to time. Therefore recommendations which are current from both local and international organisations, serve to provide the FP with updated tools in infection control.

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LEARNING POINTS

- Family Physicians have an important role to play within the community in the early detection and control of infection and disease. Current local and international recommendations provide FPs with updated tools.
- Indications for vaccinations and early screening of infectious disease vary according to different risk populations and are especially important in the young, the elderly, the immunocompromised and those with specific high risk conditions.