UNIT NO. 6

SEASONAL FLU AND TRAVELLERS VACCINE

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ABSTRACT

International travel continues despite the threat of terrorism, the reality of ward and conflict and the emergence of new diseases.

Seasonal influenza has increasingly been recognised in travellers. Pandemic influenza A (H1N1) has been included in the 2010 Southern Hemisphere trivalent influenza vaccine.

Travellers to foreign countries are often exposed to pathogens that are uncommon in their countries of residence. In preparation for a trip, travellers should be encouraged to seek pre-travel immunization. Required immunizations include yellow fever and meningococcal vaccines. The common recommended immunizations based on risk assessment include typhoid, hepatitis A and Japanese encephalitis vaccines.

Keywords: Seasonal influenza, pandemic, recommended required, immunization

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INTRODUCTION

The number of travellers crossing international borders has declined worldwide by 4% in 2009 to 880 million[1]. This has been the result of the global economic crisis and the uncertainty of pandemic influenza A (H1N1).

However, travel continues despite the threat of terrorism, the reality of war and conflict and the emergence of new diseases such as severe acute respiratory syndrome and avian influenza A (H5N1).

Influenza infection has been increasingly recognised in travellers. Therefore, influenza vaccine is considered one of the recommended travel-related vaccines.

SEASONAL INFLUENZA VACCINES

Influenza is an acute febrile respiratory illness caused by influenza type A or B viruses that occur in outbreaks and epidemics every year, usually in the winter.

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The World Health Organisation through its Global Influenza Surveillance Network (GSN) tracks influenza virus isolates throughout the world to monitor disease activity and predicts the appropriate influenza viruses to be included in the seasonal influenza vaccine in February and September for the Southern and Northern Hemisphere winters respectively.

Antigenic Variation

Influenza virus is unique for the frequency with which changes in its antigenicity occur. This is referred to as antigenic variation. This viral evolution compromises the ability of the immune system to protect against the new variants[2].

Antigenic variation involves the two envelope glycoproteins of the virus, hemagglutinin (HA) and neuraminidase (NA) and is referred to as antigenic drift or antigenic shift. Major changes in these glycoproteins are referred to as antigenic shifts and minor changes as antigenic drifts. Antigenic shifts are associated with epidemics and pandemics whereas antigenic drifts are associated with more localised outbreaks.

Influenza A viruses that infect humans have three major subtypes of hemagglutinins (H1, H2 and H3) and two subtypes of neuraminidase (N1 and N2). Influenza A viruses have a remarkable ability to undergo periodic changes in the antigenic characteristics of these glycoproteins. Influenza B viruses have a lesser propensity for antigenic changes and only antigenic drifts in hemagglutinin have been described.

The World Health Organisation has recommended that vaccines for use during the 2010 influenza season in the Southern Hemisphere include:

- An A/California/7/2009 (H1N1)-like virus (against pandemic H1N1 influenza)
- An A/Perth/16/2009-like virus
- A B/Brisbane/60/2008-like virus

Seasonal Influenza Vaccine

There are 2 types of influenza vaccines:

(i) trivalent inactivated vaccine (TIV):- whole virus or sub-virion components (split product) administered intramuscularly. Split product vaccines cause fewer adverse reactions and are preferred for use in children ≤ 12 years of age.

(ii) Trivalent live-attenuated influenza vaccine administered intra-nasally (LAIV). This vaccine uses a master attenuated cold-adapted (CA) denor virus from which reassortants are generated that have H and N antigens from currently circulating strains. This vaccine is not registered for use in Singapore.

The efficacy of the 2 available types of influenza vaccines ranged from 50% to 90%[4,5]. The protective efficacy of the vaccine is largely determined by the relationship (closeness of "fit" or "match") between the vaccine strains and viruses that circulate in an outbreak[6].

General Recommendations

The rational for immunization is that elderly individuals and with underlying health problems are at increased risk of complications of influenza. The Advisory Committee on Immunization Practices (ACIP) advocates vaccinating adults at high risk for influenza-related complications[7].

The target groups for seasonal influenza vaccination include[7]:

- Persons 50 years of age and older
- Residents of nursing homes and chronic care facilities that house persons of any age who have chronic medical conditions
- Anyone 6 months of age or older with chronic diseases such as pulmonary diseases including asthma, cardiovascular disease including congestive cardiac failure, active malignancy, chronic renal insufficiency, chronic liver disease, diabetes mellitus, hemoglobinopathies and immunosuppression including HIV infection (CD4<200 cells/mg).
- Adults with neurologic conditions that can compromise handling of respiratory secretions, cognitive dysfunction, spinal cord injuries, seizure disorders and neuromuscular disorders
- Pregnant women
- Healthcare workers, workers at long term care facilities and household contacts of persons in high risk groups.
- Children aged 6 – 24 months.

Annual vaccination is recommended even if the previous year's vaccine contained one or more of the antigens to be administered because immunity declines during the year following vaccination.

A 2008 review of literature, which included studies of individuals > 60 years old, found that seroprotection was maintained for at least 4 months after influenza vaccination in all 8 studies that assessed antibody responses to H3N2 component and in 5 of 7 studies that assessed responses to H1N1 and B components. Seroprotection rates were maintained for up to or longer than 6 months for the H3N2 and H1N1 components[8].

Pandemic Influenza A (H1N1)

In March 2009, an outbreak of influenza A (H1N1) infection was first detected in Mexico, with subsequent cases reported in many other countries worldwide[9]. On June 11, 2009, the World Health Organization (WHO) raised the influenza pandemic alert to phase 6 indicating widespread community-transmission in multiple areas of the world[10].

The signs and symptoms of novel influenza A (H1N1) virus are similar to those of seasonal influenza. Definitive diagnosis of novel influenza A (H1N1) virus infection requires specific testing for H1N1 viruses using real-time reverse transcriptase polymerase chain reaction or viral culture[11,12].

Vaccines against pandemic influenza A (H1N1) virus infection are being produced using methods similar to those for seasonal influenza vaccines. Both adjuvanted and non-adjuvanted formulations of vaccine are available. Adjuvant helps to improve immune responses to the vaccine, although it can sometimes increase local side effects[13,14]. The adjuvant can also allow a lower dose of antigen to be used.

There are no published data on the efficacy of H1N1 influenza vaccine. Studies of the immunogenicity of H1N1 influenza-vaccine evaluate the proportion of persons who achieve certain endpoints such as antibody titre of 1:40 or greater on either haemogglutination-inhibition assay or the microneutralization assay or a four-fold or greater increase in geometric mean titre (GMT) antibodies[15,16]. Several studies suggest that immunogenicity is retained if pandemic and seasonal influenza vaccines are co-administered[17].

Recommended Use of Influenza A (H1N1) Vaccine

ACIP recommends that the following 5 target groups receive the H1N1 influenza vaccine[18].

- pregnant women
- persons who live with, or provide care for infants < 6 months
- healthcare and emergency medical services personnel
- persons aged 6 months – 24 years
- persons aged 25-64 years with medical conditions associated with increased risk of influenza complications

In January 2010, CDC recommended that H1N1 influenza vaccine be given to all patients aged 6 months and older because of increased vaccine supplies and severe illness and deaths had occurred in patients > 65 years of age.

Infants and children aged 9 years or younger should receive 2 doses of H1N1 influenza vaccine at least 21 days apart and individual ≥ 10 years of age should receive one dose.

TRAVELLERS VACCINE

Travellers to foreign countries are often exposed to pathogens that are absent or uncommon in their countries of residence. In addition, the likelihood of becoming infected with familiar pathogens while travelling is greater than during daily life at home.

In preparation for a trip, travellers should be encouraged to seek pre-travel medical advice preferably 4 to 6 weeks before departure. This allows sufficient time for immunizations to be scheduled and tests of immunity to be performed. Up to date information on diseases in the destination country are provided at recognized sources such as the Centers for Disease Control and Prevention (CDC) website, www.cdc.gov/travel or the World Health Organisation's International Travel and Health website : www.who.int/ith. The common travel specific vaccines are listed in table 1.

Required Immunizations

Yellow Fever

Yellow fever is the only immunization legally required for entrance into specific countries.

Yellow fever is a potentially fatal mosquito-borne flu viral infection endemic in equatorial Central Africa and in areas of South America. Mosquitoes capable of transmitting yellow fever exist in regions where the disease does not presently occur and in regions, such as Asia, where it is has never occurred.

Yellow fever vaccine is an attenuated live virus vaccine, derived from 17D strain and is grown in chick embryo. Vaccination against yellow fever produces high levels of protection, with seroconversion rates of >95% in children and adults and duration of immunity of ≥ 10 years[20]. Ninety per cent of vaccines develop neutralizing antibody within 10 days of immunization and 99% develop neutralizing antibody within 30 days. International health regulations recommend revaccination at 10-year intervals for those who remain at risk.

Rare (~0.5/100,000 doses) complications such as viscerotrophic disease YEL-AVD (resembling wild-type yellow fever resulting in multi-organ failure) and neutrophic disease YEL-AND (causing post-vaccination encephalitis). These serious adverse events have been shown to occur more frequently in persons aged ≥ 60 and in those with thymic dysfunction[21]. Yellow fever vaccine should not be given to infants < 6 months, immuno-suppressed individuals (including symptomatic HIV infection) and pregnant females. Yellow fever vaccine must be given at official yellow fever vaccine centres and documented with an International Certificate of Vaccination.

Meningococcus

All travellers to Saudi Arabia during Hajj and Umrah are required to have a certificate of vaccination with tetravalent (A, C, Y, W-135) meningococcal vaccine.

Meningococcal disease is low risk to most travellers except those travelling to epidemic and endemic regions, particularly sub-Saharan Africa between December and June.

Meningococcal disease has mortality around 10%, with 11-19% suffering from permanent sequelee[22]. Transmission is by respiratory droplets from nasopharynx of infected persons. Transmission is highest in areas such as military recruits dormitories, refugee camps and the Hajj pilgrimage[23]. Meningococcal disease are classified into serogroups, A, B , C, X, Y and W-135. Serogroups A, B and C account for the majority of cases worldwide. In recent years, serogroups W-135, X, Y and Z have emerged as pathogens.

Polysaccharide vaccines against groups A, C, Y and W-135 (MPSV4) are most widely available formulation. Protective antibody levels against all 4 serogroups are achieved within 10-14 days. The duration of protection is 1-3 years in children

Table 1 Travel-specific vaccines

Vaccine	Type	Administration	Booster	Adverse effects
Yellow fever	Live attenuated YF 17D strain	0.5mls sc x 1 dose	10y	25% local reaction at vaccine site Rare: hypersensitivity, neurotrophic and viscerotropic complications
Typhoid fever	• Vi S. typhi purified capsule polysaccharide	0.5mls 1m x 1 dose	3y	<7% fever, headache local pain at vaccine site
	• Vivotif – live attenuated Ty 21a strain	1 cap eod x 3 doses		<5% fever, headache abdominal discomfort, nausea, vomiting
Japanese encephalitis (JE virus)	• Inactivated (mouse-brain derived) vaccine	1.0ml sc x 3 doses Day 0,7,30 or Day 0,7,14	2y	20% local reaction at vaccine site 10% fever, headache, myalgia 0.5% immediate and delayed hypersensitivity
	• Ixiaro-inactivated verocell derived SA-14-14-2	1.0mls 1m x 2 doses 0, 28	Unknown	20% headache, myalgia injection site reactions 10% rash, nausea
Hepatitis A	Inactivated Hepatitis A virus	1.0mls 1m x 2 doses 0,6 to 12 months	0	50% pain at injection site 15% headache
Meningococcal	• Meningococcal polysaccharide vaccine, quadrivalent (A,C,Y,W-135)	0.5ml sc x 1 dose	3y	Pain and redness at injection site
	• Meningococcal conjugate vaccine, quadrivalent (A,C,Y,W-135)	0.5ml sc x 1 dose		

< 3 years and 3-5 years in adolescents and adults. Unfortunately, serogroup C is poorly immunogenic and ineffective in children under 2 years of age.

Immunogenicity of polysaccharide vaccines can be improved by chemical conjugation to a protein carrier, thereby eliciting a T-cell dependent antibody response.[24] Quadrivalent meningococcal conjugate vaccine (MCV4) has been approved for use in Canada (age group 2-55 years) and USA (age group 11-55 years).

Recommended Immunizations

Typhoid

Salmonella enterica typhi infection is prevalent in many areas of Asia, Africa and Latin America. Multi-drug resistant strains of S typhi are widespread throughout the world including India and parts of Southeast Asia[25]. The risk of acquiring typhoid during travel remains low (6.1 cases per million travellers) but increases for those travelling to the Indian subcontinent (105 to 118 cases per million travellers)[26].

Typhoid vaccine should always be considered for travel to endemic areas, and recommended for stays > 2 weeks. There are 2 vaccines licenced in Singapore:

1) The Vi capsular polysaccharide vaccine for parenteral use. Primary vaccination consists of one 0.5ml administered intramuscularly. It can be to children two years of age and older. It is well tolerated and is safe for immuno-compromised individuals, including HIV-infected patients. Booster doses are administered every two years.
2) The oral live attenuated vaccine that uses Ty21a strain of S. typhi (Vivotif Berna). The vaccine is approved for those six months of age and older. It is supplied as a packet of 3 enteric-coated capsules that must be kept refrigerated. Primary vaccination consists of a total of 3 capsules, one taken every other day. Use of antimicrobials including the antimalarial agents, proguanil and atovaquone should be avoided for at least 24 hours before starting and 7-10 days after completing Vivotif.

Both vaccines have been shown to protect 50% to 80% of recipients.

Hepatitis A

Hepatitis A is prevalent in many developing countries. Transmission of this RNA picornavirus occurs by fecal contaminations of water or food in visitors to developing countries. The incidence of hepatitis A in unprotected travellers is about 3 per 1000 travellers per month of stay, and the rate rises to 20 per 1000 travellers per month for those eating or drinking under poor hygienic conditions[27,28].

Hepatitis A vaccine is recommended for all susceptible persons travelling or working in countries with intermediate or high endemicity of hepatitis A infection. One single dose of Hepatitis A vaccine administered at any time prior to departure provides adequate protection for healthy individual ≤ 40 years. A second dose of vaccine 6 to 12 months after the first dose promotes long-term protection. Once after receiving the first dose of hepatitis A vaccine, 94-100% of adults and children will have protective antibody. If immunization schedule is interrupted, the second dose can be given without restarting the series. A vaccination series started with one brand may be completed with the same or other brand of hepatitis A vaccine.

An alternative is Twinrix (GlaxoSmithKline), a combined hepatitis A and hepatitis B vaccine. Primary immunization consists of three doses administered at 0, 1 and 6 months.

Japanese B Encephalitis (JE)

Japanese encephalitis is a mosquito-borne flaviviral encephalitis that is endemic throughout much of tropical east Asia. Case fatality rate can be as high as 30%. Neuropsychiatric sequelae are reported in 50% survivors. The vector, Culex vishnui complex, is present in greatest density from June through September. Swine and certain species of wading birds are the amplifying hosts in an enzootic transmission cycle. JE transmission occurs mainly in rural agricultural locations where flooding irrigation is practiced.

The risk for short-term travellers and those who travel to urban centres is low. Expatriates and long-term traveller (> 4 weeks) in rural areas are at greatest risk.

An inactivated JE vaccine produced from infected mouse brains has been licenced for use since 1990. JE vaccine is usually given in 3 doses over a 1 month period or an accelerated 2 week schedule (0, 7 and 14 days) if travel is imminent. Neutralizing antibody titres with this shorter schedule are significantly lower although seroconversion rates among recipients are similar[29]. The longevity of JE neutralizing antibody is unknown, but seems to be at least 2 years. There is a 0.5% incidence of delayed vaccine associated hypersensitivity reactions. It is recommended for use in children older than 3 years and adults.

A new inactivated JE vaccine derived from Verocell culture of the strain SA-14-14-2 (Ixiaro, Novartis). If it met and exceeded immunogenic efficacy in phase 3 trials in 2007[30]. The primary vaccination consists of two doses given intramuscularly 28 days apart. Persistence of immunity is unknown and the timing of booster is still under investigation. It is not recommended for use in children and adolescents.

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LEARNING POINTS

- **CDC recommended that H1N1 influenza vaccine be given to all patients aged 6 months and older.**
- **Infants and children aged 9 years or younger should receive 2 doses of H1N1 influenza vaccine at least 21 days apart and individual ≥ 10 years of age should receive one dose.**
- **Yellow fever vaccine should not be given to infants < 6 months, immuno-suppressed individuals (including symptomatic HIV infection) and pregnant females.**
- **Meningococcal disease is low risk to most travellers except those travelling to epidemic and endemic regions, particularly sub-Saharan Africa between December and June.**
- **The risk of Japanese encephalitis for short-term travellers and those who travel to urban centres is low. Expatriates and long-term traveller (> 4 weeks) in rural areas are at greatest risk.**