UNIT NO. 5

TRAVEL MEDICINE IN PRIMARY CARE

A/Prof Oh May Lin Helen

ABSTRACT

International travel is growing despite economic and geographical challenges. Travellers should seek pre-travel advice 4 to 6 weeks before departure. Required immunisations include yellow fever and meningococcal vaccines. The common recommended immunisations are based on risk assessment. These include typhoid, cholera, hepatitis A, Japanese encephalitis and rabies vaccine.

Common illnesses in returned travellers are mainly due to gastrointestinal diseases, febrile diseases and dermatologic diseases. Evaluation of the travel-related illness requires an understanding of geographical distribution of infections, risk factors for transmission of infection, incubation periods of common infections, clinical presentation and appropriate laboratory investigations. Syndromic approach to the evaluation of illness in a returned traveller is important for post-travel diagnosis.

Keywords: Required, Recommended, Immunisation, Travel-related, Illness, Fever

SFP2014; 40(1): 33-38

TRAVEL VACCINE

International travel is growing. According to the World Tourism Organisation the number of international tourist arrivals grew by 5% in 2013 reaching 1057 million arrivals despite economic and geographical challenges[1].

Travellers should seek pre-travel medical advice preferably 4 to 6 weeks before departure. Immunisation needs are based on the traveller's prior immunisations, health conditions, risk of infections exposures while travelling and the countries to be visited. Up to date information on diseases in the destination countries are provided at recognised sources such as the Centres for Disease Control and Prevention (CDC) website www.cdc.gov/travel and the World Health Organisation's is International Travel and Health website, www.who.int/ith

The common travel Immunisation are listed in Table 1.

Required Immunisations

Yellow Fever

Yellow fever is the only immunisation legally required for entrance into specific countries. Yellow fever is a viral infection transmitted by Aides aegypti mosquitoes in equatorial Africa and South America[2].

OH MAY LIN HELEN, Head & Senior Consultant, Division of Infectious Disease, Changi General Hospital

Mosquitoes capable of transmitting yellow fever exist in regions where the disease does not presently occur and in regions where it has never occurred. Yellow fever vaccine is a live attenuated virus vaccine derived from 17D strain and is grown in chick embryo. The vaccine leads to seroconversion rates of 95% or higher and duration of immunity is 10 years.

The Strategic Advisory Group of Experts on immunisation (SAGE) had reviewed the latest evidence and concluded that a single dose of vaccination is sufficient to confer life-long immunity against yellow fever[3]. This has yet to be incorporated into the International Health Regulations.

Yellow fever vaccine should not be given to immuno-compromised individuals (including HIV with CD4<200/ml), infants age <6months, allergy to eggs and gelatin and thymic disorders. Rare complications such as viscerotrophic disease YEL – AVD (resembling wild type yellow fever resulting in multi-organ failure) and neurologic disease YEL–AND (causing post vaccination encephalitis). These serious adverse events have been shown to occur more frequently in persons aged ≥60 years and in those with thymic disorders[2]. Yellow fever vaccine must be given at official yellow fever vaccine centres and documented on an International Certificate of Vaccination Prophylaxis (ICVP). If YF vaccine administration is contraindicated, the traveller can be provided with a Medical Letter of Waiver.

Meningococcal vaccine

Since 2003, 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 meningitis is a serious bacterial infection transmitted by large droplet respiratory secretions with high mortality of around 10%. Meningococcal disease is low risk to most travellers except those travelling to epidemic and endemic regions, particularly sub- Saharan Africa during the dry seasons from December through June. Transmission is highest in areas such as military camps, dormitories and refugee camps. Meningococcal disease are classified into serogroups A, B, C, X, Y, W-135 and Z. 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.

There are 2 types of meningococcal vaccine[4]:

a) Quadrivalent meningococcal polysaccharide vaccine (MPSV4/Menomune) which has been around since 1980s. Protective antibody levels against all 4 serogroup are achieved within 10-14 days. The duration of protection is 1 to 3 years in children <3 years and 3 to

5 years in adolescents and adults. Serogroup C is poorly immunogenic and is ineffective in children under 2 years of age.

b) Quadrivalent meningococcal conjugate vaccine (MCV4/ Menactra)– chemical conjugation of a meningococcal capsular polysaccharide to a protein carrier elicits a T-cell dependent antibody response. MCV4 has been approved for use in Canada (age group 2-55 years) and USA (age group 11-55 years).

Recommended Immunisation

Typhoid

Typhoid fever is a systemic bacterial infection with faecal–oral transmission. It is prevalent in Asia, Africa and Latin America. Multi- drug resistant strains of S. typhoid has been endemic in most parts of Southeast Asia and the Indians subcontinent for many years[5]. Overall it has been estimated that incidence of typhoid among travellers to developing countries is 3-30 cases per 100,000 travellers.

Typhoid vaccine should be considered for travel to endemic areas and for stays >2 weeks. The only licensed vaccine available in Singapore is Vi capsular polysaccharide vaccine. Primary vaccination consists of one 0.5ml intramuscular injection. A booster dose is required 3 years later. It can be safely given to children 3 years and older and is safe for immune-compromised individuals. The vaccine has been shown to protect 50% - 80% of recipients.

Hepatitis A

Hepatitis A is a RNA picornavirus transmitted by faecal oral route. The incidence of hepatitis A in travellers to countries of high or intermediate risk was 3 to 11 per 100,000 person per month abroad and incidence for non-immune traveller was 6 to 28 per 100,000.

Hepatitis A vaccine is recommended for all susceptible persons travelling or working in countries with intermediate or high endemically of hepatitis A virus. One single dose of hepatitis A vaccine, an inactivated HAV vaccine, administered at any time prior to departure provides adequate protection for healthy persons aged <40years[8]. A second dose of vaccine 6 to 12 months after the initial dose provides longer term protection for >20years. After receiving the first dose of hepatitis A vaccine, 94 -100% of adults and children will have protective antibody. If immunisation schedule is interrupted, the second dose can be given without restarting the series. A vaccination series started with one brand of vaccine may be completed with the same or other brand of hepatitis A vaccine. A hepatitis A/B combination vaccine (Twinrix Glaxo Smith Kline Biologicals) is an alternative vaccine. Primary immunisation consists 3 doses given at 0, 1 and 6 months.

Cholera

Cholera is a severe diarrhoeal illness caused by gram negative bacillus, Vibrio cholerae. There is no WHO regulation requiring cholera vaccine for entry into any country.

There is only one oral cholera vaccine available in Singapore, the inactivated whole cell/B submit (WC/rBS) Dukoral. It is given as 2 oral doses, 7-14 days apart to person ≥ 2 years of age. Protective efficacy ranges from 50 to 80%. It offers some protection against travellers' diarrhoea due to antibodies elicited against cholera B submit toxin cross – reacting with the heat – labile toxin secreted by enterotoxin E coli[9].

Japanese Encephalitis

Japanese encephalitis is a mosquito borne flavivirus encephalitis that is endemic throughout most of Asia and parts of the western Pacific. Case fatality rate can be as high as 30%. Neuropsychiatric sequelae are reported in 50% of survivors. Pigs and some species of wading birds are natural reservoirs of the virus, while the vector, Culex mosquitoes, breed extensively in flooded rice fields and irrigation projects.

The risk for JE among persons from non-endemic countries travelling to Asia is less than 1 case per 1 million travellers. Recurrent travellers or travellers on brief trips might be at increased risk of they have extensive out door or night time exposure in rural areas during periods of active transmission. An inactivated JE vaccines produced from infected mouse brains has been licensed for use since 1990.The Green Cross JE vaccines is not licensed for use in Singapore but distributed on an exempt basis. Primary immunisation consists of 3 doses administered on 0, 7 and 14 days. A booster may be given 2-3 years after primary immunisation for continued risk of exposure. There is a 0.5% incidence of hypersensitivity reactions (namely urticarial and/ or angioedema). It may occur after any of the 3 doses and may be delayed for up to 2 weeks after the vaccine dose.

A new inactivated JE vaccine is derived from AS 14-14-2 strain JE virus and cultured in Vero cell tissue cultures (Ixiaro, Novartis). The primary vaccination consists of 2 doses given intramuscularly 28 days apart and a booster one year later. It is approved for use in person aged > 17 years[10].

In Oct 2013, the first JE vaccine was prequalified by WHO for use in children ≥ 9 months old[11]. This SA 14-14-2 live attenuated JE vaccine (CD.JEVAX) is manufactured by Chengdu Institute Biological Products. The primary vaccination consists of a single dose 0.5ml subcutaneous injection and a booster 3 to 12 months later.

Rabies

Rabies is a viral disease transmitted by animal bites (especially dog bites), that leads to encephalopathy and death. Rabies is endemic in Africa and Asia Pre-exposure rabies immunisation is recommended for travellers to remote and rural areas and expatriate workers living in countries where rabies is a recognised risk. Pre-exposure vaccination consists of three 1 ml intramuscular doses on days 0, 7 and 21 or 28.

Table 1: Travel Immunisation

Vaccine	Type	Dose/Schedule	Booster	Adverse Effects
Yellow Fever	Live attenuated YF 17D strain	>9months sc0.5mls x 1 dose	10yrs Single dose sufficient to provide lifelong immunity (SAGE 2013)	25% local reaction at vaccine site Hypersensitivity to eggs or gelatin. 1 in 131,0000 vaccinations Neurotropic and viscerotrophic complications rare.
Meningococcal	• Meningococcal polysaccharide vaccine Quadrivalent (A,G,Y,W135) (Menomune)	sc 0.5ml x 1 dose	5y if first dose given at ≥ 7yrs 3y of first dose given at 2-6yrs of age	
	• Meningococcal. Conjugate vaccine quadrivalent A,C,Y,W-135) (Menomune)	≥2yrs – 55yrs: 1m 0.5ml x 1 dose 9 – 23months: 2 dose 3 months apart	5y	
Hepatitis A	Inactivated Hepatitis A vaccine Havrix(GSK)	2y-18y im 0.5mls (720 ELU) >18y: im 1.0ml 2 doses 0, 6-12mths		50% pain at injection site 15% headache
	Avaxim	≥16y: im 5ml 2 doses, 0, 6-12mths		
Typhoid	Vi S Typhi purified capsule polysaccharide	im 0.5mls x 1 dose	3y	< 7% fever, headache, local pain of injection site
Cholera	Inactivated (WC/rBS) – Dukoral also protection against ETEC heat labile toxin (travellers'diarrhoea)	Oral 2 doses one wk apart	6 months (children 2-6yrs) 2years (>6y)	Diarrhea, abdominal pain, nausea
Japanese Encephalitis (JE vaccine)	• Inactivated vaccine SA14-14-2 strain (Ixiaro, Novartis)	>3yrs – adult im 1.0mls x 2 doses, day 0, and 28	1y after completion of primary series if on-going risk	Pain swelling at injection site, headache and myalgia
	• Live attenuated vaccine. SA 14-14-2 strain (CD. JEVAX)	Children ≥ 9 months to adults Sc 0.5 ml	3 – 12 mths	Fever, rash, nausea, crying, drowsiness or sleep problem (children)
	• Inactivated (mouse brain derived) JE vaccine (Green Cross)	im 1.0ml (aged ≥3y x 3 doses) im 0.5ml (aged ≤3y x3 doses) Day 0, 7, 14 days or 0,7,30 days	2y	20% erythema, tenderness and swelling at injection site 10% fever, headache myalgia, gastrointestinal symptoms. Allergic-hypersensitivity reactions (urticaria angioedema)
Rabies	Purified inactivated rabies vaccine Wistar Rabies strain prepared on VERO cells (Verorab)	im 0.5ml x 3 doses at 0, 7, 21 or 28 days	1y after primary vaccination and thereafter every 5 yrs	Local redness swelling at site of injection site, mild fever, nausea and muscle aches
	Purified chick embryo cell vaccine (PCEC) (Rabipur)	im1ml x 3 doses at 0,7 21 or 28 days	2y	Pain, redness and swelling of injection site, fever, headache myalgia, lymph node swelling

Without pre-exposure immunisation, the bitten person requires treatment with rabies immunoglobulin. (20IU/kg human RIG and 40IU/kg for equine RIG) and series of 4-5 dose of tissue culture derived rabies vaccine. For a bitten person who has received pre-exposure immunisation, two additional vaccine doses on days 1 & 3 are recommended. The rabies vaccine is an inactivated virus vaccine and there are 2 formulations available in Singapore. Human diploid cell vaccine (HDCV) and purified chick embryo cell vaccine (PCEC)[12].

ILLNESS IN THE RETURNED TRAVELLER

International travel has increased over the past decade with international tourist arrivals worldwide exceeding the one billion mark for the first time 2012[13]. Travel frequency has also increased for persons with co-morbid conditions, those travelling for business or visiting friends and relatives[14].

Up to 70% of travellers to developing countries report health problems, the majority of which are self-limiting; 8-15% of travellers are ill enough to seek medical advice while abroad or on returning home[15]. In the GeoSentinal Surveillance of

illness in returned travellers 2007-2011, these quarters of travel related illness was due to gastrointestinal disease (24%), febrile (23.3%) and dermatologic (19.5%) diseases[16]. Most physicians and general practitioners will encounter the returned traveller with fever which is a common symptom in those returning from the tropics[17] (Table 2).

Evaluation of fever in returned traveller requires an understanding of the geographical distribution of infections, risk factors for transmission of infections; incubation periods for travel related infections, clinical presentation and appropriate laboratory investigations.

In another report from GeoSentinal Surveillance specifically evaluating fever 28% of 24920 ill-returned travellers cited fever as a chief reason for seeking care between 1997and 200618. 35% had a febrile systemic illness; the 2 most common diagnosis were malaria (21%) and dengue (62%). 15% had febrile diarrhoeal disease and 14% had febrile respiratory illness.

History

A detailed travel history is essential; establishing the geographic region of travel, the dates of travel, duration of stay, types of accommodation, activities and exposures. Co-morbidities, pre-travel vaccinations and malaria chemoprophylaxis can affect the susceptibilities, to infection. Good resources that provide current information about infections in different geographic areas include Health Information for International Travel, Centres for Disease Control and Prevention (CDC) and International Travel and Health, World Health Organisation (WHO).

The time of the onset and duration of symptoms are important. Most tropical infections become symptomatic within 21 days of exposure (Table 3) and the majority of febrile returning travellers present within one month of leaving the endemic areas[18].

Table 2: Diagnosis among ill-returned travellers

Diagnosis	No of patients (%)	
	Freedman et al[17] n = 17353	Leder et al[16] n = 42,173
Gastrointestinal	5280 (30.43)	3651 (8.66)
- Acute diarrhoea	- 3859	
- Non-diarrhoea disorders	- 1421	
Febrile illness	3907 (22.51)	5716 (13.56)
Dermatologic	3947 (16.98)	2611 (6.19)
Respiratory		639 (1.52)
Neurologic		109 (0.26)
Others		1036 (2.46)

Table 3: Incubation periods for common infections

Disease	Usual incubation period	Geographic distribution
Incubation period <14 days		
Dengue	3 – 14 days	Tropics, subtropics
Chikungunya	1 – 14 days	Tropics, subtropics
Encephalitis (Japanese encephalitis - JE, Tickborne encephalitis, West Nile virus)	1 – 20 days	Asia (JE), Europe (Tickborne), Africa, Europe, Southwestern Asia, North America (West Nile)
Typhoid Fever	3 – 60 days	Asia, Africa, Central and South America
Acute HIV	10 days – 6 weeks	worldwide
Influenza	2 – 5 days	worldwide
Legionellosis	2 – 10 days	widespread
Leptospirosis	2 – 26 days	widespread, especially tropics
Malaria (P. falciparum)	6 – 30 days	Tropics, subtropics
Maleria	6 days – 12 months	Tropics, subtropics
Shigella	12 hrs – 4 days	Tropics
Incubation period 14 days to 6 wks		
Encephalitis, typhoid fever, acute HIV, leptospirosis, malaria	Refer above	Refer above
Amoebic Liver abscess	weeks to months	Developing countries
Hepatitis A	15 – 50 days	Developing countries
Hepatitis E	2 – 9 weeks	Asia, Mexico, Middle East, Africa
Acute schistosomiasis	4 – 8 weeks	Tropics, subtropics
Incubation period > 6 weeks		
Amoebic liver abcess, Hepatitis E, Maleria, acute schistosomiasis	Refer above	Refer above
Hepatitis B	50 – 150 days	Widespread
Visceral Leishmaniasis	10 days – years	Asia, Africa, Latin, America Middle East
Tuberculosis	Weeks to years	Global Distribution

Physical examination

The physical examination should include evaluation for jaundice, skin rashes, lymphadenopathy, enlargement of liver and/or spleen, genital lesions, signs of pneumonia, genital lesions and neurological findings.

Signs requiring urgent intervention include:
- Haemorrhagic manifestations.
- Respiratory distress.
- Hypotension.
- Confusion, drowsiness, stiff neck or focal neurologic findings.

Laboratory tests

The initial work-up of a febrile patient should include[7] full blood count, liver function test and urea electrolytes and creatinine, blood cultures (2 sets), blood films for malarial parasites (3 specimens), urinalysis and urine culture, stool culture, stool for ova and parasites and chest radiograph. Other tests to consider depending on physical examination and exposure history include serologic tests. (Widel Weil-felix, leptospiral antibody, rickettsial serology, amoebic serology, hepatitis A, B and C serologies) Blood film for microfilaria, cerebrospiral fluid for microscopic examination and culture, sputum culture, urinary, legionella and pneumococcal antigen, ultrasound scan, MRI or CT scan.

Differential Diagnosis

Routine causes of febrile illness should be considered together with tropical infections in returned traveller presenting with fever. The differential diagnosis for travel related infections should include those with a worldwide distribution, common infections occurring in developing countries and infections with focal geographic distribution such as malaria.

The most life threatening infections include P falciparum malaria, dengue and melioidosis[4]. Syndromic approach to differential diagnosis may be used in evaluating fever in a traveller returning from developing countries[19,20] (Table 4).

Table 3: Possible causes of febrile syndrome

Syndrome	Possible causes
Systemic febrile illness with non-specific symptoms	Malaria Typhoid fever Rickettsial disease (scrub thypus) Acute HIV infection Leptospirosis
Fever with skin rash	Dengue Measles Varicella Rickettsial disease Typhoid fever Panovirus B19 Mononucleosis Acute HIV infection Meningococcal disease
Fever and central nervous system involvement	Meningococcal meningitis Cerebral Malaria Arboviral encephalitis (Japanese encephalitis, West Nile virus) Rabies African trypanosomiasis
Fever with respiratory complaints	Influenza Bacterial pneumonia Acute histoplasmosis Legionella pneumonia Q fever Malaria Tularemia Pneumonia plague
Fever and eosinophilia	Acute schistosomiasis Strongyloidiasis hyperinfection Fascioliasis Filariasis Other parasitic infections eg hook worm, Ascaris lumbricordis, trichinosis Drug hypersensitivity reaction Auto immune disorders e.g. SLE
Fever and Jaundice	EBV CMV Hepatitis A - E Enteric fever (typhoid, paratyphoid) Leptospirosis Severe P falciparum Typhus Viral haemorrhagic fever Haemolytic – uremic syndrome (E Coli, Shigella)

REFERENCES

1. World Tourism Organisation (UNWTO) World Tourism Barometer. Available at www.unwto.org/barometer. Assessed 9 Feb 2014.
2. Staples UE, Gresham M, Fischer M, Center for Disease Control and Prevention (CDC). Yellow fever vaccine; Recommendations of the Advisory Committee on Immunization Practices (ACIP) MMWR Recomm Rep 2010, 59:1.
3. Vaccines and vaccination against yellow fever. WHO position paper – June 2013, Wkly Epidemol Rep 2013, 88:269
4. John AC, MacNal JR, Clark TA, Otega-Sachez JR, Briere EZ. Centre for Disease, Prevention and Control (CDC). Prevention and control of Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP) MMWR Recomm Rep 2013;62.
5. Cooke FJ, Wain J. The emergence of antibiotic resistance in typhoid fever. Trav Med & infect Dis 2004. 2, 67-74.
6. Steffen R, Richeribach M Wilhelm. U, Helminger A, Schar M. Health problems after travel to developing countries. J Infect Dis 1987156: 84-91.
7. Mutsch M, Spicher VM, Gut C, Steffen R. Hepatitis A virus infections in travellers 1988-2004 – Clin Infect Dis 2006, 42:490-7.
8. Advisory Committee on Immunization Practices (ACIP) Centre for Disease control and Prevention (CDC). Update: Prevention of hepatitis A after exposures to hepatitis A viruses and in international travellers. Updated recommendations of the Advisory committee on Immunization Practices (ACIP). MMWR Rep 2007; 56:1080.
9. Cholera vaccine: WHO position paper. Wkly Epidemiological Rep 2010;85;117-28.

10. Fischer M; Lindsey N, Staples JC, Hills S., Japanese Encephalitis Vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP) MMWR Rep 2010, 59, 1-27.

11. Newly accessible Japanese encephalitis vaccine will make saving children easier in developing countries. http://www.who.int/mediacentre/news/releases/2013/japanese_encephalitis_20131009/en/ .Accessed on 25 March 2014.

12. Manning SE, Rupprechr CE, Fishbein D, Hanlon CA, Lumiertokcha IB et al. Human Rabies protection- United State 2008. Recommendations of the Advisory Committee in Immunization Practices. (ACIP) MMWR Rep. 2008 , 57, RR-3

13. World Tourism Organisation (UNWTO), World Tourism highlights 2013 Edition. http://mkt.unwto.org/publication/unwto-tourism-highlights-2013-edition. Accessed on 25 March 2014.

14. LaRocque RC, Rao SR , Lee J, Ansdell V, Yates JA, Schwartz BS et al (Global TravEpiNet) Consortium. Global TravEpiNet a national consortium of clinics providing care to international travellers- analysis of dermographic characteristics, travel destinations and pretravel healthcare at high risk US international travellers. Clin Infect Dis 2012; 455-62.

15. Roch J Wichmann O, Kamara B, Counter M, Cramer J, Schonfield C et al. Risk and spectrum of diseases in travellers to popular tourist held destinations. J Travel Med 2005; 12:248-53

16. Leder K, Torresi J, Libmen MD, Cramer JP, Castelli F, Schlagenhanf P et el. GeoSentinel Surveilance of illness in returned travellers, 2007-2044. Ann Inern Med 2013 , 158 : 456-68.

17. Freedman DO, Weld LH, Kozarsky, PE Fisk T, Robin R, von Sonnenburg ltd et al. Spectrum of disease and relation to place of exposure among ill returned travellers. N Eng J Med 2006,354: 119-30.

18. Wilson ME, Weld LH, Boggild A, Keystone JS, Kain RC, von Sonnenburg F et al. Fever in returned travellers: results from the Geosentinel Surveillance Network. Clin Infect Dis 2007, 44:1560-8

19. Johnson V, Stockley JM, Dockrell D, Warrell D, Bailey R et al. Fever in returned travellers presenting in the United Kingdom: Recommendations for investigation and initial management. J of Infect 2009:59:1 – 18.

20. CDC, Yellow Book. Chapter 5 Post – Travel evaluation. Fever in returned travellers. http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-5.

LEARNING POINTS

- **Travellers should seek pre-travel advice 4 to 6 weeks before departure.**
- **Required immunisations are yellow fever and meningococcal vaccines.**
- **Need for recommended immunisations is based on risk assessment: typhoid, cholera, hepatitis A, Japanese encephalitis and rabies vaccine**
- **Common illnesses in returned travellers are gastrointestinal diseases, febrile diseases and dermatologic diseases.**
- **Syndromic approach to the evaluation of illness in a returned traveller is important for post-travel diagnosis.**