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Vaccine-Preventable Diseases in Travelers

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Abstract

Travel to the developing world is increasing among those from developed countries, placing them at risk for vaccine preventable and non-vaccine preventable diseases. From 2007-2011, the GeoSentinel Network reported 737 returned travelers with a vaccine preventable disease. While it is essential that clinicians use vaccines when available for a disease of risk, they should also be aware that the vast majority of diseases acquired by travelers are non-vaccine preventable. The vaccine preventable diseases can be divided into routine travel vaccines, special travel vaccines and routine vaccines used for travel. The routine travel vaccines include Hepatitis A and B, typhoid; special travel vaccine include yellow fever, meningococcal disease, rabies, polio and Japanese encephalitis; and route vaccines include influenza and tetanus-diphtheria-pertussis. Travel medicine providers should take a patient and itinerary specific approach to recommending vaccines for travel.

Introduction

The World Tourism Organization (UNWTO) reports that the number of people traveling internationally has grown substantially over the past six decades—from 25 million in 1950, to 278 million in 1980, 528 million in 1995, and 1,035 million in 2012 [1]. This number is projected to increase by 3.3% per year from 2010 to 2030 to reach 1.8 billion by 2030. Given these growing numbers, it is crucial to consider the variety of health risks that are associated with international travel. The risk of becoming ill due to an infectious disease while traveling depends on many factors, such as the region of the world visited, the traveler's age and health status, the duration of travel and the nature of the planned activities. Environmental factors such as altitude, humidity, temperature, exposure to animals and insects, hygiene, sanitation, and access to clean water also contribute to disease risk. Accordingly, all individuals planning to travel should seek the advice of health professionals to better understand the potential hazards associated with their chosen destinations. Pre-travel consultations provide the traveler with steps to undertake before, during, and after travel in order to make traveling less risky. The World Health Organization (WHO) and the Centers for Disease Control (CDC) have compiled guidelines and information that is necessary for risk assessment during pre-travel consultations. Effective pre-travel consultations require careful review of the health background of the traveler and their itinerary, including activities [2,3]. The advice provided to the patient

should be personalized, highlighting the likely exposures, food and waterborne infections, vector born, respiratory tract infections, and blood-borne infections [2]. Providing the traveler with written information of items discussed during a pre-travel visit will reinforce critical topics discussed.

Unfortunately, studies have shown that most travelers from the United States and other countries do not seek pre-travel health advice. According to GeoSentinel and Global TravEpiNet, collaborative CDC surveillance systems, ill travelers sought pre-travel advice less than 50% of the time while 75% of travelers plan to visit malaria-endemic areas.[4,5] The CDC estimates that approximately 4 million travelers going to developing regions are ill enough to seek health care, either while abroad or upon returning home.[6] Although there are limitations to these studies, they address a need for more travel medicine clinics across the globe in order to increase access and encourage international travelers to seek pre-travel medical consultation.

This article will discuss some of the most common vaccine-preventable diseases along with the disease distribution, indications and recommendations for travelers, precautions/contraindications, and vaccine administration schedules. Refer to Table 1 for available vaccines and dosing schedules.

General Precautions and Contraindications for all vaccines

Precautions: moderate to severe illness with our without fever

Contraindications: Severe allergic reaction (e.g. anaphylaxis) after a previous dose or to a vaccine component

Routine Travel Vaccines

Hepatitis A

Hepatitis A is the most common form of viral hepatitis and a common vaccine-preventable disease in travelers. [7,8] A recent population based survey estimated that the highest incidence of disease occurred in East Africa at 14.1 cases/100,000 person months.[9] The Hepatitis A virus (HAV) is transmitted via fecal-oral route from contaminated food and water or by close contact with infected individuals. Although risk of contracting the virus is highest for those who live in or visit rural areas, trek in backcountry areas, or frequently eat or drink in settings of poor sanitation, cases of travel-related hepatitis A can occur in travelers to developing countries with “standard” tourist itineraries, accommodations, and eating behaviors.[10] The incubation period for Hepatitis A averages 28 days (range, 15–50 days). Disease is most severe in older adults (50+ years) versus younger. Clinical manifestations

include the abrupt onset of fever, malaise, anorexia, nausea, and abdominal discomfort, followed within a few days by jaundice. Africa, South Asia, Central America, and Mexico are the highest-risk areas, but vaccination should be considered when traveling to all other developing countries.[11]

Indications for Travelers

- International travelers (including children over 12 months of age) to regions with high or intermediate levels of endemic HAV infection

Vaccine schedule

- Two-dose series given 1.0 mL IM in the deltoid muscle at 0 and 6-12 months (HAVRIX®) or 0 and 6-18 months (VAQTA®)
- Interrupted series do not need to be restarted
- First dose confers immunity within 2-4 weeks. Second dose sustains long term immunity.
- Clinical protection occurs even if the first dose was administered after exposure
- When less than 2 weeks before departure, CDC recommends co-administering immunglobulin intramuscular (IGIM) to adults over age 40, immunocompromised, those with chronic liver disease or chronic medical conditions
- Available as a combined vaccine with Hepatitis B (TWINRIX®), which may be given as a 3-dose series 1.0mL intramuscularly at 0, 1, and 6 months, or as an accelerated 4-dose series at days 0, 7, 21-30, and a booster at 12 months

Vaccine Specific Precautions/Contraindications

- No vaccine specific precautions/contraindications

Hepatitis B

Hepatitis B virus (HBV) is transmitted by contact with contaminated blood, blood products, and other body fluids. Infection with HBV can cause acute or chronic viral infection of the liver. Chronic infection with HBV puts people at higher risk of death from cirrhosis and liver cancer[12]. Hepatitis B virus can cause an acute illness with symptoms that last several weeks, including yellowing of the skin and eyes (jaundice), dark urine, extreme fatigue, nausea, vomiting and abdominal pain. Hepatitis B prevalence is highest in sub-Saharan Africa and East Asia[12]. The risk for

HBV infection in travelers may be higher in countries where the prevalence of chronic HBV infection is high or intermediate; expatriates, missionaries, and long-term development workers may be at increased risk for HBV infection in such countries[12]. Those traveling to provide or receive medical care, travel duration longer than 4 weeks, and possible sexual encounters while abroad should receive education about and vaccination against HBV. Since risk of developing chronic HBV is highest in young children, travelers born in high HBV endemic countries may opt to undergo HBV serology to determine need for vaccination.

Indications for Travelers

Recommended by the CDC to the following individuals:

- Unvaccinated international travelers to regions with high levels of endemic HBV infection and high risk including: prolonged stays, frequent shorter stays in the same areas, possibility of sexual encounters with new partners while traveling, those with potential to acquire medical care while traveling, health care workers, and those who may acquire tattoos, body piercings or acupuncture while traveling.

Vaccine schedule

- 1.0 ml IM in the deltoid muscle at 0, 1, and 6 months. May be accelerated to receive a 3 dose series over 1 month
- Approximately 33% develop immunity after 1 dose, 66% after 2 doses; 3 doses required for long term protection
- Prolonging interval does not require restarting the series.
- Serologic testing and booster vaccination are not recommended before travel for immunocompetent adults who have been previously vaccinated[12].

Vaccine Specific Precautions/Contraindications

None

Typhoid fever

Typhoid fever is a potentially sever and life-threatening illness cause by *Salmonella enterica* serotype Typhi, also referred to as *Salmonella typhi*. Infection by *Salmonella typhi* occurs by ingestion of food or water contaminated by the urine or feces of an infected person, making humans the sole source of typhoid fever transmission. The

incubation period of typhoid infection is 6–30 days. The onset of illness is gradual beginning with increasing fatigue and a fever that increases daily from low-grade to as high as 102°F–104°F (38°C–40°C) by the third to fourth day of illness[13]. Other symptoms include headache, malaise, anorexia, enlarged spleen and liver, a transient, macular rash of rose-colored spots occasionally seen on the trunk[13,14]. The serious complications of typhoid fever generally occur after 2–3 weeks of illness and may include intestinal hemorrhage or perforation, which can be life threatening[13].

Although the risk of typhoid fever is highest for travelers to southern Asia (6–30 times higher than for all other destinations), other areas of risk include East and Southeast Asia, Africa, the Caribbean, and Central and South America[13]. All travelers, even if vaccinated, should take food and water precautions while traveling to avoid infection.

Indications for Travelers

- Typhoid fever vaccine is recommended for those traveling to developing and/or endemic countries including those who are adventurous eaters, those who will stay longer than 4 weeks, visiting friends and relatives, and travelers to rural areas, villages and smaller towns.

Vaccine schedule

- Ty21a, live, attenuated oral vaccine
    - Given as 4 capsules to be taken on days 1, 3, 5 and 7.
    - The 7-day course must be completed 1 week prior to potential exposure to *S. typhi.*
    - If reimmunization is necessary, the 7-days course must be completed every 5 years if repeated or continued exposure to typhoid fever exists.
    - Vaccine does not confer 100% seroconversion, therefore all travelers must take food and water precautions even while vaccinated.
- Typhoid Vi inactivated polysaccharide vaccine
    - Single intramuscular injection of 0.5 mL in the deltoid muscle.
    - Vaccine efficacy is about 74% and protection persists for 2 years.
    - If reimmunization is necessary due to repeated or continued risk of exposure to S. typhi, another single 0.5 mL dose should be administered if > 2 years after the previous dose.

Vaccine Specific Precautions/Contraindications

- Ty21a
    - Vaccine is generally well tolerated. Adverse effects are infrequent and mild.
    - Reactions include abdominal pain (6.4%), nausea (5.8%), headache (4.8%), fever (3.3%), diarrhea (2.9%), vomiting (1.5%) and skin rash (1.0%)
- Typhoid Vi inactivated polysaccharide vaccine
    - Inactivated, injectable vaccine is also well-tolerated.
    - Common adverse reactions include localized injection site reactions including soreness, induration and erythema. Less common systemic reactions include headache, feverishness, and malaise.

Special Travel Vaccines

Yellow Fever

Yellow fever virus (YFV) transmission occurs via the bite of an infected mosquito the *Aedes aegypti*. Humans and non-human primates serve as the reservoirs of the YFV. Most cases of YFV infection are asymptomatic or clinically unapparent. For people who develop symptomatic illness, the incubation period is typically 3–6 days which initially presents as a nonspecific influenza-like syndrome with sudden onset of fever, chills, headache, backache, myalgia, prostration, nausea, and vomiting[15]. Most patients improve after the initial presentation but approximately 15% of patients progress to a more serious or toxic form of the disease, characterized by jaundice, hemorrhagic symptoms, and eventually shock and multisystem organ failure[15].

Yellow fever is endemic in sub-Saharan Africa and tropical South America. A traveler's risk for acquiring yellow fever is determined by various factors, including immunization status, location of travel, season, duration of exposure, occupational and recreational activities while traveling, and local rate of virus transmission at the time of travel[15]. With the exception of the Meningococcal vaccine required for the Hajj pilgrimage, the Yellow fever vaccination is the only vaccine required to enter endemic countries.

Indications for Travelers

- Recommended for persons 9 months of age or older living in or traveling to YFV endemic areas and for international travel to endemic areas.
- Travelers to YFV endemic areas must show proof of vaccination or proof of medical contraindication by means of an International Certificate of Vaccination and Prophylaxis (ICVP). Yellow fever vaccination is carried out for two different reasons: (1) to protect the individual in areas where there is a risk of yellow fever infection; and (2) to protect vulnerable countries from importation of the yellow fever virus. Travelers should therefore be vaccinated if they visit a country where there is a risk of exposure to yellow fever. In some non-endemic countries yellow fever vaccination is a prerequisite for entry for those who have recently passed through yellow fever-endemic areas.

Vaccine schedule

- The 17-D yellow fever vaccine is administered as a single 0.5 mL dose subcutaneously.
- Supplied as a lyophilized powder and must be reconstituted with the provided sterile diluent just prior to administration. Vaccine must be administered within 30 minutes of reconstitution.
- Reimmunization is recommended every 10 years for continued or repeated exposure.

Vaccine Specific Precautions/Contraindications

- Contraindicated in infants younger than 6 months of age, persons with severe egg allergy or thymus disorders.
- The severe adverse effects associated with yellow fever vaccine are yellow fever vaccine-associated neurotropic disease (YEL-AND) which is rarely fatal and yellow fever vaccine-associated viscerotropic disease (YEL-AVD). In the recent years, these effects have been seen in people of all ages, with a higher incidence in people older than 60 years of age[15]. The onset of YEL-AND for documented cases is 3-28 days after vaccination, and almost all cases were in first-time vaccine recipients. The rate is higher in people aged ≥60 years, with a rate of 1.6 per 100,000 doses in people aged 60-69 years[15].
- If travel cannot be avoided for persons at high risk of serious adverse reactions, such as travelers aged ≥ 60 years, the decision to vaccinate is based on weighing the risks and benefits of vaccination in the context of their destination-specific risk for exposure to YF.

Meningococcal Disease

Invasive meningococcal disease is rare in travelers, but its consequences can be devastating [16,17]. Meningococcal disease in travelers is caused by *Neisseria meningitidis* particularly the 5 major serogroups of A, B, C, Y, and W-135. Person-to-person transmission occurs by close contact with respiratory secretions or saliva[18]. The incidence of meningococcal disease is highest in the "meningitis belt" of sub-Saharan Africa spanning from west to east across the continent. The incidence of meningococcal disease is several times higher in the meningitis belt than in the United States, with periodic epidemics during the dry season (December–June)[18]. Generally, the risk of acquiring invasive meningococcal disease in travelers appears to be comparatively low[17]. Risk is highest in travelers to the meningitis belt who have prolonged contact with local populations during an epidemic. The Hajj pilgrimage to Saudi Arabia has been associated with outbreaks of meningococcal disease in returning pilgrims and their contacts[18]. Several significant achievements have been made in the field of meningococcal vaccine development in the past few years[19]. There are three tetravalent conjugate vaccines and one tetravalent polysaccharide vaccine currently available to protect international travelers from meningococcal disease.

Indications for Travelers

- Those traveling to endemic regions including the "Meningitis Belt" of Africa during high season and to Saudi Arabia during the Hajj.

Vaccine schedule

- MCV4-DT (Menactra)
    - Children 9 through 23 months of age receive two doses, three months apart.
    - Immunocompetent Individuals 2 through 55 years of age receive a single dose, repeated every 5 years as needed.
- MCV4-CRM (Menveo)
    - Approved for use in persons 2 months through 55 years of age.
    - Immunocompetent Individuals 2 through 55 years of age receive a single dose, repeated every 5 years as needed

- Supplied as one vial of MenA as a lyophilized powder and one diluent vial containing MenCYW-135 (vaccine must be reconstituted)

- MPSV4 (Menomune®)
  - Approved for use in persons 2 years of age or older.
  - Menomune is supplied as a single dose (or 10-dose multidose) vial of lyophilized vaccine and must be reconstituted with a corresponding diluent.
  - Administered as a 0.5 mL injection dose given subcutaneously

Vaccine Specific Precautions/Contraindications

none

Rabies

Rabies is a disease caused by a neurotropic Rhabdoviridae virus present in the saliva of an animal that is transmitted to humans by an animal bite or a bleeding scratch by a rabid animal. Rabies is nearly 100% fatal but can be efficiently averted by preexposure immunization, avoidance of contact with animals, and postexposure prophylaxis (PEP)[20]. More than 55,000 people die from rabies worldwide each year; 95% of these deaths occur in Asia and Africa, and almost all of these fatal cases result from a rabid dog bite[21]. The risk of rabies in travelers is proportional to the probability of contact with potentially rabid mammals. In most developing countries, the estimated ratio of dogs, both owned and ownerless, to humans is 1:10 and an average 100 suspected rabid dog bites per 100 000 inhabitants are reported annually[14]. Travelers should avoid contact with animals, primarily warm-blooded mammals, while traveling. Travelers with high risk of exposure including field biologists or veterinarians, spelunkers, and those staying for an extended period of time, especially children, in a high risk region should consider pre-exposure vaccination (PreP).

Indications for Travelers

- Approved for use in all age groups for PreP and PEP of rabies.
- Recommendations for PreP with rabies vaccine are grouped by the CDC into categories of exposure risk including:

- 3 dose PreP for: continuous (e.g. rabies lab workers), frequent (e.g. wildlife workers), infrequent (e.g. remote destination travelers without reliable PEP)
- No vaccine: rare (e.g. most travelers)

Vaccine Schedule

- **Imovax® (Human Diploid Cell Vaccine *HDCV*)**
  - Primary vaccination is 3 doses of 1.0 mL administered intramuscularly, preferably in the deltoid muscle in adults and in the anterolateral part of the thigh in infants and children, on days 0, 7, 21 or 28.
  - Supplied as a vial of freeze-dried vaccine with a syringe containing 1.0 mL of diluent. The vaccine must be reconstituted with the diluent and administered immediately after reconstitution.
- **RabAvert® (Purified Chick Embryo Cell *PCEC*)**
  - Primary vaccination is 3 doses of 1.0 mL administered intramuscularly, preferably in the deltoid muscle in adults and in the anterolateral part of the thigh in infants and children, on days 0, 7, 21 or 28.
  - Supplied as a lyophilized powder vaccine that should be reconstituted with the supplied diluent and administered immediately after reconstitution.

The postexposure dose in previously unvaccinated individuals is 4 doses of 1.0mL of either product given on days 0, 3, 7, and 14 with a weight-based dose of Rabies Immune Globulin (RIG) preferably given with the first vaccine dose. In previously vaccinated individuals, 2 doses of either product should be given on days 0 and 3. There is no need for RIG in previously vaccinated individuals.

Vaccine Specific Precautions/Contraindications

- Pregnancy is not a contraindication to PEP with rabies vaccine.

Poliomyelitis

Poliomyelitis is caused by a polio virus spread by the fecal-oral route by ingestion of contaminated food or water. Polio is a central nervous system disease that can cause flaccid paralysis of muscles, respiratory failure or death. The introduction of the polio vaccine drastically reduced polio cases worldwide. However, in the last decade, there

has been a reemergence of the disease due to reduced vaccination rates in various regions. In 2013, only three countries (Afghanistan, Nigeria and Pakistan) remain polio-endemic, down from more than 125 in 1988.[22] In the United States, infants and children should be vaccinated against polio as part of a routine immunization series[23]. Polio vaccination is recommended for all travelers to polio-endemic or epidemic areas[23]. Before traveling to areas where poliomyelitis cases are still occurring, travelers should ensure that they have completed the recommended age-appropriate polio vaccine series and should be adequately vaccinated with a booster dose, if necessary[23].

Indications for Travelers

- Persons with documented completed primary series of polio vaccination should receive an adult booster dose of polio vaccine when traveling to countries with current cases of polio.
- Persons traveling to areas where poliomyelitis cases are still occurring and who are unvaccinated, incompletely vaccinated, or whose vaccination status is unknown should receive a series of 3 doses: 2 doses of IPV administered at an interval of 4–8 weeks; a third dose should be administered 6–12 months after the second[23].

Vaccine schedule

- IPOL is given in a 0.5 mL dose administered intramuscularly.
- Travelers who have received their primary polio series should receive one 0.5 mL booster dose prior to travel to risk areas.

Vaccine Specific Precautions/Contraindications

- None

Japanese Encephalitis

Japanese encephalitis (JE) is caused by a *Flavivirus* transmitted to humans by the bite of an infected *Culex* mosquito. Most human infections with JE virus are asymptomatic; <1% of people infected with JE virus develop clinical disease, but of those, 20-30% are fatal and 30-50% of survivors have neurologic sequelae. The most common clinical symptom of JE infection is acute encephalitis.[24] The incubation period is 5–15 days with a sudden onset of fever, headache, and vomiting. Mental status changes, focal neurologic deficits, generalized weakness, and movement disorders may develop over the next few days. JE virus is the most common vaccine-preventable

cause of encephalitis in Asia (50% from China) and parts of the western Pacific.[25] Local transmission of JE virus has not been detected in Africa, Europe, or the Americas. Transmission principally occurs in rural agricultural areas, often associated with rice cultivation and flood irrigation, some of which may be near or within urban areas. In temperate areas of Asia, transmission is seasonal, and human disease usually peaks in summer and fall. In the subtropics and tropics, seasonal transmission varies with monsoon rains and irrigation practices and may be prolonged or even occur year-round. The overall risk of JE infection in travelers in endemic areas is low, but travelers or expatriates staying for a prolonged period of time (>4 weeks) are at a similar risk of infection from JEV as residents of the area. Travelers on even brief trips might be at increased risk if they have extensive outdoor or nighttime exposure in rural areas during periods of active transmission[24].

Indications for Travelers

- Vaccination is recommended for travelers 2 months of age or older traveling to risk areas with extensive outdoor exposure during the transmission season, particularly in endemic countries or areas where flooding irrigation is practiced. Primary prevention of JEV infection is by avoidance of mosquito bites and immunization.

Vaccine schedule

- Travelers 2 months to <3 years of age receive a 2-dose series of 0.25 mL intramuscularly administered on days 0 and 28.
- Travelers 3 years of age and older receive a 2-dose series of 0.5 mL intramuscularly on days 0 and 28
- Supplied as a 0.5 mL suspension in a prefilled syringe with a rubber stopper.

Vaccine Specific Precautions/Contraindications

- A severe allergic reaction following a previous dose of Japanese encephalitis vaccine is a contraindication to administration of subsequent doses.

<u>Routine Vaccines used for Travel</u>

Influenza Vaccine

Respiratory illness, especially influenza, is one the most common causes of morbidity in travelers, likely due to the close contact travelers have with large numbers of other people in close quarters, long haul air travel and travel to

the northern hemisphere from December-February.[26] Recent data suggest that influenza is the commonest vaccine-preventable disease of travelers occurring in an estimated 8% of returned travelers with respiratory illness.[4] Influenza is a wintertime disease in temperate climates, but there is year-round risk of transmission in tropical countries and year-round transmission on cruise ships. Influenza season in temperate climates is November–April in the northern hemisphere and April–October in the southern hemisphere.

Currently, two subtypes of influenza A (H3N2 and H1N1) and two strains of influenza B (Yamagata and Victoria lineage) circulate among humans, so seasonal influenza vaccines are trivalent and more recently, quadravalent. Recently, two new non-egg based vaccines were introduced, a canine kidney cell based and a recombinant hemagglutinin vaccine The WHO makes two sets of vaccine recommendations annually: (1) in February for the next northern hemisphere winter season (November–April), and (2) in September for the next southern hemisphere winter season (April–October). Even though northern and southern hemisphere vaccines are produced in mostly the same plants of multinational manufacturers, southern vaccine is generally not available in northern countries, and vice versa. Avian influenza has not been documented in travelers nor is there a commercial vaccine available for use. The season influenza vaccine is not expected to provide protection against avian strains.

Indications for Travelers

- 6 months and older traveling to the Northern Hemisphere (November-April), the Southern Hemisphere (April-October) or to the tropics (year round)

Vaccine schedule

- Given annually
- For those less than 9 years and receiving an influenza vaccine for the first time, they should get 2 doses separated by 28 days

Vaccine Specific Precautions/Contraindications

- All influenza vaccines: Guillain-Barré syndrome within 6 weeks of previous dose of influenza vaccine
- All egg based influenza vaccines: severe allergic reaction to eggs (RIV3 may be used)
- LAIV4: altered immune competence, pregnant, chronic medical conditions

Tetanus, Diphtheria, Pertussis

Tetanus, diphtheria and pertussis are grouped together here to match the combined vaccine. For travelers, tetanus is extremely rare while diphtheria and pertussis occasionally occur.[4] Tetanus is a non-communicable disease acquired typically by injury in the environment. While the occurrence of tetanus in travelers is rare, the consequences of acquiring it in a developing country with inadequate post-exposure care can be deadly. Unlike rabies which also rarely occurs, but has very high mortality, tetanus has an easy one dose prevention strategy that is also employed routinely in the U.S. In the U.S., someone presenting to the emergency department for a tetanus prone wound would be given a tetanus containing vaccine if more than 5 years had elapsed since the previous does. Using this strategy preventatively for travelers, tetanus vaccine should be updated, preferably with Tdap (tetanus, diphtheria and acellular pertussis), if greater than 5 years have elapsed since the last dose.

Diphtheria does not occur in the U.S., but remains endemic in much of the rest of the world, notably in Russia and the countries of the former Soviet Union. Pertussis has occurred in outbreaks around the U.S. and continues to occur globally. For both diphtheria and pertussis, it should be stressed to travelers planning to work with children or provide healthcare that need to be immunized to not only protect themselves, but also the young children they encounter.

Indications for Travelers

- Routine immunization every 10 years; consider every 5 years to travelers to developing countries
- Prefer Tdap or Td where there is no record of Tdap being given
- There is no minimum interval between Td and Tdap, especially when the traveler may interact with young children

Vaccine schedule

- 0.5 ml IM Tdap or Td

Vaccine Specific Precautions/Contraindications

- Pertussis containing vaccine – encephalopathy within 7 days of previous dose

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