

# The Medical Letter<sup>®</sup>

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# The Medical Letter®

## on Drugs and Therapeutics

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### IN THIS ISSUE

## Vaccines for Travelers

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Persons planning to travel outside the US should be up to date on routine vaccines and, depending on their destination, duration of travel, and planned activities, may also receive certain travel-specific vaccines. Tickborne encephalitis and dengue vaccines, which are not available in the US, are reviewed in a separate article available online. Detailed advice for travel to specific destinations is available from the Centers for Disease Control and Prevention (CDC) at [www.cdc.gov/travel/destinations/list](http://www.cdc.gov/travel/destinations/list). Recommendations for administration of vaccines as part of routine adult immunization are discussed in a separate issue.<sup>1</sup>

### TIMING OF VACCINE ADMINISTRATION

Multiple inactivated and/or live-attenuated vaccines can generally be given on the same day at different sites without decreasing antibody responses or increasing the risk of adverse effects. If two live-attenuated vaccines are not administered on the same day, the second one should generally be given at least one month after the first. An interrupted vaccine series does not have to be restarted; there is no maximum interval between doses of a primary series.<sup>2</sup>

Immunocompromised or pregnant patients generally should not receive live vaccines, although the benefit might outweigh the risk in some situations.<sup>3</sup>

### VACCINES

**CHOLERA** – Cholera is endemic in many countries in Africa and South and Southeast Asia. In recent years, most outbreaks have been caused by toxigenic strains of *Vibrio cholerae* serogroup O1. Cases caused by serogroup O139 have occurred in a few areas in Asia.

For most tourists, the risk of cholera is very low. Travelers who might have a higher risk of exposure

include those who plan to work in refugee camps, in outbreak settings, or as healthcare providers, and those visiting friends and relatives or staying for extended periods in affected areas.

**Recommendations** – The US Advisory Committee on Immunization Practices (ACIP) recommends vaccination for persons 18-64 years old traveling to areas with endemic or epidemic cholera caused by toxigenic *V. cholerae* serogroup O1, including areas with cholera activity within the last year that are prone to recurrences of cholera epidemics.<sup>4</sup>

**The Vaccine** – *Vaxchora*, a single-dose, oral, live-attenuated cholera vaccine, is FDA-licensed to protect against disease caused by toxigenic *V. cholerae* serogroup O1 (but not serogroup O139 or other non-O1 serogroups) in adults 18-64 years old. It should be taken at least 10 days before potential cholera exposure.<sup>5</sup>

In a randomized trial, volunteers were challenged with wild-type *V. cholerae* serogroup O1 10 days or 3 months after vaccination; the seroconversion rate was 89% at 10 days and 90% at 180 days after vaccination. Vaccine efficacy against moderate or severe diarrhea was 90% at 10 days and 80% at 3 months.<sup>6</sup>

**HEPATITIS A** – Hepatitis A virus (HAV) is common in countries where sanitation is poor and access to clean water is limited, including many parts of Africa, Asia, Central and South America, and Eastern Europe. Areas with low levels of endemic HAV transmission include Western Europe, Japan, New Zealand, and Australia. HAV vaccination has been part of routine childhood immunization in the US since 2006.

**Recommendations** – HAV vaccine is recommended by the ACIP for all unvaccinated travelers going to countries with intermediate or high HAV endemicity.<sup>7</sup> However, there is a potential risk of foodborne HAV infection even in countries with low endemicity; some experts advise all persons

Table 1. Some Vaccines for Travelers

Vaccines	Adult Dose	Pediatric Dose	Primary Schedule	Duration of Protection
<b>Cholera</b>				
<i>Vaxchora</i> (PaxVax)	18-64 yrs: 100 mL PO (reconstituted)	Not approved for <18 yrs	Single dose	► Probably at least 6 mos
<b>Hepatitis A</b>				
<i>Havrix</i> (GSK)	1 mL IM (1440 EL.U.)	1-18 yrs: 0.5 mL IM (720 EL.U.)	0 and 6-12 mos	► Probably lifelong after completion of primary series <sup>1</sup>
<i>Vaqta</i> (Merck)	1 mL IM (50 units)	1-18 yrs: 0.5 mL IM (25 units)	0 and 6-18 mos	
<b>Hepatitis B</b>				
<i>Engerix-B</i> (GSK)	1 mL IM (20 mcg)	Birth-19 yrs: 0.5 mL IM (10 mcg)	0, 1, and 6 mos <sup>2,3</sup>	► Probably lifelong after completion of primary series
<i>Recombivax-HB</i> (Merck)	1 mL IM (10 mcg)	Birth-19 yrs: 0.5 mL IM (5 mcg)	0, 1, and 6 mos <sup>3,4</sup>	
<i>Heplisav-B</i> (Dynavax)	0.5 mL IM (20 mcg)	Not approved for <18 yrs	0 and 1 mo	
<b>Hepatitis A/B</b>				
<i>Twinrix</i> (GSK) <sup>5</sup>	1 mL IM (720 EL.U./20 mcg)	Not approved for <18 yrs	0, 1, and 6 mos (alternative: 0, 7, and 21-30 days)	► Booster recommended at 12 mos with accelerated schedule; otherwise probably lifelong after completion of primary series
<b>Japanese encephalitis</b>				
<i>Ixiaro</i> (Valneva)	0.5 mL IM	2 mos-<3 yrs: 0.25 mL IM ≥3 yrs: 0.5 mL IM	0 and 28 days <sup>6</sup> (alternative: 0 and 7 days for adults 18-65 yrs old)	► A single booster ≥11 mos after completion of primary series is recommended for those ≥14 mos old with ongoing risk <sup>7,8</sup>
<b>Meningococcal</b>				
<i>Menveo</i> (GSK)	0.5 mL IM (10 mcg serogroup A, 5 mcg serogroup C, Y, W135)	≥2 mos: 0.5 mL IM (10 mcg serogroup A, 5 mcg serogroup C, Y, W135)	2 mos: 2, 4, 6, and 12 mos 7-23 mos: 0 and 3 mos <sup>9</sup> ≥2 yrs: single dose <sup>10,11</sup>	► Repeat every 5 yrs <sup>12</sup> if ongoing risk
<i>Menactra</i> (Sanofi Pasteur)	0.5 mL IM (4 mcg of each antigen)	≥9 mos: 0.5 mL IM (4 mcg of each antigen)	9-23 mos: 0 and 3 mos <sup>13</sup> ≥2 yrs: single dose <sup>11</sup>	
EL.U. = ELISA Units				
1. Protection probably lasts at least 12 months after a single dose.				
2. An alternate schedule is 3 doses given at 0, 1, and 2 months, followed by a fourth dose at 12 months.				
3. An accelerated schedule (0, 7, and 21-30 days, followed by a booster dose at 12 months) that is FDA-approved for use with <i>Twinrix</i> may also be used, if necessary, with hepatitis B vaccine.				
4. An alternate schedule for adolescents 11-15 years old is 0 and 4-6 months.				
5. Contains the same antigenic components as pediatric <i>Havrix</i> (hepatitis A) and <i>Engerix-B</i> (hepatitis B). It can be used to complete an immunization series started with monovalent hepatitis A and B vaccines.				
6. For last-minute travelers, one double dose of the vaccine (not FDA-approved) has been shown to provide 60% protection for at least one month (E Schuller et al. <i>Vaccine</i> 2009; 27:2188).				
7. One study found that a single dose of <i>Ixiaro</i> effectively boosted immunity in travelers previously vaccinated with <i>JE-Vax</i> (EO Erra et al. <i>Vaccine</i> 2013; 32:119), but the ACIP recommends that adults previously vaccinated with <i>JE-Vax</i> receive a primary series of <i>Ixiaro</i> (MMWR Morb Mortal Wkly Rep 2011; 60:661).				
8. In an observational study in adults who had completed a primary series of <i>Ixiaro</i> , the seroprotection rate was 96% six years after a booster dose (M Paulke-Korinck et al. <i>Vaccine</i> 2015; 33:3600).				
9. The second dose should be given at age 12 months and ≥3 months after the first, but can be administered as early as 8 weeks after the first dose if needed before travel.				
10. For children 2-5 years old at continued high risk, a second dose may be administered 2 months after the first.				
11. Although FDA-licensed only for persons <56 years old, the CDC states that <i>Menveo</i> or <i>Menactra</i> may be administered to travelers aged ≥56 years.				
12. Repeat after 3 years for children vaccinated at <7 years of age.				
13. The second dose can be administered 8 weeks after the first if required before travel.				

traveling outside the US to consider hepatitis A vaccination regardless of their destination.

**The Vaccines** – Monovalent HAV vaccines (*Havrix*, *Vaqta*) are usually administered in 2 IM doses at least 6 months apart. Antibodies reach protective levels 2-4 weeks after the first dose. Even when exposure to the virus occurs sooner than 4 weeks after vaccination, the traveler is usually protected because the hepatitis A incubation period is relatively long (average 28 days). Immunocompromised patients, who have reduced seroconversion rates after the first dose of HAV

vaccine, may benefit from an extra priming dose; in a study in adults with drug-induced immunosuppression given 2 doses 4 weeks apart, the seroprotection rate at 2 months was 84%.<sup>8</sup> A series started with one of the two monovalent hepatitis A vaccines may be completed with the other, or (in adults) with the combination hepatitis A/hepatitis B virus vaccine (*Twinrix*). A second dose given up to 11 years after the first has produced protective antibody levels.<sup>9</sup>

For older adults, immunocompromised patients, and those with chronic liver disease or other chronic medical

Table 1. Some Vaccines for Travelers (continued)

Vaccines	Adult Dose	Pediatric Dose	Primary Schedule	Duration of Protection
<b>Polio</b>				
<i>Ipol</i> (Sanofi Pasteur)	0.5 mL IM or SC	≥6 wks: 0.5 mL IM or SC	Adults: single dose <sup>14</sup> Children: 2, 4, 6-18 mos and 4-6 yrs <sup>15</sup>	▶ Boosters may be required for long-term travel to polio-affected countries
<b>Rabies</b>				
<i>Imovax</i> (Sanofi Pasteur)	1 mL IM (≥2.5 IU of rabies antigen)	≥Birth: 1 mL IM (≥2.5 IU of rabies antigen)	0, 7, and 21 or 28 days <sup>16</sup>	▶ Routine boosters generally not necessary; for those engaging in frequent high-risk activities (cavers, veterinarians, laboratory workers), serologic testing is recommended every 6 mos with booster doses if low levels <sup>17</sup>
<i>RabAvert</i> (GSK)	1 mL IM (≥2.5 IU of rabies antigen)	≥Birth: 1 mL IM (≥2.5 IU of rabies antigen)	0, 7, and 21 or 28 days <sup>16</sup>	
<b>Typhoid</b>				
<i>Vivotif</i> (PaxVax)	1 cap PO (contains 2.0-10.0x10 <sup>9</sup> viable CFU of <i>S. typhi</i> Ty21a)	≥6 yrs: 1 cap PO (contains 2.0-10.0x10 <sup>9</sup> viable CFU of <i>S. typhi</i> Ty21a)	1 cap every other day x 4 doses <sup>18</sup>	▶ Repeat every 5 yrs if ongoing risk
<i>Typhim Vi</i> (Sanofi Pasteur)	0.5 mL IM (25 mcg of Vi polysaccharide)	≥2 yrs: 0.5 mL IM (25 mcg of Vi polysaccharide)	Single dose	▶ Repeat every 2 yrs (3 yrs in Canada) if ongoing risk
<b>Yellow Fever</b>				
<i>YF-Vax</i> (Sanofi Pasteur) <sup>19</sup>	0.5 mL SC (4.74 log <sub>10</sub> plaque forming units of 17D204 attenuated YF virus)	≥9 mos: 0.5 mL SC (4.74 log <sub>10</sub> plaque forming units of 17D204 attenuated YF virus)	Single dose	▶ Possibly lifelong

CFU = colony-forming units

14. If primary series completed. Previously unvaccinated adults should receive 2 doses 4-8 weeks apart, followed by a third dose 6-12 months after the second.

15. Alternative for previously unvaccinated children ≥6 weeks old is a primary series consisting of 3 doses given ≥4 weeks apart, followed by a fourth dose 6 months after the third.

16. Regimen for pre-exposure prophylaxis (PrEP). The World Health Organization (WHO) recommends a 2-dose PrEP schedule on days 0 and 7, and states that, in case of time constraints, a single dose will likely confer some protection, but those who have received 1 dose should receive a 2nd dose as soon as possible and within 1 year (WHO. Rabies vaccines: WHO position paper – April 2018. Weekly Epidemiological Record 2018; 93:201. Available at [www.who.int/wer/2018/en](http://www.who.int/wer/2018/en). Accessed November 8, 2018). If a previously vaccinated traveler is exposed to a potentially rabid animal, post-exposure prophylaxis (PEP) with 2 additional vaccine doses 3 days apart should be given as soon as possible.

17. Minimal acceptable antibody level is complete virus neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test.

18. Taken about 1 hour before a meal with a cold or luke-warm drink.

19. *YF-Vax* is currently (November 2018) out of stock. Supplies are expected to be available by the middle of 2019. Another single-dose, live vaccine (*Stamaril*), which is licensed in Europe, is available at some US clinics ([www.cdc.gov/travel/page/search-for-stamaril-clinics](http://www.cdc.gov/travel/page/search-for-stamaril-clinics)).

conditions who will be traveling to an endemic area in ≤2 weeks, one dose of immune globulin (*GamaSTAN S/D*) should be given in addition to the initial dose of vaccine. Infants <6 months old and persons who elect not to receive the vaccine should receive a single dose of immune globulin before travel. Infants 6-11 months old may receive a single dose of vaccine before travel instead of immune globulin, followed by a complete 2-dose series beginning at ≥12 months of age; the rationale for off-label use of the vaccine in this age group is that HAV and live-attenuated measles, mumps, and rubella (MMR) vaccines can be administered simultaneously, but MMR vaccine cannot be administered with immune globulin.<sup>10</sup> The recommended dosage of immune globulin, which was increased in 2017, varies according to the duration of travel: 0.1 mL/kg for up to one month of travel; 0.2 mL/kg for up to 2 months; 0.2 mL/kg every 2 months for longer travel.<sup>11</sup>

**HEPATITIS B** – Hepatitis B surface antigen (HbsAg) prevalence is generally high in sub-Saharan Africa and

the Western Pacific region and low in most countries in the Americas, Western Europe, Japan, and Australia.<sup>12</sup> Hepatitis B virus (HBV) vaccine is part of routine childhood immunization in the US.

**Recommendations** – HBV vaccine is recommended by the ACIP for all travelers going to areas with intermediate or high prevalence of chronic HBV infection.<sup>9</sup> The risk for most travelers is low. Travelers who engage in behaviors that increase the risk of transmission, such as injection drug use, unprotected sexual contact with new partners, dental treatment, skin perforation practices (tattoos, acupuncture, ear piercing), or medical tourism involving invasive medical treatment, should receive the HBV vaccine regardless of their destination.<sup>13</sup>

**The Vaccines** – Three monovalent HBV vaccines are available in the US (*Engerix-B*, *Heplisav-B*, *Recombivax*). *Heplisav-B* is a 2-dose vaccine that is only FDA-licensed for use in adults. The other vaccines are usually administered in 3 doses. In randomized

clinical trials, seroprotection rates with 2 doses of *Hepelisav-B* were significantly higher than those with 3 doses of *Engerix-B*.<sup>14</sup>

The ACIP recommends using the same vaccine for all doses of a hepatitis B series, but an interrupted series does not have to be restarted if the same vaccine is not available. Two doses of *Hepelisav-B* can be used to complete a series started with a single dose of another monovalent vaccine or the combination HAV/HBV vaccine. One dose of *Hepelisav-B* can be used as part of a 3-dose series.<sup>15</sup>

**INFLUENZA** – Influenza may be a risk in temperate areas of the Southern Hemisphere from April to September and of the Northern Hemisphere from October to March, and in the tropics year-round. Increased risk has been associated with travel in large tour groups and on cruise ships and airplanes, participation in mass gatherings, and staying abroad for >30 days. Persons traveling to East and Southeast Asia appear to have a higher risk of acquiring influenza than those traveling to other regions.<sup>16</sup>

**Recommendations** – The ACIP recommends routine annual vaccination against seasonal influenza for everyone ≥6 months old; detailed recommendations are included in a separate issue.<sup>17</sup>

Travelers not vaccinated during the preceding Northern Hemisphere influenza season should consider being vaccinated before going to the Southern Hemisphere during that region's influenza season or to the tropics in any season, or when traveling in a group with persons from the Southern Hemisphere during their influenza season.<sup>18</sup>

**The Vaccines** – Northern Hemisphere influenza vaccine is usually available in the US from August until the end of June. The vaccine formulations may be the same in the Northern and Southern Hemispheres. If they are different, high-risk patients from the Northern Hemisphere who travel to the Southern Hemisphere during that region's influenza season could consider vaccination prior to departure with a US-licensed Southern Hemisphere formulation (*Fluzone Quadrivalent Southern Hemisphere*), if available, or vaccination upon arrival in the Southern Hemisphere. Serum antibody levels peak about 2 weeks after vaccination in most adults.

**JAPANESE ENCEPHALITIS** – Japanese encephalitis is an uncommon but potentially fatal mosquito-borne viral disease that occurs in rural Asia, especially near pig farms and rice paddies. It is usually seasonal

(May-October), but may occur year-round in tropical regions. The incidence in travelers has been very low.<sup>19</sup>

**Recommendations** – Vaccination is recommended for travelers who expect a long stay (≥1 month) in endemic areas or heavy exposure to mosquitoes (such as adventure travelers) during the transmission season. Vaccination should be considered for travelers spending <1 month in endemic areas during the transmission season if they will be sleeping without air conditioning, screens, or bed nets, or spending considerable time outside in rural or agricultural areas, especially in the evening or at night.<sup>20</sup>

**The Vaccine** – *Ixiaro*, an inactivated Vero cell culture-derived vaccine, is the only Japanese encephalitis vaccine currently available in the US.<sup>21</sup> It is licensed by the FDA for use in adults and children ≥2 months old.<sup>22</sup> *Ixiaro* is usually given in 2 doses 28 days apart. The FDA has now approved an accelerated schedule (0 and 7 days) of *Ixiaro* that can be used as an alternative for last-minute adult travelers ≤65 years old. In a randomized trial in healthy adults 18-65 years old, the accelerated schedule was noninferior to the standard schedule in terms of immunogenicity and safety at one month and one year after vaccination.<sup>23,24</sup>

In an observational study, 96% of adults who had completed a 2-dose primary series of *Ixiaro* and received one booster dose 15 months later were still seroprotected 6 years after their booster dose.<sup>25</sup>

A single dose of *Ixiaro* has been shown to effectively boost antibody levels in persons vaccinated with a previously available vaccine (*JE-Vax*), but the duration of protection is unknown; the ACIP recommends that persons previously vaccinated with *JE-Vax* who require continued protection receive a 2-dose primary series of *Ixiaro*.

**MEASLES** – Travel has been associated with importation of measles virus from other countries where it is endemic or large outbreaks are occurring, leading to outbreaks in the US, primarily among unvaccinated persons.<sup>26</sup>

**Recommendations** – The CDC recommends vaccination against measles for all persons without evidence of immunity, particularly international travelers. Children 6-11 months old should receive one MMR dose before traveling; they will still need 2 more doses of a measles-containing vaccine for routine immunization, beginning at ≥12 months of age. Previously unvaccinated children ≥12 months old, adolescents, and adults (born in 1957 or later

[1970 in Canada]) should receive 2 doses of a measles-containing vaccine at least 28 days apart.<sup>27,28</sup>

**The Vaccine** – The measles vaccine is available as a live-attenuated vaccine in combination with mumps and rubella (MMR; *M-M-R-II*) or with mumps, rubella, and varicella (MMRV; *ProQuad*; approved only for children 12 months-12 years old).

**MENINGOCOCCAL** – Outbreaks of meningococcal disease can occur anywhere in the world, but they are most common in the African “meningitis belt” (semi-arid areas of sub-Saharan Africa extending from Senegal and Guinea eastward to Ethiopia). Recent outbreaks have primarily been due to *Neisseria meningitidis* serogroups C and W.

**The Vaccines** – Two quadrivalent inactivated vaccines against *N. meningitidis* serogroups A, C, W, and Y (MenACWY; *Menactra*; *Menveo*) are available in the US.<sup>29,30</sup> Both contain meningococcal capsular polysaccharides conjugated to a protein carrier. A third unconjugated quadrivalent polysaccharide vaccine (*Menomune*) is no longer available in the US.

Persons traveling to Saudi Arabia during the Hajj or Umrah must present proof of immunization with MenACWY. The vaccine must be administered no fewer than 10 days and no more than 3 years before travel if the previously available polysaccharide vaccine was used and no more than 5 years before if the conjugate vaccine was used.<sup>31</sup>

Two vaccines against *N. meningitidis* serogroup B (MenB; *Trumenba*; *Bexsero*) are available for use in persons 10-25 years old. MenB vaccine is not routinely recommended for travel unless an outbreak has been reported.

**Recommendations** – Vaccination with MenACWY is recommended for travelers going anywhere in the meningitis belt during the dry season (December to June), and should also be considered for areas where outbreaks of *N. meningitidis* are occurring, particularly for travelers who will have prolonged contact with the local population, such as those living in a dormitory, military institution, or refugee camp, or working in a healthcare setting.<sup>28</sup>

**PNEUMOCOCCAL** – The incidence of pneumococcal disease is higher in some developing countries than in the US. Pneumococcal vaccination has been part of routine childhood immunization in the US since 2010.

**The Vaccines** – Two pneumococcal vaccines are available in the US: PCV13 (*Prevnar 13*), a conjugate

vaccine that contains 13 serotypes of pneumococcus, and PPSV23 (*Pneumovax 23*), a 23-valent pneumococcal polysaccharide vaccine.

**Recommendations** – Travelers should be up to date on pneumococcal vaccination. It is recommended for healthy adults  $\geq 65$  years old and for some persons  $< 65$  years old with certain immunocompromising conditions or other risk factors (e.g., smoking and chronic diseases such as diabetes). Healthy adults  $\geq 65$  years old who have not previously received either vaccine should receive PCV13 first, followed at least one year later by PPSV23. A shorter interval between doses (PCV13 followed  $\geq 8$  weeks later by PPSV23) is recommended by the ACIP for adults with immunocompromising conditions and may be appropriate for some travelers with upcoming trips.<sup>1,32</sup>

**POLIO** – In 2018, the only countries with wild poliovirus circulation during the last 12 months were Pakistan and Afghanistan. Outbreaks of vaccine-derived poliovirus have occurred in some other countries, mainly in Africa.

**Recommendations** – All persons traveling to countries with wild or vaccine-derived poliovirus circulation should complete a primary series of inactivated polio vaccine (IPV; *Ipol*) before leaving the US. Adults who have not previously been immunized against polio should receive a 3-dose primary series of IPV (2 doses 4-8 weeks apart; third dose 6-12 months after the second). If protection is needed sooner, 2 or 3 doses can be given  $\geq 4$  weeks apart; if  $< 4$  weeks are available before protection is needed, a single dose is recommended. Adults who previously completed a primary series and have never had a booster should receive a single booster dose of IPV. Previously unimmunized children should receive a 4-dose primary series of IPV beginning at age  $\geq 6$  weeks; the first 3 doses should be given  $\geq 4$  weeks apart, followed by a fourth dose  $\geq 6$  months after the third. A child who received 4 doses before age 4 should be given a fifth dose at age 4-6 years.

Travelers planning to stay for  $> 4$  weeks in a country with recent wild or vaccine-derived poliovirus circulation may be required to present proof of polio vaccination when departing that country. Polio vaccination of travelers should be documented on an International Certificate of Vaccination or Prophylaxis (ICVP; “yellow card”). Children and adults who will be in a polio-infected country for  $> 4$  weeks, and whose last dose of polio vaccine was administered  $> 12$  months before the date they will be leaving that country, should receive an additional dose of IPV

before leaving the US. Those who plan to reside in a polio-infected country for >12 months may be required to receive a dose of the polio vaccine that is available in that country (either IPV or oral polio vaccine) between 4 weeks and 12 months before their departure from the polio-infected country.<sup>33</sup>

**RABIES** – Rabies is highly endemic in many parts of Africa, Asia (particularly India, Pakistan, Bangladesh, and Bali, Indonesia), and Central and South America, but the risk to travelers is generally low.<sup>34</sup>

**Recommendations** – Pre-exposure vaccination (PrEP) against rabies is recommended for travelers with an occupational risk of exposure, for those (especially children) visiting endemic areas where immediate access to medical treatment, particularly rabies immune globulin (RIG), tends to be limited, and for outdoor-adventure travelers.<sup>35</sup>

After exposure to a potentially rabid animal, persons who received PrEP should promptly receive 2 additional doses of vaccine 3 days apart. For those who did not receive PrEP, the ACIP recommends human RIG plus 4 doses of vaccine given over 14 days; immunosuppressed patients should receive 5 doses of vaccine over 28 days.<sup>36</sup> In one retrospective study, some patients did not develop adequate antibody levels after 4 doses of vaccine.<sup>37</sup>

**The Vaccines** – Two rabies antigen vaccines are available in the US (*Imovax*; *RabAvert*). According to the CDC, cell culture rabies vaccines available outside the US are acceptable alternatives to FDA-approved vaccines, but neural tissue vaccines, which have high rates of serious adverse effects, are not. RIG is not readily available in developing countries, and even when it is, its purity and potency may be less reliable. Purified equine-derived RIG is available in some developing countries and has been used effectively, with a low incidence of adverse effects.

**TETANUS, DIPHTHERIA, AND PERTUSSIS** – Vaccination against tetanus diphtheria, and pertussis, which is part of routine childhood immunization in the US, is recommended for all travelers.

**Recommendations** – Previously unimmunized children should receive 3 or (preferably) 4 doses of pediatric diphtheria, tetanus, and acellular pertussis vaccine (DTaP) before travel. An accelerated schedule can be used beginning at age  $\geq 6$  weeks: the first 3 doses are given 4 weeks apart and the fourth dose is given at age  $\geq 12$  months and  $\geq 6$  months after the third.

Adults with an uncertain history of primary vaccination should receive 3 doses of an inactivated tetanus and diphtheria toxoid (Td) vaccine. The first 2 doses should be administered  $\geq 4$  weeks apart and the third 6-12 months after the second. One of the 3 doses (preferably the first) should contain protein components of acellular pertussis combined with diphtheria and tetanus toxoids (Tdap) to also provide protection against pertussis. Two Tdap vaccines (*Adacel*; *Boostrix*) are available for use in adults, including those  $\geq 65$  years old.<sup>38</sup>

A booster dose of inactivated Td vaccine is recommended every 10 years for adults. All persons  $\geq 11$  years old who have completed a primary childhood series and have not yet received Tdap vaccine should receive a single dose, which can be given regardless of the interval since the last Td dose to provide pertussis protection before travel. Pregnant women should receive Tdap during each pregnancy.

Tetanus and diphtheria-containing vaccines may interact with carrier proteins on conjugate vaccines, suppressing the immune response to these vaccines; Tdap administration should be deferred until after administration of a meningococcal or pneumococcal conjugate vaccine.<sup>39</sup>

**TYPHOID** – Typhoid fever is usually acquired through consumption of food or water contaminated with *Salmonella typhi*. The risk is highest in South Asia. Other risk areas are East and Southeast Asia, Central and South America, the Caribbean, and Africa.

**Recommendations** – Vaccination is recommended for travelers going to areas where there is an increased risk of typhoid fever, especially if they expect a long stay or will be visiting friends or relatives or traveling outside routine tourist destinations.<sup>40,41</sup>

**The Vaccines** – A live-attenuated oral typhoid vaccine (*Vivotif*) is available for adults and children  $\geq 6$  years old. It is taken every other day as a single capsule (at least 1 hour before eating) for a total of 4 doses, beginning at least 2 weeks before departure. The capsules must be refrigerated. Antibiotics should be avoided for at least 24 hours before administration of the first dose and for 1 week after administration of the last dose. The vaccine provides protection for about 5 years.

A purified capsular polysaccharide parenteral vaccine (*Typhim Vi*) is FDA-licensed for use in adults and children  $\geq 2$  years old. It is given at least 2 weeks before departure and provides protection for about 2 years.

A combined hepatitis A/typhoid vaccine (*Vivaxim*) is available in Canada.

**VARICELLA** – Varicella is endemic worldwide. Vaccination against varicella has been part of routine childhood immunization in the US since 1996.

**Recommendations** – Persons born in the US before 1980 are generally considered immune to varicella.<sup>1</sup> Vaccination is recommended for all travelers  $\geq 12$  months old without evidence of immunity. Before traveling abroad, children 1–3 years old should receive 1 dose of vaccine and persons  $\geq 4$  years old should receive 2 doses. The minimum interval between doses should be 3 months for persons  $< 13$  years old and 4 weeks for those  $\geq 13$  years old.<sup>28</sup>

**The Vaccines** – Two varicella-containing vaccines are available in the US: single-antigen varicella vaccine (*Varivax*), which is licensed for use in persons  $\geq 12$  months old, and combination measles-mumps-rubella-varicella vaccine (MMRV; *ProQuad*), which is only licensed for use in children 12 months–12 years old.

**YELLOW FEVER** – Yellow fever virus is transmitted by the bite of an infected mosquito. It is endemic in tropical South America and sub-Saharan Africa.

**Recommendations** – The ACIP recommends administration of a single dose of yellow fever vaccine at least 10 days before travel to endemic areas.<sup>42</sup> Booster doses are no longer recommended for most travelers because a single dose has been shown to provide protection for many decades. Additional doses are still recommended for certain populations: women who were pregnant when they received their initial dose should receive one additional dose before traveling to an endemic area; persons who underwent a hematopoietic stem cell transplantation after being vaccinated should be revaccinated before traveling if they are sufficiently immunocompetent; persons who were infected with HIV when they received their last dose should receive a booster dose every 10 years if they continue to be at risk. A booster dose given at least 10 years after the previous dose may also be considered for travelers at increased risk of exposure, such as those planning prolonged travel in an endemic area or those traveling to highly endemic areas during peak transmission season or to an area with an ongoing outbreak.<sup>43</sup>

Some countries require an International Certificate of Vaccination or Prophylaxis (ICVP, "yellow card") as proof of vaccination against yellow fever, or a physician's waiver letter, from all entering travelers; other countries require evidence of vaccination from

travelers coming from or traveling through endemic or infected areas, including brief airport transits. An updated list of countries requiring proof of yellow fever vaccination is available at [www.cdc.gov/travel](http://www.cdc.gov/travel).

**The Vaccine** – US-licensed yellow fever vaccine (*YF-Vax*) is a live-attenuated vaccine prepared in eggs. It is usually available from providers certified by state health departments, but at press time it is temporarily out of stock; supplies are expected to be available by the middle of 2019. Some clinics are offering an alternative single-dose live vaccine (*Stamaril* – Sanofi Pasteur). A list of these clinics is available at [wwwnc.cdc.gov/travel/page/search-for-stamaril-clinics](http://wwwnc.cdc.gov/travel/page/search-for-stamaril-clinics). *Stamaril*, which has been used for decades in Europe, is available in the US under an investigational new drug program. It is comparable in efficacy and safety to *YF-Vax*.

Yellow fever vaccine-associated viscerotropic disease, a severe systemic illness that can cause fatal organ failure, has been reported rarely. It has occurred only in first-time recipients and is most common in persons  $> 60$  years old. Vaccine-associated neurologic disease (encephalitis, Guillain-Barré syndrome, Bell's palsy) has also occurred almost exclusively in first-time recipients; the risk is increased in infants and persons  $> 60$  years old.<sup>44,45</sup>

Caution is advised for vaccination of infants 6–8 months old, first-time recipients  $\geq 60$  years old, and those with asymptomatic HIV infection and moderate immune suppression (CD4 counts 200–499 cells/mm<sup>3</sup>). In a small study, relapse rates were significantly higher among travelers with multiple sclerosis who received yellow fever vaccine.<sup>46</sup> There have been case reports of vaccine-associated neurologic disease in breastfed infants of recently vaccinated women.<sup>47</sup> The vaccine is contraindicated in infants  $< 6$  months old, in persons with immunodeficiencies or receiving immunosuppressive or immunomodulatory therapies, and in those with HIV infection and CD4 counts  $< 200$  cells/mm<sup>3</sup>.<sup>42</sup> ■

#### Additional Content Available Online

Expanded Table: Some Vaccines for Travel  
<http://medicalletter.org/TML-article-1560b>  
Tickborne Encephalitis and Dengue Vaccines  
<http://medicalletter.org/TML-article-1560c>

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