Vaccines for Travel

- Clinical Policy Bulletins
- Medical Clinical Policy Bulletins

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses vaccines for travel.

1. **Medical Necessity**

   The following table lists vaccines that may be required for travel, and their medically necessary indications, standard administration schedule, and contraindications:

Table: List of Vaccines*

Vaccine	Standard Schedule	Indications	Precautions and Contraindications
Chikungunya	Single intramuscular dose of chikungunya vaccine, live (Ixchiq, Valneva USA)	For persons 18 years of age and older who are at increased risk of exposure to chikungunya virus (i.e., travelng to endemic areas).	Contraindicated in immunocompromised individuals. Safety and effectiveness in persons younger than 18 years have not been established
Cholera	Lyophilized *Vibrio cholerae* CVD 103-HgR (Vaxchora, Emergent Travel Health), after preparation, a single-dose, live attenuated oral cholera vaccine is administered a minimum of 10 days before potential exposure.	For persons 2 through 64 years of age traveling to endemic areas. **Note:** vaccination is not routinely recommended because cholera is rare in travelers and most travelers do not visit areas of active transmission (CDC, 2023).	Safety in pregnancy unknown. Safety and effectiveness have not been established in persons 65 years of age or older, or in immunocompromised individuals.
Dengue	see CPB 1010 - Dengue Vaccine		
Hepatitis A	see CPB 0048 - Hepatitis A Vaccine		
Hepatitis B	see CPB 0410 - Hepatitis B Vaccine		
Inactivated polio	see CPB 0402 - Polio Vaccine		
Japanese B encephalitis	Primary: 3 doses (1.0 ml) subcutaneously on days 0, 7,	Travel to areas of risk with rural exposure or prolonged residence.	Pregnancy; allergy to mice or rodents; immuno-compromised host.†

	and 30 or at weekly intervals.		
Lyme vaccine (LYMErix)††	Primary: 3 doses, 30 mg/0.5 ml, with the second dose 1 month after the first, and the third dose given at 1 year. Booster: The need for periodic booster doses has not been established.	Age 15 to 70 and live, work,* or travel or take part in regular recreational activities that make them likely to come into contact with infected deer ticks.	Hypersensitivity to vaccine; safety in pregnancy unknown; not tested in pediatric patients less than 15 years of age.
Measles	Infants 6 months through 11 months of age should receive 1 dose of MMR vaccine. Infants who get 1 dose of MMR vaccine before their 1st birthday should get 2 more doses (1 dose at 12 through 15 months of age and another dose at least 28 days later). Children 12 months of age and older should receive 2 doses of MMR vaccine separated by at least 28 days. Teenagers and adults who do not have evidence of immunity against measles should get 2 doses of MMR vaccine separated by at least 28 days. Acceptable presumptive evidence of immunity against measles includes at least one of the following: written documentation	Risk of exposure to measles.	Contraindications: Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, or long-term immunosuppressive therapy or patients with human immunodeficiency virus [HIV] infection who are severely immunocompromised). Vaccine should be deferred for the appropriate interval if replacement immune globulin products are being administered. HIV-infected children may receive varicella and measles vaccine if CD4+ T-lymphocyte count is greater than 15 %.Pregnancy Precautions: Moderate or severe acute illness with or without feverRecent (within 11 months) receipt of antibody-containing blood product (specific interval depends on product). Vaccine should be deferred for

	of adequate vaccination, laboratory evidence of immunity, laboratory confirmation of measles, or birth in the United States before 1957.		the appropriate interval if replacement immune globulin products are being administered History of thrombocytopenia or thrombocytopenic purpura Need for tuberculin skin testing. Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine can be administered on the same day as tuberculin skin testing. If testing cannot be performed until after the day of MMR vaccination, the test should be postponed for at least 4 weeks after the vaccination. If an urgent need exists to skin test, do so with the understanding that reactivity might be reduced by the vaccine.
Meningococcal vaccines	see CPB 0356 - Meningococcal Vaccines		
Oral polio	see CPB 0402 - Polio Vaccine		
Rabies (human diploid-cell vaccine)	Pre-exposure: 1 ml intramuscularly in deltoid on days 0, 7, and 21 or 28; or 0.1 ml intradermally, on days 0, 7, and 21 or 28. Booster: every 2 years or when antibody titer falls below acceptable level.	For persons at high-risk of rabies exposure including international travelers who are likely to come in contact with animals in areas where dog rabies is enzootic.	Allergy to previous doses; may be given in pregnancy if indicated; intradermal route should be completed 30 days or more before travel; intradermal route should not be used with concurrent chloroquine administration.
Tick-borne encephalitis virus vaccine (Ticovac)	Primary: 3 intramuscular doses 1 through 15 years of age: each dose 0.25 mL ◦ First dose: Day 0; ◦ Second dose: 1 to	Indicated for active immunization to prevent tick-borne encephalitis (TBE). Ticovac is approved for use in individuals 1 year of age and older.	Contraindicated in those with severe allergic reaction (e.g., anaphylaxis) to any component of Ticovac. There are no adequate and well-controlled studies of Ticovac in pregnant women. Some individuals with altered

	3 months after 1st dose; ◦ Third dose: 5 to 12 months after 2nd dose. 16 years of age and older: each dose 0.5 mL ◦ First dose: Day 0; ◦ Second dose: 14 days to 3 months after 1st dose; ◦ Third dose: 5 to 12 months after 2nd dose. Booster: A booster dose (fourth dose) may be given at least 3 years after completion of the primary immunization series if ongoing exposure or re-exposure to tickborne encephalitis virus (TBEV) is expected.		immunocompetence may have reduced immune responses to Ticovac. Ticovac contains albumin. There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) Adverse reactions: 1 through 15 years of age: Local tenderness, local pain, headache, fever and restlessness. 16 through 65 years of age: Local tenderness, local pain, fatigue, headache and muscle pain.
Typhoid, attenuated live bacteria	Primary: 4 oral doses; re-immunize every 5 years.	Risk of exposure to typhoid fever.	Immuno-compromised host†; enteric illness; concurrent antimicrobial treatment.
Typhoid, inactivated bacteria	Primary: 2 doses (0.5 ml) subcutaneously given 4 or more weeks apart. Booster: 0.5 ml subcutaneously or 0.1 ml intradermally, every 3 years.	Risk of exposure to typhoid fever.	Previous severe local or systemic reaction.
Yellow fever	Primary: 1 dose (0.5 ml) subcutaneously, 10 days to 10 years before	As requested by individual countries.	Avoid in pregnant women, unless engaged in high-risk travel; immuno-compromised host†;

	travel. Booster: every 10 years.		hypersensitivity to eggs.
Zaire ebolavirus vaccine, live (Ervebo)	Primary: single 1 mL dose administered intramuscularly. Booster: Not recommended.	Indicated for the prevention of disease caused by Zaire ebolavirus in individuals 18 years of age and older. Limitations: The duration of protection conferred is unknown. Vaccine does not protect against other species of Ebolavirus or Marburgvirus. Effectiveness of the vaccine when administered concurrently with antiviral medication, immune globulin (IG), and/or blood or plasma transfusions is unknown.	Anaphylaxis has been observed following administration of vaccine. Vaccinated individuals should continue to adhere to infection control practices to prevent Zaire ebolavirus infection and transmission. Vaccine virus RNA has been detected in blood, saliva, urine, and fluid from skin vesicles of vaccinated adults; transmission of vaccine virus is a theoretical possibility.

† Persons who are immunocompromised because of immune deficiency diseases, leukemia, lymphoma, generalized cancer, or the acquired immunodeficiency syndrome, or who are receiving immunosuppressive therapy with corticosteroids, alkylating agents, anti-metabolites, or radiation.

†† LYMErix was withdrawn from the U.S. market in February 2002.

* Most Aetna benefit plans exclude coverage of vaccines for work. Please check benefit plan descriptions.

Note: The Advisory Committee on Immunization Practices (1996) states that plague vaccination is not indicated for most travelers to countries in which cases of plague have been reported.

2. **Experimental, Investigational, or Unproven**

The following vaccines for travel are considered experimental, investigational, or unproven (not an all-inclusive list):

1. Malaria vaccine for travel because an effective malaria vaccine has yet to be developed.
2. Cholera vaccine for all other indications not listed in Section 1 including prevention of entero-toxigenic *Escherichia coli* diarrhea because the clinical value has not been established.

3. **Policy Limitations and Exclusions**

Note: Most Aetna HMO plans exclude coverage of vaccines for travel. Most Aetna traditional plans cover medically necessary travel vaccines for members of plans with preventive services benefits. Please check benefit plan descriptions.

Note: Many of these vaccines may also be considered medically necessary for reasons other than travel, and may be covered when medically necessary in members with preventive benefits, regardless of whether the plan excludes coverage of travel vaccines.

CPT Codes/ HCPCS Codes / ICD-10 Codes

CPT codes covered if selection criteria are met:

Code	Code Description
90589	Chikungunya virus vaccine, live attenuated, for intramuscular use
90625	Cholera vaccine, live, adult dosage, 1 dose schedule, for oral use [covered for age 2 – 64 only]
90626	Tick-borne encephalitis virus vaccine, inactivated; 0.25 mL dosage, for intramuscular
90627	0.5 mL dosage, for intramuscular use
90675	Rabies vaccine, for intramuscular use
90676	Rabies vaccine, for intradermal use
90690	Typhoid vaccine, live, oral
90691	Typhoid vaccine, Vi capsular polysaccharide (ViCPs), for intramuscular use
90707	Measles, mumps and rubella virus vaccine (MMR), live, for subcutaneous use
90710	Measles, mumps, rubella, and varicella vaccine (MMRV), live, for subcutaneous use
90717	Yellow fever vaccine, live, for subcutaneous use
90738	Japanese encephalitis virus vaccine, inactivated, for intramuscular use
90758	Zaire ebolavirus vaccine, live, for intramuscular use

Other CPT codes related to the CPB:

90460	Immunization administration through 18 years of age via any route of administration, with counseling by physician or other qualified health care professional; first vaccine/toxoid component
+90461	each additional vaccine/toxoid component
90471	Immunization administration (includes percutaneous, intradermal, subcutaneous, or intramuscular injections); one vaccine (single or combination vaccine/toxoid)
+ 90472	each additional vaccine (single or combination vaccine/toxoid) (list separately in addition to code for primary procedure)
90473	Immunization administration by intranasal or oral route; one vaccine (single or combination vaccine/toxoid)
+ 90474	each additional vaccine (single or combination vaccine/toxoid) (list separately in addition to code for primary procedure)
90644	Meningococcal conjugate vaccine, serogroups C & Y and Haemophilus influenzae type b vaccine (Hib-MenCY), 4 dose schedule, when administered to children 6 weeks-18 months of age, for intramuscular use

HCPCS codes covered if selection criteria are met:

G0010	Administration of hepatitis B vaccine

Other HCPCS codes related to the CPB:

G0310	Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service, 5 to 15 mins time (this code is used for Medicaid billing purposes)
G0311	Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service, 16-30 mins time (this code is used for Medicaid billing purposes)
G0312	Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service for ages under 21, 5 to 15 mins time (this code is used for Medicaid billing purposes)
G0313	Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service for ages under 21, 16-30 mins time (this code is used for Medicaid billing purposes)

ICD-10 codes covered if selection criteria are met:

Z23	Encounter for immunization

Background

The Centers for Disease Control and Prevention (CDC)'s recommended vaccinations for travelers can be found at the following website: Destinations and Travelers Health.

In a Cochrane review on vaccines for preventing malaria, Graves and Gelband (2006a) concluded that there is no evidence for protection by SPf66 vaccines against P. falciparum in Africa. There is a modest reduction in attacks of P. falciparum malaria following vaccination with SPf66 in South America. There is no justification for further trials of SPf66 in its current formulation. Further research with SPf66 vaccines in South America or with new formulations of SPf66 may be justified.

In another Cochrane review, Graves and Gelband (2006b) concluded that the MSP/RESA (Combination B) vaccine shows promise as a way to reduce the severity of malaria episodes, but the effect of the vaccine is MSP2 variant-specific. Pre-treatment for malaria during a vaccine trial makes the results difficult to interpret, particularly with the relatively small sample sizes of early trials. The results show that blood-stage vaccines may play a role and merit further development.

Vaughan et al (2009) presented a comprehensive meta-analysis of more than 500 references, describing nearly 5,000 unique B cell and T cell epitopes derived from the Plasmodium genus, and detailing thousands of immunological assays. This was the first inventory of epitope data related to malaria-specific immunology, plasmodial pathogenesis, and vaccine performance. The survey included host and pathogen species distribution of epitopes, the number of antibody versus CD4(+) and CD8(+) T cell epitopes, the genomic distribution of recognized epitopes, variance among epitopes from different parasite strains, and the characterization of protective epitopes and of epitopes associated with parasite evasion of the host immune response. The results identified knowledge gaps and areas for further investigation. This information has relevance to issues, such as the identification of epitopes and antigens associated with protective immunity, the design and development of candidate malaria vaccines, and characterization of immune response to strain polymorphisms.

Currently, there is an ongoing phase III clinical trial of a candidate vaccine for malaria, but the study has not been completed (Birkett, 2010).

The Advisory Committee on Immunization Practices (ACIP) of the CDC provided the following recommendations regarding the prevention of plague (1996):

- Routine plague vaccination is not necessary for individuals living in areas in which plague is enzootic.
- Plague vaccination is not indicated for hospital staff or other medical personnel in such areas.
- Plague vaccination is not indicated for most travelers to countries in which cases of plague have been reported.

In a Cochrane review, Ahmed et al (2013) evaluated the safety, effectiveness, and immunogenicity of vaccines for preventing entero-toxigenic Escherichia coli (ETEC) diarrhea. These investigators searched the Cochrane Infectious Disease Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, and ClinicalTrials up to December 2012. Randomized controlled trials (RCTs) and quasi-RCTs comparing use of vaccines to prevent ETEC with use of no intervention, a control vaccine (either an inert vaccine or a vaccine normally given to prevent an unrelated infection), an alternative ETEC vaccine, or a different dose or schedule of the same ETEC vaccine in healthy adults and children living in endemic regions, intending to travel to endemic regions, or volunteering to receive an artificial challenge of ETEC bacteria were included for analysis. Two authors independently assessed each trial for eligibility and risk of bias. Two independent reviewers extracted data from the included studies and analyzed the data using Review Manager (RevMan) software. They reported outcomes as risk ratios (RR) with 95 % confidence intervals (CI) and assessed the quality of the evidence using the GRADE approach. A total of 24 RCTs, including 53,247 participants, met the inclusion criteria – 4 studies assessed the protective efficacy of oral cholera vaccines when used to prevent diarrhea due to ETEC and 7 studies assessed the protective efficacy of ETEC-specific vaccines. Of these 11 studies, 7 studies presented efficacy data from field trials and 4 studies presented efficacy data from artificial challenge studies. An additional 13 trials contributed safety and immunological data only. The currently available, oral cholera killed whole cell vaccine (Dukoral®) was evaluated for protection of people against "travelers' diarrhea" in a single RCT in people arriving in Mexico from the USA. These researchers did not identify any statistically significant effects on ETEC diarrhea or all-cause diarrhea (1 trial, 502 participants; low-quality evidence). Two earlier trials, one undertaken in an endemic population in Bangladesh and one undertaken in people travelling from Finland to Morocco, evaluated a precursor of this vaccine containing purified cholera toxin B subunit rather than the recombinant subunit in Dukoral®. Short-term protective efficacy against ETEC diarrhea was demonstrated, lasting for around 3 months (RR 0.43, 95 % CI: 0.26 to 0.71; 2 trials, 50,227 participants). This vaccine is no longer available. An ETEC-specific, killed whole cell vaccine, which also contains the recombinant cholera toxin B-subunit, was evaluated in people traveling from the USA to Mexico or Guatemala, and from Austria to Latin America, Africa, or Asia. These investigators did not identify any statistically significant differences in ETEC-specific diarrhea or all-cause diarrhea (2 trials, 799 participants), and the vaccine was associated with increased vomiting (RR 2.0, 95 % CI: 1.16 to 3.45; 9 trials, 1,528 participants). The other ETEC-specific vaccines in development have not yet demonstrated clinically important benefits. The authors concluded that there is currently insufficient evidence from RCTs to support the use of the oral cholera vaccine Dukoral® for protecting travelers against ETEC diarrhea. Moreover, they stated that further research is needed to develop safe and effective vaccines to provide both short- and long-term protection against ETEC diarrhea.

Also, an UpToDate review on "Travelers' diarrhea" (Wanke, 2014) states that "Use of vaccines to protect against travelers' diarrhea is hindered by the varied pathogens that can cause it. Although enterotoxigenic E. coli (ETEC) predominates as an etiology of travelers' diarrhea, vaccination strategies that have focused on this pathogen as a target have been suboptimal.

Although vaccination to protect against cholera is not routinely recommended for travelers, a number of trials suggest that the oral, killed whole-cell vaccine given with the nontoxic B subunit of cholera toxin (Dukoral) provides protection for travelers against ETEC infection. The rationale for such protection is that the B subunit of cholera is antigenically similar to the heat-labile enterotoxin of ETEC. In two randomized trials, the killed whole-cell vaccine combined with the B subunit of cholera toxin reduced the incidence of diarrhea caused by ETEC by 67 percent in a trial in Bangladesh and 52 percent among travelers to Morocco. The Dukoral vaccine was approved in the United States in late 2006 for use as a travelers' diarrhea vaccine. However, a conservative estimate that took into account the incidence of ETEC infection throughout the world and the efficacy of the vaccine suggested that it may prevent ≤7 percent of travelers' diarrhea cases. The 2006 guidelines on travel medicine from the Infectious Diseases Society of America concluded that the decision to use the vaccine to prevent travelers' diarrhea must balance its cost, adverse effects, and limited utility against the known effectiveness and costs of self-treatment as described above. A separate vaccination strategy for ETEC also appears to have limited utility. Despite initial promising data on vaccination with heat-labile enterotoxin from ETEC via a skin patch, it was not effective in decreasing the incidence of moderate to severe diarrhea due to either ETEC or any cause in a randomized, placebo controlled trial that included 1,644 individuals who traveled to Mexico or Guatemala. In a subgroup analysis, the vaccine provided modest protection against ETEC that produced only heat-labile enterotoxin (vaccine efficacy 61 percent [95 % CI, 7 to 84 percent]), but not ETEC that produced heat-stable toxin or both. This highlights the limitations of a single-antigen vaccine for travelers’ diarrhea".

An UpToDate review on "Immunizations for travel" (Freedman and Leder, 2015) states that "In general, severely immunocompromised patients should not receive live vaccines. Live vaccines include yellow fever vaccine, oral typhoid vaccine, nasal influenza vaccine, oral polio vaccine (OPV), MMR, and varicella vaccine. Inactivated vaccines include meningococcal vaccine, parenteral typhoid vaccine, hepatitis A and B vaccines, rabies vaccine, Japanese encephalitis vaccine, inactivated influenza vaccine, inactivated polio vaccine (IPV), Tdap, and Td".

Chikungunya Vaccine

Chikungunya is primarily a mosquito-borne alphavirus caused by the chikungunya virus (CHIKV) that is often associated with fever and debilitating joint pain. Rarely, the virus can be transmitted via blood products, laboratory and maternal-fetal transmission. Outbreaks typically occur in tropical and subtropical regions of Africa, Asia, Oceania, and parts of the Americas and Europe where chikungunya virus-carrying mosquitos are endemic (Bettis et al, 2022; Wilson and Lenschow, 2022). Between 2014 and 2016, 3,941 cases were reported in the United States among travelers; 92% were associated with travel in the Americas (most commonly the Dominican Republic, Puerto Rico, and Haiti). The remaining 8% had traveled to Asia, Africa, or the Western Pacific (Lindsey et al, 2018; Wilson and Lenschow, 2022).

Management of the chikungunya virus is supportive (i.e., rest, fluids, antiinflammatory and analgesic agents). Systemic glucocorticoids or treatment with a disease-modifying antirheumatic drug (DMARD) has been used in refractory or chronic arthritis cases. The cornerstone of prevention has been minimizing mosquito exposure (Lenschow and Wilson, 2023). In November 2023, the FDA approved the first chikungunya vaccine (Ixchiq, Valneva Scotland Ltd) for the prevention of disease caused by chikungunya virus (CHIKV) in individuals 18 years of age and older who are at increased risk of exposure to CHIKV. "This indication is approved under accelerated approval based on anti-CHIKV neutralizing antibody titers. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory studies" (Valneva, 2023).

FDA approval was based on two clinical trials conducted in North America that evaluated the safety of Ixchiq in adults 18 years or older. In clinical studies, the most common solicited injection site reaction (greater than 10%) was tenderness (10.6%). The most common solicited systemic adverse reactions (greater than 10%) were headache (31.6%), fatigue (28.5%), myalgia (23.9%), arthralgia (17.2%), fever (13.5%) and nausea (11.2%). The effectiveness was based on immune response data from a clinical study conducted in the US in adults. "In this study, the immune response of 266 participants who received the vaccine was compared to the immune response of 96 participants who received placebo. The level of antibody evaluated in study participants was based on a level shown to be protective in non-human primates that had received blood from people who had been vaccinated. Almost all vaccine study participants achieved this antibody level" (FDA, 2023).

Ixchiq is administered as a single intramuscular injection. Ixchiq contains a live, weakened version of the chikungunya virus and may cause symptoms in the vaccine recipient similar to those experienced by people who have chikungunya disease. It is contraindicated in immunocompromised individuals or those with a history of a severe allergic reaction to any component of Ixchiq. Vertical transmission of wild-type CHIKV from pregnant individuals with viremia at delivery is common and can cause potentially fatal CHIKV disease in neonates. Vaccine viremia occurs in the first week following administration of Ixchiq, with resolution of viremia by 14 days after vaccination. It is not known if the vaccine virus can be vertically transmitted and cause fetal or neonatal adverse reactions. A decision to administer during pregnancy should take into consideration the individual’s risk of wild-type CHIKV infection, gestational age, and risks to the fetus or neonate from vertical transmission of wild-type CHIKV. Labeled warnings and precautions also include risk of syncope associated with administration of injectable vaccines (Valneva, 2023).

The Centers for Disease Control's (CDC) Advisory Committee on Immunization Practices (ACIP) met in October 2023 to discuss recommendations for the chikungunya vaccine. Draft recommendations include chikungunya vaccine recommendation for persons 18 years of age and older traveling to a country or territory where there is a chikungunya outbreak. In addition, the

vaccine may be considered for persons traveling to a country or territory without an outbreak but with evidence of chikungunya virus transmission among humans within the last 5 years:

- Older persons (e.g., >65 years), particularly those with underlying medical conditions, who are likely to have at least moderate exposure (moderate exposure could include travelers who might have at least 2 weeks (cumulative) of exposure to mosquitoes in indoor and/or outdoor settings) to mosquitoes
- Persons staying for a cumulative period of 6 months or more during a 2-year period

The ACIP is an anticipated to vote on the drafted recommendations at the February 2024 ACIP meeting (CDC, 2023).

Japanese Encephalitis Vaccine for Pediatric Travelers

Taucher and colleagues (2020) stated that in an initial study among children from non-Japanese encephalitis (JE)-endemic countries, sero-protection rates (SPRs) remained high 6 months following completion of the primary series with IXIARO. In an open-label, follow-up study, a subset of 23 children who received a 2-dose primary series of IXIARO in the parent study, were examined for safety and neutralizing antibody persistence for 36 months. SPRs remained high but declined from 100 % 1 month after primary immunization to 91.3 % at month 7 and 89.5 % at month 36. Geometric mean titers (GMTs) declined considerably from 384.1 by day 56-60.8 at month 36. No long-term safety concerns were identified. The authors concluded that the substantial decline in GMT observed in this study, together with previously published data on children vaccinated with IXIARO supported the recommendation for a booster dose in children who remain at risk of JE from 1 year after the primary series of IXIARO, consistent with the recommendation for adults.

Measles

Jost and colleagues (2015) evaluated the relevance of travel-related measles, a highly transmissible and vaccine-preventable disease. Between 2001 and 2013, surveillance and travel-related measles data were systematically reviewed according to the PRISMA guidelines with extraction of relevant articles from Medline, Embase, GoogleScholar and from public health authorities in the Region of the Americas, Europe and Australia. From a total of 960 records, 44 articles were included and they comprised 2,128 imported measles cases between 2001 and 2011. The proportion of imported cases in Europe was low at 1 to 2 %, which reflected the situation in a measles-endemic region. In contrast, imported and import-related measles accounted for up to 100 % of all cases in regions with interrupted endemic measles transmission; 11 air-travel related reports described 132 measles index cases leading to 47 secondary cases. Secondary transmission was significantly more likely to occur if the index case was younger or when there were multiple infectious cases on board. Further spread to health care settings was found. Measles cases associated with cruise ship travel or mass gatherings were sporadically observed. The authors concluded that within both, endemic and non-endemic home countries, pre-travel health advice should assess MMR immunity routinely to avoid measles spread by non-immune travelers. They stated that to identify measles spread as well as to increase and sustain high vaccination coverages, joint efforts of public health specialists, health care practitioners and travel medicine providers are needed.

An UpToDate review on "Immunizations for travel" (Freedman and Leder, 2016) states that "Children traveling outside the United States should receive MMR vaccination sooner than the standard immunization schedule. Prior to departure, children 12 months of age or older should have received 2 doses of MMR vaccine separated by at least 28 days, with the first dose administered on or after the first birthday. Children aged 6 to 11 months should receive 1 dose of MMR before departure. MMR vaccination for adults is indicated for individuals born in 1957 or later in the United States (before 1970 in Canada; before 1966 in Australia) without evidence of immunity or without evidence of 2 doses of an adequate live vaccine at any time after age 12 months. Although individuals born before 1957 in the United States are presumed to be immune (exceptions include United States healthcare workers and women of childbearing age), 2 doses of MMR vaccine spaced by 1 month should be strongly considered for unvaccinated individuals without other evidence of immunity who were born before 1957 (in the United States) and are traveling for purposes of healthcare or humanitarian work potentially entailing close contact with ill individuals. MMR vaccination is contraindicated in pregnant and immunocompromised patients".

The CDC (2015) states that anyone who is not protected against measles is at risk of getting infected when they travel internationally. It recommends the following: Centers for Disease Control and Prevention.

- Infants 6 months through 11 months of age should receive 1 dose of MMR vaccine†
- Children 12 months of age and older should receive 2 doses of MMR vaccine separated by at least 28 days.
- Teenagers and adults who do not have evidence of immunity* against measles should get 2 doses of MMR vaccine separated by at least 28 days.

† Infants who get 1 dose of MMR vaccine before their first birthday should get 2 more doses (1 dose at 12 through 15 months of age and another dose at least 28 days later).

* Acceptable presumptive evidence of immunity against measles includes at least one of the following: written documentation of adequate vaccination, laboratory evidence of immunity, laboratory confirmation of measles, or birth in the United States before 1957.

Contraindications and Precautions: Vaccine Recommendations and Guidelines of the ACIP.

Contraindications

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component
- Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, or long-term immunosuppressive therapy† or patients with human immunodeficiency virus [HIV] infection who are severely immunocompromised)*
- Pregnancy

† Vaccine should be deferred for the appropriate interval if replacement immune globulin products are being administered.

* HIV-infected children may receive varicella and measles vaccine if CD4+ T-lymphocyte count is greater than 15 %.

Precautions

- Moderate or severe acute illness with or without fever
- Recent (within 11 months) receipt of antibody-containing blood product (specific interval depends on product)†
- History of thrombocytopenia or thrombocytopenic purpura
- Need for tuberculin skin testing*

† Vaccine should be deferred for the appropriate interval if replacement immune globulin products are being administered

* Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine can be administered on the same day as tuberculin skin testing. If testing cannot be performed until after the day of MMR vaccination, the test should be postponed for at least 4 weeks after the vaccination. If an urgent need exists to skin test, do so with the understanding that reactivity might be reduced by the vaccine.

Tick-Borne Encephalitis Vaccine

Rampa et al (2020) state that tick-borne encephalitis (TBE) is increasing in Europe and has become one of the most important causes of viral encephalitis, as well as the most frequent cause of viral meningitis, in Europe. The authors note that there is no antiviral treatment against TBE and that active vaccination is a practical preventive measure to reduce the number of cases. There are two inactivated virus vaccines licensed in Europe: FSME-Immun® (Pfizer), in some countries distributed as Ticovac®, and Encepur® (Bavarian Nordic). FSME-Immun is based on the TBE virus strain Neudoerfl (Nd), whereas Encepur is based on the TBE virus strain Karlsruhe-23 (K23). Both vaccines have a pediatric TBE vaccine variant. Thus, the authors conducted a systematic review (registered at PROSPERO (#CRD42020155737) and conducted in accordance with PRISMA guidelines) of the immunogenicity and safety of the tick-borne encephalitis vaccine (2009-2019). Of a total of 2464 records, 49 original research publications included evaluation for immunogenicity and safety. The authors found that TBE-vaccines showed adequate immunogenicity, good safety and interchangeability in adults and children with some differences in long-term protection (seropositivity in 90.6–100% after primary vaccination; 84.9%–99.4% at 5 year follow up). Primary conventional vaccination schedule (days 0, 28, and 300) demonstrated the best immunogenic results (99–100% of seropositivity). Mixed brand primary vaccination presented adequate safety and immunogenicity with some exceptions. After booster follow-ups, accelerated conventional and rapid vaccination schedules were shown to be comparable in terms of immunogenicity and safety. First booster vaccinations five years after primary vaccination were protective in adults aged less than 50 years, leading to protective antibody levels from at least 5 years up to 10 years after booster vaccination. In older vaccinees, 50 years and older, lower protective antibody titers were found. Allergic individuals showed an adequate response and immunosuppressed individuals a diminished response to TBE-vaccination. The authors concluded that the TBE-vaccination with Encepur or FSME-Immun to be highly immunogenic, well tolerated and in all studies except one to be interchangeable. Schedules should, if possible, use the same vaccine brand (non-mixed). TBE-vaccines are immunogenic in terms of antibody response but less so when vaccination is started after the age of 50 years. Age at priming is a key factor in the duration of protection. In terms of safety, the European, licensed vaccines were found to be well tolerated in both children (aged 1–17 years) and in adults, with local injection site reactions in 24.8% (4.3–54%) and systematic reactions in 30% (0.6–45.9%) of vaccinees. Vaccine related serious adverse events (SAE) were rare.

In February 2021, the U.S. FDA accepted for Priority Review Pfizer’s Biologics License Application (BLA) for TicoVac, its tick-borne encephalitis (TBE) vaccine for active immunization to prevent TBE in individuals 1 year of age and older. If approved, TicoVac would be the first vaccine in the U.S. to help protect adults and children who are visiting or living in TBE endemic areas. In line with Priority Review designation, the FDA will target an action within six months of the application submission date, with the anticipated Prescription Drug User Fee Act (PDUFA) action date expected for August 2021.

The BLA is based on results from "more than 40 years of experience and evidence outside the U.S. In clinical trials, the safety and immunogenicity of TicoVac was assessed across two age groups (1-15 years of age and 16-65 years of age). In these studies, pooled seropositivity rates were 99-100% in 1-15 year olds and 94-99% in adults >15 years following three doses. Clinical studies demonstrated that TicoVac was well-tolerated with no unexpected adverse events or vaccine-related serious

adverse events observed. Subsequent real-world studies have shown that the vaccine is 96-99% effective in people who have received at least two doses of the vaccine, and two to three doses of the vaccine were shown to be sufficient to provide a long-lasting immune memory" (Pfizer, 2021b).

On August 13, 2021, the U.S. FDA approved Ticovac (Pfizer Inc.), tick-borne encephalitis (TBE) vaccine, for active immunization to prevent TBE in individuals 1 year of age and older. FDA approval was based on the safety and immunogenicity of Ticovac that were assessed cross two age groups (Study 209: 1 to15 years of age and Studies 213 and 690601: persons 16 years of age and older). In these studies, seropositivity rates were 99.5% in the group of 1 to 15 year olds and 98.7-100% in persons older than 15 years following three primary doses. Clinical studies demonstrated that Ticovac was generally well-tolerated with no unexpected adverse events or vaccine-related serious adverse events observed. The most common adverse reactions across both age groups were local tenderness, headache, local pain, fever, restlessness, fatigue, and muscle pain. Real-world studies from Austria have shown that the vaccine is 96-98.7% effective in people who have received at least three doses of the vaccine (Pfizer, 2021a, 2021c).

Two open-label, multi-center, follow-up studies which enrolled subjects who were seropositive 1 month after the third vaccination from Studies 213 (N=252, ages 16 through 65 at the time of first TICOVAC dose) and 209 (N=358, ages 1 through 15 at the time of first Ticovac dose) were conducted to assess the seropersistence of TBE antibodies after completion of the primary vaccination series and the antibody response to a booster administration. Three years after the primary series of Ticovac , neutralization test (NT) seropositivity in follow-up studies 223 and 700401 ranged from 82.9% to 100% depending on age. Following a booster dose the NT seropositivity rates were 100% (Pfizer, 2021a).

Vaccines for Pregnant Travelers

Nasser and colleagues (2020) noted that pregnant travelers and their offspring are vulnerable to severe outcomes following a wide range of infections. Vaccine-preventable diseases can have a particularly severe course in pregnant women, but little is known about the safety of travel vaccines in pregnant women. These investigators carried out a systematic review of all published literature concerning the safety of vaccines frequently given to travelers such as yellow fever, MMR (mumps, measles and rubella), influenza, Tdap (tetanus, diphtheria and pertussis), meningococcus, hepatitis A and B, rabies, polio, typhoid fever, tick-borne encephalitis and Japanese encephalitis vaccines. They included case series, cohort studies and RCTs. For the meta-analysis, these researchers included only RCTs that compared the administration of a vaccine to placebo or to no vaccine. Outcome measures included severe systemic adverse events (AEs), maternal outcomes related to the course of pregnancy, neonatal outcomes and local AEs. They calculated the RR and its 95 % CI as the summary measure. The safety of influenza vaccine is supported by high-quality evidence. For Tdap vaccine, no evidence of any harm was found in the meta-analysis of RCTs. A slight increase in chorioamnionitis rate was reported in 3 out of 12 observational studies. However, this small possible risk is far out-weighed by a much larger benefit in terms of infant morbidity and mortality. Meningococcal vaccines are probably safe during pregnancy, as supported by RCTs comparing meningococcal vaccines to other vaccines. Data from observational studies support the safety of hepatitis A, hepatitis B and rabies vaccines, as well as that of the live attenuated yellow fever vaccine. The authors found little or no data about the safety of polio, typhoid, Japanese encephalitis, tick-borne encephalitis and MMR vaccines during pregnancy.

Yellow Fever Vaccine Safety in Immunocompromised Individuals

de Araujo Lagos et al (2023) stated that yellow fever (YF) is an arbovirus with variable severity, including severe forms with high mortality; and vaccination is the most effective measure to protect against the disease . Non-serious and serious AEs have been described in immunocompromised individuals; however, previous studies have failed to show this association. In a systematic review, these investigators examined the risk of AEs following YF vaccination in immunocompromised individuals compared with its use in non-immunocompromised individuals. They carried out a literature search in the Medline, LILACS, Embase, SCOPUS, DARE, Toxiline, Web of Science and grey literature databases for publications until February 2021. Randomized and quasi-randomized clinical trials and observational studies that included immunocompromised subjects (individuals with HIV infection, organ transplantation, cancer, who used immunosuppressive drugs for rheumatologic diseases and those on immunosuppressive therapy for other diseases) were selected. The methodological quality of observational or non-randomized studies was assessed by the ROBINS-I tool. These researchers carried out 2 meta-analyses, proportion and risk factor analyses, to identify the summary measure of RR in the studies that had variables suitable for combination. A total of 25 studies were included, most with risk of bias classified as critical; 13 studies had enough data to perform the proposed meta-analyses; 7 studies without a comparator group had their results aggregated in the proportion meta-analysis, identifying an 8.5 % (95 % CI: 0.07 to 21.8] risk of immunocompromised individuals presenting AEs following vaccination; 6 cohort studies were combined, with an RR of 1.00 (95 % CI: 0.78 to 1.29). Subgroup analysis was conducted according to the etiology of immunosuppression and was also unable to identify an increased risk of AEs following vaccination. The authors concluded that it was not possible to affirm that immunocompromised individuals, regardless of etiology, had a higher risk AEs, following receiving the YF vaccine.

Schnyder et al (2024) noted that long-term immunity following yellow fever vaccination remains controversial. In a systematic review and meta-analysis, these investigators examined the available evidence regarding the long-term protection (10 years or longer) conveyed by a single-dose of yellow fever vaccination. They searched 11 databases from their inception to August 24, 2023. These researchers included cohort and cross-sectional studies reporting immunogenicity outcomes for children or adults who received a single-dose of yellow fever vaccination 10 or more years ago. Case series and single case reports were

excluded. Participants who received more than 1 dose of yellow fever vaccination before measurement of the outcome were excluded. Identified records were reviewed by 2 independent reviewers. The primary outcome of the meta-analysis was the pooled sero-protection rate. Risk of bias was assessed with the Risk Of Bias In Non-randomized Studies of Interventions tool, and the Joanna Briggs Institute tool for analytical cross-sectional studies. Studies of moderate or good quality that reported sero-protection were included for random-effects meta-analysis and stratified by endemicity and specific risk groups. Of the 7,363 articles identified by the search, 39 were eligible for inclusion for systematic review. These studies comprised 2,895 individuals vaccinated 10 to 60 years ago. A total of 20 studies were included in the meta-analysis. Pooled sero-protection rates were 94 % (95 % CI: 86 to 99) among healthy adults in a non-endemic setting (mostly travelers) and 76 % (65 to 85) in an endemic setting (all Brazilian studies). The pooled sero-protection rate was 47 % (35 to 60) in children (aged 9 to 23 months at time of vaccination) and 61 % (38 to 82) in individuals living with HIV. Reported criteria for sero-protection were highly heterogeneous. The authors concluded that the gathered evidence suggested that a single-dose of yellow fever vaccination provided lifelong protection in travelers; however, in individuals living with HIV and children (younger than 2 years), booster doses might still be needed because lower proportions of vaccinees were sero-protected 10 or more years post-vaccination. Lower observed sero-protection rates among residents of endemic areas were partly explained by the use of a higher cut-off for sero-protection that was applied in Brazil. Studies from sub-Saharan Africa were scarce and of low-quality; therefore, no conclusions could be drawn for this region.

Zaire Ebolavirus Vaccine

The Ebola virus [Zaire ebolavirus (EBOV)] vaccine is a replication-competent, live, attenuated recombinant vesicular stomatitis virus (rVSV) vaccine. It contains a gene from the Ebola virus, not the whole virus, which means persons cannot become infected with EBOV from the vaccine. The vaccine is known as rVSVΔG-ZEBOV-GP Ebola vaccine, brand name Ervebo (manufactured by Merck). The vaccine was approved by the U.S. FDA on December 19, 2019, for the prevention of Ebola virus disease (EVD) caused by EBOV in people 18 years of age and older, based on the data from 12 clinical trials that included a total of 15,399 adults (CDC, 2021).

Study 3 (Ring vaccination study) was an open-label, randomized cluster (ring) vaccination study conducted in the Republic of Guinea during the 2014 outbreak. Each cluster was composed of contacts and contacts of contacts of individuals with laboratory-confirmed Ebola virus disease (EVD). Clusters were randomized to receive either an “immediate” vaccination or a 21-day “delayed” vaccination. In the primary efficacy analysis, 3,537 subjects 18 years of age and older were considered contacts and contacts of contacts of an index case with laboratory-confirmed EVD. Of these, 2,108 were included in 51 immediate vaccination clusters, and 1,429 were included in 46 delayed vaccination clusters. In the primary efficacy analysis, the number of cases of laboratory-confirmed EVD in subjects vaccinated in immediate vaccination clusters was compared to the number of cases in subjects in delayed vaccination clusters. Cases of EVD that occurred between Day 10 and Day 31 post-randomization of the cluster were included in the analysis. Vaccine efficacy was 100%; no cases of confirmed EVD were observed in the immediate vaccination clusters, and 10 confirmed cases of EVD were observed in a total of 4 delayed vaccination clusters between Day 10 and Day 31 post-randomization (Merck, 2019).

On February 26, 2020, the Advisory Committee on Immunization Practices (ACIP) recommended pre-exposure vaccination with Ervebo® for adults aged 18 years or older in the U.S. population who are at potential risk of exposure to EBOV. This recommendation includes adults who are responding or may respond to an outbreak of EVD; laboratorians or other staff working at biosafety-level 4 facilities in the United States; or healthcare personnel (HCP) working at federally designated Ebola Treatment Centers in the United States. HCP refers to all paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials, including body substances (e.g., blood, tissue, and specific body fluids); contaminated medical supplies, devices, and equipment; contaminated environmental surfaces; or contaminated air. These HCP include, but are not limited to, emergency medical service personnel, nurses, nursing assistants, physicians, technicians, clinical laboratory personnel, autopsy personnel, therapists, phlebotomists, pharmacists, students and trainees, contractual staff not employed by the healthcare facility, and persons not directly involved in patient care, but who could be exposed to infectious agents that can be transmitted in the healthcare setting (e.g., clerical, dietary, environmental services, laundry, security, engineering and facilities management, administrative, billing, and volunteer personnel) (CDC, 2021).

Ervebo (Merck Sharp & Dohme Corporation) is a vaccine indicated for the prevention of disease caused by Zaire ebolavirus in individuals 18 years of age and older. Immunization with Ervebo results in an immune response and protection from disease caused by Zaire ebolavirus. The relative contributions of innate, humoral and cell-mediated immunity to protection from Zaire ebolavirus are unknown.

Limitations of use include:

- The duration of protection conferred by Ervebo is unknown;
- Ervebo does not protect against other species of Ebolavirus or Marburgvirus;
- Effectiveness of the vaccine when administered concurrently with antiviral medication, immune globulin (IG), and/or blood or plasma transfusions is unknown.

Ervebo is available as 1 mL suspension for injection supplied as a single-dose vial and is to be administered intramuscularly.

Ervebo label carries warnings and precautions for anaphylaxis. Vaccinated individuals should continue to adhere to infection control practices to prevent Zaire ebolavirus infection and transmission. Vaccine virus RNA has been detected in blood, saliva, urine, and fluid from skin vesicles of vaccinated adults; transmission of vaccine virus is a theoretical possibility. The most common injection-site adverse events were injection-site pain (70%), swelling (17%), and redness (12%). The most common systemic adverse events reported were headache (37%), feverishness (34%), muscle pain (33%), fatigue (19%), joint pain (18%), nausea (8%), arthritis (5%), rash (4%) and abnormal sweating (3%) (Merck, 2019).

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Policy History

- Last Review 11/05/2024

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- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes