

TYPHOID VACCINE

Typhoid Vaccine

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Introduction

Typhoid vaccine is available as an oral live, attenuated vaccine (typhoid vaccine live oral Ty21a; Vivotif[®])¹⁰³, and a parenteral inactivated Vi polysaccharide vaccine (typhoid Vi polysaccharide vaccine; Typhim Vi[®]).¹²³

Uses

■ Prevention of Typhoid Fever

Typhoid vaccine live oral Ty21a and typhoid Vi polysaccharide vaccine are used to stimulate active immunity to prevent typhoid fever.^{103,123}

There are currently 2 preparations of typhoid vaccine commercially available in the US.^{103,123} Typhoid vaccine live oral Ty21a (Vivotif[®]) is an oral vaccine containing live, attenuated *Salmonella typhi* (*S. typhi*) of the Ty21a strain and is used for immunization against disease caused by *S. typhi* in adults and pediatric patients >6 years of age.¹⁰³ Typhoid Vi polysaccharide vaccine (Typhim Vi[®]) is a parenteral inactivated vaccine containing polysaccharide antigens extracted from *S. typhi* of the Ty2 strain and is used for active immunization for the prevention of typhoid fever caused by *S. typhi* in adults and pediatric patients ≥2 years of age.¹²³ Although a parenteral whole-cell heat/phenol-inactivated typhoid vaccine was previously used in the US, this vaccine was associated with a high rate of adverse effects and is no longer available.¹⁰³ Other typhoid vaccines (e.g., inactivated protein-conjugated Vi polysaccharide vaccines) may be available in other countries.¹¹⁵

Typhoid fever is a potentially severe and occasionally life-threatening, febrile, enteric illness caused by *Salmonella enterica* serovar Typhi and usually is acquired by ingestion of food and/or water contaminated with feces from individuals who have typhoid fever or are chronic typhoid carriers.^{102,105,115} The usual incubation period for typhoid fever is 6–30 days; however, the range may vary depending on infectious dose and host factors.¹¹⁵ Onset of illness is gradual with increasing fatigue and a fever that starts as low-grade and increases to 39–40°C by the third or fourth day of illness.¹¹⁵ Almost all patients have symptoms of anorexia, headache, and malaise with illness; abdominal pain, constipation, and diarrhea are also common.¹¹⁵ Serious complications include life-threatening GI hemorrhage, intestinal perforation, and encephalopathy, and generally occur after 2–3 weeks of illness.¹¹⁵ The overall case-fatality rate of typhoid fever in patients who receive early and appropriate antibacterial treatment is typically less than 1%;¹⁰² however, the case-fatality rate for untreated disease from the pre-antibiotic era has been reported at >10%.^{102,115}

Typhoid fever is uncommon in the US.¹⁰² The risk for infection is high in countries with endemic disease, poor access to safe food and water, and poor sanitation.¹¹⁵ About 9.2 million cases of typhoid fever occur worldwide each year.¹¹⁵ In 2019, there were about 450 culture-confirmed cases of typhoid fever reported in the US.¹¹⁵ During 2020–2021, when US travel patterns were affected by COVID-19, there were about 150–160 reported cases of typhoid fever each year.¹¹⁵ About 85% of cases in the US occur among international travelers, with >70% of cases in those returning from South Asia.¹¹⁵ While the risk of acquiring illness increases with the duration of stay, travelers to areas where the disease is highly endemic have acquired typhoid fever during visits lasting <1 week.¹¹⁵

Routine vaccination against typhoid fever is not recommended in the US.^{103,123} Selective immunization is recommended for travelers to areas in which there is a recognized risk of exposure to *S. typhi*, individuals with intimate exposure (e.g., household contact) to a *S. typhi* carrier, and microbiology laboratory personnel who work frequently with *S. typhi*.^{103,123}

Vaccination against typhoid is not required for international travel, but is recommended for travelers to areas with a recognized risk of exposure to *S. typhi*.¹²³ For travelers who will have prolonged exposure to potentially contaminated food and water, vaccination is particularly recommended.¹²³ However, all travelers, regardless of their vaccination status, should still use caution in selecting food and water.¹²³

There is no evidence to support typhoid vaccination to control common source outbreaks, disease following natural disasters, or in persons attending rural summer camps. ^{103,123,}

Not all recipients of typhoid vaccine will be fully protected against typhoid fever. ^{103,} Individuals who are vaccinated should continue to take personal precautions against exposure to typhoid organisms. ^{103,}

Vaccination does not protect against species of *Salmonella* other than *S. typhi* or other bacteria that cause enteric infections; vaccination is also not suitable for the treatment of acute infections with *S. typhi*. ^{103,} Typhoid vaccine should not be used to treat a patient with typhoid fever or a chronic typhoid carrier. ^{123,}

Experience using typhoid vaccines in individuals from areas without endemic disease (e.g., US residents) who travel to endemic regions is limited; however, seroconversion rates following primary immunization with typhoid vaccine live oral Ty21a or typhoid Vi polysaccharide vaccine in these individuals appear to be comparable to or higher than seroconversion rates attained in residents of endemic areas. ^{102,103,123,} Because of the low incidence of typhoid fever in the US, efficacy studies are not possible in this population; however, evidence from antibody-titer studies suggests that both the oral and parenteral vaccines provide protection in vaccine recipients residing in nonendemic areas. ^{102,103,123,129,}

Clinical Experience with Typhoid Vaccine Live Oral Ty21a (Vivotif®)

Efficacy of typhoid vaccine live oral Ty21a (Vivotif®) for the prevention of typhoid fever has been assessed in several clinical studies. ^{101,103,117,120,266,267,} Results of these studies indicate that adults and pediatric patients ≥6 years of age may be protected against typhoid fever after oral ingestion of 4 doses of typhoid vaccine live oral Ty21a. ^{103,} In a controlled study in Alexandria, Egypt, a typhoid fever endemic area, 32,388 pediatric patients 6–7 years of age received either 3 doses of the vaccine or placebo. ^{103,266,} There was a 95% decrease in the incidence of typhoid fever due to immunization over a 3-year surveillance period. ^{103,} In the placebo group, there were 22 confirmed cases of typhoid fever versus a single confirmed case in the vaccine group. ^{266,}

A series of trials were also conducted in Santiago, Chile, another typhoid fever endemic area, to evaluate the efficacy of the vaccine strain when administered in the form of an acid-resistant enteric-coated capsule. ^{103,} One of these trials randomized 82,543 pediatric patients 5 to >14 years of age to receive 1 or 2 doses of typhoid vaccine live oral Ty21a in enteric-coated capsules or placebo. ^{103,117,} After a 2-year surveillance period, the vaccine efficacy was found to be 29% with a single dose and 59% with 2 doses. ^{103,117,} The second trial in Santiago, Chile was conducted in 109,594 school-aged children 6–21 years of age; participants were randomized to receive either 3 scheduled doses of typhoid vaccine live oral Ty21a in an enteric-coated formulation or placebo. ^{101,103,} The 3-dose series of the enteric-coated capsules was administered either on alternating days (short immunization schedule) or 21 days apart (long immunization schedule). ^{103,} After 3 years of surveillance, 3 doses of enteric-coated typhoid vaccine live oral Ty21a resulted in a 67% decrease in the incidence of typhoid fever in the short immunization schedule group and a 49% reduction in the long immunization schedule group. ^{101,103,} The short immunization schedule also resulted in a 69% decrease in typhoid fever after 48 months of surveillance. ^{103,} In the third trial in Santiago, Chile, 189,819 school-aged children were randomized to receive 2, 3, or 4 doses of enteric-coated typhoid vaccine live oral Ty21a. ^{103,120,} Vaccine doses were administered on alternate days. ^{103,120,} The incidence of typhoid fever was lowest in patients who received the 4-dose regimen with an incidence of 95.8 cases per 105 study subjects versus an incidence of 160.5 and 184.6 cases per 105 subjects with the 3- and 2-dose regimens, respectively. ^{103,120,} Another study assessed typhoid vaccine live oral Ty21a in Plaju, Indonesia in 20,543 patients 3–44 years of age. ^{103,267,} Patients were randomized to receive either 3 doses of enteric-coated vaccine capsules or placebo at weekly intervals. ^{103,267,} After a 30 month surveillance period, the vaccine had a protective efficacy of 42.2%. ^{103,267,}

In another study, the seroconversion rate (defined as a ≥0.15-unit increase in optical density over baseline) after 3 doses of typhoid vaccine live oral Ty21a was compared between adults living in typhoid fever endemic areas (Chile) and non-endemic areas (the US and Switzerland). ^{103,} Seroconversion rates were comparable between the groups. ^{103,}

Based on challenge studies in North American volunteers, the Ty21a strain vaccine has shown protection from an experimental challenge of *S. typhi*. ^{103,113,}

Clinical Experience with Typhoid Vi Polysaccharide Vaccine (Typhim Vi®)

The efficacy of 2 formulations of typhoid Vi polysaccharide vaccine, a liquid formulation identical to Typhim Vi® and a lyophilized formulation, was assessed independently in 2 randomized, double-blind, controlled trials in typhoid fever endemic areas. ^{123,124,125,} The efficacy of the liquid formulation of Typhim Vi® was assessed in a trial in Kathmandu, Nepal, with 6908 vaccinated subjects; 6439 subjects were in the target population of 5–44 years of age. ^{123,124,} Patients in this study were randomized to receive either Typhim Vi® or a 23-valent pneumococcal polysaccharide vaccine. ^{123,124,} For blood culture confirmed cases of typhoid fever during 20 months of post-vaccination follow-up, the overall efficacy of Typhim Vi® was 74%. ^{123,} In the second trial, the typhoid Vi polysaccharide vaccine lyophilized formulation was evaluated in 11,384 children 5–15 years of age in South Africa. ^{123,125,} In this study, patients were randomized to receive either the typhoid Vi capsular polysaccharide vaccine or a meningococcal polysaccharide (groups A+C) vaccine. ^{123,125,} During a 21-month follow-up, comparison of cases of typhoid in the typhoid vaccine group and meningococcal group showed a typhoid Vi polysaccharide vaccine efficacy of 60%. ^{125,} During 3 years of post-vaccination follow-up, the overall efficacy of typhoid Vi polysaccharide vaccine, based on blood culture-confirmed cases of typhoid fever, was 55%. ^{123,}

A specific correlation between post-vaccination antibody levels after immunization with the typhoid Vi polysaccharide vaccine and subsequent protection is not available; the Vi antibody level that provides protection has not been determined. ^{123,} In endemic regions where trials have been conducted (e.g., Nepal, South Africa), pre-vaccination geometric mean antibody levels suggest infection with *S. typhi* had previously occurred in a large percentage of vaccine recipients. ^{123,} Specific antibody levels increased 4-fold or more in 68–87.5% of older children and adults following vaccination in this population. ^{123,}

Immunogenicity of Typhim Vi® has been assessed in adults in the US. ^{123,129,} A single dose increased antibody levels by 4-fold or greater in 88% of adults in a study with 2 different lots of the vaccine, and in 96% of adults in a study with a single lot of the vaccine. ^{123,} No studies of immunogenicity have been conducted in US children. ^{123,} However, a double-blind, randomized, controlled trial evaluated the immunogenicity of Typhim Vi® vaccine in 175 Indonesian children 2–5 years of age. ^{123,} At 4 weeks post-vaccination, 96.3% of children achieved a 4-fold or greater increase in antibody levels. ^{123,}

In a reimmunization study in the US, adults previously vaccinated with Typhim Vi® in prior studies were reimmunized with a 25 mcg dose at 27 or 34 months after the primary dose. ^{123,} Antibody levels attained following reimmunization were similar to levels attained following primary immunization. ^{123,}

Clinical Perspective

The US Public Health Service Advisory Committee on Immunization Practices (ACIP) and other experts (e.g., the American Academy of Pediatrics [AAP]) state that routine vaccination against typhoid fever is not recommended for individuals residing in the US, but is recommended for those ≥ 2 years of age traveling to areas with a recognized risk of exposure to *Salmonella* Typhi.^{102,105,115} The CDC maintains a list of regions for travelers for which the typhoid vaccine is recommended.¹¹⁵ All travelers should also follow safe food and water precautions and frequent handwashing, especially before meals, to prevent typhoid fever.¹¹⁵ In addition, vaccination against typhoid fever is recommended in individuals with intimate exposure (e.g., household contact) to a documented *Salmonella* serotype Typhi chronic carrier (defined as excretion of *Salmonella* Typhi in urine or stool for >1 year).^{102,105} Vaccination is also recommended in laboratory personnel with frequent contact with *Salmonella* serotype Typhi or specimens containing this organism, or in those who work in laboratory environments where these cultures or specimens are routinely handled.^{102,105}

When vaccination against typhoid fever is indicated, either typhoid vaccine live oral Ty21a or typhoid Vi polysaccharide vaccine can be used; vaccine selection is based on the age of the patient, need for booster doses, and possible contraindications and reactions.^{102,105,115} The efficacy of both vaccines ranges from 50–80%.^{105,115} Since neither vaccine is 100% effective, safe food and water precautions for travelers should be reinforced.¹¹⁵ Patients who receive primary vaccination with typhoid Vi polysaccharide vaccine should receive the vaccine at least 2 weeks before potential exposure; for those who remain at risk, a dose is recommended every 2 years.^{102,105,115} For patients who receive the typhoid vaccine live oral Ty21a vaccine, primary vaccination consists of 4 total capsules with 1 capsule taken every other day.^{102,105,115} The entire regimen of the live oral Ty21a vaccine should be completed at least 1 week before potential exposure; revaccination with the entire 4-dose series is recommended every 5 years for patients who remain at risk.^{102,105,115}

Dosage and Administration

■ General

Pretreatment Screening

- Prior to administration of typhoid vaccine live oral Ty21a or typhoid Vi polysaccharide vaccine, conduct a review of the patient's history with respect to health status and possible sensitivity to the vaccine, similar vaccines, or vaccine components.^{103,123}

Other General Considerations

- Individuals who have been vaccinated against typhoid fever should be advised to continue to take other precautions against exposure to *Salmonella* Typhi (e.g., safe food and water precautions, frequent handwashing).^{103,123}
- Epinephrine should be available for immediate treatment if an anaphylactic or other serious allergic reaction occurs.¹²³

■ Administration

Typhoid vaccine live oral Ty21a is administered orally.¹⁰³

Typhoid Vi polysaccharide vaccine is administered by IM injection.¹²³

Typhoid Vaccine Live Oral Ty21a

Typhoid vaccine live oral Ty21a is administered orally as enteric-coated capsules.¹⁰³

The vaccine capsules should be given with cold or lukewarm (not exceeding a temperature of about 37°C [body temperature]) liquid approximately 1 hour before a meal.¹⁰³

The vaccine capsules should be swallowed whole immediately after placement in the mouth and should not be chewed.¹⁰³

Typhoid vaccine live oral Ty21a should not be administered to individuals with acute GI illness or persistent diarrhea or vomiting.¹⁰³

Typhoid vaccine live oral Ty21a enteric-coated capsules should be stored at 2–8°C in a dry place protected from light.¹⁰³ The vaccine capsules should be shipped and stored only at 2–8°C.¹⁰³

Vaccine recipients should be advised that the capsules must be refrigerated (2–8°C) until just prior to administration since potency is adversely affected by exposure to warmer temperatures.¹⁰³ It is essential that remaining capsules are placed back in the refrigerator after each dose is taken until the 4-dose vaccination series is completed.¹⁰³

Typhoid vaccine live oral Ty21a does not contain thimerosal or any other preservatives.¹⁰³

Typhoid Vi Polysaccharide Vaccine

Typhoid Vi polysaccharide vaccine is administered by IM injection.¹²³

The vaccine should appear clear and colorless and should be discarded if it is turbid or contains particulates.¹²³

Typhoid Vi polysaccharide vaccine should be administered undiluted and should not be mixed with any other vaccine.¹²³

Data are not available regarding use of typhoid Vi polysaccharide vaccine following previous vaccination with typhoid vaccine live oral Ty21a or any other typhoid vaccine.¹²³

Typhoid Vi polysaccharide vaccine should be stored at 2–8°C and should not be frozen.¹²³ The vaccine does not contain thimerosal, but contains phenol 0.25% as a preservative.¹²³

In adults, IM injections of typhoid Vi polysaccharide vaccine preferably should be made into the deltoid area.¹²³ In pediatric patients, IM injections of the vaccine should be made into the deltoid or the anterolateral thigh.¹²³ The vaccine should not be injected into the gluteal area or any area where there may be a nerve trunk.¹²³

To ensure delivery of vaccine into muscle, IM injections should be made at a 90° angle to the skin using a needle length appropriate for the individual's age and body mass, thickness of adipose tissue and muscle at the injection site, volume to be administered, and injection technique.¹³⁴

Syncope (vasovagal or vasodepressor reaction; fainting) may occur following vaccination¹³⁵ and has been reported following administration of typhoid Vi polysaccharide vaccine.¹²³ Syncope occurs most frequently in adolescents and young adults.¹³⁵ Appropriate measures should be taken to prevent injuries if a patient becomes dizzy or loses consciousness.¹³⁵ Syncope and secondary injuries may be averted if vaccine recipients sit or lie down during vaccination; providers should also consider observing patients for 15 minutes after vaccination.¹³⁵ If syncope occurs, the patient should be observed until symptoms resolve.¹³⁵

When multiple vaccines are administered during a single health-care visit, each parenteral vaccine should be given with a different syringe and at different injection sites.¹³⁴ Injection sites should be separated by at least 1 inch (if anatomically feasible) to allow appropriate attribution of any local adverse effects that may occur.¹³⁴

■ Dosage

Dosing schedules (i.e., number of doses, timing prior to potential exposure to typhoid fever) differ between typhoid vaccine live oral Ty21a and typhoid Vi polysaccharide vaccine.^{103,123} Dosage recommendations for the specific preparation used should be followed.^{102,103,123}

Adults

Prevention of Typhoid Fever

Typhoid Vaccine Live Oral Ty21a: Primary immunization with typhoid vaccine live oral Ty21a in adults consists of 4 doses given as 1 capsule every other day (e.g., Sunday, Tuesday, Thursday, and Saturday or day 0, 2, 4, and 6).^{102,103}

The 4-dose regimen of typhoid vaccine live oral Ty21a should be completed at least 1 week prior to potential exposure to Salmonella enterica serovar Typhi.^{102,103}

The duration of response and optimum revaccination or booster schedule for typhoid vaccine live oral Ty21a have not been established.^{102,103} The efficacy of typhoid vaccine live oral Ty21a has been shown to persist for at least 5 years.¹⁰³ Revaccination with the same 4-dose regimen of typhoid vaccine live oral Ty21a (i.e., 1 capsule every other day for 4 doses) is recommended every 5 years in individuals with continuing or repeated exposure to Salmonella Typhi.^{102,103}

Data are not available regarding use of typhoid vaccine live oral Ty21a as a booster in individuals previously vaccinated with typhoid Vi polysaccharide vaccine or any other typhoid vaccine.¹⁰³

Typhoid Vi Polysaccharide Vaccine: For primary immunization in adults, typhoid Vi polysaccharide vaccine is administered as a single 25-mcg dose (0.5 mL from the commercially available prefilled single-dose syringe or multidose vial).^{102,123}

Typhoid Vi polysaccharide vaccine should be administered at least 2 weeks prior to potential exposure to Salmonella Typhi.^{102,123}

The duration of response and optimum revaccination or booster schedule for typhoid Vi polysaccharide vaccine have not been established.^{102,123} Pending further accumulation of data, revaccination with a single 0.5-mL dose of typhoid Vi polysaccharide vaccine is recommended every 2 years in individuals with continuing or repeated exposure to Salmonella Typhi.^{102,123}

Data are not available regarding use of typhoid Vi polysaccharide vaccine following previous vaccination with typhoid vaccine live oral Ty21a or any other typhoid vaccine.¹²³

Pediatric Patients

Prevention of Typhoid Fever

Typhoid Vaccine Live Oral Ty21a: Primary immunization with typhoid vaccine live oral Ty21a in pediatric patients 6 years of age and older consists of 4 doses given as 1 capsule every other day (e.g., Sunday, Tuesday, Thursday, and Saturday or day 0, 2, 4, and 6).^{102,103}

The 4-dose regimen of typhoid vaccine live oral Ty21a should be completed at least 1 week prior to potential exposure to Salmonella enterica serovar Typhi.^{102,103}

The duration of response and optimum revaccination or booster schedule for typhoid vaccine live oral Ty21a have not been established.^{102,103} The efficacy of typhoid vaccine live oral Ty21a has been shown to persist for at least 5 years.¹⁰³ Revaccination with the same 4-dose regimen of typhoid vaccine live oral Ty21a (i.e., 1 capsule every other day for 4 doses) is recommended every 5 years in individuals with continuing or repeated exposure to *Salmonella* Typhi.^{102,103}

Data are not available regarding use of typhoid vaccine live oral Ty21a as a booster in individuals previously vaccinated with typhoid Vi polysaccharide vaccine or any other typhoid vaccine.¹⁰³

Typhoid Vi Polysaccharide Vaccine: For primary immunization in pediatric patients 2 years of age and older, typhoid Vi polysaccharide vaccine is administered as a single 25-mcg dose (0.5 mL from the commercially available prefilled single-dose syringe or multidose vial).^{102,123}

Typhoid Vi polysaccharide vaccine should be administered at least 2 weeks prior to potential exposure to *Salmonella* Typhi.^{102,123}

The duration of response and optimum revaccination or booster schedule for typhoid Vi polysaccharide vaccine have not been established.^{102,123} Pending further accumulation of data, revaccination with a single 0.5-mL dose of typhoid Vi polysaccharide vaccine is recommended every 2 years in individuals with continuing or repeated exposure to *Salmonella* Typhi.^{102,123}

Data are not available regarding use of typhoid Vi polysaccharide vaccine following previous vaccination with typhoid vaccine live oral Ty21a or any other typhoid vaccine.¹²³

■ Special Populations

Hepatic Impairment

The manufacturer makes no specific dosage recommendations in hepatic impairment.^{103,123}

Renal Impairment

The manufacturer makes no specific dosage recommendations in renal impairment.^{103,123}

Geriatric Patients

The manufacturer makes no specific dosage recommendations in geriatric patients.^{103,123}

Cautions

■ Contraindications

- Typhoid vaccine live oral Ty21a: Hypersensitivity to any component of the vaccine or the enteric-coated capsule.¹⁰³
- Typhoid Vi polysaccharide vaccine: Hypersensitivity to any component of the vaccine.¹²³

■ Warnings/Precautions

Individuals with Altered Immunocompetence

Because typhoid vaccine live oral Ty21a contains live, attenuated bacteria, it should not be used in immunocompromised individuals.^{102,103} Safety of the live, attenuated oral vaccine has not been established in individuals deficient in an ability to mount a humoral or cell-mediated immune response, and the manufacturer states that the vaccine should not be used in such individuals, regardless of any possible benefits.¹⁰³

If indicated, typhoid Vi polysaccharide vaccine may be used in patients with altered immunocompetence, including HIV-infected patients; those who are severely immunocompromised because of congenital immunodeficiency, leukemia, lymphoma, aplastic anemia, generalized malignancy, or therapy with alkylating agents, antimetabolites, radiation, or corticosteroids; patients with solid organ transplants or chronic immunosuppressive therapy; or patients with asplenia, renal failure, diabetes mellitus, alcoholism, or alcoholic cirrhosis.^{102,123} The US Public Health Service Advisory Committee on Immunization Practices (ACIP) states that recommendations concerning use of typhoid Vi polysaccharide vaccine in patients with altered immunocompetence are the same as those for individuals who are not immunocompromised.¹³⁴ However, immunization may be less effective in individuals with altered immunocompetence since antibody responses to vaccine antigens may be reduced in such individuals.¹²³

Hypersensitivity Reactions

Prior to administration of typhoid vaccine live oral Ty21a or typhoid Vi polysaccharide vaccine, all known precautions should be taken to prevent adverse reactions, including a review of the patient's history with respect to health status and possible sensitivity to the vaccine, similar vaccines, or vaccine components.^{103,123} Epinephrine should be available for immediate treatment if an anaphylactic or other serious allergic reaction occurs.¹²³

Gastrointestinal Illness

Typhoid vaccine live oral Ty21a should not be administered to individuals with an acute GI illness; vaccination should be deferred in those with persistent diarrhea or vomiting.¹⁰³

Acute Illness

The typhoid vaccine live oral Ty21a should not be administered to individuals with acute febrile illness.^{102,103}

The manufacturer states that administration of typhoid Vi polysaccharide vaccine may be deferred in individuals with acute infection or febrile illness, unless withholding the vaccine poses a greater risk.¹²³

Limitations of Vaccine Effectiveness

Typhoid vaccine live oral Ty21a and typhoid Vi polysaccharide vaccine may not protect all vaccine recipients against typhoid fever.^{102,103,123} Vaccine-induced immunity can be overwhelmed by a large inoculum of *Salmonella* Typhi.¹⁰²

Individuals who have been vaccinated against typhoid fever should be advised to continue to take precautions against exposure to *Salmonella* Typhi (e.g., safe food and water precautions, frequent handwashing).¹⁰²

Patients should be advised that it is essential that all 4 doses of typhoid vaccine live oral Ty21a be administered as recommended; an optimum immune response may not be achieved if the complete 4-dose regimen is not used.¹⁰³

Typhoid vaccines will not provide protection against *Salmonella* Paratyphi or any *Salmonella* other than *Salmonella* Typhi and will not provide protection against other bacteria known to cause enteric disease.^{103,123}

Typhoid vaccines are not used for the treatment of typhoid fever and should not be used in individuals with acute *Salmonella* Typhi infection^{103,123} or in chronic typhoid carriers.¹²³

There is no evidence to support the use of typhoid vaccine to control common source outbreaks or disease following natural disasters or in individuals attending rural summer camps.^{103,123}

Specific Populations

Pregnancy

Data are not available regarding use of typhoid vaccine live oral Ty21a or typhoid Vi polysaccharide vaccine in pregnant women.^{102,123} Animal reproduction studies have not been performed with either vaccine, and it is not known whether the vaccines can cause fetal harm or affect reproduction capacity when administered to pregnant women.^{103,123}

The manufacturer of typhoid vaccine live oral Ty21a states that the vaccine should be used during pregnancy only when clearly needed.¹⁰³ ACIP states that live vaccines generally are contraindicated during pregnancy.¹⁰²

Typhoid Vi polysaccharide vaccine should be used during pregnancy only when clearly needed.^{102,123} The manufacturer suggests that delaying vaccination until the second or third trimester is a reasonable precaution to minimize the possibility of teratogenicity.¹²³

Lactation

Data are not available regarding use of typhoid vaccine live oral Ty21a or typhoid Vi polysaccharide vaccine in nursing women.^{103,123} It is not known whether typhoid vaccine live oral Ty21a is distributed into human milk.¹⁰³ ACIP states that, although live vaccines multiply in the body, most have not been shown to distribute into human milk.¹³⁶

It is not known whether typhoid Vi polysaccharide vaccine is distributed into human milk.¹²³ The manufacturer recommends that the vaccine be used with caution in nursing women.¹²³ Although specific data are not available, ACIP states that non-live vaccines pose no risk for mothers who are breast-feeding or their infants.¹³⁶

Pediatric Patients

*Safety and efficacy of typhoid vaccine live oral Ty21a have not been established in pediatric patients younger than 6 years of age and the vaccine is not indicated in this age group.¹⁰³ Safety and efficacy of typhoid Vi polysaccharide vaccine have not been established in pediatric patients younger than 2 years of age.¹²³ As with other polysaccharide vaccines, the antibody response to typhoid Vi polysaccharide vaccine may be inadequate in pediatric patients younger than 2 years of age.¹²³ The manufacturer states that a decision whether to use typhoid Vi polysaccharide vaccine in **pediatric patients younger than 2 years of age [off-label]**⁺ depends on the risk incurred by the child on the basis of the epidemiological context.¹²³*

Geriatric Patients

Pharmacokinetics of typhoid vaccine live oral Ty21a or typhoid Vi polysaccharide vaccine have not been evaluated in geriatric patients.^{103,123}

■ Common Adverse Effects

In individuals who received 3 doses of typhoid vaccine live oral Ty21a, the most common adverse effects included abdominal pain (6.4%), nausea (5.8%), headache (4.8%), fever (3.3%), diarrhea (2.9%), vomiting (1.5%), and skin rash (1%), with only nausea occurring at a substantially higher rate than placebo.¹⁰³

Within the first 48 hours of vaccination with the typhoid Vi polysaccharide vaccine, the most common local adverse effects experienced in adults were tenderness (98%) and pain (40.7%); the most common systemic adverse effects included malaise (24%) and headache (20.4%).¹²³ In children, local reactions such as soreness and pain were the most common, and occurred in 13 and 14.3% of children, respectively.¹²³ Feverishness (a subjective feeling of fever) occurred in 2.9% of children, and was the most common systemic adverse effect.¹²³

Drug Interactions

■ Anti-infective Agents

Anti-infective agents may be active against *Salmonella* enterica serovar Typhi contained in typhoid vaccine live oral Ty21a and may reduce immunogenicity.¹⁰² The manufacturer of typhoid vaccine live oral Ty21a states that the vaccine should not be used in individuals receiving sulfonamides or other anti-infectives.¹⁰³ The US Public Health Service Advisory Committee on Immunization Practices (ACIP) states that typhoid vaccine live oral Ty21a should not be given until at least 3 days (72 hours) after the last dose of anti-infective agent and, if feasible, anti-infective agents should not be initiated or resumed until at least 3 days after the last dose of the oral vaccine.¹⁰²

The manufacturer of typhoid Vi polysaccharide vaccine states that specific studies evaluating drug interactions between the parenteral vaccine and anti-infective agents have not been conducted to date.¹²³

■ Anti-malarial Agents

Several antimalarial agents (e.g., chloroquine, mefloquine, proguanil) have antibacterial activity against *Salmonella* and have the potential to interfere with the immunogenicity of typhoid vaccine live oral Ty21a.¹⁰³ In one study of 45 healthy adults, concomitant use of typhoid vaccine live oral Ty21a and mefloquine or chloroquine did not significantly reduce serum anti-*S. typhi* immune response compared to patients receiving vaccine only, indicating that mefloquine and chloroquine can be used concomitantly.¹⁰³ Concurrent use of proguanil (200 mg daily; not commercially available in the US as a single-entity preparation) and typhoid vaccine live oral Ty21a in healthy adults resulted in a decreased immune response to the live, attenuated vaccine.¹⁰³ Therefore, the manufacturer of typhoid vaccine live oral Ty21a states that proguanil should not be administered until at least 10 days after the final dose of typhoid vaccine live oral Ty21a.¹⁰³

ACIP states that the fixed combination of atovaquone and proguanil (atovaquone/proguanil) in dosages used for prophylaxis of malaria may be used concurrently with typhoid vaccine live oral Ty21a.¹⁰²

The manufacturer of typhoid Vi polysaccharide vaccine states that specific studies evaluating drug interactions between the parenteral vaccine and other drugs, including antimalarial agents, have not been conducted to date.¹²³

■ Immune Globulins

Although the manufacturer of typhoid vaccine live oral Ty21a states that data are not available regarding concurrent use with immune globulins,¹⁰³ ACIP states that the oral vaccine may be administered simultaneously with or at any time before or after immune globulin preparations.¹⁰²

The manufacturer of typhoid Vi polysaccharide vaccine states that specific studies evaluating drug interactions between the parenteral vaccine and immune globulin have not been conducted to date.¹²³

■ Immunosuppressive Agents

Individuals receiving immunosuppressive therapy (e.g., alkylating agents, antimetabolites, corticosteroids, radiation) may have decreased antibody response to typhoid vaccine live oral Ty21a, and the vaccine should not be used in individuals receiving such therapy.¹⁰³ ACIP states that live, attenuated vaccines should not be administered for at least 3 months after immunosuppressive therapy is discontinued.¹³⁷ ACIP states that vaccination with live, attenuated vaccines should be deferred for at least 1 month after completion of therapy in patients receiving high-dose corticosteroids (e.g., ≥20 mg/day prednisone or equivalent for ≥14 days in individuals weighing ≥10 kg).¹³⁷ Corticosteroids are not a contraindication to the administration of live virus vaccines when steroid use is 1) short-term, 2) given in low to moderate doses, 3) used as long-term, alternate-day treatment with short-acting agents, 4) given in maintenance, physiologic doses, or 5) when administered inhaled, topically, or by intraarticular, bursal, or tendon injection.¹³⁷

■ Vaccines

Inactivated Vaccines and Toxoids

The manufacturer of typhoid Vi polysaccharide vaccine states that specific studies evaluating interactions between the parenteral inactivated vaccine and other vaccines (e.g., hepatitis A vaccine, tetanus toxoid adsorbed, poliomyelitis vaccine) have not been conducted to date.¹²³

Meningococcal Vaccine

MenACWY-D (Menactra[®]) and typhoid Vi polysaccharide vaccine (Typhim Vi[®]) have been administered concomitantly at different sites in adults 18–55 years of age without reduced immune responses to either vaccine.^{123,}

Live Vaccines

ACIP states that typhoid vaccine live oral Ty21a may be administered concurrently with or at any interval before or after other live vaccines (e.g., measles, mumps, and rubella virus vaccine live [MMR], varicella virus vaccine live, yellow fever vaccine).^{102,134,}

The manufacturer of typhoid Vi polysaccharide vaccine states that specific interaction studies evaluating drug interactions between the parenteral inactivated vaccine and live vaccines have not been conducted to date.^{123,}

Description

Typhoid vaccines stimulate active immunity to typhoid fever in individuals at high risk of exposure to *Salmonella* enterica serovar Typhi.^{103,123,}

Response to Typhoid Vaccine Live Oral Ty21a

The exact mechanism by which typhoid vaccine live oral Ty21a elicits an immune response is not known; however, the oral vaccine is thought to produce a local immune response in the GI tract.^{103,} Seroconversion rates in healthy US adults following primary immunization with 3 doses of typhoid vaccine live oral Ty21a are similar to those attained in residents of typhoid-endemic areas.^{103,} Following ingestion, virulent strains of *Salmonella* Typhi can pass through the stomach acid barrier, colonize the intestinal tract, penetrate the intestinal lumen, and enter the lymphatic system and blood stream, resulting in infection.^{103,} It has been suggested that oral administration of typhoid vaccine containing a live, attenuated strain of the bacilli may elicit a local immune response in the intestinal tract while undergoing an aborted infection, with resultant protection against subsequent infection with a virulent strain.^{103,} However, the ability of *Salmonella* Typhi to elicit a protective immune response depends on possession by the bacilli of a complete lipopolysaccharide.^{103,} The ability of the live, attenuated strain present in the oral typhoid vaccine to produce a complete lipopolysaccharide is limited since this strain is deficient in enzymes essential for lipopolysaccharide biosynthesis; however, sufficient complete lipopolysaccharide apparently is produced to elicit an adequate immune response.^{103,} In addition, despite low levels of lipopolysaccharide biosynthesis by the vaccine strain, sufficient quantities of intermediates of this synthesis accumulate and induce cell lysis before the organism can gain a virulent phenotype.^{103,}

In a series of field trials in Chile, efficacy of the live, attenuated vaccine (as enteric-coated capsules) given as a 1- or 2-dose regimen in school-aged children was 21 or 54%, respectively, after 33 months of surveillance.^{103,} When a 3-dose regimen (as enteric-coated capsules) was administered on alternate days (short-schedule immunization) or 21 days apart (long-schedule immunization) in Chilean school-age children, vaccine efficacy was 67 or 49%, respectively, after 36 months of surveillance; after 48 months, efficacy of the short-schedule immunization was 69%.^{103,} The level of immune protection was undiminished during the fifth year of surveillance.^{103,}

Experience in individuals from areas without endemic disease (e.g., US residents) who travel to endemic regions also is limited, but seroconversion rates reported following a 3-dose primary immunization series with the live, attenuated vaccine in such individuals are comparable to those in residents of endemic areas.^{103,} Because of the low incidence of typhoid fever in the US, efficacy studies are not possible in this population; however, evidence from antibody-titer studies suggests that the live, attenuated vaccine will provide protection to vaccine recipients residing in nonendemic areas such as the US.^{103,} The duration of response after primary immunization with typhoid vaccine live oral Ty21a has not been established.^{103,}

Response to Typhoid Vi Polysaccharide Vaccine

Administration of typhoid Vi polysaccharide vaccine stimulates immunity to *Salmonella* Typhi by inducing production of antibodies to the Vi antigen.^{123,} Antibodies to the Vi antigen confer protection against typhoid fever.^{123,} IM administration of a single dose of typhoid Vi polysaccharide vaccine in most healthy adults and children 2 years of age or older generally results in a 4-fold or greater increase in serum antibodies specific for the Vi antigen within 4 weeks.^{123,} Results of several US studies indicate that a single 25-mcg dose of Vi polysaccharide vaccine results in a 4-fold or greater increase in serum antibodies in 88–96% of healthy adults.^{123,} Because baseline antibody titers from individuals from typhoid-endemic areas (i.e., Nepal, South Africa, Indonesia) indicate prior exposure to *Salmonella* Typhi, vaccine-induced antibody response in these individuals differs from that produced in “typhoid naive” populations (e.g., most travelers from the US).^{123,} In studies conducted in Nepal, administration of a single 25-mcg dose of typhoid Vi polysaccharide vaccine in children 5–14 years of age, adolescents and adults 15–44 years of age, or adults 45–55 years of age produced a 4-fold or greater increase in antibody titers within 4 weeks in approximately 77, 79, or 63% of individuals, respectively.^{123,} A single 25-mcg dose of the vaccine produced a 4-fold or greater increase in serum antibodies within 4 weeks in about 96% of Indonesian children aged 2–5 years of age.^{123,} The titer of antibody that is protective against typhoid has not been determined to date.^{123,}

Limited evidence indicates that antibody titers against the Vi antigen remain elevated for at least 12 months following administration of typhoid Vi polysaccharide vaccine in children 5–15 years of age residing in typhoid-endemic areas and for at least 36 months in healthy US adults.^{123,} Administration of an additional dose of typhoid Vi polysaccharide vaccine in healthy US adults 27–34 months after the initial dose produces antibody titers comparable to those obtained following the primary dose.^{123,}

Efficacy of a single 25-mcg dose of typhoid Vi polysaccharide vaccine in preventing typhoid fever has been demonstrated in a series of field trials in typhoid-endemic areas.^{123,} In a trial in Nepal in individuals 5–44 years of age, those who received the vaccine had 74% fewer cases of culture-confirmed *Salmonella* Typhi infection over a 20-month period follow-up period.^{123,} Surveillance in immunized South African children indicated that vaccine efficacy was 61, 52, or 50% after 1, 2, or 3 years; overall vaccine efficacy was 55%.^{123,}

Advice to Patients

The following information contains important points for the clinician to discuss with patients during counseling. For more comprehensive monographs suitable for distribution to the patient, please refer to the *AHFS Patient Medication Information* monographs available from [MedlinePlus](#) (in English and Spanish; written at a 6th- to 8th-grade reading level).

- Prior to administration of typhoid vaccine, provide a copy of the appropriate CDC Vaccine Information Statement (VIS) to the patient or patient's legal representative (VISs are available at [\[Web\]](#)).^{103,123,}

- Advise patient and/or patient's parent or guardian of the risks and benefits of vaccination with typhoid vaccine. ^{103,123,}
- Advise patient and/or patient's parent or guardian that routine typhoid vaccination is not recommended in the US, but may be used to prevent typhoid in individuals at high risk of exposure to typhoid (e.g., certain travelers, household contacts of a typhoid carrier, certain laboratory personnel). ^{103,123,}
- Advise patient and/or patient's parent or guardian that oral or parenteral typhoid vaccine may not provide protection in all vaccine recipients. ^{102,103,123,} In addition to vaccination, advise patients of the importance of taking other precautions against exposure to typhoid fever (e.g., safe food and water precautions, frequent handwashing). ^{102,103,123,}
- When using typhoid vaccine live oral Ty21a, advise patients to complete the 4-dose vaccination series as directed (i.e., dose every other day for 4 doses). ^{103,} Advise vaccine recipients to swallow capsules whole with cool or lukewarm liquid on an empty stomach 1 hour before a meal and store remaining capsules in the refrigerator until entire 4-dose regimen is completed. ^{102,103,} Stress importance of completing the vaccination series ≥ 1 week prior to possible exposure to typhoid fever and importance of revaccination with the 4-dose series every 5 years if at continued or repeated risk of exposure. ^{102,103,}
- When using typhoid Vi polysaccharide vaccine, advise patients of the importance of receiving the dose ≥ 2 weeks prior to possible exposure to typhoid fever and importance of revaccination every 2 years if at continued or repeated risk of exposure. ^{102,123,}
- Advise patients to notify clinicians if patient is immunocompromised since oral typhoid vaccine should not be used in individuals with a weakened immune system (e.g., leukemia, lymphoma, HIV/AIDS) or in those receiving treatment that may weaken the immune system (e.g., high-dose corticosteroids). ^{102,103,}
- Stress importance of informing clinicians of a history of allergic reactions to typhoid vaccine or any ingredient in the formulation. ^{103,123,}
- Stress importance of informing clinicians if any adverse reactions (including allergic reactions) occur with typhoid vaccine. ^{103,123,} Clinicians or individuals can report any adverse reactions that occur following vaccination to the Vaccine Adverse Event Reporting System (VAERS) at 800-822-7967 or [Web] . ^{103,123,} Also can be reported to the manufacturer at 800-533-5899 (PaxVax) ^{103,} or 800-822-2463 (Sanofi Pasteur). ^{123,}
- Stress importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, and any concomitant illnesses. ^{103,123,} Stress importance of notifying clinicians if receiving therapy with anti-infective or antimalarial agents. ^{103,}
- Stress importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed. ^{103,123,}
- Inform patients of other important precautionary information. ^{103,123,}

Additional Information

The American Society of Health-System Pharmacists, Inc. represents that the information provided in the accompanying monograph was formulated with a reasonable standard of care, and in conformity with professional standards in the field. Readers are advised that decisions regarding use of drugs are complex medical decisions requiring the independent, informed decision of an appropriate health care professional, and that the information contained in the monograph is provided for informational purposes only. The manufacturer's labeling should be consulted for more detailed information. The American Society of Health-System Pharmacists, Inc. does not endorse or recommend the use of any drug. The information contained in the monograph is not a substitute for medical care.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Typhoid Vaccine Live Oral Ty21a

<i>ROUTES</i>	<i>FORMS</i>	<i>STRENGTHS</i>	<i>BRAND NAMES</i>	<i>MANUFACTURER</i>
<i>Oral</i>	<i>Capsules, enteric-coated</i>	<i>2–10 × 10⁹ CFU of viable Salmonella Typhi Ty21a</i>	<i>Vivotif[®]</i>	<i>Bavarian Nordic A/S Denmark</i>

Typhoid Vi Polysaccharide Vaccine

<i>ROUTES</i>	<i>FORMS</i>	<i>STRENGTHS</i>	<i>BRAND NAMES</i>	<i>MANUFACTURER</i>
<i>Parenteral</i>	<i>Injection, for IM use</i>	<i>25 mcg Vi capsular polysaccharide per 0.5 mL</i>	<i>Typhim Vi[®]</i>	<i>Sanofi Pasteur</i>

† Use is not currently included in the labeling approved by the US Food and Drug Administration.

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