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Typhoid Immunization

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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Washington, DC

The following CDC staff members prepared this report:

Paul R. Cieslak, MD
Robert V. Tauxe, MD, MPH
Division of Bacterial and Mycotic Diseases
National Center for Infectious Diseases

John C. Watson, MD, MPH
Epidemiology and Surveillance Division
National Immunization Program

Typhoid Immunization

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

*These revised recommendations of the Advisory Committee on Immunization Practices update previous recommendations (*MMWR *1990;39[RR-10]:1–5). They include information on the Vi capsular polysaccharide (ViCPS) vaccine, which was not available when the previous recommendations were published.*

INTRODUCTION

The incidence of typhoid fever declined steadily in the United States from 1900 to 1960 and has since remained low. From 1975 through 1984, the average number of cases reported annually was 464. During that period, 57% of reported cases occurred among persons ≥20 years of age; 62% of reported cases occurred among persons who had traveled to other countries. From 1967 through 1976, only 33% of reported cases occurred among travelers to other countries (*1*).

TYPHOID VACCINES

Three typhoid vaccines are currently available for use in the United States: a) an oral live-attenuated vaccine (Vivotif Berna™ vaccine, manufactured from the Ty21a strain of *Salmonella typhi* (*2*) by the Swiss Serum and Vaccine Institute); b) a parenteral heat-phenol-inactivated vaccine that has been widely used for many years (Typhoid Vaccine, manufactured by Wyeth-Ayerst); and c) a newly licensed capsular polysaccharide vaccine for parenteral use (Typhim Vi, manufactured by Pasteur Mérieux). A fourth vaccine, an acetone-inactivated parenteral vaccine, is currently available only to the armed forces.

Although no prospective, randomized trials comparing any of the three U.S.-licensed typhoid vaccines have been conducted, several field trials have demonstrated the efficacy of each vaccine. In controlled field trials conducted among schoolchildren in Chile, three doses of the Ty21a vaccine in enteric-coated capsules administered on alternate days reduced laboratory-confirmed infection by 66% over a period of 5 years (95% confidence interval [CI]=50%–77%) (*3,4*). In a subsequent trial in Chile, efficacy appeared to be lower: three doses resulted in only 33% (95% CI=0%–57%) fewer cases of laboratory-confirmed infection over a period of 3 years. When the data were stratified by age in this trial, children ≥10 years of age had a 53% reduction in incidence of culture-confirmed typhoid fever (95% CI=7%–77%), whereas children 5–9 years of age had only a 17% reduction (95% CI=0%–53%). This difference in age-related efficacy, however, is not statistically significant (*5*). In another trial in Chile, a significant decrease in the incidence of clinical typhoid fever occurred among persons receiving four doses of vaccine compared with persons receiving two ($p<0.001$) or

three (p=0.002) doses. Because no placebo group was included in this trial, absolute vaccine efficacy could not be calculated (*6*).

Weekly and triweekly dosing regimens have been less effective than alternate-day dosing (*3*). A liquid formulation of Ty21a is more effective than enteric-coated capsules (*5,7,8*), but only enteric-coated capsules are available in the United States. The efficacy of vaccination with Ty21a has not been studied among persons from areas without endemic disease who travel to disease-endemic regions. The mechanism by which Ty21a vaccine confers protection is unknown; however, the vaccine does elicit both serum (*2,9*) and intestinal (*10*) antibodies and cell-mediated immune responses (*11*). Vaccine organisms can be shed transiently in the stool of vaccine recipients (*2,9*). However, secondary transmission of vaccine organisms has not been documented.

In field trials involving a primary series of two doses of heat-phenol-inactivated typhoid vaccine (which is similar to the currently available parenteral inactivated vaccine), vaccine efficacy over the 2½- to 3-year follow-up periods ranged from 51% to 77% (*12–14*). Efficacy for the acetone-inactivated parenteral vaccine, available only to the armed forces, ranges from 75% to 94% (*12,14,15*).

The newly licensed parenteral vaccine (Vi capsular polysaccharide [ViCPS]) is composed of purified Vi ("virulence") antigen, the capsular polysaccharide elaborated by *S. typhi* isolated from blood cultures (*16*). In recent studies, one 25-μg injection of purified ViCPS produced seroconversion (i.e., at least a fourfold rise in antibody titers) in 93% of healthy U.S. adults (*17*); similar results were observed in Europe (*18*). Two field trials in disease-endemic areas have demonstrated the efficacy of ViCPS in preventing typhoid fever. In a trial in Nepal, in which vaccine recipients were observed for 20 months, one dose of ViCPS among persons 5–44 years of age resulted in 74% (95% CI=49%–87%) fewer cases of typhoid fever confirmed by blood culture than occurred with controls (*19*). In a trial involving schoolchildren in South Africa who were 5–15 years of age, one dose of ViCPS resulted in 55% (95% CI=30%–71%) fewer cases of blood-culture-confirmed typhoid fever over a period of 3 years than occurred with controls. The reduction in the number of cases in years 1, 2, and 3, was 61%, 52%, and 50%, respectively (*20,21*). The efficacy of vaccination with ViCPS has not been studied among persons from areas without endemic disease who travel to disease-endemic regions or among children <5 years of age. ViCPS has not been tested among children <1 year of age.

VACCINE USAGE

Routine typhoid vaccination is not recommended in the United States. However, vaccination is indicated for the following groups:

- Travelers to areas in which there is a recognized risk of exposure to *S. typhi*. Risk is greatest for travelers to developing countries (e.g., countries in Latin America, Asia, and Africa) who have prolonged exposure to potentially contaminated food and drink (*22*). Multidrug-resistant strains of *S. typhi* have become common in some areas of the world (e.g., the Indian subcontinent [*23*] and the Arabian peninsula [*24,25*]), and cases of typhoid fever that are treated with ineffective drugs can be fatal. Travelers should be cautioned that typhoid vaccination is not a substitute for careful selection of food and drink. Typhoid vaccines are not 100% effective, and the vaccine's protection can be overwhelmed by large inocula of *S. typhi*.

- Persons with intimate exposure (e.g., household contact) to a documented *S. typhi* carrier.
- Microbiology laboratorians who work frequently with *S. typhi* (*26*).

Routine vaccination of sewage sanitation workers is not warranted in the United States and is indicated only for persons living in typhoid-endemic areas. Also, typhoid vaccine is not indicated for persons attending rural summer camps or living in areas in which natural disasters (e.g., floods) have occurred (*27*). No evidence has indicated that typhoid vaccine is useful in controlling common-source outbreaks.

CHOICE OF VACCINE

The parenteral inactivated vaccine causes substantially more adverse reactions but is no more effective than Ty21a or ViCPS. Thus, when not contraindicated, either oral Ty21a or parenteral ViCPS is preferable.

Each of the three vaccines approved by the Food and Drug Administration has a different lower age limit for use among children (Table 1). In addition, the time required for primary vaccination differs for each vaccine. Primary vaccination with ViCPS can be accomplished with a single injection, whereas 1 week is required for Ty21a, and 4 weeks are required to complete a primary series for parenteral inactivated vaccine (Table 1). Finally, the live-attenuated Ty21a vaccine should not be used for immunocompromised persons or persons taking antibiotics at the time of vaccination (see Precautions and Contraindications).

TABLE 1. Dosage and schedules for typhoid fever vaccination

Vaccination	Age	Dosage			
		Dose/mode of administration	Number of doses	Interval between doses	Boosting interval
Oral live-attenuated Ty21a vaccine					
Primary series	≥6 yrs	1 capsule*	4	2 days	—
Booster	≥6 yrs	1 capsule*	4	2 days	every 5 yrs
Vi capsular polysaccharide vaccine					
Primary series	≥2 yrs	0.50 mL†	1	—	—
Booster	≥2 yrs	0.50 mL†	1	—	every 2 yrs
Heat-phenol-inactivated parenteral vaccine					
Primary series	6 mos–10 yrs	0.25 mL§	2	≥4 wks	—
	≥10 yrs	0.50 mL§	2	≥4 wks	—
Booster	6 mos–10 yrs	0.25 mL§	1	—	every 3 yrs
	≥10 yrs	0.50 mL§	1	—	every 3 yrs
	≥6 mos	0.10 mL¶	1	—	every 3 yrs

*Each orally administered capsule contains contains 2–6 x 10^9 viable *S. typhi* Ty21a and 5–50 x 10^9 nonviable *S. typhi* Ty21a.
†Intramuscularly.
§Subcutaneously.
¶Intradermally.
— Not applicable.

VACCINE ADMINISTRATION

Ty21a

Primary vaccination with live-attenuated Ty21a vaccine consists of one enteric-coated capsule taken on alternate days for a total of four capsules. The capsules must be kept refrigerated (not frozen), and all four doses must be taken to achieve maximum efficacy (*6*). Each capsule should be taken with cool liquid no warmer than 37 C (98.6 F), approximately 1 hour before a meal. Although adverse reactions to Ty21a are uncommon among children 1–5 years of age (*28,29*), data are unavailable regarding efficacy for this age group. This vaccine has not been studied among children <1 year of age. The vaccine manufacturer recommends that Ty21a *not* be administered to children <6 years of age.

ViCPS

Primary vaccination with ViCPS consists of one 0.5-mL (25-μg) dose administered intramuscularly. This vaccine has not been studied among children <1 year of age. The vaccine manufacturer does not recommend the vaccine for children <2 years of age.

Parenteral Inactivated Vaccine

Primary vaccination with parenteral inactivated vaccine consists of two 0.5-mL subcutaneous injections, each containing approximately 5×10^8 killed bacteria, separated by ≥4 weeks. The vaccine manufacturer does not recommend the vaccine for use among children <6 months of age. If the two doses of parenteral inactivated vaccine cannot be separated by ≥4 weeks because of time constraints, common practice has been to administer three doses of the vaccine at weekly intervals in the volumes listed above. Vaccines administered according to this schedule may be less effective, however.

Booster Doses

If continued or repeated exposure to *S. typhi* is expected, booster doses of vaccine are required to maintain immunity after vaccination with parenteral typhoid vaccines (Table 1). The ViCPS manufacturer recommends a booster dose every 2 years after the primary dose if continued or renewed exposure is expected. In a study in which efficacy was not examined, revaccination of U.S. adults at either 27 or 34 months after the primary vaccination increased mean antibody titers to the approximate levels achieved with the primary dose (*17*). The optimal booster schedule for persons administered Ty21a for primary vaccination has not been determined; however, the longest reported follow-up study of vaccine trial subjects indicated that efficacy continued for 5 years after vaccination (*4*). The manufacturer of Ty21a recommends revaccination with the entire four-dose series every 5 years if continued or renewed exposure to *S. typhi* is expected. This recommendation may change as more data become available about the period of protection produced by the Ty21a vaccine. If the parenteral inactivated vaccine is used initially, booster doses should be administered every 3 years if continued or renewed exposure is expected. A single booster dose of parenteral inactivated vaccine is sufficient, even if >3 years have elapsed since the prior vaccination. When the heat-phenol-inactivated vaccine is used for booster

vaccination, the intradermal route causes less reaction than the subcutaneous route (*30*). The acetone-inactivated vaccine should not be administered intradermally or by jet- injector gun because of the potential for severe local reactions (*31*).

No information has been reported concerning the use of one vaccine as a booster after primary vaccination with a different vaccine. However, using either the series of four doses of Ty21a or one dose of ViCPS for persons previously vaccinated with parenteral vaccine is a reasonable alternative to administration of a booster dose of parenteral inactivated vaccine.

ADVERSE REACTIONS

Ty21a produces fewer adverse reactions than either ViCPS or the parenteral inactivated vaccine. During volunteer studies and field trials with oral live-attenuated Ty21a vaccine, side effects were rare and consisted of abdominal discomfort, nausea, vomiting, fever, headache, and rash or urticaria (*2,7,32*) (Table 2). In placebo-controlled trials, monitored adverse reactions occurred with equal frequency among groups receiving vaccine and placebo.

In several trials, ViCPS produced fever (occurring in 0%–1% of vaccinees), headache (1.5%–3% of vaccinees), and erythema or induration ≥1 cm (7% of vaccinees) (*17,20,33*) (Table 2). In the study conducted in Nepal, the ViCPS vaccine produced fewer local and systemic reactions than did the control (the 23-valent pneumococcal vaccine) (*19*). Among schoolchildren in South Africa, ViCPS produced less erythema and induration than did the control bivalent meningococcal vaccine (*20*). In a direct comparison, ViCPS produced reactions less than half as frequently as parenteral inactivated vaccine, probably because ViCPS contains negligible amounts of bacterial lipopolysaccharide (*33*).

Parenteral inactivated vaccines produce several systemic and local adverse reactions, including fever (occurring in 6.7%–24% of vaccinees), headache (9%–10% of vaccinees), and severe local pain and/or swelling (3%–35% of vaccinees) (Table 2); 21%–23% of vaccinees missed work or school because of adverse reactions (*12,13,34*). More severe reactions, including hypotension, chest pain, and shock, have been reported sporadically.

TABLE 2. Common adverse reactions of typhoid fever vaccines

Vaccine	Reactions		
	Fever	Headache	Local reactions
Ty21a*	0%– 5%	0%– 5%	Not applicable
ViCPS	0%– 1%	1.5%– 3%	Erythema or induration ≥1 cm: 7%
Parenteral inactivated	6.7%–24%	9%–10%	Severe local pain or swelling: 3%–35%

*The side effects of Ty21a are rare and mainly consist of abdominal discomfort, nausea, vomiting, and rash or urticaria.

PRECAUTIONS AND CONTRAINDICATIONS

The theoretical possibility for decreased immunogenicity when Ty21a, a live bacterial vaccine, is administered concurrently with immunoglobulin, antimalarials, or viral vaccines has caused concern (35). However, because Ty21a is immunogenic even in persons with preexisting antibody titers (*29*), its immunogenicity should not be affected by simultaneous administration of immunoglobulin. Mefloquine can inhibit the growth of the live Ty21a strain in vitro; if this antimalarial is administered, vaccination with Ty21a should be delayed for 24 hours. The minimum inhibitory concentration of chloroquine for Ty21a is >256 μg/mL; this antimalarial should not affect the immunogenicity of Ty21a (*36,37*). The vaccine manufacturer advises that Ty21a should not be administered to persons receiving sulfonamides or other antimicrobial agents; Ty21a should be administered ≥24 hours after an antimicrobial dose. No data exist on the immunogenicity of Ty21a when administered concurrently or within 30 days of viral vaccines (e.g., oral polio, measles/mumps/rubella, or yellow fever vaccines). In the absence of such data, if typhoid vaccination is warranted, it should not be delayed because of the administration of viral vaccines.

No data have been reported on the use of any of the three typhoid vaccines among pregnant women. Live-attenuated Ty21a should not be used among immunocompromised persons, including those persons known to be infected with human immunodeficiency virus. The two available parenteral vaccines present theoretically safer alternatives for this group. The only contraindication to vaccination with either ViCPS or with parenteral inactivated vaccine is a history of severe local or systemic reactions following a previous dose.

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