EVIDENCE SYNOPSIS

Title: Benefits and Harms of Immunization Against Typhoid Fever in Travelers Who Have Not Been Previously Exposed

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Clinical question: What are the benefits and harms of immunization against typhoid fever in travelers who have not been previously exposed?

Author recommendations:

For adult travelers who have never been exposed to typhoid fever, prior to vaccinating, clinicians should assess the risk of typhoid fever by travel destination, purpose of travel, and exposure to unsanitary conditions or poor quality drinking water and food.

If clinicians choose to vaccinate, they may administer either of the two available vaccines, with the choice based on the individual traveler's characteristics, as both are reasonably and equally—but not completely—effective. Adverse events are infrequent, generally mild, and self-limiting.

Evidence and recommendations:

Quality of Evidence[a]	Strength of Recommendations[b]	Conclusion
Moderate	Strong	Evidence favors typhoid fever risk mitigation strategies for high-risk travelers to typhoid fever–endemic areas, including vaccination and dietary and hygiene precautions

[a]Quality of evidence scale (GRADE): high, moderate, low, and very low.
[b]Strength of recommendations scale (GRADE): strong, weak, or no recommendation. For more information on the GRADE rating system, see http://www.gradeworkinggroup.org/index.htm.

What are the parameters of our evidence search?

Population	Healthy adults 18 years of age or older with no exposure or past immunization to typhoid fever traveling to areas where the disease is endemic (developing countries)
Intervention	Oral typhoid vaccine (Ty21a strain), parenteral Vi polysaccharide vaccine, Vi-rEPIA, oral M01ZH09 vaccine, or older whole-cell vaccine, with or without food precautions; time before travel
Comparator	No immunization against typhoid or placebo; food precautions only
Primary outcome(s)	Incident typhoid fever with positive blood, urine, or stool culture or positive Widal test; harms of vaccines

What is the basis for our conclusion(s)?

Patients or population: Healthy adults 18 years of age or older with no exposure or past immunization to typhoid fever traveling to areas where the disease is endemic (developing countries)

Intervention: Oral typhoid vaccine (Ty21a strain), parenteral Vi polysaccharide vaccine, Vi-rEPIA, oral M01ZH09 vaccine, or older whole-cell vaccine, with or without food precautions; time before travel

Comparison: No immunization against typhoid or placebo; food precautions only

Outcome: Incident typhoid fever with positive blood, urine, or stool culture or positive Widal test; harms of vaccines

Setting: Various destination countries where typhoid fever is endemic: areas of Eastern and Southern Europe, the African continent, Asia (excluding Japan), Central and South America, the Middle East, and the Caribbean

TABLE 1 Typhoid Fever Vaccine Efficiency

OUTCOME: PROPORTION OF PARTICIPANTS ATTAINING A FOUR-FOLD INCREASE IN ANTIBODY TITER (OVER BASELINE)

Study (Year) Design Intervention Sex Age	Comparator (Regime) Sex Age	Intervention Probability of Success (Sufficiently Protective Titer) Estimate (95% CI) n	Comparator Probability of Success (Sufficiently Protective Titer) Estimate (95% CI) n	Risk Difference Estimate (95% CI)	Quality of Evidence (GRADE)	Comment
Overbosch (2005)[1] RCT Combined hepatitis A + typhoid fever vaccine—ViCPS Female 61.5% Age 29.3 (±10) years	Monovalent vaccines for hepatitis A and ViCPS for typhoid Female 58.6% Age 29.2 (±10.5)	0.893 (0.84, 0.93) 177	0.894 (0.84, 0.93) 176	0.001 (–0.065, 0.066)	Low	No difference At day 14 post-vaccination. Approximately 5% titer reduction for both at 28 days and 50% at 1 year Risk of bias: no report of random sequence generation or concealment; differential loss to follow-up; industry involvement Netherlands and France
Overbosch (2005)[1] RCT Combined hepatitis A + typhoid fever vaccine—ViCPS	Monovalent vaccines for hepatitis A and ViCPS for typhoid	0.673 (0.54, 0.80) 56	0.698 (0.54, 0.83) 43	–0.025 (–0.20, 0.17)	Low	No difference Subgroups revaccinated at 3 years. Outcome at 3 years + 28 days Risk of bias: no report of random sequence generation or concealment; differential loss to follow-up; industry involvement Netherlands and France

Sanofi- Aventis (2014)[2] Prospective pre-post Typhoid Typhoid ViCPS Adults (single 0.5-mL dose) Female 38.3% Age 37.2 (±11.4) years	NA	0.92 (0.87, 0.95) 188	NA	NA	Unclear	Geometric mean antibody titers increased from baseline of 6.6 (5.8, 7.4) to 148.6 (126.9, 174.0) at 28 days The quality of evidence is unclear, as the study description is minimal on clinicaltrials.gov Industry-sponsored, -designed, and -run Japan
Adolescents (single 0.5-mL dose) Female 43% Age 15.6 (±2.0)	NA	0.86 (0.42, 1.0) 7	NA	NA	Unclear	Geometric mean antibody titers increased from baseline of 10.2 (2.9, 35.9) to 320.0 (230.6, 442.2) at 28 days The quality of evidence is unclear, as the study description is minimal on clinicaltrials.gov Industry-sponsored, -designed and -run Japan
Children (single 0.5-mL dose) Female 20% Age 5.2 (±3.8) years	NA	1.0 (0.48, 1.0) 5	NA	NA	Unclear	Geometric mean antibody titers increased from baseline of 3.7 (NA, NA)[a] to 501.7 (305.3, 824.5) at 28 days The quality of evidence is unclear, as the study description is minimal on clinicaltrials.gov Industry-sponsored, -designed and -run Japan

[a]The 95% CI was not calculated, as the titer values are less than the lower level of quantitation.
CI, Confidence interval; *NA,* not applicable; *RCT,* randomized controlled trial; *ViCPS,* Vi capsular polysaccharide vaccine.

Outcome: Proportion of typhoid fever patients who had been vaccinated within 5 years or less

Study (Year) Design Cases Sex Age	Controls (Regime) Sex Age	Cases Proportion of Typhoid Fever Cases Previously Vaccinated Estimate (95% CI) Cases/ Vaccinated	Controls Proportion of Paratyphoid Cases Previously Vaccinated Estimate (95% CI) Cases/ Vaccinated	Odds Ratio (95% CI) Vaccine Effectiveness Estimate (95% CI)	Quality of Evidence (GRADE)	Comment
Mahon B (2014)[3] Case-control (adjusted) Typhoid fever cases Female 48% Age 23 (2-86) median (range)	Paratyphoid A cases Age 25 (2-74) median (range) Female 43%	0.05 (29/602)[a]	0.20 (29/142)[b]	Odds ratio 0.20 (0.10, 0.36) Vaccine effectiveness 0.80 (0.66, 0.89)	Low	Compared vaccination rates in cases with vaccination status (within 5 years of illness) and estimated typhoid vaccine effectiveness as (1-OR) × 100% Risk of bias: some cases may have had pre-existing infection, and others have gone undiagnosed and unreported South Asia
Wagner K (2014)[4] (Case-control) Typhoid fever cases Female 47% Age 25 (2-83) mean (range)	Paratyphoid A cases	0.18 (118/640)	0.40 (247/616)	Odds ratio 0.34 (0.26, 0.44) Vaccine effectiveness (adjusted) 0.65 (0.53, 0.73)	Low	Compared vaccination rates in cases with vaccination status (within 3 years of illness) and estimated typhoid vaccine effectiveness Risk of bias: well-conducted case-control study Statistically significant reduction in vaccine effectiveness at 1-2 years post-vaccine from 0.72 (0.61, 0.80) to 0.37 (–0.12, 0.65)

[a]Of all registered cases of typhoid fever (609), 29 were vaccinated.
[b]Of all registered cases of paratyphoid A fever (142), 29 were vaccinated.
CI, Confidence interval; *OR*, odds ratio.

Outcome: Typhoid fever vaccine efficiency with concomitant travel vaccines; measured by 29-day post-vaccination geometric mean concentrations and geometric mean titers of typhoid fever antibodies

Study (Year) Design Intervention Sex Age	Comparator (Regime) Sex Age	Intervention Geometric Mean Concentration or Geometric Mean Titer Estimate (95% CI) N	Comparator Geometric Mean Concentration or Geometric Mean Titer Estimate (95% CI) N	Vaccine Group Ratio Comparator: Intervention Estimate (95% CI)	Quality of Evidence (GRADE)	Comment
Alberer M (2015)[5] RCT ViCPS + yellow fever vaccine (live, attenuated) Female 44% 36.5 (±10.8) years	Typhoid fever ViCPS + live attenuated yellow fever + quadrivalent meningococcal glycoconjugate ACWY-CRM vaccine Female 44% 35.1 (±11.0) years	Typhoid fever GMC 134 (101, 174) 99 Yellow fever GMT 5244 (3929, 7000) 100	Typhoid fever GMC 153 (118, 197) 99 Yellow fever GMT 5022 (3754, 6717) 100	Typhoid fever 1.14 (0.81, 1.60) Yellow fever 0.96 (0.65, 1.41)	High	Non-inferiority study Protective immunogenicity of monovalent typhoid and/or yellow fever vaccines is not compromised when given in combination with meningococcal vaccine

All comparative risks are reported as risk differences (RD) with 97.5 1-sided % confidence intervals. Studies in bold font have statistically significant differences in probability of prevention.
Because of rounding, the intervention and comparator numbers may not add up to the actual reported risk difference.
ACWY-CRM reflects the quadrivalent (A, C, W-135, and Y serogroups) conjugated to CRM_{197}, a nontoxic mutant of diphtheria toxin as a carrier protein.
CI, Confidence interval; *GMC*, geometric mean concentrations; *GMT*, geometric mean titers; *NNT*, number needed to treat; *RCT*, randomized controlled trial; *ViCPS*, Vi capsular polysaccharide.

TABLE 2 Adverse Events

Adverse Event	STUDY AND INTERVENTION GROUPS									
	ALBERER M[6]			OVERBOSCH D[7]				SANOFI-AVENTIS[2]		
	Typhoid and Yellow Fever Monovalents (N = 101)	Typhoid and Yellow Fever Monovalents + Meningococcal Vaccine (N = 100)	Meningococcal Vaccine Alone (N = 100)	Hepatitis A / ViCPS Mono-Components (N = 179)	Hepatitis A / ViCPS Re-vaccination (N = 43)	Combined Hepatitis A + ViCPS (N = 176)	Combined Hepatitis A + ViCPS Revaccination (N = 53) C	Adults (N = 188)	Adolescents (N = 7)	Children (N = 6)
Serious or severe adverse event[a]	2% (2)	3% (3)	3% (3)	2.8% (5)	28% (12)	4.5% (8)	17% (9)	0	0	17% (1)
Injection-site pain, edema, induration, or erythema	2-12% across groups			84% (150)	56% (24)	92.1% (162)	15.7% (8)	74% (139)	86% (6)	50% (3)
Headache (mild, moderate, or severe)	4-8% across groups			13.3% (24)	0	15.2% (27)	5.6% 3	7.4% (14)	0	0
Asthenia	NR	NR	NR	19.4% (35)	0	16.9% (30)	8% (4)	NR	NR	NR
Diarrhea	NR	NR	NR	5% (9)	0	2.8% (5)	0	NR	NR	NR
Malaise, influenza-like illness, or nasopharyngitis	1-8% across groups			3.3% (6)	2% (1)	3.4% (6)	6% (3)	16% (30)	0	17% (1)
Fever	NR	NR	NR	0.6% (1)	0	4.5% (8)	3.7% (2)	1% (2)	0	17% (1)

[a]As reported in the studies.
NR, Not reported; *ViCPS*, Vi capsular polysaccharide.

Guidelines: Newton A, et al. The 2014 Yellow Book; Chapter 3: Infectious Diseases Related to Travel: Typhoid Fever.[8] (AGREE II Score: unavailable) There is no evidence or strength of recommendations ratings or methods described.

- Vaccinate travelers who are traveling to areas of increased risk of exposure to *Salmonella enterica* serotype Typhi. The two vaccines available in the United States are an oral live attenuated vaccine (Vivotif®) and an intramuscular capsular polysaccharide vaccine, Typhim Vi®.
- The oral vaccine requires a booster every 5 years, and the intramuscular product requires a booster every 2 years.
- Adverse reactions to Ty21a vaccine are rare and mainly consist of abdominal discomfort, nausea, vomiting, and rash. ViCPS vaccine is most often associated with headache (16-20%) and injection-site reactions (7%).

International Travel and Health: Typhoid Fever. Chapter 6. World Health Organization, 2012.[9] (AGREE II Score: unavailable) There are no evidence or strength of recommendations ratings or methods described.

- A combination hepatitis A/typhoid (ViCPS) vaccine, administered as a single dose, confers high levels of protection against both of these water-borne diseases.
- The risk for travelers is generally low, except in parts of northern and western Africa, in southern Asia, in parts of Indonesia, and in Peru. Elsewhere, travelers are usually at risk only when exposed to low standards of hygiene. Even vaccinated travelers should take care to avoid potentially contaminated food and water, as the vaccine does not confer 100% protection.
- Both typhoid vaccines are safe, and there are no contraindications to their use other than previous severe hypersensitivity reactions to vaccine components. Proguanil, mefloquine, and antibiotics should be stopped from 3 days before until 3 days after the administration of Ty21a. These vaccines are not recommended for use in infant immunization programs due to insufficient information on their efficacy in children under 2 years of age.
- There are two vaccines available: (1) The oral vaccine based on the live, attenuated mutant strain of *Salmonella typhi* Ty21a (Ty21a vaccine) is supplied in enteric coated capsules. In Australia and Europe, three tablets are given on days 1, 3, and 5; this series is repeated every year for individuals traveling from non-endemic to endemic countries and every 3 years for individuals living in countries or areas at risk. In North America, four tablets are given on days 1, 3, 5, and 7, and revaccination is recommended only after 7 years (Canada) or 5 years (United States) for all, regardless of typhoid fever risk in the country or area of residence. The duration of protection following Ty21a immunization is not well defined and may vary with vaccine dose and possibly with subsequent exposures to *S. typhi* (natural booster).
- (2) The injectable Vi capsular polysaccharide vaccine (ViCPS vaccine) is given intramuscularly in a single dose. Protection is induced about 7 days after the injection. In countries or areas at risk, the protective efficacy 1.5 years after vaccination is about 72%; after 3 years it is about 50%. The vaccine is licensed for individuals aged >2 years. To maintain protection, revaccination is recommended every 3 years.

Hill DR, Ericsson CD, Pearson RD, et al. The Practice of Travel Medicine: Guidelines by the Infectious Diseases Society of America, 2006.[10] (AGREE II Score: unavailable) Infectious Diseases Society of America-United States Public Health Service grading system for ranking recommendations in clinical guidelines.

- Typhoid fever should be administered on the basis of a risk assessment. (Strength of recommendation, A; good evidence to support a recommendation for use. Quality of evidence III; evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.)
- Travelers to the Indian subcontinent, particularly those visiting friends and relatives, are at greatest risk. Immunization is indicated when traveling to destinations with poor-quality sanitation and hygiene and endemic areas. In addition to the Indian subcontinent, endemic areas include Central and South America, Asia, and Africa.

Johnson KJ, Gallagher NM, Mintz ED, Newton AE, Brunette GW, Kozarsky PE. New country-specific recommendations for pre-travel typhoid vaccinations from the CDC, 2011.[11] (AGREE II Score: unavailable) Infectious Diseases Society of America–United States Public Health Service grading system for ranking recommendations in clinical guidelines.

- Twenty-six countries were downgraded to the Centers for Disease Control and Prevention low-risk category.
- The change in recommendations for 26 Eastern European and two Middle Eastern destinations is an encouraging reflection of reduced disease risk due to improvements in water and sanitation coverage. However, the fact that pre-travel vaccination is still recommended for 175 (74%) of 238 destinations demonstrates that typhoid continues to remain a serious risk to travelers in many parts of the world.

Jackson BR, Iqbal S, Mahon B. Updated recommendations for the use of typhoid vaccine—Advisory Committee on Immunization Practices, United States, 2015.[12] (AGREE II Score: unavailable) There is no evidence or strength of recommendations ratings or methods described.

- Vaccination is recommended for the following groups:
  - Travelers to areas where there is a recognized risk for exposure to *Salmonella* serotype Typhi (the most recent guidelines are available at http://wwwnc.cdc.gov/travel). Risk is greatest for travelers who have prolonged exposure to possibly contaminated foods and beverages, although short-term travelers are also at risk. Most travel-associated typhoid fever cases in the United States occur among travelers who are visiting friends or relatives; many travelers in this group do not seek pre-travel health care. Multidrug-resistant strains of *Salmonella* serotype Typhi have become common in many regions, and cases of typhoid fever that are treated with drugs to which the organism is resistant can be fatal. Travelers should be cautioned that typhoid vaccination is not a substitute for careful selection of food and beverages. Typhoid vaccines are not 100% effective, and vaccine-induced protection can be overwhelmed by large inocula of *Salmonella* serotype Typhi.
  - Persons with intimate exposure (e.g., household contact) to a documented *Salmonella* serotype Typhi chronic carrier (defined as excretion of *Salmonella* serotype Typhi in urine or stool for >1 year).

Author commentary: Though the evidence supporting the recommendations is low quality, the recommendation is strong. The intermediate outcome, vaccine immunogenicity, appears first in the table, as this outcome is a prerequisite for vaccine effectiveness, while the more clinically relevant result, vaccine effectiveness based on observational studies, follows.

The risks of bias encountered are balanced by the consistency of findings and the magnitude of studies' effect estimates. The randomized controlled trials show convincing immunogenic response by 28 days post-vaccination. Given the geometric mean titer reduction at 1 year, those travelers who were vaccinated 1 year or more prior to a planned trip to a typhoid fever–endemic area, especially if they are visiting friends and family, may be candidates for revaccination, though clinical practice guidelines tend to recommend doing so after 2 years for the intramuscular and 5 years for the oral vaccine.

The two registry-based observational studies are well designed and executed and indicate that, of those vaccinated, up to 80% will be protected by the vaccine. However, the authors consider this estimate an overestimation of the actual vaccine efficiency, especially in areas of intense exposure to serotype Typhi. Additionally, travelers may have a lower risk of exposure as a result of short exposure times and less exposure to contaminated water and food than the local population.

Either the oral or intramuscular typhoid fever vaccine may be used with confidence of a solid immunogenic response with few and generally mild side effects; the most frequent of these are local injection-site reactions and headaches. The decision to vaccinate should be based on a detailed risk assessment for typhoid fever that includes destination, purpose,

exposure to contaminated water and food, immunocompetence, and prior or potential allergic reactions to the vaccine.

The clinical practice guidelines are consistent with these recommendations.

Update alerts: Important new citations relevant to this topic are added here as they become available.

Glossary: AGREE II, Appraisal of Guidelines for Research and Evaluation; CI, confidence interval; CPG, Clinical Practice Guideline; GMC, geometric mean concentrations; GMT, geometric mean titers; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NA, not applicable; NNT, number needed to treat; NR, not reported; OR, odds ratio; RCT, randomized controlled trial; ViCPS, Vi capsular polysaccharide.

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