STATEMENT ON INTERNATIONAL TRAVELLERS AND TYPHOID

AN ADVISORY COMMITTEE STATEMENT (ACS)

COMMITTEE TO ADVISE ON TROPICAL MEDICINE AND TRAVEL (CATMAT)

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

—Public Health Agency of Canada

Également disponible en français sous le titre :
Déclaration concernant les voyageurs internationaux et la typhoïde

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This publication can be made available in alternative formats upon request.

Publication date: February 2014

Cat.: HP40-98/2014E-PDF
ISBN: 978-1-100-23223-2
Pub.: 130582

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PREAMBLE

The Committee to Advise on Tropical Medicine and Travel (CATMAT) provides the Public Health Agency of Canada with ongoing and timely medical, scientific, and public health advice relating to tropical infectious disease and health risks associated with international travel. The Agency acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and medical practices, and is disseminating this document for information purposes to both travellers and the medical community caring for travellers.

Persons administering or using drugs, vaccines, or other products should also be aware of the contents of the product monograph(s) or other similarly approved standards or instructions for use. Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) or other similarly approved standards or instructions for use by the licensed manufacturer(s). Manufacturers have sought approval and provided evidence as to the safety and efficacy of their products only when used in accordance with the product monographs or other similarly approved standards or instructions for use.

Key points/Messages

- Recommendations for use of typhoid vaccine were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. They consider the balance of benefits (efficacy) and harms of typhoid vaccine, the confidence in the estimates of effect for vaccination (high, moderate, low or very low), and what is believe to be the values and preferences of the traveller regarding prevention of typhoid through vaccination.
- This is the first time that the GRADE approach has been used for a statement developed by CATMAT. The terminology used to express the strength of recommendations has been changed to strong and conditional. The meaning of these terms is explained in Boxes 1 and 2.
- Typhoid vaccine is only moderately effective (~50%) but is well tolerated with very low risk of serious adverse events. We have moderate confidence in the estimate of effect for vaccine efficacy. Confidence was reduced, i.e. not high, because the included studies assessed efficacy of vaccination in populations living in countries with elevated typhoid risk and then these data were extrapolated to travellers.
- The strongest and most consistent predictor of typhoid risk in travellers is destination of travel. The estimated risk of developing travel associated typhoid is about: 1/3,000 travellers for travel to the South Asia (high risk), 1/50,000–100,000 for travel to Sub-Saharan Africa, North Africa and the Middle East, or South America (intermediate risk), and < 1/300,000 for travel to the Caribbean and Central America (low risk). The confidence in the baseline estimates of typhoid risk by destination (quality of the data) was moderate. Confidence was reduced, i.e. not high, because of the intermediate risk of bias of included studies due to the possibility of under-ascertainment of cases and to imprecision (i.e. unable to calculate confidence intervals due to incomplete stratified denominator data).

- Several studies have identified travelling children, those visiting friends and relatives (VFRs), the presence of achlorhydria or use of acid suppression therapy and longer duration of travel to be factors that increase the risk of travel associated typhoid. The incremental magnitude of risk that these factors contribute in addition to travel destination is unclear. The confidence in the effect estimates (quality of the data) for these factors was very low.
- No data on the values and preferences of travellers or practitioners regarding the use of typhoid vaccine for prevention of typhoid were found. In the absence of such data, recommendations were made under the belief that the majority of Canadian travellers would consider the decrease in typhoid risk worth the cost and inconvenience of the vaccine if the absolute risk of typhoid was 1 in 10,000 or higher but not if the risk was less than this. Among destinations for which data are available, travel to South Asia was the only region where risk exceeded this threshold.
- The vaccine recommendations are conditional due to the modest efficacy of typhoid vaccine; the relatively poor quality of risk factor data; and uncertainty about traveller/practitioner values and preferences.
- Providers should discuss with the traveller the anticipated benefits and harms (including financial costs) associated with vaccination, and help the traveller reach a decision that is consistent with his/her values and preferences.
- Available injectable polysaccharide vaccines do not protect against enteric fever (paratyphoid) caused by *Salmonella paratyphi* serovars. Current evidence is not sufficient to recommend oral typhoid vaccine (Ty21a) for protection against paratyphoid.

GRADE Recommendations

- CATMAT suggests that typhoid vaccine (Ty21a or Vi polysaccharide vaccine) be used for Canadian travellers visiting South Asia*; ***Conditional recommendation, moderate confidence in estimate of effect***.
- CATMAT suggests that typhoid vaccine (Ty21a or Vi polysaccharide vaccine) not be used for Canadian travellers visiting destinations other than the South Asia; ***Conditional recommendation against (immunization), moderate confidence in estimate of effect.***
    - The decision of whether or not to use typhoid vaccination for destinations other than South Asia might be influenced by: other factors associated with risk of travel associated typhoid such as pediatric travel, visiting friends and relatives, longer duration of travel, the presence of achlorhydria or use of acid suppression therapy; and/or patient preferences.

* South Asia is defined as per the World Bank classification and includes Afghanistan, Pakistan, India, Nepal, Bangladesh, Maldives, Sri Lanka, Bhutan. Among these countries, the large majority (≥90%) of cases of typhoid among travellers were reported from India, Pakistan and Bangladesh (1;2).

For implications of what a conditional recommendation means, see Box 1*: Recommendation categories* and Box 2: *What does a conditional recommendation mean in practice?*

BOX 1: Recommendation categories

Strong*-recommendation for	The committee believes that all or almost all well informed people would want the recommended course of action and only a small number would not. Implication for practitioners: The balance of risks and benefits are such that most travellers would choose the intervention.
Strong-recommendation against	The committee believes that all or almost all well informed people would not want the recommended course of action and only a small number would. Implication for practitioners: The balance of risks and benefits are such that most travellers would not choose the intervention.
Conditional recommendation for**	The committee believes that the majority of well-informed people would want the recommended course of action, but a minority (perhaps a large minority) would not. Implication for practitioners: With a conditional recommendation different travellers may make different choices. Practitioners should present the risks and benefits of the intervention and help each traveller make a decision consistent with his/her values and preferences.
Conditional recommendation against	The committee believes that the majority of well-informed people would not want the recommended course of action, but a minority (perhaps a large minority) would. Implication for practitioners: With a conditional recommendation different travellers may make different choices. Practitioners should present the risks and benefits of the intervention and help each traveller make a decision consistent with his/her values and preferences.

Adapted from the GRADE handbook for grading quality of evidence and strength of recommendations and GRADE guidelines 14 and 15 (3–5).

* The GRADE working group suggests that if a recommendation is "strong", then it is expected that 90% or more of informed individuals would choose (or not choose) the recommended course of action.

** The GRADE working group suggests that if a recommendation is "conditional", then it is expected that less than 90% of informed individuals would choose (or not choose) the recommended course of action.

BOX 2: What does a conditional recommendation mean in practice?

GRADE-based recommendations in this statement are "conditional", which means that we believe that the majority of well-informed travellers would choose the recommended course of action; however a minority (perhaps a large minority) would not. This is because the benefit of typhoid vaccine is modest and the decision to use it should consider: the risk of travel associated typhoid in different destinations; the relatively poor quality of risk factor data (i.e., VFR, pediatric travel, duration of stay, achlorhydria/acid suppression and asplenia); and divergent individual traveller preferences.

Examples of traveller decisions in the context of conditional typhoid vaccine recommendations:

- In situations where the risk is particularly low, we believe that the majority of travellers would not use vaccine. For example, a visit to a Caribbean resort for a short period is associated with a very low risk of typhoid and travellers are very unlikely to choose to use typhoid vaccine. On the other hand, when the risk is relatively high, such as a family going to a rural area of South Asia for several months/years, travellers are very likely to choose to use typhoid vaccine.
- Travellers with short stays in South Asia, living in lower risk environments, and/or who place a relatively lower value on protection against typhoid for themselves or family members might decide not to use typhoid vaccine.
- The majority of travellers to Africa would likely choose not to use typhoid vaccine. However, those travelling for a long period of time, visiting rural areas, VFR travel, those with achlorhydria/acid suppression, asplenia, and/or who place a relatively higher value on protection against typhoid for themselves or family members might decide to receive vaccine.

INTRODUCTION

Typhoid fever is an enteric febrile illness that, among Canadians, is usually acquired during travel to a typhoid endemic country (6–9). Prevention involves vaccination, personal hygiene and food and water precautions. This statement updates previous recommendations on typhoid and overseas travel (10) and was deemed necessary based on: the datedness of the existing statement; the availability of new interventions; and, the publication of new evidence related to the prevention of typhoid. The typhoid vaccine-based recommendations were developed using the evidence-based medicine approach Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (11;12).

BACKGROUND

Clinical and epidemiological features

Typhoid fever is caused by *Salmonella enterica* subsp. *enterica* serovars Typhi (S. typhi) (13;14). Exposure to the causative pathogen is usually through ingestion of water or food that has been contaminated by feces from an ill individual or a chronic carrier (15;16). Humans are the only reservoir for this disease. The incubation period is normally eight to 14 days but can vary from three to over 60 days (15). Individuals infected with *S. typhi* are infectious for as long as they are excreting the bacilli, generally from the first week of infection until symptoms have resolved. However, 10% of untreated individuals excrete the bacilli for three months or more after initially contracting the disease and 2% to 5% of untreated individuals become asymptomatic chronic carriers (15).

The majority of the global burden of typhoid occurs in low income countries. The World Health Organization (WHO) estimates there to be 21 million cases and 210,000 to 840,000 deaths annually worldwide (17;18). In endemic countries transmission is facilitated by poorly developed sanitation infrastructure and almost the entire population can be exposed (19). Most cases and deaths (more than 90%) occur in Asian countries, predominantly in South Asia (17). Incidence in high income countries is low (e.g., <15/100,000 persons per year) (13;15;20), and cases are most often associated with travel. Based on reporting to the Public Health Agency of Canada, there was an average of 127 (range: 77 to 183) cases per year in Canada from 1999 to 2011; with a mean annual incidence of 0.39/100,000 (range: 0.25 to 0.53/100,000) (21).

The clinical course of typhoid ranges from mild illness with low-grade fever to severe systemic disease with abdominal perforation and extra intestinal infection that, if untreated, can be fatal (14;15). Symptoms are non-specific and can include fever, headache, abdominal pain, nausea, vomiting, malaise, anorexia, bradycardia, splenomegaly, cough, rose spots on trunk and constipation (15). Hospitalization in North America and Europe is common (75%-90%) with a mean length of stay ranging from 6–10 days (2;22;23). The case fatality rate is approximately 10% for untreated cases in low income settings and <1% for patients receiving care in high income countries (2;22–25).

METHODS

This statement was developed by a working group comprised of volunteers from the CATMAT committee, none of whom declared a relevant conflict of interest. All working group members were approved by the CATMAT secretariat and chair. The working group, with support from the secretariat, was responsible for: literature retrieval, synthesis and analysis; and the development of key questions and draft recommendations. The final statement was approved by the full CATMAT membership.

Vaccine-recommendations in this statement were developed using the GRADE methodology. This approach has been increasingly adopted by guideline developers (26;27). It stresses transparency and provides an explicit framework in which the following factors are considered and weighed when making a recommendation(s): confidence in the estimate of effect (quality of data), balance of benefits and harms and values and preferences. This is the first CATMAT statement to use the GRADE methodology. Resulting recommendations are expressed as strong or conditional (see Box 1 for details), which differs from the evidence-based grading system of the Canadian Preventive Task Force[i] on Preventive Health Care (e.g., AI-III, BI-III) used in previous CATMAT statements (28;29). Examples of how a conditional recommendation may be applied in practice are presented in Box 1.

The following summarizes the process used to develop this statement:

1. An analytic framework identifying clinical preventive actions (interventions) for typhoid and risk factors for typhoid disease was developed (see Appendix 1).
2. From the analytic framework, the following key "PICO" (population of interest, intervention, comparison and outcome) question was identified:
    a. *Among Canadian travellers, does the administration of typhoid vaccine versus no vaccine decrease the incidence of typhoid and the associated morbidity and mortality?*
3. From the analytic framework, key questions to define the magnitude of benefits and harms were identified:
    a. *What harms are associated with typhoid vaccination?*
    b. *What are the important risk factors for typhoid among travellers (e.g., destination, duration of travel, age, VFRs, comorbidities such as infection with HIV or acid suppression/achlorhydria)?*
    c. *What are the values and preferences of travellers regarding the magnitude of risk reduction in typhoid that would make use of the vaccine worthwhile given the cost and inconvenience associated with the vaccine?*
4. Additional contextual questions that were considered included:
    a. *Does antimicrobial treatment reduce typhoid mortality and morbidity among travellers; and does pathogen susceptibility to antimicrobial treatment vary by destination?*
    b. *Do hygiene and/or food and water precautions reduce the risk of acquiring typhoid among travellers?*

[i] The task force has since updated its system for grading evidence, and now deploys the GRADE approach (www.canadiantaskforce.ca/methods/grade)

5. With the aid of a reference librarian, a strategy was developed to identify relevant literature. Two electronic databases (Ovid MEDLINE and Embase) were searched using the terms "typhoid fever" and "travel". The search spanned the publication period of January 1, 2000 to August 14, 2012. In addition, the Cochrane Review Database was searched using the term "typhoid" from the start of the database up to and including July 2012. For all searches, only articles in English and/or French were retained.
6. From these searches, literature addressing the PICO and other questions was identified. Systematic reviews that addressed the efficacy of typhoid vaccine were specifically sought. In addition, studies that addressed: burden of disease (incidence, morbidity, mortality, hospitalizations), especially for travellers; disease pathogenesis; population-specific risk factors (e.g., age, VFR); itinerary-specific risk factors (e.g., destination, duration of travel); efficacy of preventive measures (e.g., sanitation and hygiene); and/or disease treatment/management, were identified.
7. A quality assessment of studies on the efficacy of typhoid vaccine was performed, and results were collated into evidence profile and summary of findings tables (see Appendices 2 and 3) as per the GRADE methodology (30;31).
8. An approach to assess the confidence in estimates of baseline risk from observational, non-intervention studies using the GRADE framework is under development. Currently, the GRADE group recommends assessing quality by applying the same elements that are used for intervention-based data, i.e. risk of bias, publication bias, imprecision, inconsistency, and indirectness (32). A notable difference is that, for baseline risk, observational studies start out as high quality data. This is because they are often more suited than are clinical trials (which often include highly selected populations) to provide population based estimates of risk (Guyatt, personal communication, 2013). The evaluation of studies of baseline risk of typhoid to travellers within the GRADE framework is presented in Appendices 4a and 4b (32). Studies on other risk factors, i.e. VFRs, age, duration of travel, acid suppression/achlorhydria, were judged to be of very low quality and are described in a narrative fashion.
9. Benefits and harms associated with vaccination were estimated. The absolute risks of developing typhoid with and without vaccine and of typhoid associated hospitalization or death were calculated by region and are presented in Tables 3a and 3b.
10. Recommendations were developed for use of typhoid vaccination taking into consideration: a) our confidence in the estimates of the efficacy and harms of typhoid vaccine and the baseline risk of typhoid to travellers by destination, b) the balance of vaccine-associated harms and benefits, and c) the values and preferences of travellers. The cost of the vaccine, normally borne by the traveller, was not explicitly considered as there were no data on willingness to pay (WTP) for typhoid vaccine in travellers.
11. Non-GRADE recommendations were developed based on expert opinion. There were certain interventions (such as hand washing and avoiding high risk foods), that entail minimal or no risk, inconvenience, or cost and for which there is appreciable indirect evidence of benefit in terms of reducing typhoid incidence. We did not conduct a formal GRADE assessment for such interventions and consider them "best practice" or "common sense" recommendations. We did not assess use and choice of antibiotic for treatment of typhoid with GRADE. Guidance in this regard was developed based on a more superficial evaluation of the evidence and expert opinion.

RESULTS

Our initial literature search identified 227 studies of which 75 were excluded (19 due to language other than English or French; 56 due to non-relevance) based on screening of titles and abstracts. Full texts of the remaining 152 studies were reviewed; one was excluded due to language and four others due to non-relevance. The remaining 147 articles were included and addressed: typhoid epidemiology (N=39), disease characteristics (N=17), risks in specific populations (N=16), preventive measures (N=38), and/or disease management (N=54) (numbers add to >147 as some articles addressed > one subject). Two additional studies on baseline risk (33;34) were identified after the initial literature review.

All included vaccine efficacy studies were conducted in populations living in typhoid endemic countries. No studies that addressed efficacy of typhoid vaccine in travellers; or associated reductions in morbidity and mortality for this population were found. A Cochrane Collaboration systematic review published in 2006 was identified, and assessed 17 randomized or quasi-randomized trials (35) of typhoid vaccine among residents of endemic areas. It was rated as a high quality systematic review using the AMSTAR measurement tool for the assessment of methodological quality of systematic reviews (36). An additional three randomized or quasi-randomized controlled clinical trials (RCTs) published after this systematic review were also identified and are included in our analyses (37–39).

Quality Assessments

Clinical trials assessed with GRADE

To assess efficacy of typhoid vaccine, three trials for each of Ty21a oral vaccine (40–42) and Vi polysaccharide vaccine were included (37;39;43) (see Appendices 2a–c)[ii]. Studies that were identified and included in the Cochrane Review on typhoid vaccine but excluded from our analysis and the corresponding reason for exclusion are listed in the same appendix. For adverse events (AE), three trials for Ty21a oral vaccine (40;42;46) and two trials for Vi polysaccaride vaccine were included (38;47) (see Appendices 3a–c). For Ty21a, only AE data for enteric-coated tablets were included. The evidence from clinical trials on the efficacy and harms of typhoid vaccine are summarized in the evidence profile and a summary of findings tables (see Appendices 2b, 2c, 3b and 3c). No data on the impact of typhoid vaccination on morbidity and mortality were found. Thus, the primary outcome for our assessment was vaccine-associated reduction in typhoid incidence. These data (37;38;40–43;48–53), along with adverse effects recorded from these and additional trials, were assessed with GRADE. Estimates of effect were deemed to be without serious risk of bias; but were universally rated down for indirectness as they only included residents of endemic areas (not travellers) and often were done with younger age groups. Thus, we had moderate confidence in the estimate of effect for vaccine efficacy. Estimates for adverse effects were also rated down for indirectness; and sometimes for imprecision and/or inconsistency.

[ii] Follow-up studies were used for Klugman 1987 (43) (in Klugman 1996 (44), i.e. Vi to 3 yrs), Levine 1987 (42) (Levine 1999 (45), i.e. Ty21a to 7 years).

Observational studies on risk factors

The assessment of the studies of the baseline risk of typhoid in travellers by destination is shown in Appendix 3a and 3b. We have moderate confidence in the baseline estimates of risk. The confidence in these estimates was downgraded from high to moderate as we believed that the data were at intermediate risk of bias due to under-ascertainment of cases and imprecision (unable to calculate confidence intervals due to incomplete stratified denominator data). The studies describing risk from factors other than destination of travel were considered to be very low quality. For example, risk of typhoid due to VFR travel or length of stay only reported data on the proportion of cases occurring in VFRs or for different time periods. The magnitude of risk due to these factors therefore, could not be determined (54–57). Only one study reported the risk of travel associated typhoid in different age groups and expressed this as an odds ratio (1). Another study only reported the proportion of cases of typhoid occurring in each age group (54). Furthermore, the number of children in these studies was low resulting in moderate imprecision. The quality of data for the risk of typhoid in those with achlorhydria was considered to be very low quality due to the case control design of the included studies (58).

Data synthesis to address specific questions

DOES THE ADMINISTRATION OF TYPHOID VACCINE VERSUS NO VACCINE DECREASE THE INCIDENCE OF TYPHOID AND THE ASSOCIATED MORBIDITY AND MORTALITY AMONG CANADIAN TRAVELLERS?

No studies that measured the effect of typhoid vaccine on typhoid-associated hospitalizations or mortality in travellers were found. The primary outcome of the analysis was vaccine efficacy to prevent cases of typhoid. Two types of typhoid vaccine are licensed in Canada (Table 1): a live oral vaccine (Ty21a), and injectable Vi polysaccharide vaccines. Only evidence for these types of vaccines was reviewed. Data for the Vi conjugate vaccine (50), though included in the Cochrane systematic review, were not considered in our analyses.

Vaccine efficacy to prevent typhoid: Expressed as three year cumulative risk of typhoid, persons receiving typhoid vaccine (Ty21a or Vi polysaccharide) were significantly less likely to develop typhoid fever than those who did not (Relative Risk (RR), 95% CI =0.51 (0.42 to 0.62). For the same outcome, but measured as a two year cumulative risk of typhoid, RR was lower at 0.43 (0.34 to 0.54). Expressed by vaccine type, estimates ranged from RR=0.34 (0.19 to 0.60) for Ty21a after two years of follow-up to 0.53 (0.43 to 0.54) for Ty21a after three years of follow-up; efficacy of Vi polysaccharide vaccine was intermediate to these values (Appendices 2b and 2c). We also assessed vaccine efficacy for different age groups (Appendices 2b and 2c). This was done separately for the respective vaccines due to reporting results on different age stratifications. For both types of vaccine, the RR estimate was lower in older than in younger persons. However, these differences were not significant; and we thus decided against making age-specific recommendations for vaccine use.

Harms associated with typhoid vaccine: Based on clinical trial data, adverse events (AE) associated with typhoid vaccines (Appendices 3 a-c) are generally mild and not significantly different from controls for: fever, vomiting, diarrhea, headaches, rash, or erythema. With Vi polysaccharide, pain at the injection site was more common among the vaccine recipients (RR=3.68; CIs=1.96 to 6.93). For enteric coated Ty21a, there was increased risk of: any mild

adverse event (RR=1.78; CIs=1.08 to 2.95) (35) and nausea or abdominal pain (RR=2.13; CIs=1.33 to 3.41). Based on these data, it was estimated that there would be one additional AE due to pain for every 13 persons receiving Vi polysaccharide vaccine; and one mild AE and one nausea and abdominal pain AE for every 18 and 31 persons, respectively, receiving Ty21a.

In Canada, there were 1,216 adverse events following immunization with typhoid vaccines reported from 1987 to March 2013. Most reports were for vaccination site reactions, fever, gastrointestinal symptoms, systemic symptoms, skin and allergic reactions, and neurological symptoms such as paresthesia and dizziness (59). These are consistent with AEs reported in the product monographs (60;61). Post marketing surveillance from the United States (62) indicated 666 AEs associated with Ty21a or Vi polysaccharide vaccines (1990 and 2002). Event rates in this study were 9.7 and 4.5/100,000 doses for all AE with these vaccines, respectively; with serious AE rates of 0.59 and 0.34 events/100,000 doses.

WHAT ARE THE IMPORTANT RISK FACTORS FOR TYPHOID AMONG TRAVELLERS (E.G., DESTINATION, DURATION OF TRAVEL, AGE, VFRS, COMORBIDITIES SUCH AS INFECTION WITH HIV OR ACHLORHYDRIA)?

Destination: Seven observational studies estimating typhoid incidence by destination were identified and six were included (1;2;24;33;34;54;63). Studies were included if they expressed risk based on bacteriologically confirmed cases of typhoid (through mandated surveillance systems) in national-level databases for the numerator and used validated travel survey methods to determine population based travel volume for the denominator (Appendix 4a). Four of the studies included hundreds of cases over multi-year periods: two of which were from the United States (2;24), the others were from the Netherlands (33) and Switzerland (34). Two studies were based on smaller cohorts of travellers, and were from Sweden and Quebec. Four of these studies were used to estimate baseline risk (1;2;33;54) (Table 3). Two were not included because: more recent data were available (24); or because incomplete data on case numbers/rates were provided (34). For the included (and excluded) studies, risk was consistently highest in South Asia (accounting for around 70% of travel associated typhoid cases), followed by: Sub-Saharan Africa, other low/middle income countries, and higher income countries. This ranking is similar to baseline risk estimates for residents of endemic areas (64;65).

Visiting Friends and Relatives (VFRs): Referring to persons and their families who return to their birth country to visit friends or relatives, VFRs are at increased risk for typhoid (55;56). In an observational study (n=36 cases) from Quebec, VFRs accounted for more than 90% of reported cases of typhoid despite comprising less than 15% of the "at risk" travelling population (54). Similarly, VFRs accounted for 66% of reported travel-related cases of typhoid in the United States (1999–2006) compared to only 9% among persons categorized as "tourists" (41). These data suggest that VFR travellers are at higher risk for typhoid, but were judged to be very low quality.

Age: Children are at increased risk of typhoid, either as residents of typhoid endemic countries or as travellers (1;66;67). They also have higher rates of typhoid-associated complications, hospitalizations and death as compared to adults (13;17;67). In a Quebec case series, approximately 50% of cases occurred among persons less than 20 years of age (54). Similarly, children aged 0 to 6 years accounted for 17% of typhoid cases in a Swedish study (1), but only 5% of the exposed population. In this study, those 0–6 years of age had a

44.2 (10.6–184) higher odds ratio (OR) of having typhoid compared to those 46–65 years of age. In addition, those 7–18 years of age had an OR of 14.2 (3.8–52.9) and those 19–45 years of age had an OR of 10.8 (3.3–35.5) compared to travellers aged 46–65 years. These data were judged to be very low quality due to study design and imprecision. Evidence addressing whether older travellers are at increased risk of acquiring typhoid or developing complications post infection were not found.

Length of stay: Several studies have demonstrated that risk of exposure to typhoid increases with duration of travel. In a study in Quebec, no cases occurred in persons travelling less than two weeks (54). Similarly, in a larger case series from the US, less than 20% of cases occurred in persons travelling for less than two weeks (56). Finally, long term travellers (length of stay more than six months) were more likely than short term travellers to be diagnosed with enteric fever (typhoid and paratyphoid) in a study of patients identified in the GeoSentinel Surveillance Network (57). To conclude, the majority of cases in the reviewed studies occurred after two weeks of travel, however a time duration below which there was negligible risk of typhoid could not be determined.

HIV positive travellers: HIV infection is recognized to predispose to more severe and complicated infections with non-typhoidal salmonellosis but does not appear to increase the risk of *S. typhi* infection (68); though a small study in Peru suggested an association between HIV and increased severity and relapse rate of typhoid disease (69). While not conclusive, these studies suggest that infection with HIV is not a critical risk factor for typhoid.

Achlorhydria/acid suppression: Given the important role that gut acidity plays in destroying microbes, it is reasonable to expect that achlorhydria or acid suppression therapy could potentially enhance the risk of typhoid. In a recent systematic review of 11,280 patients in 6 studies, those taking acid suppression had a 2.6 higher odds (95% CI 1.53–4.25) of developing an enteric infection (e.g., salmonella, campylobacter and other enteric organisms) as compared to those not on acid suppression (58). No data on the risk of developing enteric infections in travellers with achlorhydria or on acid suppression therapy were found, but there is no biologic reason why travellers should be different from those found in these studies.

Asplenia: Splenectomized patients are at increased risk for encapsulated organisms but there were no published data that specifically address this issue for salmonella in asplenic travellers. In patients with asplenia, despite lack of typhoid specific risk data, it may be prudent to have a low threshold to use vaccine in this population. The decision to use (or not) vaccine should be guided through a discussion of the benefits and risks of typhoid vaccination with the patient.

WHAT ARE THE VALUES AND PREFERENCES OF TRAVELLERS REGARDING THE BALANCE OF HARMS AND BENEFITS OF PREVENTING TYPHOID WITH TYPHOID VACCINATION?

There is evidence that typhoid vaccine is cost effective for residents of some endemic areas (70;71). However, compared to most travellers, cumulative risk is much higher among resident populations; and cost-effectiveness in resident populations (from a societal perspective) is not an appropriate measure to extrapolate to travellers who are paying for their own vaccine. Studies on Willingness to Pay (WTP) for typhoid (72) or other travel-related immunizations would be a more relevant measure of risk acceptance of travellers; however no such studies were identified. Furthermore, we did not find data describing non-economic based values and preferences of travellers related to typhoid prevention.

DO ANTIMICROBIAL TREATMENTS REDUCE TYPHOID MORTALITY AND MORBIDITY; AND DOES PATHOGEN SUSCEPTIBILITY TO ANTIMICROBIAL TREATMENT VARY BY DESTINATION?

The WHO presently considers fluoroquinolones to be the first line agents for typhoid treatment (Table 4) (73;74). In a 2011 Cochrane review, fluoroquinolones were found to result in fewer clinical failures compared to chloramphenicol, co-trimoxazole, amoxicillin and ampicillin (73). When the performance of quinolones was compared to other agents including cephalosporins (ceftriaxone and cefixime) or azithromycin, clinical outcomes appeared to be equivalent in most studies. Definitive conclusions however, could not be made given that most of the data came from small underpowered studies and because resistance patterns differ between geographic regions and over time. When deciding on the optimal empiric therapy for typhoid, antibiotic resistance patterns in the travel destination countries should be considered (15;67). Of particular importance is the increasing prevalence of fluoroquinolone resistance among *Salmonella tyhpi* isolates from Asia (73).

DO HYGIENE AND/OR FOOD AND WATER PRECAUTIONS REDUCE THE RISK OF ACQUIRING TYPHOID?

There are a number of "common sense" or "best practice" interventions that are thought to reduce the risk of typhoid. They include hand washing and precautions for safe consumption of food and drink (74). As these are non-invasive interventions with broad applicability, they were not subjected to a GRADE evaluation. For further information on these interventions, see the Statement on Travellers' Diarrhea (75).

EFFICACY OF TYPHOID VACCINE TO PREVENT SALMONELLA PARATYPHI

Paratyphoid fever, caused by *Salmonella enterica* serovar Paratyphi A, B and C, is a systemic disease with clinical features indistinguishable from typhoid fever. The global burden, estimated at 5.4 million cases annually, is thought to be increasing (18); as is the prevalence of antibiotic resistance and the number of travel-related cases. A question often raised about paratyphoid is whether available typhoid vaccines provide protection. It is unlikely that Vi vaccines would provide protection because the vaccine elicits antibodies for an antigen that is not present in *S. paratyphi* A and B. In contrast, Ty21a vaccines elicit serum and mucosal antibodies to *S. typhi* O, H and other antigens, which are shared with *S. paratyphi*. Pooled analyses of randomized controlled field trials done with Ty21a (among children) in Chile suggest that Ty21a provides some protection against *S. paratyphi* B [protective efficacy of 0.49 (95% CI 0.08–0.73) (76); and a descriptive analysis of national enteric fever surveillance data among Israeli travellers suggested that Ty21a vaccine may protect against *S. paratyphi* A (63). Immunologic data support these clinical findings (77). We judged that, although the evidence is suggestive of protection, it is not sufficient to recommend Ty21a vaccine (as an unlabeled use) to prevent paratyphoid.

GRADE RECOMMENDATIONS

- CATMAT suggests that typhoid vaccine (Ty21a or Vi polysaccharide vaccine) be used for Canadian travellers visiting South Asia*; ***Conditional recommendation, moderate confidence in estimate of effect.***
- CATMAT suggests that typhoid vaccine (Ty21a or Vi polysaccharide vaccine) not be used for Canadian travellers visiting destinations other than South Asia; ***Conditional recommendation against (immunization), moderate confidence in estimate of effect.***
    - The decision of whether or not to use typhoid vaccination for destinations other than South Asia might be influenced by: other factors associated with risk of travel associated typhoid such as pediatric travel, visiting friends and relatives, longer duration of travel, the presence of achlorhydria or use of acid suppression therapy; and/or patient preferences ***(very low quality data)***.

* South Asia is defined as per the World Bank classification and includes Afghanistan, Pakistan, India, Nepal, Bangladesh, Maldives, Sri Lanka, Bhutan. Among these countries, the large majority (≥90%) of cases of typhoid among travellers were reported from India, Pakistan and Bangladesh (1;2).

BASIS OF RECOMMENDATIONS

Balance of benefits and harms

Most travellers are at low risk for acquiring typhoid during travel with destination being an important predictor of risk. Travel to South Asia (~1/3,000 travellers) consistently has at least a several fold higher risk than does travel to other regions such as Sub-Saharan Africa, North Africa/the Middle East and South America (~1/50,000–100,000 travellers); or to the Caribbean/ Central America and the Eastern Mediterranean (<1/300,000 travellers) (Table 2). Although rates of travel associated typhoid are low, the proportion of cases resulting in hospitalization in high incomes countries is high (68%-90%) with a mean length of stay ranging from 6–10 days (2;22;23;34). The case fatality rate for typhoid in high income countries is <1%.

Vaccination against typhoid is moderately effective, reducing the risk of clinical typhoid by ~50% over a three year period (RR 0.51; 95% CI 0.42–0.62; Appendix 2b). Vaccines are well-tolerated, i.e. they have a very low rate of reported major adverse events (0.59–0.34 events/100,000 doses; 46), with a modest increased risk of mild AE or nausea or abdominal pain for Ty21a and pain for Vi polysaccharide. The benefit of vaccine for travellers to South Asia, the highest risk destination, is modest: one case of typhoid would be prevented for every ~6,000 travellers vaccinated. Correspondingly, vaccinating this many travellers is estimated to be associated with about 460 injection site pain AE for Vi polysaccharide, and about 333 mild AE and 194 nausea or abdominal pain AE for Ty21a vaccine. In this same circumstance, estimates are of one typhoid associated hospitalization avoided for every ~8,500 travellers vaccinated and one typhoid associated death avoided for every ~2 million travellers vaccinated. Estimates for other endemic regions (Table 3) are correspondingly higher.

Confidence in Estimate (Quality of evidence)

Typhoid vaccination efficacy to prevent typhoid cases (moderate confidence) and vaccine adverse events (very low to moderate confidence). Risk of developing typhoid in travellers by destination (moderate confidence). Risk of developing typhoid by age, VFR status, duration of travel and achlorhydria (very low confidence).

Values and preferences

We believe that the majority of Canadian travellers would consider the use of typhoid vaccine worth the cost and inconvenience of the vaccine where the risk of typhoid was > 1 in 10,000 travellers. These recommendations are conditional given that: several other identified (but relatively poorly characterized) risk factors for typhoid such as age (children), VFR travel and duration of stay might increase/decrease risk for a given itinerary, typhoid vaccine has moderate efficacy (for a vaccine) and travellers values and preferences including willingness to pay for such protection is poorly characterized and might show substantial heterogeneity.

OTHER RECOMMENDATIONS (NON-GRADE)

- Practitioners should advise travellers to adhere to basic sanitation and food and water precautions.
- Providers should discuss with the traveller the anticipated benefits and harms (including financial costs) associated with vaccination, and support the traveller in reaching a decision that is consistent with his/her values and preferences.
- While there is evidence that suggests Ty21a protects against paratyphoid, it is not sufficient to recommend this vaccine (as an unlabelled use) for this purpose.
- The first line drug of choice to treatment typhoid are fluoroquinolones however, local antimicrobial resistance patterns in the country of travel need to be considered when choosing empiric therapy.

CONCLUSIONS AND RESEARCH NEEDS

Risk of typhoid is generally low, but is highest for travellers to South Asia. The low risk of typhoid combined with the moderate efficacy of the vaccine mean that the benefits of vaccination are modest (efficacy ~50%); however, the vaccines have good safety profiles. Given these (and other) considerations, CATMAT suggests that the majority of travellers going to South Asia be given typhoid vaccine whereas the majority travellers going to all other endemic areas not be given typhoid vaccine. More effective vaccines to enhance the protection against typhoid in populations living in typhoid endemic countries as well as travellers to these countries are needed. In addition, there are several gaps in the knowledge base related to typhoid fever in travellers. Large studies that estimate the travel associated typhoid risk attributable to pediatric travel, VFR travel and length of stay would help practitioners to more accurately estimate typhoid risk in individual travellers. Studies on WTP of travellers for protection against typhoid would also aid practitioners to more accurately determine benefits of typhoid vaccine to individual travellers.

ACKNOWLEDGEMENTS

† **CATMAT Members:** Dr. A. McCarthy (Chair), Dr. A. Boggild, Dr. J. Brophy, Dr. Y. Bui, Dr. M. Crockett, Dr. W. Ghesquiere, Dr. C. Greenaway, Ms. A. Henteleff, Dr. M. Libman, Dr. P. Teitelbaum.

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CATMAT gracefully acknowledges the contribution of Dr. Gordon Guyatt, Distinguished Professor of Medicine, McMaster University, GRADE methodological support.

TABLES

TABLE 1: Typhoid vaccines licensed for use in Canada

VACCINE	PARENTERAL, CAPSULAR POLYSACCHARIDE VACCINES (TYPH-I)*	ORAL, LIVE ATTENUATED VACCINE (TYPH-O)	COMBINED VACCINE
Brand Name	Typhim Vi® (61) (Sanofi Pasteur) TYPHERIX® (60) (GlaxoSmithKline Inc)	Vivotif ® (capsules) (78) (Crucell Switzerland Ltd)	ViVAXIM® (79) (Sanofi Pasteur) (combination of purified Vi polysaccharide typhoid with inactivated hepatitis A)
Authorized for use in persons	> 2 years of age	adults and children > 5 years of age	≥16 years of age
Protection begins	14 days following vaccination	7 days following vaccination	14 days following vaccination
Dosage	0.5 ml	4 enteric-coated capsules taken on alternate days	1.0 ml
Route	Single intramuscular injection	Orally in a series of doses	Single intramuscular injection
Contraindications	A severe local or systemic reaction to a previous dose of the vaccine	Individuals with hypersensitivity to any component of the vaccine or the enteric-coated capsule. Persons with an acute gastrointestinal condition or inflammatory bowel disease. Vaccine should not be administered to persons deficient in their ability to mount a humoral or cell-mediated response due to either a congenital or acquired immunodeficient state including treatment with immunosuppressive or antimitotic drugs.	Known systemic hypersensitivity reaction to any component of ViVAXIM® or a life-threatening reaction after previous administration of the vaccine or a vaccine containing one or more of the same components

VACCINE	PARENTERAL, CAPSULAR POLYSACCHARIDE VACCINES (TYPH-I)*	ORAL, LIVE ATTENUATED VACCINE (TYPH-O)	COMBINED VACCINE
Drug Interactions	There are no known interactions	Antibiotics: Ty21a vaccination should be completed 3 days before commencing treatment with sulfonamides or other antibiotics. Antibiotic exceptions: Chloroquine, Mefloquine and Malarone do not influence the immune response of Ty21A and can be administered at any interval When using any other antimalarial, immunization with Vivotif ® should precede antimalarial prophylaxis using the three day interval	
Adverse Events	Typhim Vi®:Pain at injection site, edema, redness, headache and malaise (61) TYPHERIX®: Pain at injection site, fever, headache,general aches, malaise, nausea and itching. These mild reactions occur in less than 10% of individuals vaccinated (60).	Adverse reactions are infrequent and mild; nausea, abdominal pain, headache, fever, diarrhea, vomiting and skin rash	ViVAXIM® Pain, edema or erythema at the injection site, myalgia, headache, fever, malaise, nausea and diarrhea (79).
Efficacy with immunosuppression	Immunocompromised persons (whether from disease or treatment) may not obtain the expected immune response.		
Revaccination[1]	Typhim Vi®—every 3 years TYPHERIX®—every 3 years	Vivotif®—every 7 years[2]	Hepatitis A—Boost with a single dose of inactivated hepatitis A vaccine 6–36 months later for long term protection Typhoid—Revaccination with a single dose of purified Vi polysaccharide vaccine can be given at an interval of not more than 3 years

VACCINE	PARENTERAL, CAPSULAR POLYSACCHARIDE VACCINES (TYPH-I)*	ORAL, LIVE ATTENUATED VACCINE (TYPH-O)	COMBINED VACCINE
Interchangeability	Although there are no data regarding the interchangeability of typhoid vaccines, it is presumed that re-immunization can be performed with any of the available formulations regardless of the vaccine used initially.		
Safety in Pregnancy	Safety in pregnancy has not been studied for any of the typhoid vaccines. Therefore, the benefits of vaccination must be carefully weighed against potential adverse events before it is given to pregnant women. Vaccine should only be used in pregnancy when there is a high risk of infection. There is no expected effect with purified polysaccharide vaccines.		

Sources: (60;61;78;79)

* The parenteral formulation (Typh-I) is licensed but is no longer available in Canada.

[1] Revaccination should be carried out when subjects remain at risk in conditions of repeated or continuous exposure. The Cochrane review presented data that sero protection continues for up to three years after immunization in endemic populations; there are data to indicate that protection from Ty21a extends to seven years (45). There are no data on continued protection in travellers.

[2] CATMAT is aware that The Yellow Book—CDC Health Information for International Travellers 2012 advises repeat immunization with oral live attenuated Ty21a vaccine every five years however the CATMAT statement is consistent with the Health Canada Biologics and Genetic Therapies Directorate vaccine approval for re-immunization every seven years.

TABLE 2: Typhoid risk by destination[1]

REGION/STUDY POPULATION	SWEDEN[2] 1997–2003 (1)		CANADA 2004–2007 (54;80)		UNITED STATES[3] 1999–2006 (2)		NETHERLANDS[4] 1995–2006 (33)		MEAN ESTIMATE[5]
	Cases	Rate/ 100,000	Cases	Rate/ 100,000	Cases	Rate/ 100,000	Cases	Rate/ 100,000	
Eastern Mediterranean	7	0.09	/	/	/	/	/	/	0.09
North America/Europe[6]	0	/[7]	0	N/A	/	/	/	/	/
Russia/former USSR	0	/	/	/	/	/	/	/	/
North Africa/Middle East[8]	16	1.47	2	1.78	51[9]	**0.76**	91	1.2	1.48
Sub-Saharan Africa[10]	5	2.50	1	0.92			29	2.1	1.84
Southern Africa	0	/	/	/	/	/	/	/	/
Caribbean, Central America[11]	2	0.36	6	0.23	217[12]	**0.13**	13	0.4	0.33
South America	3	1.20	1	0.70			/	/	0.95
East Asia[13]	5	0.24	1	0.30	140	0.2	242	**5.2** (19.7[14])	0.25
South Asia[15]	50	41.6	27	60.7	856	8.9			32.73
Pacific	0	/	/	/	/	/	/	/	/

[1] Rates in bold were not used to determine the mean estimate of baseline risk.

[2] Does not include travellers/cases to/from Nordic countries and Western, Southern and Eastern Europe.

[3] 1439 cases were identified as travel related; of which 1277 were for persons visiting a single country.

[4] Median annual rate over study period.

[5] Arithmetic mean.

[6] For Ekdahl et al.(1) is North America, for Bui et al.(54) and Trépanier et al.(80) is Europe.

[7] '/' represents no data available or no cases reported.

[8] Data from Ekdahl et al.(1) for North Africa and the Middle East were combined into a single estimate.

[9] Estimate for all of Africa.

[10] Data from Ekdahl et al.(1) for West, East and Central Africa were combined into a single estimate.

[11] Data from Ekdahl et al.(1) for the Caribbean and Central America were combined into a single estimate; this grouping also includes Mexico for Bui et al.(54) and Trépanier et al.(80)

[12] Includes Mexico. 25 cases were attributed to exposure in Haiti.

[13] Bui et al.(54) and Trépanier et al.(80), this is referred to as "Asia, excluding Indian sub-continent". For the Lynch et al.(2) data, the rate was interpolated by determining the number of cases (n=140) in Asia outside the subcontinent and assuming that travel to this region represents 25% of the total travel to Asia (estimated at 95 million for 1999-2006). As India accounted for about 12% of all Asian travel from 1999–2006 (travel data from: US International Trade Administration) the 25% estimate is likely generous.

[14] Value in parentheses is estimate for "Indian subcontinent"; estimate for remainder Asia (not Indian subcontinent) was not available.

[15] South Asia defined as: India, Pakistan and Bangladesh in Lynch et al.(2); these countries as well as Afghanistan, Bhutan, Maldives, Nepal and Sri Lanka in Ekdahl et al.(1); in accordance with the United Nations Development Agency in Batten et al. (33), and was not specified in Bui et al.(54) or Trépanier et al.(80).

TABLE 3A: Vaccine Benefit[1,2]

REGION OF ORIGIN	RISK TYPHOID (NO VACCINE)	RISK TYPHOID (WITH VACCINE)	RISK HOSPITALIZATION (NO VACCINE)	RISK HOSPITALIZATION (WITH VACCINE)	RISK MORTALITY (NO VACCINE)	RISK MORTALITY (WITH VACCINE)
Eastern Mediterranean	1,111,111	2,222,222	1,587,302	3,174,603	370,370,370	740,740,741
North Africa/Middle East	67,568	135,135	96,525	193,050	22,522,523	45,045,045
South Asia	3,055	6,111	4,365	8,729	1,018,434	2,036,867
Sub-Saharan Africa	54,348	108,696	77,640	155,280	18,115,942	36,231,884
South America	105,263	210,526	150,376	300,752	35,087,719	70,175,439
Caribbean, Central America	303,030	606,061	432,900	865,801	101,010,101	202,020,202
East Asia	400,000	800,000	571,429	1,142,857	133,333,333	266,666,667
North America/Europe	/	/	/	/	/	/
Russia/former USSR	/	/	/	/	/	/
Pacific	/	/	/	/	/	/

[1] Estimated absolute risk of typhoid, typhoid-associated hospitalization and typhoid mortality by geographic region, with or without vaccine expressed as number of exposed travellers per event (case, hospitalization or death).

[2] Assumptions: The estimated baseline risks for typhoid by destination are found in table 3. Vaccine efficacy was assumed to be 50%, the probability of hospitalization 70% and case fatality rate 0.3%.

TABLE 3B: Vaccine Risk[1,2]

REGION OF ORIGIN	TYPHOID CASE		TYPHOID HOSPITALIZATION		TYPHOID DEATH	
	Vi	Ty21a	Vi	Ty21a	Vi	Ty21a
Eastern Mediterranean	170,940	194,932	244,200	278,474	56,980,057	64,977,258
North Africa/Middle East	10,395	11,854	14,850	16,934	3,465,003	3,951,320
South Asia	470	536	671	766	156,682	178,673
Sub-Saharan Africa	8,361	9,535	11,945	13,621	2,787,068	3,178,235
South America	16,194	18,467	23,135	26,382	5,398,111	6,155,740
Caribbean, Central America	46,620	53,163	66,600	75,947	15,540,016	17,721,070
East Asia	61,538	70,175	87,912	100,251	20,512,821	23,391,813
North America/Europe	/	/	/	/	/	/
Russia/former USSR	/	/	/	/	/	/
Pacific	/	/	/	/	/	/

[1] Estimated absolute risk of typhoid vaccine associated mild adverse events to prevent one case of typhoid, typhoid-associated hospitalization or typhoid mortality by geographic region.

[2] Assumptions: Rates of adverse events (AE) associated with vaccination were held constant and assumed to be: pain for every 13 persons receiving Vi polysaccharide vaccine; and a mild AE and nausea or abdominal pain for every 18 and 31 persons, respectively, receiving Ty21a. For Ty21a, values represent the aggregate estimate for a mild AE and nausea or abdominal pain (i.e. an AE for approx. every 11.4 vaccine recipients).

TABLE 4: Treatment of uncomplicated typhoid fever

	OPTIMAL THERAPY			ALTERNATIVE EFFECTIVE DRUGS		
Susceptibility	**Antibiotic**	**Daily dose mg/kg**	**Days**	**Antibiotic**	**Daily dose mg/kg**	**Days**
Fully Sensitive	Fluoroquinolone e.g., ofloxacin or ciprofloxacin	15	5–7[1]	Amoxicillin TMP-SMX	75–100 8–40	14 14
Multidrug resistance	Fluoroquinolone or cefixime	15 15–20	5–7 7–14	Azithromycin Cefixime	8–10 15–20	7 7–14
Quinolone Resistance[2]	Azithromycin or ceftriaxone	8–10 75	7 10–14	Cefixime	20	7–14

[1] Three day courses are also effective and are particularly so in epidemic containment.

[2] The optimum treatment for quinolone-resistant typhoid fever has not been determined. Azithromycin, the third generation cephalosporins, or a 10–14 day course of high dose fluoroquinolones, is effective. Combinations of these are now being evaluated.

SOURCE: WHO Background Document (74)

NOTE: WHO recommends chloramphenicol as an alternative effective drug—however due to safety concerns and availability of safer options in Canada—CATMAT recommends avoiding chloramphenicol.

NOTE: There is some evidence that the newest fluoroquinolone, gatifloxacin, remains effective in some regions where resistance to older fluoroquinolones has developed. However, the different fluoroquinolones have not been compared directly in trials (73).

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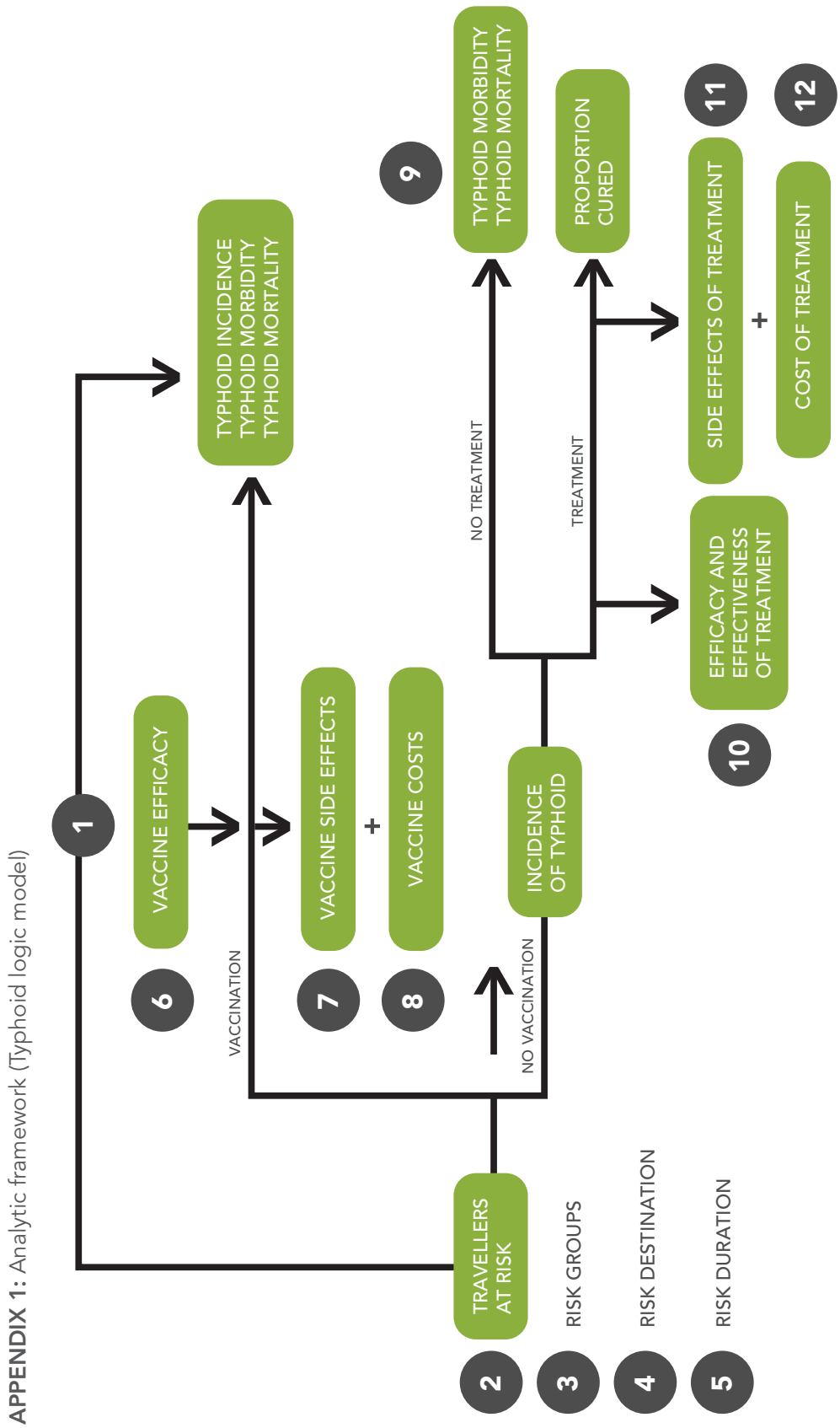

APPENDIX 1: Analytic framework (Typhoid logic model)

APPENDIX 2A: Trials of typhoid vaccine efficacy considered for inclusion in analysis

AUTHOR/YEAR	COUNTRY	VACCINE DOSE/ROUTE	TOTAL POPULATION	AGE (YRS)	FOLLOW-UP (YRS)	RELATIVE RISK	COMMENTS
Ty21a: Oral Typhoid Vaccine							
Levine 1987 (42)	Chile	Ty21a, 3 doses @ 2 or 21 d intervals ECV, GCV, placebo	109,000	6–21	3	0.60 (0.43–0.83)	Include arm with ECV @ 3 day intervals as is closest to Canadian schedule.
Levine 1990 (41)	Chile	Ty21a, 3 doses @ 2 day intervals ECV, LSV, placebo	81,621	5–19	3	0.44 (0.29–0.60)	Include arm with ECV @ 3 day intervals as is closest to Canadian schedule.
Simanjuntak 1991(40)	Indonesia	Ty21a, 3 doses @ weekly intervals ECV, LSV	20,543	3–44	2.5	0.52 (0.42–0.66)	Include but only ECV.
Black 1990 (49)	Chile	Ty21a, 2 doses vs placebo	82,543	5–22	5	0.59 (0.43–0.83)	**Excluded** as only two doses used & given at weekly intervals. Not sufficiently similar to Canadian schedule.
Fereccio 1989 (81)	Chile	Ty21a, 2, 3 or 4 doses, no placebo	189,819	?	3	0.59 (0.43–0.83)	**Excluded** as no placebo arm.
Wahdan 1982 (51)	Egypt	Ty21a, 3 doses LSV vs placebo	32,388	6–7	3	0.04 (0.01–0.33)	**Excluded** as only LSV used and not sufficiently similar to Canadian formulations.
Typhoid Vi: Injectable Vaccine							
Klugman 1987 (43)	South Africa	Vi Polysaccharide	11,384	5–15	3	0.45 (0.3–0.7)	Include.
Sur 2009 (37)	Kolkata, India	Vi Polysaccharide	37,673	2+	2	0.60 (0.41–0.75)	Include.
Khan 2012 (39)	Pakistan	Vi Polysaccharide	27,231	2–16	2	0.65 (0.48–0.55)	Include.

AUTHOR/YEAR	COUNTRY	VACCINE DOSE/ROUTE	TOTAL POPULATION	AGE (YRS)	FOLLOW-UP (YRS)	RELATIVE RISK	COMMENTS
Acharya 1987 (48)	Nepal	Vi Polysaccharide	6,907	5–44	1	0.28 (0.13–0.59)	**Excluded** as only 1 year of F/U.
Wang 1997 (52)	China	Vi Polysaccharide	81,506	5–55	1	0.29 (0.12–0.66)	**Excluded** as only 1 year of F/U.
Yang 2001 (53)	China	Vi Polysaccharide	131,271	3–19	19 mo	0.31 (0.13–0.72)	**Excluded** as only 1 year of F/U.

Ty21a attenuated oral typhoid vaccine; ECV=enteric coated vaccine; GCV=gelatin capsule vaccine; LSV=liquid suspension vaccine; F/U=follow-up.

APPENDIX 2B: Evidence profile for the efficacy of typhoid vaccine

QUALITY ASSESSMENT							NO OF PATIENTS		EFFECT		
NO OF STUDIES	DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	TYPHOID VACCINE	CONTROL	RELATIVE (95% CI)	ABSOLUTE	QUALITY
Three year cumulative risk of typhoid fever combined											
4	randomised trials	no serious risk of bias	no serious inconsistency	serious	no serious imprecision	none	177/67767 (0.26%)	370/48168 (0.77%)	RR 0.51 (0.42 to 0.62)	4 fewer per 1000 (from 3 fewer to 4 fewer)	⊕⊕⊕⊖ **moderate**
Two year cumulative risk of typhoid fever combined											
4	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	no serious imprecision	none	100/59969 (0.17%)	237/60395 (0.39%)	RR 0.43 (0.34 to 0.54)	2 fewer per 1000 (from 2 fewer to 3 fewer)	⊕⊕⊕⊖ **moderate**
Three year cumulative risk of typhoid fever Ty21a											
3	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	no serious imprecision	none	147/62075 (0.24%)	304/42476 (0.72%)	RR 0.53 (0.43 to 0.65)	3 fewer per 1000 (from 3 fewer to 4 fewer)	⊕⊕⊕⊖ **moderate**
Two year cumulative risk of typhoid fever Ty21a											
1	randomised trials	no serious risk of bias[3]	no serious inconsistency	serious[2]	no serious imprecision	none	15/22170 (0.07%)	44/21906 (0.2%)	RR 0.34 (0.19 to 0.61)	1 fewer per 1000 (from 1 fewer to 2 fewer)	⊕⊕⊕⊖ **moderate**
Three year cumulative risk of typhoid fever Vi polysaccharide											
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	30/5692 (0.53%)	66/5692 (1.2%)	RR 0.45 (0.30 to 0.7)	6 fewer per 1000 (from 3 fewer to 8 fewer)	⊕⊕⊕⊖ **moderate**
Two year cumulative risk of typhoid fever Vi polysaccharide											
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	85/37799 (0.22%)	193/38489 (0.5%)	RR 0.45 (0.35 to 0.58)	3 fewer per 1000 (from 2 fewer to 3 fewer)	⊕⊕⊕⊖ **moderate**

QUALITY ASSESSMENT							NO OF PATIENTS		EFFECT		
NO OF STUDIES	DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	TYPHOID VACCINE	CONTROL	RELATIVE (95% CI)	ABSOLUTE	QUALITY
Cumulative risk of typhoid fever by age Ty21a											
2	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	no serious imprecision	none	86/56864 (0.15%)	98/32206 (0.3%)	RR 0.45 (0.33 to 0.63)	2 fewer per 1000 (from 1 fewer to 2 fewer)	⊕⊕⊕⊖ **moderate**
Cumulative risk of typhoid fever by age Ty21a—Age 5-<10											
2	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	no serious imprecision	none	54/28162 (0.19%)	40/13182 (0.3%)	RR 0.61 (0.39 to 0.97)	1 fewer per 1000 (from 0 fewer to 2 fewer)	⊕⊕⊕⊖ **moderate**
Cumulative risk of typhoid fever by age Ty21a—Age ≥ 10											
2	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	no serious imprecision	none	32/28702 (0.11%)	58/19024 (0.3%)	RR 0.34 (0.21 to 0.54)	2 fewer per 1000 (from 1 fewer to 2 fewer)	⊕⊕⊕⊖ **moderate**
Cumulative risk of typhoid fever by age Vi polysaccharide											
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	64/32107 (0.2%)	145/32797 (0.44%)	RR 0.45 (0.34 to 0.6)	2 fewer per 1000 (from 2 fewer to 3 fewer)	⊕⊕⊕⊖ **moderate**
Cumulative risk of typhoid fever by age Vi polysaccharide—Age 2-<5											
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	21/4251 (0.49%)	40/4419 (0.91%)	RR 0.54 (0.32 to 0.91)	4 fewer per 1000 (from 1 fewer to 6 fewer)	⊕⊕⊕⊖ **moderate**
Cumulative risk of typhoid fever by age Vi polysaccharide—Age ≥ 5											
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[4]	none	43/27856 (0.15%)	105/28378 (0.37%)	RR 0.42 (0.29 to 0.59)	2 fewer per 1000 (from 2 fewer to 3 fewer)	⊕⊕⊖⊖ **low**

[1] Two studies did not correct for cluster design; this was judged not to present a serious risk of bias.

[2] Studies with endemic populations, generally children; not with travellers. For Ty21a data based on three not four doses of vaccine.

[3] Study did not correct for cluster design, this was judged not to present a serious risk of bias.

[4] Heterogeneity in estimates of efficacy across studies.

APPENDIX 2C: Summary of findings for the efficacy of typhoid vaccine

OUTCOMES	ILLUSTRATIVE COMPARATIVE RISKS* (95% CI) ASSUMED RISK CONTROL	CORRESPONDING RISK TYPHOID VACCINE	RELATIVE EFFECT (95% CI)	NO OF PARTICIPANTS (STUDIES)	QUALITY OF THE EVIDENCE (GRADE)
Three year cumulative risk of typhoid fever combined	**8 per 1000**	**4 per 1000** (3 to 5)	**RR 0.51** (0.42 to 0.62)	115935 (4 studies)	⊕⊕⊕⊖ **moderate**
Two year cumulative risk of typhoid fever combined	**4 per 1000**	**2 per 1000** (1 to 2)	**RR 0.43** (0.34 to 0.54)	120364 (4 studies)	⊕⊕⊕⊖ **moderate**[1,2]
Three year cumulative risk of typhoid fever Ty21a	**7 per 1000**	**4 per 1000** (3 to 5)	**RR 0.53** (0.43 to 0.65)	104551 (3 studies)	⊕⊕⊕⊖ **moderate**[1,2]
Two year cumulative risk of typhoid fever Ty21a	**2 per 1000**	**1 per 1000** (0 to 1)	**RR 0.34** (0.19 to 0.61)	44076 (1 study)	⊕⊕⊕⊖ **moderate**[2,3]
Three year cumulative risk of typhoid fever Vi polysaccharide	**12 per 1000**	**5 per 1000** (3 to 8)	**RR 0.45** (0.30 to 0.7)	11384 (1 study)	⊕⊕⊕⊖ **moderate**[2]
Two year cumulative risk of typhoid fever Vi polysaccharide	**5 per 1000**	**2 per 1000** (2 to 3)	**RR 0.45** (0.35 to 0.58)	76288 (3 studies)	⊕⊕⊕⊖ **moderate**[2]
Cumulative risk of typhoid fever by age Ty21a	**3 per 1000**	**1 per 1000** (1 to 2)	**RR 0.45** (0.33 to 0.63)	89070 (2 studies)	⊕⊕⊕⊖ **moderate**[1,2]
Cumulative risk of typhoid fever by age Ty21a—Age 5-<10	**3 per 1000**	**2 per 1000** (1 to 3)	**RR 0.61** (0.39 to 0.97)	41344 (2 studies)	⊕⊕⊕⊖ **moderate**[1,2]
Cumulative risk of typhoid fever by age Ty21a—Age ≥ 10	**3 per 1000**	**1 per 1000** (1 to 2)	**RR 0.34** (0.21 to 0.54)	47726 (2 studies)	⊕⊕⊕⊖ **moderate**[1,2]
Cumulative risk of typhoid fever by age Vi polysaccharide	**4 per 1000**	**2 per 1000** (1 to 3)	**RR 0.45** (0.34 to 0.6)	64904 (2 studies)	⊕⊕⊕⊖ **moderate**[2]
Cumulative risk of typhoid fever by a ge Vi polysaccharide—Age 2-<5	**9 per 1000**	**5 per 1000** (3 to 8)	**RR 0.54** (0.32 to 0.91)	8670 (2 studies)	⊕⊕⊕⊖ **moderate**[2]
Cumulative risk of typhoid fever by age Vi polysaccharide—Age ≥ 5	**4 per 1000**	**2 per 1000** (1 to 2)	**RR 0.42** (0.29 to 0.59)	56234 (2 studies)	⊕⊕⊖⊖ **low**[2,4]

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 Two studies did not correct for cluster design; this was judged not to present a serious risk of bias.

2 Studies with endemic populations, generally children; not with travellers. For Ty21a data based on three not four doses of vaccine.

3 Study did not correct for cluster design, this was judged not to present a serious risk of bias.

4 Heterogeneity in estimates of efficacy across studies.

APPENDIX 3A: Adverse Events During Typhoid Vaccine Efficacy Trials Considered for Inclusion in Analysis

AUTHOR/YEAR	COUNTRY	VACCINE DOSE/ ROUTE	TOTAL POPULATION	AGE (YRS)	FOLLOW-UP	ADVERSE EVENTS	COMMENTS
Ty21a: Oral Typhoid Vaccine							
Levine 1986 (46)	Chile	Ty21a, 3 doses ECV, placebo	539	children		Fever, vomiting, diarrhea, nausea, abdominal pain and headache	Include.
Levine 1986 (46)	Chile	Ty21a, 3 doses ECV, placebo	751	adults		Fever, vomiting, diarrhea, nausea, abdominal pain and headache	Include.
Simanjuntak 1991 (40)	Indonesia	Ty21a, 3 doses @ weekly intervals ECV, LSV	1190	3–44		Fever, vomiting, diarrhea, nausea, rash, headache and any side effect	Include.
Wahdan 1982 (51)	Egypt	Ty21a, 3 doses LSV vs placebo	884	6–7		Fever and vomiting	**Excluded** as ECV not tested.
Cryz 1993 (82)	Thailand	Ty21a, 3 doses LSV vs placebo	634		Up to 21 days post vaccine		**Excluded** as denominators not provided therefore could not calculate rates of adverse events
Olanatmanee 1992 (83)	Thailand	Ty21a, 3 doses LSV vs placebo	170	Children		Mild adverse events	**Excluded** because only observed x 1.5 hrs post vaccine and classified as mild adverse events

AUTHOR/YEAR	COUNTRY	VACCINE DOSE/ ROUTE	TOTAL POPULATION	AGE (YRS)	FOLLOW-UP	ADVERSE EVENTS	COMMENTS
Typhoid Vi: Injectable Vaccine							
Keitel 1994 (47)	Texas	Vi Polysaccharide	378	18–40 yrs	Adverse events 28 days post vaccine	Pain, erythema, and fever	Only included data for primary vaccination, not for boosters..
Zhou 2007 (38)	China	Vi Polysaccaride Primary vac (N=331), Revaccination (N=334) Placebo (N=333)	998	9–14		Local reaction (erythema, swelling, pain) Systemic (Rash, fever, headache, dizziness, itching, other)	Only included data for primary vaccination; and for the first three days following vaccination.
Yang 2001(53)	China	Vi Polysaccharide	131,271	3–19	Passive reporting 48 hours post vaccine	Fever, local reaction	**Excluded** as AE collected for 3 schools; not the entire cohort.
Sur 2009 (37)	Kolkata, India	Vi Polysaccharide	37,673	2+			**Excluded** as comparator arm was hepatitis B vaccine.
Khan 2012 (39)	Karachi Pakistan	Vi Polysaccharide		2–16			**Excluded** as comparator arm was hepatitis B vaccine.
Wang 1997 (52)	China	Vi Polysaccharide	777				**Excluded** as comparator was meningococcal vaccine.

Not included as no reported adverse event data: Acharya 1987, Black 1990, Levine 1987, Levine 1990, Klugman 1987, Ferrecio 1989.

APPENDIX 3B: Evidence profile for adverse event from typhoid vaccine

QUALITY ASSESSMENT							NO OF PATIENTS		EFFECT		
NO OF STUDIES	DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	TYPHOID VACCINE	CONTROL	RELATIVE (95% CI)	ABSOLUTE	QUALITY
Any mild adverse event by vaccine type—Ty21a Enteric Coated Vaccine											
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	40/311 (12.9%)	21/291 (7.2%)	RR 1.78 (1.08 to 2.95)	56 more per 1000 (from 6 more to 141 more)	⊕⊕⊕⊖ **moderate**
Fever by vaccine type											
5	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	28/1435 (2%)	21/1444 (1.5%)	RR 1.24 (0.71 to 2.19)	3 more per 1000 (from 4 fewer to 17 more)	⊕⊕⊕⊖ **moderate**
Fever by vaccine type—Ty21a Enteric Coated Vaccine											
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	17/867 (2%)	8/1025 (0.78%)	RR 2.15 (0.93 to 4.96)	9 more per 1000 (from 1 fewer to 31 more)	⊕⊕⊕⊖ **moderate**
Fever by vaccine type—Vi Polysaccharide Vaccine											
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	11/568 (1.9%)	13/419 (3.1%)	RR 0.72 (0.32 to 1.62)	9 fewer per 1000 (from 21 fewer to 19 more)	⊕⊕⊕⊖ **moderate**
Vomiting by vaccine type—Ty21a Enteric Coated Vaccine											
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	9/867 (1%)	15/1025 (1.5%)	RR 0.86 (0.38 to 1.97)	2 fewer per 1000 (from 9 fewer to 14 more)	⊕⊕⊕⊖ **moderate**

Diarrhea by vaccine type—Ty21a Enteric Coated Vaccine											
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	21/867 (2.4%)	21/1025 (2%)	RR 1.14 (0.61 to 2.14)	3 more per 1000 (from 8 fewer to 23 more)	⊕⊕⊕⊖ **moderate**
Nausea or abdominal pain by vaccine type—Ty21a Enteric Coated Vaccine											
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	48/867 (5.5%)	29/1025 (2.8%)	RR 2.13 (1.33 to 3.41)	32 more per 1000 (from 9 more to 68 more)	⊕⊕⊕⊖ **moderate**
Headache by vaccine type											
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	33/1026 (3.2%)	25/991 (2.5%)	RR 1.25 (0.75 to 2.07)	6 more per 1000 (from 6 fewer to 27 more)	⊕⊕⊕⊖ **moderate**
Headache by vaccine type—Ty21a Enteric Coated Vaccine											
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	33/695 (4.7%)	24/658 (3.6%)	RR 1.3 (0.78 to 2.18)	11 more per 1000 (from 8 fewer to 43 more)	⊕⊕⊖⊖ **low**
Headache by vaccine type—Vi Polysaccharide Vaccine											
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	0/331 (0%)	1/333 (0.3%)	RR 0.34 (0.01 to 8.2)	2 fewer per 1000 (from 3 fewer to 22 more)	⊕⊕⊖⊖ **low**
Rash by vaccine type											
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	5/1026 (0.49%)	4/991 (0.4%)	RR 1.17 (0.34 to 4.08)	1 more per 1000 (from 3 fewer to 12 more)	⊕⊕⊖⊖ **low**
Rash by vaccine type—Ty21a Enteric Coated Vaccine											
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	5/695 (0.72%)	3/658 (0.46%)	RR 1.58 (0.38 to 6.59)	3 more per 1000 (from 3 fewer to 25 more)	⊕⊕⊖⊖ **low**

Rash by vaccine type—Vi Polysaccharide Vaccine											
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2,3]	none	0/331 (0%)	1/333 (0.3%)	RR 0.34 (0.01 to 8.2)	2 fewer per 1000 (from 3 fewer to 22 more)	⊕⊖⊖⊖ **very low**
Erythema by vaccine type—Vi Polysaccharide Vaccine											
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	16/568 (2.8%)	0/419 (0%)	RR 12.06 (0.73 to 198.92)	-	⊕⊕⊖⊖ **low**
Pain by vaccine type—Vi Polysaccharide Vaccine											
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	91/568 (16%)	12/419 (2.9%)	RR 3.68 (1.96 to 6.93)	77 more per 1000 (from 27 more to 170 more)	⊕⊕⊕⊖ **moderate**

[1] Studies with endemic populations, generally children; not travellers.

[2] 95% CI around relative risk fails to exclude important benefit or important harm.

[3] Small sample size and low number of events.

APPENDIX 3C: Summary of findings for the adverse events of typhoid vaccine

OUTCOMES	ILLUSTRATIVE COMPARATIVE RISKS* (95% CI) ASSUMED RISK CONTROL	CORRESPONDING RISK TYPHOID VACCINE	RELATIVE EFFECT (95% CI)	NO OF PARTICIPANTS (STUDIES)	QUALITY OF THE EVIDENCE (GRADE)
Any mild adverse event by vaccine type—Ty21a Enteric Coated Vaccine	72 per 1000	128 per 1000 (78 to 213)	RR 1.78 (1.08 to 2.95)	602 (1 study)	⊕⊕⊕⊖ moderate[1]
Fever by vaccine type	Moderate		RR 1.24 (0.71 to 2.19)	2879 (5 studies)	⊕⊕⊕⊖ moderate[1]
	12 per 1000	15 per 1000 (9 to 26)			
Fever by vaccine type—Ty21a Enteric Coated Vaccine	Moderate		RR 2.15 (0.93 to 4.96)	1892 (3 studies)	⊕⊕⊕⊖ moderate[1]
	5 per 1000	11 per 1000 (5 to 25)			
Fever by vaccine type—Vi Polysaccharide Vaccine	Moderate		RR 0.72 (0.32 to 1.62)	987 (2 studies)	⊕⊕⊕⊖ moderate[1]
	24 per 1000	17 per 1000 (8 to 39)			
Vomiting by vaccine type—Ty21a Enteric Coated Vaccine	Moderate		RR 0.86 (0.38 to 1.97)	1892 (3 studies)	⊕⊕⊕⊖ moderate[1]
	17 per 1000	15 per 1000 (6 to 33)			
Diarrhea by vaccine type—Ty21a Enteric Coated Vaccine	Moderate		RR 1.14 (0.61 to 2.14)	1892 (3 studies)	⊕⊕⊕⊖ moderate[1]
	22 per 1000	25 per 1000 (13 to 47)			
Nausea or abdominal pain by vaccine type—Ty21a Enteric Coated Vaccine	Moderate		RR 2.13 (1.33 to 3.41)	1892 (3 studies)	⊕⊕⊕⊖ moderate[1]
	25 per 1000	53 per 1000 (33 to 85)			
Headache by vaccine type	Moderate		RR 1.25 (0.75 to 2.07)	2017 (3 studies)	⊕⊕⊕⊖ moderate[1]
	34 per 1000	42 per 1000 (26 to 70)			
Headache by vaccine type—Ty21a Enteric Coated Vaccine	Moderate		RR 1.3 (0.78 to 2.18)	1353 (2 studies)	⊕⊕⊖⊖ low[1,2]
	36 per 1000	47 per 1000 (28 to 78)			
Headache by vaccine type—Vi Polysaccharide Vaccine	Moderate		RR 0.34 (0.01 to 8.2)	664 (1 study)	⊕⊕⊖⊖ low[1,3]
	3 per 1000	1 per 1000 (0 to 25)			

OUTCOMES	ILLUSTRATIVE COMPARATIVE RISKS* (95% CI)		RELATIVE EFFECT (95% CI)	NO OF PARTICIPANTS (STUDIES)	QUALITY OF THE EVIDENCE (GRADE)
	ASSUMED RISK	CORRESPONDING RISK			
	CONTROL	TYPHOID VACCINE			
Rash by vaccine type	**Moderate**		**RR 1.17** (0.34 to 4.08)	2017 (3 studies)	⊕⊕⊖⊖ **low**[1,2]
	3 per 1000	**4 per 1000** (1 to 12)			
Rash by vaccine type—Ty21a Enteric Coated Vaccine	**Moderate**		**RR 1.58** (0.38 to 6.59)	1353 (2 studies)	⊕⊕⊖⊖ **low**[1,2]
	4 per 1000	**6 per 1000** (2 to 26)			
Rash by vaccine type—Vi Polysaccharide Vaccine	**Moderate**		**RR 0.34** (0.01 to 8.2)	664 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3]
	3 per 1000	**1 per 1000** (0 to 25)			
Erythema by vaccine type—Vi Polysaccharide Vaccine	**Moderate**		**RR 12.06** (0.73 to 198.92)	987 (2 studies)	⊕⊕⊖⊖ **low**[1,3]
	0 per 1000	**0 per 1000** (0 to 0)			
Pain by vaccine type—Vi Polysaccharide Vaccine	**Moderate**		**RR 3.68** (1.96 to 6.93)	987 (2 studies)	⊕⊕⊕⊖ **moderate**[1]
	40 per 1000	**147 per 1000** (78 to 277)			

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 Studies with endemic populations, generally children; not travellers.

2 95% CI around relative risk fails to exclude important benefit or important harm.

3 Small sample size and low number of events.

APPENDIX 4A: Quality assessment for risk of typhoid by destination: Risk of bias assessment by study

	STUDY SETTING	TOTAL NUMBER OF TYPHOID CASES	REPRESENTATIVE SAMPLE	OUTCOME MEASUREMENT	OUTCOME ASCERTAINMENT
Bui 2011/ Trépanier 2010 (54;80)	Quebec, Canada 2004–2007	34	Numerator: Population based case series of reported cases of typhoid in provincial notifiable disease database in Quebec from Jan 2004-Dec 2007. Denominator: Estimates of travellers from Statistics Canada. **Low Risk**	Laboratory confirmed cases of S.typhi from clinical specimens. **Low Risk**	• Only most severe cases reported. • Uncertain of differential bias due to health seeking behavior or missed cases due to presentation in country of travel prior to return. **Moderate Risk**
Ekdahl 2005 (1)	Sweden 1997–2003	115	Numerator: Population based case series of reported cases of typhoid in Swedish notifiable disease database from 1997–2003. Denominator: Swedish tourist and travel database obtained from monthly telephone interviews. Database has been externally validated with in-flight passenger data. **Low Risk**	As above. **Low Risk**	As above. **Moderate Risk**
Baaten 2010 (33)	Netherlands 1995–2006	375	Numerator: Population based case series of reported cases of typhoid in Dutch notifiable disease database from 1995–2006. Denominator: Dutch tourist and travel database obtained from quarterly surveys. Database has been externally validated with in-flight passenger data. National estimates of travellers. **Low Risk**	Laboratory confirmed cases of S.typhi from clinical specimens (94% or reports) or serology (6% of cases). **Low Risk**	As above. **Moderate Risk**

	STUDY SETTING	TOTAL NUMBER OF TYPHOID CASES	REPRESENTATIVE SAMPLE	OUTCOME MEASUREMENT	OUTCOME ASCERTAINMENT
Keller 2008 (34)	Switzerland 1993–2004	208	Numerator: Population based case series of reported cases of typhoid in Swiss notifiable disease database from 1993–2004. Denominator: National estimates of travellers from Swiss Office of Statistics. **Low Risk**	Laboratory confirmed cases of S.typhi from clinical specimens. **Low Risk**	As above. **Moderate Risk**
Lynch 2009 (2)	US 1999–2006	1902	Numerator: Population based case series of all reported cases of typhoid in the United States notifiable disease database from 1999–2006. Denominator: Travellers (excluding immigrants) in the Tourism industries, International Trade Administration, United States Department of Commerce database. **Low Risk**	As above. **Low Risk**	As above. **Moderate Risk**
Mermin 1998 (24)	US 1985–1994	2445	As above. **Low Risk**	As above. **Low Risk**	As above. **Moderate Risk**

APPENDIX 4B: Quality assessment for risk of typhoid by destination: Evidence profile for assessment of confidence in estimates of baseline risk by region

NO OF STUDIES	DESIGN[1]	RISK OF BIAS[2]	INCONSISTENCY	INDIRECTNESS	IMPRECISION[3]	OTHER CONSIDERATIONS	ESTIMATE (CASES/100,000)	CONFIDENCE IN BASELINE ESTIMATE
Eastern Mediterranean								
1	Observational cohort	intermediate risk of bias	no serious inconsistency	no serious indirectness	intermediate risk of imprecision	none	0.09	⊕⊕⊕◯ MODERATE
North Africa/Middle East								
3	Observational cohort	intermediate risk of bias	no serious inconsistency	no serious indirectness	intermediate risk of imprecision	none	1.48	⊕⊕⊕◯ MODERATE
Sub-Saharan Africa								
3	Observational cohort	intermediate risk of bias	no serious inconsistency	no serious indirectness	intermediate risk of imprecision	none	1.84	⊕⊕⊕◯ MODERATE
Caribbean, Central America								
3	Observational cohort	intermediate risk of bias	no serious inconsistency	no serious indirectness	intermediate risk of imprecision	none	0.33	⊕⊕⊕◯ MODERATE
South America								
2	Observational tcohort	intermediate risk of bias	no serious inconsistency	no serious indirectness	intermediate risk of imprecision	none	0.95	⊕⊕⊕◯ MODERATE
East Asia								
3	Observational cohort	intermediate risk of bias	no serious inconsistency	no serious indirectness	intermediate risk of imprecision	none	0.25	⊕⊕⊕◯ MODERATE
South Asia								
4	Observational cohort	intermediate risk of bias	no serious inconsistency	no serious indirectness	intermediate risk of imprecision	none	32.73	⊕⊕⊕◯ MODERATE

[1] Observation studies start as high quality.

[2] For all destinations, intermediate risk of bias due to possible under-ascertainment of cases.

[3] For all destinations, intermediate risk of imprecision because estimates of error (e.g., confidence limits) could not be derived across the body of evidence.