



Published in final edited form as:

*Vaccine*. 2014 June 17; 32(29): 3577–3579. doi:10.1016/j.vaccine.2014.04.055.

## Effectiveness of typhoid vaccination in US travelers

Barbara E. Mahon<sup>a,\*</sup>, Anna E. Newton<sup>a</sup>, and Eric D. Mintz<sup>b</sup>

<sup>a</sup>Enteric Diseases Epidemiology Branch, Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Mailstop C-09, 1600 Clifton Road, Atlanta, GA 30030, USA

<sup>b</sup>Waterborne Disease Prevention Branch, Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Mailstop C-09, 1600 Clifton Road, Atlanta, GA 30030, USA

### Abstract

Typhoid vaccination is recommended in the United States before travel to countries where typhoid fever is endemic, though little information is available on its effectiveness in travelers.

We estimated typhoid vaccination effectiveness (VE) by comparing vaccination status in cases of typhoid fever and paratyphoid fever (*Salmonella Paratyphi A* infection, against which typhoid vaccine offers no protection) reported in the United States. We included travelers to Southern Asia and excluded persons <2 years old and cases in which vaccination status was not reported.

From 2008 through 2011, 744 eligible cases (602 typhoid, 142 paratyphoid A) were reported to CDC. Typhoid vaccination was reported for 5% (29/602) of typhoid patients and for 20% (29/142) of paratyphoid A patients. Estimated VE was 80% (95% confidence interval, 66–89%). Because of missing data, we could not estimate VE for specific vaccines.

We demonstrated moderate effectiveness of typhoid vaccination in US travelers, supporting vaccination recommendations.

### Keywords

Typhoid vaccination; Vaccination effectiveness; United States; Travelers

## 1. Introduction

Typhoid vaccination is recommended in the United States before travel to countries where typhoid fever is endemic [1–3]. Two vaccines are available – live, oral Ty21a (Vivotif<sup>®</sup>, Crucell/Berna) and typhoid Vi polysaccharide (Typhim Vi<sup>®</sup>, Sanofi Pasteur) – but little information exists on their effectiveness in travelers.

\*Corresponding author. Tel.: +1 404 718 1157; fax: +1 404 639 2205. bmahon@cdc.gov. aenewton@cdc.gov (A.E. Newton), emintz@cdc.gov (E.D. Mintz).

Conflict of interest statement

All author declare no conflict of interests.

Typhoid fever is caused by infection with *Salmonella enterica* serotype Typhi. It is clinically indistinguishable from paratyphoid fever, which is most often caused by infection with *S. enterica* serotype Paratyphi A but can also be caused by Paratyphi B and C. Illness is characterized by fever, abdominal pain, and malaise that can last for weeks and can cause severe outcomes such as intestinal perforation or death [4]. Both are transmitted primarily through contaminated food or water and are uncommon in the United States; most cases occur in persons who have recently traveled in countries where these diseases are endemic. Travel to Southern Asia, (primarily India, Pakistan, and Bangladesh) accounts for most typhoid and paratyphoid fever cases in the United States [5–7].

Although Ty21a may provide some protection against Paratyphi B infection, neither vaccine provides protection against paratyphoid fever caused by Paratyphi A [8,9]. Therefore, vaccination rates among returning travelers with typhoid fever can be compared with rates among those with paratyphoid fever caused by Paratyphi A to infer the degree of protection provided by vaccination. We used surveillance data to estimate the effectiveness of typhoid vaccination in US travelers.

## 2. Material and methods

State and local health officials report culture-confirmed typhoid and paratyphoid fever to the Centers for Disease Control and Prevention (CDC) through the National Typhoid and Paratyphoid Fever Surveillance (NTPFS) system [10]. This system, which initially included only typhoid fever, was expanded in 2007 to include paratyphoid fever. The standard case report includes information on patient demographics, travel history including destination countries and reason for travel, whether the patient received a typhoid vaccine in the 5 years before illness onset, and, if so, which vaccine.

We analyzed data on reported cases of typhoid fever (hereafter called typhoid) and of paratyphoid fever caused by *Salmonella* serotype Paratyphi A infection (hereafter called paratyphoid A) occurring from 2008 through 2011. For the vaccine effectiveness analysis, we included cases in travelers, defined as persons who spent time outside of the United States in the 30 days before illness began. Because Paratyphi A is primarily reported from Southern Asia<sup>1</sup>, we excluded travelers who did not travel to this region [11]. Children <2 years old, who were too young for typhoid vaccination, and cases in which vaccination status was not reported were excluded.

We calculated descriptive statistics for typhoid and paratyphoid A. Using conditional logistic regression, we calculated the odds ratio (OR) with 95% confidence intervals (95% CI) for vaccination among travelers with typhoid, compared with those with paratyphoid A, and we estimated typhoid vaccination effectiveness (VE) as  $(1 - \text{OR}) \times 100\%$ . We assessed confounding by constructing models that included citizenship status and reason for travel, considering a change in the OR for vaccination of >10% as indicating confounding. We used SAS 9.3 (Cary, NC) for analyses.

---

<sup>1</sup>As defined by the United Nations, includes Afghanistan, Bangladesh, Bhutan, India, Iran (Islamic Republic of), Maldives, Nepal, Pakistan, and Sri Lanka.

### 3. Results

During 2008–2011, 1171 travelers 2 years old were reported with typhoid and 318 with paratyphoid A; 956 (82%) with typhoid and 306 (96%) with paratyphoid A reported travel to Southern Asia. Among these, vaccination status was available for 602 (63%) typhoid and 142 (43%) paratyphoid A patients; these 744 cases were included in the analysis.

Demographic characteristics were similar among typhoid and paratyphoid A patients (Table 1). Travel destinations were also similar. Visiting friends and relatives was the most common reason for travel and was more commonly reported for typhoid patients (71%) than paratyphoid A patients (66%,  $p = 0.04$ ). United States citizenship was reported for a somewhat lower percentage of typhoid patients (221/331, 67%) than paratyphoid A patients (75/96, 78%,  $p = 0.03$ ), though data were frequently missing (45% for typhoid, 33% for paratyphoid A).

Typhoid vaccination within 5 years before illness began was reported for 5% (29/602) of typhoid fever patients but for 20% (29/142) of paratyphoid A fever patients, yielding an estimated VE of 80% (95% CI, 66–89%). Estimated VE did not change substantially in models adjusting for reason for travel or US citizenship status or both. The type of vaccine received was often not known; this information was missing for 69% (20/29) vaccinated typhoid patients and 28% (8/29) vaccinated paratyphoid A patients. Among vaccinated typhoid patients for whom the type of vaccine was reported, 3 (33%) had received the oral vaccine and 6 (67%) the parenteral vaccine. Among vaccinated paratyphoid A patients, 6 (29%) had received the oral vaccine and 15 (71%) the parenteral vaccine.

### 4. Discussion

This study demonstrates moderate effectiveness of typhoid fever vaccination in US travelers and provides the first direct evidence of effectiveness in this group. This result reflects the effectiveness of adherence to the recommendation for typhoid vaccination for travelers in general, because we could not estimate the effectiveness of either US-licensed vaccine individually. Our estimate of 80% effectiveness is on the high end of the range of previous estimates of protection by both typhoid vaccines [12]. Typhoid vaccines have been less effective in situations with intense exposure to serotype Typhi than when the risk of exposure is lower [9]. Therefore, our relatively high effectiveness estimate suggests that the risk of serotype Typhi exposure might be lower, on average, for travelers than for persons living in endemic areas, perhaps because many travelers do not stay in endemic areas for months or years before returning to the United States or because they have less exposure to contaminated water and food than the local population.

We used paratyphoid A patients as controls for typhoid patients for a case-control analysis. This approach assumes that paratyphoid A and typhoid patients arise from the same source population and have the same risk of exposure to serotype Typhi during travel and the same likelihood of being diagnosed and reported after travel, and thus that the observed difference in vaccination rates between the two groups is due to protection induced by vaccination. A strength of our study is that the risk factors, clinical manifestations, and public health surveillance for paratyphoid A and typhoid in travelers are similar, so the likelihood of

exposure, diagnosis, and reporting to CDC were likely very similar as well. By restricting analysis to cases related to travel to Southern Asia, we further ensured similar opportunity for exposure. The fact that these groups were similar in terms of demographics, reasons for travel, and citizenship and that controlling for these factors did not substantially change the vaccination effectiveness estimate is also reassuring.

A second assumption is that typhoid vaccination provides no protection against paratyphoid A. Vi polysaccharide vaccine is thought to protect through stimulating a humoral response to Vi antigen, which is not present on Paratyphi A; thus, Vi vaccine does not protect against Paratyphi A infection. For Ty21a, the situation is less certain, because the mechanism of protection is not fully understood and because of laboratory evidence of some immunologic cross-reactivity to Paratyphi A after Ty21a vaccination [13–15]. However, efficacy studies in endemic areas have found no evidence of actual protection against infection [8,9]. If Ty21a did protect against Paratyphoid A, it would tend to lower our estimate of vaccine effectiveness.

Although NTPFS collects information on both diseases, only typhoid is nationally notifiable. Therefore, it is possible that reporting is more complete for typhoid than for paratyphoid A. However, unless reporting is associated with vaccination status, this difference would not bias the estimate of vaccination effectiveness. The lack of vaccination information for many reported cases of both diseases is more problematic. By decreasing the power of our analysis, this missing information likely lowered the precision of our vaccination effectiveness estimate. Again, though, it would not have biased the vaccination effectiveness estimate unless missing data led to spurious differences in the rates of vaccination in the two groups. Many reports in both groups that included vaccination information did not identify the specific vaccine administered; as a result, we could not estimate the effectiveness of each vaccine individually, only of typhoid vaccination in general.

Less than a quarter of paratyphoid A patients in our study had been vaccinated against typhoid. The fact that they acquired paratyphoid A shows that they were also at risk for typhoid, since both infections are transmitted by the same routes. This result is consistent with other studies that have shown a great deal of room for improvement in preventive measures for travelers, especially travelers visiting friends and relatives [16], the majority in our study.

In conclusion, our analysis of 4 years of US national surveillance data indicates that travelers to endemic areas can expect moderate protection from typhoid vaccination. It supports the recommendation for vaccination before travel to endemic areas and also emphasizes the importance of careful attention to food and water safety. Increased vaccination rates among travelers to endemic areas, especially travelers visiting friends and relatives, could have a substantial impact on travel-associated typhoid in the United States. Our results also highlight the need for an effective vaccine against paratyphoid A, which is an increasingly important cause of enteric fever in Asia [17] and could spread to other regions.

## Acknowledgements

We gratefully acknowledge the many state and local health officials who reported cases to NTPFS. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

## References

- [1]. Johnson K, Gallagher N, Mintz E, Newton A, Brunette G, Kozarsky P. From the CDC: new country-specific recommendations for pre-travel typhoid vaccination. *J Trav Med*. 2011; 18:430–3.
- [2]. Centers for Disease Control and Prevention. *CDC health information for international travel 2014*. Oxford University Press; New York: 2014.
- [3]. Centers for Disease Control and Prevention. Typhoid immunization—recommendations of the Advisory Committee on Immunization Practices (ACIP) (no. RR-14), 43. Centers for Disease Control and Prevention. 1994:1–8.
- [4]. Levine, M.; Tapia, M.; Zaidi, A. Pathogens and practice. 3rd ed. Elsevier, Inc; Edinburgh: 2002. Typhoid and paratyphoid (enteric) fever. *Tropical infectious diseases: principles*.
- [5]. Centers for Disease Control and Prevention. [accessed on January 21, 2014] National typhoid and paratyphoid fever surveillance annual summary. Centers for Disease Control and Prevention. 2011. Available from <http://www.cdc.gov/ncezid/dfwed/pdfs/typhi-annual-summary-2011-508c.pdf>
- [6]. Gupta S, Medalla F, Omondi M, Whichard J, Fields P, Gerner-Smidt P, et al. Laboratory-based surveillance of paratyphoid fever in the United States: travel and antimicrobial resistance. *Clin Infect Dis*. 2008; 46:1656–63. [PubMed: 18422453]
- [7]. Lynch M, Blanton E, Bulens S, Polyak C, Vojdani J, Stevenson J, et al. Typhoid fever in the United States, 1999–2006. *JAMA*. 2009; 302:859–65. [PubMed: 19706859]
- [8]. Levine M, Ferreccio C, Black R, Lagos R, San Martin O, Blackwelder W. Ty21a live oral typhoid vaccine and prevention of paratyphoid fever caused by *Salmonella enterica* serovar Paratyphi B. *Clin Infect Dis*. 2007; 45(Suppl 1):S24–8. [PubMed: 17582564]
- [9]. Simanjutak C, Paleologo F, Punjabi N, Darmowigoto P, Suprijanto E, Witham N, et al. Oral immunisation against typhoid fever in Indonesia with Ty21a vaccine. *Lancet*. 1991; 338:1055–9. [PubMed: 1681365]
- [10]. Centers for Disease Control and Prevention. [accessed on January 3, 2014] Surveillance system overview: national typhoid and paratyphoid fever surveillance 2011. Centers for Disease Control and Prevention. 2014. Available from [http://www.cdc.gov/ncezid/dfwed/PDFs/typhi\\_surveillance\\_overview\\_508c.pdf](http://www.cdc.gov/ncezid/dfwed/PDFs/typhi_surveillance_overview_508c.pdf)
- [11]. United Nations Statistics Division. [accessed on January 3, 2014] Composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and other groupings 2013. United Nations Statistics Division. 2014. Available from <http://unstats.un.org/unsd/methods/m49/m49regin.htm>
- [12]. Fraser A, Paul M, Goldberg E, Acosta C, Leibovici L. Typhoid fever vaccines: systematic review and meta-analysis of randomised controlled trials. *Vaccine*. 2007; 25:7848–57. [PubMed: 17928109]
- [13]. Wahid R, Simon R, Zafar S, Levine M, Sztein M. Live oral typhoid vaccine Ty21a induces cross-reactive humoral immune responses against *Salmonella enterica* serovar Paratyphi A and S. Paratyphi B in humans. *Clin Vaccine Immunol*. 2012; 19:825–33. [PubMed: 22492745]
- [14]. Tagliebue A, Villa L, De Magistris M, Romano M, Silvestri S, Boraschi D, et al. IgA-driven T cell-mediated anti-bacterial immunity in man after live oral Ty 21a vaccine. *J Immunol*. 1986; 137:1504–10. [PubMed: 3489034]
- [15]. Kantele A, Pakkanen S, Karttunen R, Kantele J. Head-to-head comparison of humoral immune responses to Vi capsular polysaccharide and *Salmonella* Typhi Ty21a typhoid vaccines—a randomized trial. *PLoS One*. 2013; 8:e60583. [PubMed: 23593253]

- [16]. Angell S, Cetron M. Health disparities among travelers visiting friends and relatives abroad. *Ann Intern Med.* 2005; 142:67–72. [PubMed: 15630110]
- [17]. Shastrabuddhe S, Carbis R, Wierzba T, Ochiai R. Increasing rates of *Salmonella* Paratyphi A and the current status of its vaccine development. *Expert Rev Vaccines.* 2013; 12:1021–31. [PubMed: 24053396]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

**Table 1**

Characteristics of patients with typhoid (*Salmonella* serotype Typhi infection) or paratyphoid A (*Salmonella* serotype Paratyphi A infection) who were  $\geq 2$  years old, traveled to Southern Asia, and had known vaccination status reported to the National Typhoid and Paratyphoid Fever Surveillance (NTPFS) system, United States, 2008–2011.

	<b>Typhoid N = 602</b>	<b>Paratyphoid A N = 142</b>	<b>p-Value</b>
Median age, years (range)	23 (2–86)	25 (2–74)	0.07
Female n/N (%)	284/587 (48%)	60/141 (43%)	0.20
Travel destination in Southern Asia			
Single country	596	140	
India n (%)	416 (70%)	102 (73%)	0.53*
Bangladesh n (%)	97 (16%)	25 (18%)	
Pakistan n (%)	75 (13%)	9 (6%)	
Nepal n (%)	8 (4%)	4 (3%)	
2 countries <sup>†</sup>	6	2	
Reason for travel			
Visit friends and relatives <sup>‡</sup> (VFR)	425 (71%)	93 (66%)	0.04
Business	28 (5%)	10 (7%)	
Tourism	24 (4%)	18 (13%)	
Immigration to US	35 (6%)	4 (3%)	
Other	38 (6%)	10 (7%)	
Unknown	52 (9%)	7 (5%)	
United States citizen n/N (%)	221/331 (67%)	75/96 (78%)	0.03
Typhoid vaccination n/N (%)	29/602 (5%)	29/142 (20%)	<0.0001

\* p-Value is for comparison of travel to India vs travel to a single country other than India.

<sup>†</sup> Included combinations of India, Bangladesh, Pakistan, Nepal, and Sri Lanka.

<sup>‡</sup> p-Value is for comparison of VFR travel vs any other reason for travel, including “other”, but excluding “unknown”.

Reported typhoid vaccination within 5 years before illness onset.