Typhoid fever in travellers: estimating the risk of acquisition by country

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Abstract

Background: Typhoid fever is a notifiable disease within Australia. Although studies in endemic regions give an indication of acquisition risk, many countries lack reliable data, and little is known of the absolute or relative risk in Australian travellers. By combining notified case data with travel statistics provided by the Australian Bureau of Statistics, the aim of this study was to give an indication of risk for typhoid acquisition among Australian travellers.

Methods: Australian typhoid notifications between 1st January 2010 and 30th June 2017 were grouped by country of acquisition and age category (<15 or ≥15 years). Australian travel data were used to inform time at risk and incidence rate of Australian typhoid notifications pertaining to country and region of acquisition. Salmonella Paratyphi infections, though notifiable, were excluded as the focus was vaccine preventable illness. Data from New South Wales and Victoria were used to examine the incidence in those acquiring infection in their country of birth (COB) against travellers who did not.

Results: Nine hundred twenty-three cases of typhoid were notified over the period of review, 96% of which were acquired overseas. The greatest determinant of risk was travel destination, with countries in south Asia associated with highest crude incidence rate (252 per 100 000 person-years), particularly Bangladesh. Younger age and immigrants returning to their COB were generally associated with higher risk of acquisition.

Conclusions: The risk of typhoid fever in Australian travellers to endemic regions is considerable. Immigrants returning to their COB appear to be at higher risk and it is likely that this risk extends to their traveling dependents. These findings help clinicians and public health officials to plan and advise pre-travel vaccination strategies with at-risk individuals and groups. Additional sociodemographic data collection with Australian typhoid notifications would enhance the surveillance of differing international travel risk groups leaving Australia.

Key words: Enteric fever, salmonella typhi, vaccine-preventable disease, travel, imported infection, surveillance, visiting friends and relatives (VFR)

Introduction

Typhoid fever is a systemic illness that causes considerable worldwide morbidity and mortality. Salmonella enterica subspecies enterica serovar Typhi (Salmonella Typhi) is the causative bacterium, transmitted primarily via the faecal oral route and with humans acting as the sole reservoir. Noted to be a disease of poverty, the illness disproportionately affects countries and regions with poor water supply and sanitation with south and southeast Asia, western and eastern sub-Saharan Africa and Oceania identified as regions of highest incidence.1

Travellers to these regions are at risk of acquiring infection, and in addition to advice to optimize safe food and water practices, may be offered the oral or injectable typhoid vaccine pre-travel. Salmonella enterica subspecies enterica serovar Paratyphi (Salmonella Paratyphi) causes paratyphoid fever which has a similar route of acquisition and clinical presentation to typhoid fever. However, despite limited data suggesting the oral typhoid vaccine may provide cross-protection for Salmonella Paratyphi B (albeit without established effectiveness for either Salmonella...

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Paratyphi A or C); Salmonella Paratyphi currently has no licensed vaccines available.1

Diagnosis of typhoid fever is typically made via culturing Salmonella Typhi from blood. The sensitivity of culture is dependent both on the volume of blood collected and prior antibiotic use.2–4 Bone marrow sampling for culture may increase diagnostic sensitivity, but this is offset by added resource use, procedural risks and patient discomfort which preclude its routine use in the work-up of suspected cases. In most regions of high typhoid endemicity, underdiagnosis related to low rates of presentation to health care, as well as lack of diagnostic testing facilities, making it difficult to accurately measure the burden of typhoid disease on a global scale.6–11

Existing estimates of typhoid fever incidence in higher incidence settings have typically relied on control arms of vaccine trials, population-based or household-level active surveillance, sentinel studies or prospective observational studies.11 Multipliers are often applied to derive incidence estimates which account for known difficulties in case detection and underdiagnosis.11,12

Studies and reviews from low incidence countries, including the USA, UK, Israel, Canada and the Netherlands, have noted predominant overseas acquisition of the disease and sought to estimate risk and/or vaccine efficacy to help guide pre-travel vaccine recommendations.13–17 Risk estimates for travellers have typically been recorded as incidence proportions (notifications per 100 000 travellers) rather than incidence rates [notifications per 100 000 person-years (PY)] with a lack of data obtained for travellers to endemic Oceanic countries.16,17

Australia, a high-income country, is the largest country both by population size and geographical area in the Oceania region which consists of 14 member countries. Typhoid is a notifiable disease in Australia, with reporting of cases from both the diagnostic laboratory and treating clinician required by law to the National Notifiable Diseases Surveillance System (NNDSS). Confirmed cases are notifiable with diagnostic confirmation the National Notifiable Diseases Surveillance System (NNDSS). Notified typhoid case data were recorded in 6-month time periods, population-based or household-level active surveillance, sentinel studies or prospective observational studies.11

Methods

Notified typhoid fever cases

Case data for the period 1st January 2010–30th June 2017 in 6 monthly time periods were requested from NNDSS, including classification by age (<15 or ≥15 years) and COA. NNDSS coordinates the national surveillance of more than 50 communicable diseases, including typhoid. Data collected by State and Territory Health departments are de-identified prior to forwarding to the NNDSS. Reason for travel, residency status and COA are not routinely collected at the national level, so were instead sought from individual state and territory health departments. COB data for notified cases were able to be provided by the two largest Australian state health departments, New South Wales (NSW) and Victoria (VIC), but reason for travel and residency status was not routinely recorded and not obtainable.

Travel data

Travel statistics collected by the ABS include aggregated information on departing travellers from, and incoming travellers to, Australia. A distinction is made between short-term (<12 months travel) and long-term travel (>12 months) and category of traveller—Australian resident (all Australian citizens, permanent visa holders and any New Zealand citizens who can be identified as a resident) or visitor. Until 30th June 2017, all individuals departing Australia were required to complete a departure card which recorded main destination, duration and reason for travel (Appendix S1, Supplementary data are available at JTM online). Collated data on short-term travellers are publicly available,24 but we requested additional aggregated data from the ABS on departing Australian residents (with <12 months planned travel) grouped by age (<15 or ≥15 years), resident state or territory, main destination country and main reason for travel. Aggregated number of movements and duration of overseas travel (days) were supplied for Australian-born, overseas-born (returning to COB) and overseas-born (not returning to COB) individuals. The Standard Australian Classification of Countries, 2016, was used to classify countries into major and minor world groupings.25

Data analysis

Notified typhoid case data were recorded in 6-month time periods against age category of case (<15 or ≥15 years) and COA.
ABS outbound travel data included intended travel duration which was used to provide time at risk, enabling calculation of incidence rates for major and minor world group sets and individual countries. Incidence rates (cases per 100 000 PY) were calculated using the formula: \( n \times d \times 365.25 \times 100,000 \), where \( n \) = number of typhoid notifications and \( d \) = total days exposure. Calculations assumed that travellers with multiple destinations spend their entire travel time in the main country visited, that all cases were notified and that notifications were acquired through short-term travel of Australian residents. Population level data were obtained; therefore, risk estimates were calculated without confidence intervals.

For notifications from NSW and VIC, the dataset additionally recorded if COB and COA were the same (COB = COA), and incidence rates were additionally calculated according to whether this variable was recorded as ‘Yes’, ‘No’ or ‘Unknown’. ‘Unknown’ results for this variable were imputed in the base case analysis assuming that results were missing at random. To examine the effect of missing data assumptions, a sensitivity analysis was undertaken with all missing data for the dummy variable imputed as ‘Yes’ then ‘No’ to create high and low estimates.

Data were received and recorded de-identified in a secure electronic database (excel). Statistical analyses were performed using statistical software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Results
Over the 7.5 years of this retrospective review, 923 cases of typhoid were notified within Australia, 887 (96%) of which were acquired overseas. Only 36 cases (4%, <5 notifications per year) were acquired locally (from an approximate Australian population of 23 million).\(^1\) Most notifications were attributable to acquisition in south Asia (\( n = 668, 72\% \)) followed by southeast Asia (\( n = 94, 10\% \)), and Oceania (\( n = 75, 8\% \)), with India being the most common COA (\( n = 496, 54\% \)). Individuals aged ≥15 years (\( n = 669, 72\% \)) were predominant in notifications.

When denominator data were applied, south Asia (252 cases per 100 000 PY) still had the highest crude incidence rates for acquisition, but Bangladesh had the highest rate (584 cases per 100 000 PY), followed by India (282 cases per 100 000 PY), Pakistan (264 cases per 100 000 PY) and Nepal (189 cases per 100 000 PY) (Table 1). Samoa (342 cases per 100 000 PY) in Oceania and Myanmar (101 cases per 100 000 PY) in southeast Asia were also found to be associated with high acquisition risk. Of 10 destination countries with comparative data, seven were found to have incidence rates higher in individuals aged <15 years compared with ≥15 years (Table 1).

COB was available only for notifications from NSW and VIC (\( n = 615 \)), representing two-thirds of all cases (Appendix S1B, Supplementary data are available at JTM online) and ~62% of total Australian resident travel. NSW/VIC travellers returning to their COB were found to have greater relative risk of acquiring typhoid regardless of destination country (Table 2). Stratification by this variable showed every destination country to have greater relative risk in individuals aged <15 years compared with ≥15 years, including the three countries—Samoa, Nepal and Indonesia—that did not show this age association unstratified (Table 1). Sensitivity analyses showed altered magnitude of relationships but a consistent increase in relative risk for those returning to their COB (Appendix S2, Supplementary data are available at JTM online).

Discussion
We have used notification and travel pattern data to determine the incidence of typhoid notification among Australian travellers. As has been shown previously,\(^11-17\) we confirm that travel destination is the most important risk factor for typhoid acquisition and that south Asia is associated with the largest number of notifications and highest crude incidence rates. India, Pakistan, Bangladesh and Nepal had rates of infections in travellers broadly consistent with that of a recent systematic review of internal studies from this region,\(^11\) and our findings align with previous reports suggesting that notified typhoid cases in Australia are predominantly acquired in India.\(^22\) Sri Lanka, compared with its neighbouring countries in south Asia, was notable for lowered apparent risk. Although recent published comparative data are sparse, national surveillance and vaccination programs exist within Sri Lanka and our data support the effectiveness of control measures in place.

Acquisition of typhoid in southeast Asia appeared to be an order of magnitude lower than south Asia. Frequently travelled countries in this region including Vietnam, Singapore, Malaysia and Laos were associated with very few or no notifications, which is consistent with published literature of lowered endemic rates in these countries.\(^5,27-31\) The greatest number of typhoid notifications were associated with travel to Indonesia, but Myanmar (101 cases per 100 000 PY) was associated with the highest regional risk and would meet the definition of a high incidence country at >100 cases per 100 000 PY.\(^33\) While our results are based on only a small number of case notifications, they are broadly comparable to a study from Yangon, Myanmar that combined sentinel hospital surveillance and multipliers derived from a household healthcare utilization survey in determining an estimated incidence of 391 cases per 100 000 PY in 2015/16.\(^31\)

Within Oceania, the risk of acquiring typhoid was notable for Samoa (342 cases per 100 000 PY) which was higher than most countries of south Asia. This is potentially an alarming finding and suggests possible under-reporting of cases locally in Samoa. A study that was published recently reported that, based on internal health data, annual incidence rates over the same period ranged between 27.5 cases and 101.9 cases per 100 000 PY in 2014 and 2012, respectively.\(^35\)

Data from New Zealand tend to support our findings, indicating prominent acquisition of typhoid associated with travel to Samoa. The calculated incidence for Auckland resident travellers to Samoa between 2005 and 2010 was determined to be 19.7 per 100 000 travellers.\(^34\) Annual reports from New Zealand, where typhoid is also notifiable, indicate that Samoa was either the first or second (after India) most common place of travel-associated infection between 2010 and 2017, with 5–21 case notifications per year.\(^36,37\)

Incidence rates from studies and reviews of Fiji are more comparable to our results (12.5 cases per 100 000 PY), placing Fiji in a moderate range of 10 to <100 cases per 100 000 PY.\(^38,39\)
Table 1. Incidence of Australian typhoid notifications in Australian travellers—1 January 2010 to 30 June 2017

| Typhoid Acquisition World Region Minor Region Country | Australian notified typhoid cases (n) | Travel exposure (days)—returning Australian residents | Travel episodes (n) | Typhoid incidence (per 100 000 PY)—crude estimates |
|-------------------------------------------------------|---------------------------------------|--------------------------------------------------------|-------------------|-----------------------------------------------------|
| Age (years)                                           | <15   | ≥15   | Total           | <15   | ≥15   | Total           | <15   | ≥15   | Total   |<15   | ≥15   | Total   |
| OCEANIA                                               |       |       |                 |       |       |                 |       |       |         |       |       |         |
| Melanesia                                             | 13    | 14    | 27              | 2.338450 | 22.422110 | 24.760560 | 1.330140 | 203.05 | 22.81 | 39.83 |
| Papua New Guinea                                      | 13    | 14    | 27              | 1.112110 | 13.941580 | 15.053690 | 0.684540 | 426.96 | 36.68 | 65.51 |
| Micronesia                                            | 1     | 0     | 1               | 73.650 | 1.626280 | 1.699930 | 83.580 | 495.93 | —     | 21.49 |
| Nauru                                                 | 1     | 0     | 1               | 40.710 | 10.844880 | 1.125190 | 57.340 | 897.20 | —     | 32.46 |
| Polynesia (excl Hawaii)                               | 5     | 41    | 46              | 7.231480 | 30.109400 | 37.340880 | 2.924590 | 25.25  | 49.74 | 44.99 |
| Samoa                                                 | 5     | 29    | 34              | 668.830 | 2.959370 | 3.628200 | 178.130 | 273.05 | 357.92 | 342.28 |
| Fiji                                                  | 0     | 10    | 10              | 5.954790 | 23.285330 | 29.240120 | 2.478910 | —     | 15.69 | 12.49 |
| Tonga                                                 | 0     | 1     | 1               | 264.960 | 1.485900 | 1.750860 | 88.350 | 410     | —     | 37.00 | 28.61 |
| American Samoa                                        | 0     | 1     | 1               | 870     | 777     | 8640     | 410     | —     | 4700.77 | 4227.43 |
| New Zealand                                           | 0     | 1     | 1               | 14.432300 | 99.198980 | 113.631280 | 8.866990 | —     | 0.37  | 0.32  |
| SOUTH AND CENTRAL ASIAa                                |       |       |                 |       |       |                 |       |       |         |       |       |         |
| Southern Asia                                         | 203   | 466   | 669             | 21.616460 | 79.132940 | 100.749400 | 2.909480 | 343.01 | 215.09 | 242.53 |
| India                                                 | 131   | 365   | 496             | 21.148900 | 75.555110 | 96.704010 | 2.824880 | 350.59 | 224.31 | 251.93 |
| Bangladesh                                            | 30    | 49    | 79              | 14.636840 | 49.691910 | 64.256750 | 1.843930 | 326.90 | 286.67 | 281.94 |
| Pakistan                                              | 41    | 22    | 63              | 1.209710 | 3.728000 | 4.937710 | 123.850 | 905.80 | 480.08 | 584.38 |
| Nepal                                                 | 1     | 24    | 25              | 5.85310 | 4.257510 | 4.843020 | 147.250 | 62.38  | 203.89 | 188.34 |
| Sri Lanka                                             | 0     | 4     | 4               | 2.067220 | 10.648650 | 12.715870 | 449.970 | —     | 13.72 | 11.49 |
| Central Asia                                          | 0     | 1     | 1               | 467.560 | 3.577830 | 4.045390 | 84.600 | —     | 10.21 | 9.03  |
| Afghanistan                                           | 0     | 1     | 1               | 363.520 | 2.406080 | 2.769600 | 55.500 | —     | 15.18 | 13.19 |
| SOUTH EAST ASIAa                                       | 10    | 84    | 94              | 41.965140 | 316.516140 | 358.381280 | 197.76840 | 8.72   | 9.69  | 9.58  |
| Mainland SE Asia                                      | 1     | 16    | 17              | 13.11310 | 1.17742960 | 131.134770 | 6.366810 | 2.72   | 4.96  | 4.73  |
| Cambodia                                              | 1     | 4     | 5               | 906.520 | 8.135380 | 9.041900 | 339.300 | 40.29  | 17.96 | 20.20 |
| Myanmar                                               | 0     | 7     | 7               | 2.30910 | 2.291390 | 2.532300 | 99.110 | —     | 111.58 | 101.37 |
| Thailand                                              | 0     | 5     | 5               | 7.044990 | 66.714380 | 73.759370 | 4.159450 | —     | 2.74  | 2.48  |
| Maritime SE Asia                                      | 9     | 67    | 76              | 28.453330 | 198.773180 | 227.226510 | 13.390030 | 11.55  | 12.31 | 12.22 |
| Indonesia                                             | 6     | 49    | 55              | 14.084330 | 89.352890 | 103.437220 | 7.450130 | 15.56  | 20.03 | 19.42 |
| Philippines                                           | 3     | 12    | 15              | 4.238970 | 31.936290 | 36.175260 | 1.369260 | 25.85  | 13.72 | 15.15 |
| Singapore                                             | 0     | 2     | 2               | 4.948020 | 36.710070 | 41.658090 | 2.469210 | —     | 1.99  | 1.75  |
| Timor-Leste                                            | 0     | 2     | 2               | 33.1570 | 3.249200 | 3.580770 | 115.900 | —     | 22.48 | 20.40 |
| Malaysia                                              | 0     | 2     | 2               | 47.28210 | 36.622180 | 41.350390 | 1.954490 | —     | 1.99  | 1.77  |
| NORTH EAST ASIAa                                       | 0     | 2     | 2               | 24.712470 | 181.363230 | 206.075700 | 7.237700 | —     | 0.40  | 0.35  |
| Chinese Asia (incl Mongolia)                          | 0     | 2     | 2               | 18.600930 | 139.855720 | 158.456650 | 5.035370 | —     | 0.52  | 0.46  |
| Hong Kong                                             | 0     | 1     | 1               | 3.902970 | 39.247730 | 43.150700 | 1.620550 | —     | 0.93  | 0.85  |

(Continued)
| Typhoid Acquisition | Australian notified typhoid cases (n) | Travel exposure (days)—returning Australian residents | Travel episodes (n) | Typhoid incidence (per 100 000 PY)—crude estimates |
|---------------------|--------------------------------------|--------------------------------------------------------|-------------------|--------------------------------------------------|
| **World Region**    | **Minor Region**                     | **Country**                                             |                   | **Age (years)**                                   | **<15** | **≥ 15** | **Total** | **<15** | **≥ 15** | **Total** | **Total** | **<15** | **≥ 15** | **Total** |
| SUB-SAHARAN AFRICA  |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Central & W Africa  |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Ghana               |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| South and East Africa|                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Zambia              |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Tanzania            |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| South Africa        |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Somalia             |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Djibouti            |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| NTH AFRICA AND MIDDLE EAST |                  |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| North Africa        |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Sudan               |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Middle East         |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Lebanon             |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Iraq                |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Syria               |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Iraq                |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Saudi Arabia        |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| AMERICAS            |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Central America     |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| El Salvador         |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Mexico              |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| SOUTHERN AND EASTERN EUROPE |            |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Eastern Europe      |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |
| Czechia             |                                      |                                                          |                   |                                                 |
|                     |                                      |                                                          |                   |                                                 |

NDSS data were provided by the Office of Health Protection, Department of Health, on behalf of the Communicable Diseases Network Australia—2019 August 20.

Additional 23 cases with unknown COA (age < 15 years n = 6, age ≥ 15 years n = 17) and 36 cases locally acquired in Australia (age < 15 years n = 13, age ≥ 15 years n = 23).

Based on ABS, Customized Report, 2019.

Total travel episodes—returning Australian residents < 12 months overseas travel.

Crude incidence estimates under assumption that 100% of typhoid notifications were in returning Australian residents.

Includes 1 case attributed to region but not specific country.
### Table 2. Typhoid fever incidence in NSW/VIC travellers acquiring infection in their COB vs not acquiring in COB—1st January 2010–30th June 2017

| Country of typhoid acquisition and age category (years) | Typhoid notifications—n (adjusted)* | Travel exposure—days | Incidence—per 100 000 PY∧ | IRR (COB=COA: COB ≠ COA) |
|--------------------------------------------------------|-------------------------------------|----------------------|----------------------------|-----------------------------|
|                                                       | COB=COA | COB ≠ COA | Total | COB=COA | COB ≠ COA | Total | COB=COA | COB ≠ COA | Total |
| India <15                                              | 31 (33) | 53 (57)  | 90    | 24 583 50 | 7 314 130 | 9 772 480 | 490.30 | 284.64 | 336.38 | 1.72  |
| India ≥15                                              | 199 (214)| 26 (28)  | 242   | 24 009 050| 9 580 680 | 33 589 730| 325.56 | 106.75 | 263.15 | 3.05  |
| Bangladesh <15                                         | 5 (6)   | 13 (15)  | 21    | 147 540  | 777 310  | 924 850  | 148.56 | 704.83 | 829.35 | 2.11  |
| Bangladesh ≥15                                         | 35 (36) | 3 (3)  | 39    | 2 390 850| 410 240  | 2 801 090 | 549.97 | 267.10 | 508.54 | 2.06  |
| Pakistan <15                                           | 9 (10)  | 17 (18)  | 28    | 471 920  | 1 374 330 | 1 846 250 | 773.97 | 478.38 | 553.93 | 1.62  |
| Pakistan ≥15                                           | 12 (12) | 4 (4)  | 16    | 2 659 520| 1 619 370 | 4 278 890 | 164.80 | 90.22  | 136.58 | 1.83  |
| Nepal <15                                              | 1 (1)   | 0 (0)  | 1     | 45 630   | 380 980  | 426 610  | 800.46 | −      | 85.62  | −     |
| Nepal ≥15                                              | 14 (14) | 2 (2)  | 16    | 1 099 050| 1 699 910 | 2 798 960 | 465.27 | 42.97  | 208.79 | 10.83 |
| Indonesia <15                                          | 0 (0)   | 2 (2)  | 2     | 453 870  | 6 463 260| 6 917 130 | −      | 11.30  | 10.56  | −     |
| Indonesia ≥15                                          | 13 (14) | 9 (10)  | 24    | 7 343 050| 35 296 800| 42 639 850| 69.64 | 10.35  | 20.56  | 6.73  |
| Cambodia <15                                           | 0 (0)   | 1 (1)  | 1     | 59 670   | 580 010  | 639 680  | −      | 62.97  | 57.10  | −     |
| Cambodia ≥15                                           | 2 (2)   | 2 (2)  | 4     | 1 658 970| 3 234 180| 4 893 150 | 44.03 | 22.59  | 29.86  | 1.95  |
| Thailand <15                                           | 0 (0)   | 0 (0)  | 0     | 412 880  | 4 033 630| 4 446 510 | −      | −      | −      | −     |
| Thailand ≥15                                           | 1 (1)   | 4 (4)  | 5     | 3 493 310| 34 443 340| 37 936 650| 10.46 | 4.24   | 4.81   | 2.46  |
| Samoa <15                                              | 0 (0)   | 2 (2)  | 2     | 21 950   | 398 230  | 420 180  | −      | 183.44 | 173.85 | −     |
| Samoa ≥15                                              | 11 (15) | 1 (2)  | 17    | 884 680  | 937 030  | 1 821 710 | 619.29 | 77.96  | 340.85 | 7.94  |
| Fiji <15                                               | 0 (0)   | 0 (0)  | 0     | 98 920   | 4 261 850| 4 360 770 | −      | −      | −      | −     |
| Fiji ≥15                                               | 4 (5)   | 3 (0)  | 8     | 3 314 770| 12 657 660| 15 972 430| 55.09 | 8.66   | 18.29  | 6.36  |

*IRR = Incidence rate ratio.
Only countries with at least one available comparison shown.
*(Adjusted) includes imputed cases with unknown COB assumed to be missing at random.
∧Incidence = notifications (adjusted)/travel exposure × 365.25 × 100 000.
See Appendix S2, Supplementary data are available at JTM online, for extended countries data and sensitivity analysis for effect of missing data assumptions.
We found that Papua New Guinea was a prominent place of acquisition (65 cases per 100 000 PY) with a high rate detected particularly in the ≤15 age category. Unfortunately, a paucity of published data exist to compare this finding and most of the notifications in this study were from outside NSW/VIC, making it impossible to investigate the effect of COB on acquisition risk. Nauru, Tonga and American Samoa each had single notifications over the study period, but small populations and relatively little returning travel from Australia mean risk assessments are imprecise. Likewise, small numbers of notifications and relatively little travel limited the assessment of other known endemic regions of the world including Africa and South and Central America. The low case numbers from these areas, particularly from sub-Saharan Africa, are in line with other reports among travellers from sub-Saharan Africa, are in line with other reports among travellers\textsuperscript{16,17,18}; although not well-understood generally, these findings may be explained in our study by the predominance of South Africa as the exposure country and its presumed lower risk compared with others in the region.

Younger age has frequently been associated with higher risk of acquiring typhoid in a variety of study types and locations, as reflected in a recent systematic analysis informing global disease burden.\textsuperscript{3} While neonates appear relatively protected through exclusive breastfeeding, the risk rapidly rises with considerable burden in pre-school aged children and peak incidence occurs under the age of 10.\textsuperscript{19} Consistent with prior studies, our data showed that most locations had higher incidence rates for age <15 compared with ≥15 years, with exceptions being Indonesia, Nepal and Samoa.

For the subset of NSW/VIC travellers for whom COB data were available, we assumed that those returning to their COB would likely be engaged in VFR travel, a factor that has been previously established as greater risk for acquisition of typhoid.\textsuperscript{21,22} Unfortunately, this was likely a sub-optimal stratification method for age <15 years, where Australian-born children of immigrant parents (often referred to as second generation VFRs)\textsuperscript{23} were unable to be distinguished. A better division would likely be achieved in this age group by categorizing based on their parents’ COB, or ideally on reason for travel, but unfortunately neither of these data was available.

Only India, Pakistan and Bangladesh had sufficient attributable notifications in the ≤15 years age group to examine the relative risk of children returning to their COB vs not traveling to their COB, with RR of 1.72, 1.62 and 2.11, respectively.

For age ≥15 years, the greater relative risks of travellers returning to their COB were most pronounced for Nepal (RR 10.83), Indonesia (RR 6.73), Samoa (RR 7.94) and Fiji (RR 6.36) and were also seen to a lesser degree for India (RR 3.05), Bangladesh (RR 2.11), Pakistan (RR 1.83), Cambodia (RR 1.95) and Thailand (RR 2.46).

Overall, our findings concur with previous studies of travellers from low-incidence countries in identifying south Asia as a prominent region for acquisition of typhoid.\textsuperscript{14–17,40} Importantly, however, our analysis provides a contemporaneous assessment of the Asia-Pacific region including Oceanic countries that to date have had little data evaluation. The limited ability to assess subcategories of risk, including reason for travel, highlights that such information ideally should be routinely captured in case notification data to help identify and focus preventive strategies on those with greatest need.

Our study has several limitations. Firstly, we may have underestimated typhoid acquisition since case ascertainment required diagnosis of typhoid to occur in Australia following return from abroad. We may have also underestimated the absolute risks given some (unknown proportion of) travellers may have received typhoid vaccine prior to travel. However, our data are directly relevant for Australian healthcare utilization estimates.

Secondly, data were gained retrospectively and are subject to several limitations. Exposure data were based on aggregated estimates of intended rather than confirmed travel duration. Additionally, travel time was apportioned to the main country of destination and therefore could not account for travel to multiple destinations, potentially resulting in misclassification when assessing results for individual countries.

Thirdly, detailed denominator data were obtained only for returning Australian residents with less than 12 months of travel, with exclusion of newly arrived immigrants, those involved in long-term travel and short-term visitors to Australia, the latter being the largest in number.\textsuperscript{24} Unfortunately, residency status was not routinely recorded for cases, so there was no instance to examine this. Publicly available short-term visitor data to Australia over the period of this study indicate that short-term visitors account for 8–50% of travel episodes between typhoid endemic countries and Australia,\textsuperscript{24} with variation across countries and regions.

Finally, the period of 7.5 years for this study was used to allow for greater numbers of notifications for individual countries, to mitigate seasonal effects and to balance the concern that time periods for notifications and travel could not be perfectly aligned. However, this period was insufficient to enable an assessment of risk variability over time for different destinations.

**Conclusion**

This study of typhoid acquisition in returning Australian travellers gives important information on several factors crucial to understanding disease transmission and risks associated with disease acquisition. Our findings particularly shed light on risks among travellers to destinations within Oceania and will help clinicians to provide informed advice regarding pre-travel typhoid vaccination. Additionally, we have identified areas where capture of enhanced notification information on reason for travel and residency status would be beneficial, ideally extending data collection to the parent(s) of notified traveling dependents. Capturing the vaccination status of cases would also be informative. Such data could be used to provide more precise risk characterization that could underpin future targeted public health strategies.

**Supplementary data**

Supplementary data are available at JTM online.

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Authors’ contributions
DF—literature search, study design, data collection, analysis, writing. 
KL—study design, review, writing.

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References
1. Stanaway JD, Reiner RC, Blacker BF et al. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the global burden of disease study 2017. Lancet Infect Dis 2019; 19: 369–81.
2. Levine MM, Ferreccio C, Black RE et al. Ty21a live oral typhoid vaccine and prevention of paratyphoid fever caused by Salmonella enterica serovar Paratyphi B. Clin Infect Dis 2007; 45: S24–8.
3. Manesh A, Meltzer E, Jin C et al. Typhoid and paratyphoid fever: a clinical seminar. J Travel Med 2021; 28:taab012.
4. Gilman RH, Termnel M, Levine MM et al. Relative efficacy of blood, urine, rectal swab, bone-marrow, and rose-spot cultures for recovery of Salmonella Typhi in typhoid fever. Lancet 1975; 1:1211–3.
5. Wain J, Pham VB, Ha V et al. Quantitation of bacteria in bone marrow from patients with typhoid fever: relationship between counts and clinical features. J Clin Microbiol 2001; 39:1571–6.
6. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bull World Health Organ 2004; 82:346–53.
7. Mogasale V, Maskery B, Ochiai RL et al. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. Lancet Glob Health 2014; 2:e570–80.
8. Mogasale V, Mogasale VV, Ramani E et al. Revisiting typhoid fever surveillance in low and middle income countries: lessons from systematic literature review of population-based longitudinal studies. BMC Infect Dis 2016; 16:35.
9. Antillón M, Warren JL, Crawford FW et al. The burden of typhoid fever in low- and middle-income countries: a meta-regression approach. PLoS Negl Trop Dis 2017; 11:1–21.
10. Radhakrishnan A, Alu D, Mintz ED et al. Introductory article on global burden and epidemiology of typhoid fever. Am J Trop Med Hyg 2018; 99:4–9.
11. Marchello CS, Hong CY, Crump JA. Global typhoid fever incidence: a systematic review and meta-analysis. Clin Infect Dis 2019; 68:S105–16.
12. Crump JA, Youssef FG, Luby SP et al. Estimating the incidence of typhoid fever and other febrile illnesses in developing countries. Emerg Infect Dis 2003; 9:539–44.
13. Mahon BE, Newton AE, Mintz ED. Effectiveness of typhoid vaccination in US travelers. Vaccine 2014; 32:3577–9.
14. Wagner KS, Freedman JL, Andrews NJ, Jones JA. Effectiveness of the typhoid vi vaccine in overseas travelers from England. Clin Infect Dis 2015; 22:87–93.
15. Connor BA, Schwartz E. Typhoid and paratyphoid fever in travelers. Lancet Infect Dis 2005; 5:623–8.
16. Greenaway C, Schofield S, Henteljeff A et al. Summary of the statement on international travelers and typhoid by the committee to advise on tropical medicine and travel (CATMAT). Can Commun Dis Rep 2014; 40:60–70.
17. Suryapranata FS, Prins M, Sonder GJ. Low and declining attack rates of imported typhoid fever in the Netherlands 1997–2014, in spite of a restricted vaccination policy. BMC Infect Dis 2016; 16:731.
18. Communicable Diseases Network Australia. Australian national notifiable diseases case definitions. Typhoid fever case definition [Internet]. Canberra (ACT): Australian Government Department of Health; 2021 [updated 2013; cited 7 September 2021]. https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-su rveil-rndss-casedefs-cd_typhi.htm.
19. Communicable Diseases Network Australia. National Notifiable Diseases Surveillance System [Internet]. Canberra (ACT): Australian Government Department of Health; 2021 [updated 2021; cited 28 May 2021]. http://www9.health.gov.au/cda/source/cda-index.cfm.
20. Australian Bureau of Statistics. Migration, Australia. Reference period 2017-18 financial year. Australia’s population by country of birth [Internet]. [Released 3/04/2019; cited 10 March 2021]. https://www.abs.gov.au/statistics/population/migration/a ustralian-classification-countries-sacc/2016#data-downloads.
21. Paudel P, Raina Mac Intyre C, Zwar N et al. Risk activities and pre-travel health seeking practices of notified cases of imported infectious diseases in Australia. J Travel Med 2017; 24:ta044.
22. Heywood AE, Zwar N, Forsman BL et al. The contribution of travelers visiting friends and relatives to notified infectious diseases in Australia: state-based enhanced surveillance. Epidemiol Infect 2016; 144:3554–63.
23. Yap N, Purcell R, Butterly J. Pre-traveler typhoid vaccinations for Australian children visiting friends and relatives overseas. A call to (inject) arms. J Paediatr Child Health 2020; 56:956–8.
24. Australian Bureau of Statistics. Visitor arrivals and resident returns by country, Industry, tourism and transport, overseas arrivals and departures [Internet - table]. 2021 [updated 2021; cited 28 May 2021]. http://stat.data.abs.gov.au/#.
25. Australian Bureau of Statistics. Standard Australian Classification of Countries (SACC). 2016 [Internet]; [updated 2016; cited 10 March 2021]. https://www.abs.gov.au/statistics/classifications/standard-au stralian-classification-countries-sacc/2016#data-downloads.
26. Australian Bureau of Statistics. 2016 Census Quick Stats Australian population [Internet]. 2016 [updated 2020; cited 01 March 2021]. https://quickstats.censusdata.abs.gov.au/census_services/getproduct/census/2016/quickstat/0336/opendocument.
27. Ochiai RL, Acosta C, Danovaro-Holliday MC et al. A study of typhoid fever in five Asian countries: disease burden and implications for controls. Bull World Health Organ 2008; 86:260–8.
28. Nga TVT, Duy PT, Lan NPH et al. The control of typhoid fever in Vietnam. Am J Trop Med Hyg 2018; 99:72–8.
29. Chanthavily P, Mayxay M, Xongmixe P et al. Estimation of incidence of typhoid and paratyphoid fever in Vientiane, Lao People’s Democratic Republic. Am J Trop Med Hyg 2020; 102:744–8.
30. Roberts T, Rattananovong S, Phommasone K et al. Typhoid in Laos: an 18-year perspective. Am J Trop Med Hyg 2020; 102:749.
31. Pitzer VE, Meiring J, Martineau FP et al. The invisible burden: diagnosing and combatting typhoid fever in Asia and Africa. Clin Infect Dis 2019; 69:S395–401.
32. Oo WT, Myat TO, Htike WW et al. Incidence of typhoid and paratyphoid fevers among adolescents and adults in Yangon. Myanmar Clin Infect Dis 2019; 68:S124–9.
33. Sikorski MJ, Desai SN, Tupua S et al. Tenacious endemic typhoid fever in Samoa. Clin Infect Dis 2020; 71:S120–6.
34. Lane RJ, Holland D, McBride S et al. Enteric fever in the Pacific: a regional retrospective study from Auckland, New Zealand. Intern Med J 2015; 45:148–55.

35. ESR, funded by the Ministry of Health, New Zealand. Annual Surveillance Summary. Notifiable diseases in NZ: annual reports 2010–2017 [Internet], [updated 2019; cited 01 March 2021]. https://surv.esr.cri.nz/surveillance/annual_surveillance.php.

36. Getahun Strobel A, Parry CM, Crump JA et al. A retrospective study of patients with blood culture-confirmed typhoid fever in Fiji during 2014–2015: epidemiology, clinical features, treatment and outcome. Trans R Soc Trop Med Hyg 2019; 113:764–70.

37. Thompson CN, Kama M, Acharya S et al. Typhoid fever in Fiji: a reversible plague? Trop Med Int Health 2014; 19:1284–92.

38. Date KA, Newton AE, Medalla F et al. Changing patterns in enteric fever incidence and increasing antibiotic resistance of enteric fever isolates in the United States, 2008-2012. Clin Infect Dis 2016; 63:322–9.

39. Britto C, Pollard AJ, Voysey M, Blohmke CJ. An appraisal of the clinical features of pediatric enteric fever: systematic review and meta-analysis of the age-stratified disease occurrence. Clin Infect Dis 2017; 64:1604–11.

40. Dave J, Millar M, Maxeiner H et al. East London experience with enteric fever 2007-2012. PLoS One 2015; 10:e0120926.

41. O’Brien DP, Leder K, Matchett E et al. Illness in returned travelers and immigrants/refugees: the 6-year experience of two Australian infectious diseases units. J Travel Med 2006; 13:145–52.