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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*

Paratyphi A or C),[2] *Salmonella* Paratyphi currently has no licensed vaccines available.[3]

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.[3–5] 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 dependent on definitive laboratory evidence via culture.[18] Serological testing is not accepted as a confirmatory test and with rare exceptions (most commonly stool culture in the setting of screening known contacts); a positive blood culture is the predominant form of diagnosis.

Access to health care and diagnostic testing capability are excellent in Australia, so combined with mandatory notification of confirmed typhoid, case capture is considered high. Notification data confirm that most diagnosed cases are acquired overseas, with overall notification rates consistently <1 per 100 000 PY,[19] well within the definition of a low-incidence country (<10 cases per 100 000 PY).[6]

In 2018, an estimated 29% of Australian residents were born overseas.[20] Prior to the COVID-19 pandemic, international travel for tourism or business, or by those returning to their country of birth (COB) to visit friends and relatives (VFR) occurred at a high rate. VFR travellers compared with other travellers have been established as having higher relative risk for several infectious diseases endemic to their country of origin, including typhoid.[21,22] This is presumed to relate to a range of factors including under-recognition of potential risks from consuming local food and water.[21,22] Temporary visitors from endemic regions may be another source of typhoid notifications; while unable to be distinguished from routine travellers in case notification data, they are unlikely to be a prominent source of typhoid notifications.[22,23]

Australians frequently travel to high-risk destinations within the Asia-Pacific region, so notification rates and risks may differ from those reported in other studies. Therefore, we have examined Australia's typhoid notifications, and combined these data with travel statistics kept by the Australian Bureau of Statistics (ABS) to estimate the risk of typhoid following travel to a range of countries to help guide optimal vaccine prevention strategies.

The specific aims of this study were to (i) provide a summary of Australian *Salmonella* Typhi notifications for period of 1st January 2010 to 30th June 2017, (ii) apply denominator travel data to enable the estimation of typhoid fever incidence rates for Australian travellers by age and country of acquisition (COA) and (iii) where possible, examine the relative risk of infection for travellers returning to their COB vs other travellers.

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 COB 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: $x/d \times 365.25 \times 100\,000$, where x = 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).[26] 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, 73%) 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,[14–17] 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.[1,27–31] 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.[6] 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.[32]

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.[33]

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.[35]

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.[36,37]

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[δ]		
Age (years)	<15	≥15	Total	<15	≥15	Total	Total	<15	≥15	Total
OCEANIA	**19**	**56**	**75**	**24 180 310**	**154 700 970**	**178 881 280**	**13 336 120**	**28.7**	**13.22**	**15.31**
Melanesia	13	14	27	2 338 450	22 422 110	24 760 560	1 330 140	203.05	22.81	39.83
Papua New Guinea	13	14	27	1 112 110	13 941 580	15 053 690	684 540	426.96	36.68	65.51
Micronesia	1	0	1	73 650	1 626 280	1 699 930	83 580	495.93	–	21.49
Nauru	1	0	1	40 710	1 084 480	1 125 190	57 340	897.20	–	32.46
Polynesia (excl Hawaii)	5	41	46	7 231 480	30 109 400	37 340 880	2 924 590	25.25	49.74	44.99
Samoa	5	29	34	668 830	2 959 370	3 628 200	178 130	273.05	357.92	342.28
Fiji	0	10	10	5 954 790	23 285 330	29 240 120	2 478 910	–	15.69	12.49
Tonga	0	1	1	264 960	1 485 900	1 750 860	88 350	–	24.58	20.86
American Samoa	0	1	1	870	7770	8640	410	–	4700.77	4227.43
New Zealand	0	1	1	14 432 300	99 198 980	113 631 280	8 866 990	–	0.37	0.32
SOUTH AND CENTRAL ASIA*	**203**	**466**	**669**	**21 616 460**	**79 132 940**	**100 749 400**	**2 909 480**	**343.01**	**215.09**	**242.53**
Southern Asia	203	464	667	21 148 900	75 555 110	96 704 010	2 824 880	350.59	224.31	251.93
India	131	365	496	14 636 840	49 619 910	64 256 750	1 843 930	326.90	268.67	281.94
Bangladesh	30	49	79	1 209 710	3 728 000	4 937 710	123 850	905.80	480.08	584.38
Pakistan	41	22	63	2 555 090	6 175 260	8 730 350	178 230	586.09	130.12	263.57
Nepal	1	24	25	585 510	4 257 510	4 843 020	147 250	62.38	205.89	188.54
Sri Lanka	0	4	4	2 067 220	10 648 650	12 715 870	449 970	–	13.72	11.49
Central Asia	0	1	1	467 560	3 577 830	4 045 390	84 600	–	10.21	9.03
Afghanistan	0	1	1	363 520	2 406 080	2 769 600	55 500	–	15.18	13.19
SOUTH EAST ASIA*	**10**	**84**	**94**	**41 865 140**	**316 516 140**	**358 381 280**	**19 756 840**	**8.72**	**9.69**	**9.58**
Mainland SE Asia	1	16	17	13 411 810	117 742 960	131 154 770	6 366 810	2.72	4.96	4.73
Cambodia	1	4	5	906 520	8 135 380	9 041 900	339 300	40.29	17.96	20.20
Myanmar	0	7	7	230 910	2 291 390	2 522 300	99 110	–	111.58	101.37
Thailand	0	5	5	7 044 990	66 714 380	73 759 370	4 159 450	–	2.74	2.48
Maritime SE Asia	9	67	76	28 453 330	198 773 180	227 226 510	13 390 030	11.55	12.31	12.22
Indonesia	6	49	55	14 084 330	89 352 890	103 437 220	7 450 130	15.56	20.03	19.42
Philippines	3	12	15	4 238 970	31 936 290	36 175 260	1 369 260	25.85	13.72	15.15
Singapore	0	2	2	4 948 020	36 710 070	41 658 090	2 469 210	–	1.99	1.75
Timor-Leste	0	2	2	331 570	3 249 200	3 580 770	115 900	–	22.48	20.40
Malaysia	0	2	2	4 728 210	36 622 180	41 350 390	1 954 490	–	1.99	1.77
NORTH EAST ASIA*	**0**	**2**	**2**	**24 712 470**	**181 363 230**	**206 075 700**	**7 237 700**	–	**0.40**	**0.35**
Chinese Asia (incl Mongolia)	0	2	2	18 600 930	139 855 720	158 456 650	5 035 370	–	0.52	0.46
Hong Kong	0	1	1	3 902 970	39 247 730	43 150 700	1 620 550	–	0.93	0.85

(Continued)

Table 1. Continued

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$^{\delta}$		
Age (years)	<15	≥15	Total	<15	≥15	Total	Total	<15	≥15	Total
SUB-SAHARAN AFRICA	**3**	**6**	**9**	**4 058 440**	**31 538 300**	**35 596 740**	**1 132 060**	**27.0**	**6.95**	**9.23**
Central & W Africa	1	1	2	201 860	3 062 860	3 264 720	74 060	180.94	11.93	22.38
Guinea	1	0	1	2520	135 390	137 910	5380	14 494.1	–	264.85
Ghana	0	1	1	87 550	980 050	1 067 600	22 920	–	37.27	34.21
South and East Africa	2	5	7	3 856 580	28 475 440	32 332 020	1 058 000	18.94	6.41	7.91
Zambia	2	1	3	87 720	742 070	829 790	20 300	832.76	49.22	132.05
Tanzania	0	1	1	85 590	1 694 940	1 780 530	51 210	–	21.55	20.51
South Africa	0	1	1	1 967 220	15 578 790	17 546 010	649 080	–	2.34	2.08
Somalia	0	1	1	57 720	213 300	271 020	4100	–	171.24	134.77
Djibouti	0	1	1	60	26 850	26 910	420	–	1360.34	1357.30
NTH AFRICA AND MIDDLE EAST	**0**	**12**	**12**	**11 334 600**	**55 663 150**	**66 997 750**	**1 549 120**	–	**7.87**	**6.54**
North Africa	0	3	3	1 151 570	6 319 330	7 470 900	176 530	–	17.34	14.67
Sudan	0	3	3	302 700	1 061 530	1 364 230	23 550	–	103.22	80.32
Middle East	0	9	9	10 183 030	49 343 820	59 526 850	1 372 590	–	6.66	5.52
Lebanon	0	4	4	3 203 360	10 568 350	13 771 710	273 000	–	13.82	10.61
Iran	0	1	1	742 530	3 705 950	4 448 480	102 670	–	9.86	8.21
Syria	0	1	1	148 090	498 690	646 780	10 830	–	73.24	56.47
Iraq	0	2	2	873 800	2 398 430	3 272 230	58 560	–	30.46	22.32
Saudi Arabia	0	1	1	450 050	2 886 890	3 336 940	64 000	–	12.65	10.95
AMERICAS	**0**	**2**	**2**	**20 216 630**	**208 978 210**	**229 194 840**	**8 499 370**	–	**0.35**	**0.32**
Central America	0	2	2	323 070	5 456 600	5 779 670	155 210	–	13.39	12.64
El Salvador	0	1	1	45 720	393 370	439 090	8510	–	92.85	83.18
Mexico	0	1	1	203 470	3 771 880	3 975 350	117 130	–	9.68	9.19
SOUTHERN AND EASTERN EUROPE	**0**	**1**	**1**	**10 785 160**	**117 876 480**	**128 661 640**	**3 226 650**	–	**0.31**	**0.28**
Eastern Europe	0	1	1	1 743 000	13 402 960	15 145 960	366 730	–	2.73	2.43
Czechia	0	1	1	277 680	1 744 580	2 022 260	47 950	–	20.94	18.06

NNDSS 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 $n = 17$) and 36 cases locally acquired in Australia (age < 15 years $n = 13$, age ≥ 15 $n = 23$).
^Based on ABS, Customized Report, 2019.
£Total travel episodes—returning Australian residents <12 months overseas travel.
$^{\delta}$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 June2017

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	2 458 350	7 314 130	9 772 480	490.30	284.64	336.38	1.72
	≥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	1485.36	704.83	829.35	2.11
	≥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
	≥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	–
	≥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	–
	≥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	–
	≥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	–	–	–	–
	≥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	–
	≥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	–	–	–	–
	≥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[16,17,38]; 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.[1] 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.[39] 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.[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)[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 RRs 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.[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.[41] Unfortunately, residency status was not routinely recorded for cases, so it was not possible 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,[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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