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Original Article

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 \geq 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 pretravel. *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),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 \geq 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 \geq 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 \geq 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: $x/d \times 365.25 \times 100000$, 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 \geq 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 \geq 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}

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Mainland SE Asia11617134118101177429601311547706366810 2.72 4.96 4.73 $Cambodia$ 1459065208135380904190033930040.2917.962020 $Mjanmar$ 07723091022913902522330099110-111.158101.37 $Tbailand$ 0557044990 66714380 737593704159450-2.142.48 $Maritime SE Asia964955140843308935289010347220745013011.5520.0319.42Maritime SE Asia955140843308935289010347220745013015.5620.0319.42Maritime SE Asia31215153622033193629031937220745013015.5620.0319.42Maritime SE Asia312154733601339003011.5520.0319.42Maritime SE Asia31215448200367100704165800025.8513.7215.15Nidopresia02224948003507700115900-1.9417.72Nidopresia0222413563501357260135020025.8513.7215.15Nidopresia02223492003580770115900-1.991.77NoRTH EAST022218136323$	SOUTH EAST ASIA*	10	84	94	41865140	316516140	358381280	19756840	8.72	9.69	9.58
Cambodia145906 5208135 380904 1900339 30040.2917.9620.20Myanmar0777230 9102.291 390252 30099110-111.58101.37Thailand0557044 990 $66714 380$ 7375 93704159 450-2.742.48Maritime SE Asia9 677 7628 453 330198 773 1802.522 50099110-2.7742.48Maritime SE Asia9 677 7628 453 330198 773 1802.57226 51013 390 03011.551.2.311.2.22Indonesia6495514084 33089 352 890103 4372207450 13015.5620.0319.42Philippines31121215423 897031 95 22036 175 26013 390 03011.5520.0319.42Singapore0222449 802036 71007041 658 0902469 210-1.1991.75Timor-Leste022224712470181 363 230266075700733790-1.1991.77NoRTH EAST ASIA*022222222224728 20.40Maloyia0222222221<771<7NoRTH EAST ASIA*022222221<771<7	Mainland SE Asia	1	16	17	13411810	117742960	131154770	6366810	2.72	4.96	4.73
Myanmar0777230 910252 30099110-111.58101.37Thailand055704499066714380737593704159450-111.58101.37Thailand055704499066714380737593704159450-2.742.48Maritime SE Asia96776284533301987731802272265101339003011.5512.3112.22Indonesia6495514 08433089352890103 437220745013015.5620.0319.42Philippines3112151542389703193629036175260136926025.8513.7215.15Philippines0223193629036710070416580902469210-1.991.75Singapore02233157032492003580770115900-1.991.75Ninor-Leste02223492003580770115900-1.991.75NoRTH EAST ASIA*022247124701813632302060757007237700-0.400.35OKTH EAST ASIA*02222186009301398557201584566505033370-0.400.35NoRTH EAST ASIA*02222186009301398557201584566505035370-0.400.35Norese Asia (i	Cambodia	1	4	5	906 520	8135380	9041900	339300	40.29	17.96	20.20
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	Myanmar	0	7	~	230910	2291390	2522300	99110	Ι	111.58	101.37
Maritime SE Asia96776284533301987731802272265101339003011.5512.3112.22Indonesia649551408433089352890103437220745013015.5620.031942Philippines3121542389703193629036175260136926025.8513.7215.15Philippines022494802036710070416580902469210-1.991.75Singapore0223315703597700115900-1.991.75Malaysia02224712470181363230198577007357700-0.400.35NORTH EAST ASIA*022247124701813632302060757007237700-0.400.35Chinese Asia (incl Mongolia)022213855720158456650503537001237700-0.400.35Mong Kong01139029703924773043150700162055007035370-0.520.46	Thailand	0	5	5	7044990	66714380	73759370	4159450	Ι	2.74	2.48
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	Maritime SE Asia	6	67	76	28453330	198773180	227226510	$13\ 390\ 030$	11.55	12.31	12.22
Philippines3121542389703193629036175260136926025.8513.7215.15Singapore022494802036710070416580902469210-1.991.75Timor-Leste02233157032492003580770115900-1.991.75Madrysia022472821036622180413503901954490-1.991.77NORTH EAST ASIA*022247724701813632302060757007237700-0.400.35Chinese Asia (incl Mongolia)02221398557201584566505035370-0.520.46Hong Kong011390297039247730431507001620550-0.930.85	Indonesia	9	49	55	14084330	89352890	103437220	7450130	15.56	20.03	19.42
Singapore0224948020 36710070 41658090 2469210 -1.99 1.75 Timor-Leste022 331570 3249200 3580770 115900 -1.99 1.77 Malaysia022 4728210 36622180 41350390 1954490 -1.99 1.77 NoRTH EAST ASIA*022 24712470 181363230 206075700 7237700 - 0.40 0.35 Chinese Asia (incl Mongolia)022 24712470 181363230 206075700 7237700 - 0.40 0.35 Chinese Asia (incl Mongolia)022 24712470 181363230 206075700 7237700 - 0.40 0.35 Chinese Asia (incl Mongolia)022 24712470 139855720 158456650 5035370 $-0.520.46Hong Kong011390297039247730431507001620550-0.930.85$	Philippines	ŝ	12	15	4238970	31936290	36175260	1369260	25.85	13.72	15.15
Timor-Leste02233157032492003580770115900-22.4820.40 $Malaysia$ 022472821036622180413503901954490-12991.77 $Malaysia$ 022247124701813632302060757007.237700-0.400.35 $NORTHEASTASIA*$ 022247124701813632302060757007.237700-0.400.35 $NorthEastaincl Mongolia)$ 0222247124701813632302060757007.237700-0.400.35 $NorthEastaincl Mongolia)$ 0222247124701813632302060757007.237700-0.400.35 $NorthEastaincl Mongolia)$ 0222247124701813632302060757007.237700-0.400.35 $NorthEastaincl Mongolia)$ 02221813632302060757007.237700-0.400.35 $Northeastaincl Mongolia)$ 011390297039247730431507001620550-0.930.930.83	Singapore	0	2	2	4948020	36710070	41658090	2469210	I	1.99	1.75
Malaysia 0 2 2 4728210 36622180 41350390 1954490 - 1.99 1.77 NORTH EAST ASIA* 0 2 2 24712470 181363230 206075700 7237700 - 1.99 1.77 NORTH EAST ASIA* 0 2 2 24712470 181363230 206075700 7237700 - 0.40 0.35 Chinese Asia (incl Mongolia) 0 2 2 183855720 158456650 50353700 - 0.52 0.46 Hong Kong 0 1 3902970 39247730 43150700 1620550 - 0.93 0.85	Timor-Leste	0	2	2	331570	3249200	3 580 770	115900	I	22.48	20.40
NORTH EAST ASIA* 0 2 24712470 181363230 206075700 7237700 - 0.40 0.35 Chinese Asia (incl Mongolia) 0 2 2 13855720 13845650 5 035 370 - 0.40 0.35 Hong Kong 0 1 1 3902970 39247730 43150700 1620 550 - 0.93 0.85	Malaysia	0	2	2	4728210	36622180	41350390	1954490	I	1.99	1.77
Chinese Asia (incl Mongolia) 0 2 2 18 600 330 139 855 720 158 456 650 5 035 370 - 0.52 0.46 Hong Kong 0 1 1 3902 970 39247730 43 150 700 1 620 550 - 0.93 0.85	NORTH EAST ASIA*	0	7	2	24 712 470	181363230	206075700	7237700	I	0.40	0.35
Hong Kong 0 1 1 1 3902970 39247730 43150700 1 620 550 – 0.93 0.85	Chinese Asia (incl Mongolia)	0	2	2	18600930	139855720	158456650	5 035 370	I	0.52	0.46
	Hong Kong	0	1	1	3 902 970	39247730	43150700	1620550	I	0.93	0.85

	Typhoid Acquisition World Region Minor Region Country	Australian 1	notified typhoid ca	ises (n)	Travel exposur residents	e (days)—returning	ç Australian	Travel episodes $(n)^{\pounds}$	Typhoid incid estimates ^ô	ence (per 100 000	PY)—crude
GBS-MHARAN AFRCA 3 6 9 4088440 3158330 3596740 1132060 27.0 6.95 9.23 Geneal & Mfrica 1 1 2 201860 3063800 324720 7400 1133 2238 Geneal & Mfrica 1 1 2 201860 3063800 3247470 5370 5418 771 Geneal & Mfrica 2 1 1 233200 1667600 22920 44144.1 791 Geneal 0 1 1 1 25750 88050 1667600 22920 441 791 Geneal 0 1 1 1 110 2000 1894 402 13730 Geneal 0 1 1 1 7770 839370 51910 6907 6912 13737 Geneal 0 1 1 1 1 113460 5664150 52910 64917 1314753 Geneal 0 </th <th>Age (years)</th> <th><15</th> <th>≥15</th> <th>Total</th> <th><15</th> <th>≥15</th> <th>Total</th> <th>Total</th> <th><15</th> <th>≥15</th> <th>Total</th>	Age (years)	<15	≥15	Total	<15	≥15	Total	Total	<15	≥15	Total
	SUB-SAHARAN AFRICA	e e	6	6	4 058 440	31 538 300	35 596 740	1 132 060	27.0	6.95	9.23
Gained 1 0 1 230 13530 137910 5380 149411 - 2418 Gained 1 0 1 1 8750 98050 137700 23200 294941 - 2418 Guinal 2 3 5 7 38550 98050 137050 23200 2930 1341 791 Combinal 2 1 1 87500 74070 8279700 23300 81216 4932 13330 Combinal 0 1 1 1 85500 740700 82370 233200 23330 2113 31330 Combination 0 1 <th1< th=""> <th1< th=""> <th1< th=""></th1<></th1<></th1<>	Central & W Africa	1	1	2	201860	3062860	3264720	74060	180.94	11.93	22.38
Ghana 0 1 1 87530 396030 1067600 22200 - 3727 34.1 Zambia 2 1 3 365630 2475440 233200 1093000 18.94 6.41 791 Zambia 0 1 1 1 85590 169440 173600 18.94 6.41 731 Zambia 0 1 1 1 97720 1257790 1754010 6.913 6.41 731 Dibout 0 1 1 1 97720 215300 26910 490 14347 203 1447 Dibout 0 1 1 1 97720 213300 27690 1754010 1754010 1447 203 1447 Dibout 0 1 1 1 1 1 1<1	Guinea	1	0	1	2520	135390	137910	5380	14494.1	I	264.85
South and East Africa 2 7 385580 247540 333200 105800 1894 641 791 Tatarian 0 1 1 87720 74070 837790 53030 51210 6912 13205 Tatarian 0 1 1 197720 153790 178030 51210 490 2.34 208 South Africa 0 1 1 197720 153790 17300 4100 -723 13770 South Africa 0 1 1 1697720 15378790 175600 699750 174770 174770 137730 5363150 6997750 154730 55730 55730 55730 55730 55730 55730 55730 55730 55730 55730 55730 55730 55730 55730 55730 55730 55730 557300 557300 557300 556580 1577510 5537580 1573590 <td>Ghana</td> <td>0</td> <td>1</td> <td>1</td> <td>87 550</td> <td>980 050</td> <td>1067600</td> <td>22920</td> <td>I</td> <td>37.27</td> <td>34.21</td>	Ghana	0	1	1	87 550	980 050	1067600	22920	I	37.27	34.21
Zambia2138772074070829790203083.2769.2212.05Tatemia011186720016587901674601069.080 $-$ 2.132.03Tatemia0111186722015587301754610 $-$ 2.142.03Somalia01111867720213300271020 $-$ 2.142.03Diboti011115677202133002774010 $-$ 2.142.03Diboti01111602.68302.6910 $+$ 207.712413.7730Diboti011111602.68301754510 $-$ 7.732.08Diboti01111602.683013775102.7300 $-$ 7.732.03Sodiff033.027005.6631506.99750159120177530 $-$ 7.74137730Modific East00111742303.73590 $-$ 0.0212.330.02500Midfic East000111742303.73590 $-$ 0.17341467Midfic East0000000.8635013777102.73000 $-$ 0.17340.6547Midfic East000000	South and East Africa	2	5	7	3 856 580	28475440	$32\ 332\ 020$	1058000	18.94	6.41	7.91
	Zambia	2	1	33	87 720	742 070	829 790	20300	832.76	49.22	132.05
South Africa011 167720 1578790 1746010 649080 - 2.34 2.08 South Africa011 17720 213300 271020 4100 - $2.171.34$ 137730 Diplomi011 1 7720 213300 271020 4100 - 2.737 5.44 Diplomi0111 60^{-} 2683150 6697750 1549120 - 2.737 5.44 Diplomi0331151570 6139330 277090 16617530 278750 278750 278750 $2647565555565565565565565565565655656565565$	Tanzania	0	1	1	85 590	$1\ 694\ 940$	1780530	51210	I	21.55	20.51
Somula011 57720 213300 271020 4100 -1 171.24 13477 Difiouri0111 60 5633150 6697750 159120 - 171.24 13477 Difiouri0111 60 5663150 5663150 6697760 1569120 - 171.24 137730 ASTNorth Africa0111 60 5563150 6697760 1569120 - 7.87 654 ASTNorth Africa033 1151570 6319330 7470900 176530 17.34 137730 North Africa033 1151570 6319330 1364230 2356850 17.34 137730 North Africa011 173230 1377110 237580 17.34 1367 Sudam011 742330 376850 1448480 102670 12066 52.232 Sudaf Arabia0011 742330 377580 1448480 102670 12053 1264 Inam011 74230 376940 646780 1387250 12066 52.232 Sudaf Arabia011 74230 377580 1377710 27790 1264 532447 Inam011 148000 498690 3372230 53690 64000 1265 12364 Inam <t< td=""><td>South Africa</td><td>0</td><td>1</td><td>1</td><td>1967220</td><td>15578790</td><td>17546010</td><td>649080</td><td>I</td><td>2.34</td><td>2.08</td></t<>	South Africa	0	1	1	1967220	15578790	17546010	649080	I	2.34	2.08
	Somalia	0	1	1	57 720	$213\ 300$	271 020	4100	I	171.24	134.77
	Djibouti	0	1	1	60	26 850	26910	420	I	1360.34	1357.30
EASTNorth Africa11515706 31933017553017341467North Africa03311515706 3193301364230136530-17341467North Africa033330270015643023550-17341467Middle East033302360195432035628501377290-103.22803Middle East0117425303705950444840102670-103.22803Lebmon0117425303705950444840102670-9.368.21Syria0117425303705950444840102670-9.368.21Syria0117425303705950444840102670-9.368.21Syria011742530377550-13321061Inaq011742530377550-0.2550-0.366Saudi Ambia02222335405530.32545Inaq0111742530377550646780102670-13.4613.46Saudi Ambia0222222233333333 <th< td=""><td>NTH AFRICA AND MIDDLE</td><td>0</td><td>12</td><td>12</td><td>11334600</td><td>55 663 150</td><td>66 997 750</td><td>1549120</td><td>I</td><td>7.87</td><td>6.54</td></th<>	NTH AFRICA AND MIDDLE	0	12	12	11334600	55 663 150	66 997 750	1549120	I	7.87	6.54
North Africa0331151570 6319330 7470900 176530 - 17.34 1467 Sudar033302700 1061330 1364230 23550 - 17.34 1467 Sudar033302700 1061330 1364230 23550 - 17.34 1467 Middle East09 10183030 0958350 137590 23550 - 10322 8032 Middle East0011 722330 375950 494890 45660 6665 5.52 Middle East011 742330 3705950 4948690 646780 1372300 $= 6.66$ 5.232 Sudar Arabia0111 742330 370590 4448490 102670 $= 0$ 3364 22324 5647 Sudar Arabia0111 742330 3775230 58560 $= 0$ 13.82 1061 Sudar Arabia022 2372330 33753690 3272230 58560 $= 0$ 3364 22324 5647 Saudi Arabia022 237230 58760 102670 $= 0$ 2324 5647 Saudi Arabia02 237230 33753690 327230 58760 $= 0$ 3364 22324 5647 Saudi Arabia022 22323070 5375300 117130 $= 0$ 2326650 $= 03$	EAST										
Sudar 0 3 302700 1061330 1364230 23550 23550 -1 103.22 80.32 Middle Eat 0 9 9 10183030 4934320 5956850 13771710 273000 -1 6.66 5.52 Lebaron 0 1 1 1 745303 370550 4448400 102670 -1 6.66 5.23 Niddle Eat 0 1 1 1 745303 370550 4448400 102670 -1 5.66 5.23 Syria 0 1 1 1 1 1 1 273300 493670 -1 5.66 5.23 Syria 0 1 1 1 1 1 1 13830 -1 5.66 5.23 Saudi Arabia 0 0 1 1 1 1 13830 -1 5.66 5.23 America 0 1 1 1 1 148090 3376940 64000 -1 12.64 Saudi Arabia 0 0 1 1 1 45050 2386890 337230 439370 499370 -1 2.66 America 0 0 1 1 1 45005 5779670 155210 -1 10.35 0.35 America 0 1 1 1 1 1 1 10785400 5779670 155210 -1 10.36 Mexico 0 1	North Africa	0	33	ŝ	$1\ 151\ 570$	6319330	7470900	176530	I	17.34	14.67
Middle East099101830304934382059568501372590-6.665.52Lebanon0117425303705950448480102670-6.665.52Ibanon0117425303705950448480102670-6.665.52Ibanon0117425303705950448480102670-6.665.22Ibanon0117425303705950448480102670-6.665.22Syria01117425303705950448480102670-6.665.22Syria01117425303705950448480102670-6.665.22Saudi Arabia01117425303356906.467806.9336012.670.53Saudi Arabia022220166302.9868903356406.4000-12.650.35Saudi Arabia01114500505356002.2919484084993706.01350.35America01145005053560053560012.650.330.35Saudi Arabia0145005053868903337053991064000-12.65Saudi Arabia0111078516057967012367013.6412.6512.65Saudi Arabia </td <td>Sudan</td> <td>0</td> <td>ŝ</td> <td>ŝ</td> <td>302700</td> <td>$1\ 061\ 530$</td> <td>1364230</td> <td>23550</td> <td>I</td> <td>103.22</td> <td>80.32</td>	Sudan	0	ŝ	ŝ	302700	$1\ 061\ 530$	1364230	23550	I	103.22	80.32
	Middle East	0	6	6	$10\ 183\ 030$	49343820	59 526 850	1372590	Ι	6.66	5.52
Iran01174253037059504448480102670-9.868.21Syria011114809049869064678010830-73.2456.47Syria022287380023984303.37223058560-73.2456.47Saudi Arabia01114500502.3984303.37594064000-12.6510.95Saudi Arabia01114500502.3984303.37594064000-0.3462.2.32Saudi Arabia0222220216630298782102291948408499370-0.350.32AMERICAS02222202166305776670155210-0.350.32AMERICAS011120347037718803775670155210-9.689.19Mexico011110785160178764801286616403226650-9.689.19SOUTHERN AND EASTERN0111787648013764803226650-0.310.2812.64Easten Europe0111178764801374596055210-9.199.19SOUTHERN AND EASTERN0111787648013764801374596056650-0.310.23Easten Europe011 <td>Lebanon</td> <td>0</td> <td>4</td> <td>4</td> <td>$3\ 203\ 360$</td> <td>10568350</td> <td>$13\ 771\ 710$</td> <td>273000</td> <td>I</td> <td>13.82</td> <td>10.61</td>	Lebanon	0	4	4	$3\ 203\ 360$	10568350	$13\ 771\ 710$	273000	I	13.82	10.61
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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 $\ge 15 n = 17$) and 36 cases locally acquired in Australia (age < 15 years n = 13, age $\ge 15 n = 23$). ^Based on ABS, Customized Report, 2019. L 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 1. Continued

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Table 2. Typhoid fever incidence in NSW/VIC travelle

Country of typh and age category	oid acquisition (years)	Typhoid notific	cations—n (adjusted)	*_	Travel exposur	e—days		Incidence-per	· 100 000 PY^		IRR (COB=COA: COB ≠ COA)
		COB=COA	COB ≠ COA	Total	COB=COA	$COB \neq COA$	Total	COB=COA	COB ≠ COA	Total	
India	<15	31 (33)	53 (57)	90	2458350	7314130	9 772 480	490.30	284.64	336.38	1.72
	≥ 15	199 (214)	26 (28)	242	24009050	9580680	33 589 730	325.56	106.75	263.15	3.05
Bangladesh	<15	5 (6)	13(15)	21	147540	777 310	924850	1485.36	704.83	829.35	2.11
	≥ 15	35 (36)	3 (3)	39	2390850	410240	$2\ 801\ 090$	549.97	267.10	508.54	2.06
Pakistan	<15	9 (10)	17(18)	28	471 920	1374330	1846250	773.97	478.38	553.93	1.62
	≥ 15	12 (12)	4 (4)	16	2659520	1619370	4278890	164.80	90.22	136.58	1.83
Nepal	<15	1 (1)	0 (0)	1	45630	380 980	426610	800.46	I	85.62	I
	≥ 15	14(14)	2 (2)	16	1099050	1699910	2 798 960	465.27	42.97	208.79	10.83
Indonesia	<15	0 (0)	2 (2)	2	453870	6463260	6 917 130	Ι	11.30	10.56	I
	≥ 15	13 (14)	9 (10)	24	7343050	35296800	42 639 850	69.64	10.35	20.56	6.73
Cambodia	<15	0 (0)	1 (1)	1	59670	580010	639680	I	62.97	57.10	I
	≥ 15	2 (2)	2 (2)	4	1658970	3234180	$4\ 893\ 150$	44.03	22.59	29.86	1.95
Thailand	<15	0 (0)	0 (0)	0	412880	4033630	4446510	I	I	Ι	I
	≥ 15	1 (1)	4 (4)	5	3493310	$34\ 443\ 340$	37 936 650	10.46	4.24	4.81	2.46
Samoa	<15	0 (0)	2 (2)	2	21950	398230	420180	I	183.44	173.85	I
	≥ 15	11 (15)	1 (2)	17	884680	937030	$1\ 821\ 710$	619.29	77.96	340.85	7.94
Fiji	<15	0 (0)	0 (0)	0	98920	4261850	4360770	Ι	I	I	I
	≥ 15	4 (5)	3 (0)	8	3314770	12657660	15972430	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 22, 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 \geq 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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Departments along with Communicable Diseases Network Australia for provision of national notification data.

Authors' contributions

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

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Conflict of interest: The authors have no conflicts of interest to declare.

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