Title: Epidemiology of non-typhoid *Salmonella* infection in the Australian Capital Territory over a 10 year period

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Aim: Describe the epidemiology of non-typhoid *Salmonella* (NTS) infection in the Australian Capital Territory (ACT), including factors associated with hospitalisation.

Methods: Retrospective descriptive and observational study of culture-confirmed NTS infections using data collected from ACT public health, public pathology and hospital services, 2003-2012. Outcome measures include incidence and NTS serotype for total reported and hospitalised cases; and focus of infection, complications and antibiotic susceptibility for hospitalised cases.

Results: 1469 cases of NTS infection were reported, with the crude annual incidence increasing from 24.4 to 61.3 cases per 100,000 population. Fourteen percent were hospitalised, representing an incidence of 5.9 hospitalisations per 100,000 population, without significant change over time. Hospitalisation incidence peaked at the extremes of age. Comorbid disease and age ≥80 years were associated with complications during hospitalisation. *S*. Typhimurium was the most common serotype, accounting for 64% of NTS. Independent risk factors for invasive disease included non-*S*. Typhimurium serotype (aRR 5.46, 95%CI 1.69-17.65 p=0.005), ischaemic heart disease (aRR 4.18, 95%CI 1.20-14.60 p=0.025) and haematological malignancy (aRR 6.93, 95%CI 2.54-18.94 p<0.001). Among hospitalised patients, resistance to ampicillin, ceftriaxone, trimethoprim-sulfamethoxazole and quinolones was 9.9%, 0%, 4.4% and 2.5%, respectively.

Conclusions: NTS notifications in the ACT have increased over time, with outbreaks of foodborne disease contributing to this increase. Crude age-specific incidence is highest in the very young, while rates of hospitalisation are highest in the elderly. Comorbid disease and infection with a non-*S*. Typhimurium serotype was associated with complicated NTS disease course. Antimicrobial resistance in NTS is low and has not increased over time.

Keywords: *Salmonella*, epidemiology, foodborne diseases, bacteraemia, hospitalisation

Introduction

Non-typhoid *Salmonella* (NTS) is a major foodborne pathogen with the global burden of gastroenteritis estimated at 150 million cases annually[1]. The incidence and mortality varies widely between geographic regions[1]. While most NTS gastroenteritis is self-limiting in nature, infections due to NTS result in greater morbidity and more deaths than any other foodborne pathogen [1,2]. This is in part due to the ability of NTS to cause invasive disease, especially in those at extremes of age or with impaired cellular immunity[1,3,4].

The emergence of antibiotic resistance in NTS isolates is a major public health problem, threatening the successful treatment of serious *Salmonella* infections. Antimicrobial resistance varies depending on geographic region. However, extended-spectrum beta-lactam, quinolone and multi-drug resistant NTS isolates have been identified globally[5].

Given the geographical variations in incidence, antimicrobial resistance and outcome determinants, it is important to understand the local epidemiology. This study examines NTS infections occurring in residents of the Australian Capital Territory (ACT) over a ten year period.

Materials and Methods

The ACT has a population of almost 400,000 people. All emergency department presentations in the ACT are managed by the two public hospitals using a single public pathology provider. Laboratories and clinicians (both public and private) are required to notify all cases of *Salmonella* infection to the ACT Health Protection Service (HPS) under the ACT Public Health Act 1997.

A population-based, retrospective review of NTS cases was undertaken between January 1 2003 and December 31 2012. A NTS case was defined as any ACT resident with a culture-confirmed NTS infection (including *S*. Paratyphi B biovar Java[6]). Each case was registered once per episode of salmonellosis, regardless of the number of specimens of the same serotype or the time between positive specimens. Data for total ACT salmonellosis cases was obtained from the HPS and included age, sex, serotype and whether the case had been epidemiologically linked to a confirmed outbreak via public health investigation.

Hospitalised cases were defined as cases that were admitted to hospital under the care of a medical or surgical team and formed a subset of total ACT notified cases. They were identified through a combined search of public hospital medical records using diagnostic ICD-10 codes (A01 and A02), infection control records and pathology records. Medical record and pathology review was used to document comorbidities, focus of infection, complications, in-hospital mortality, serotype and antimicrobial susceptibility. The Charlson Comorbidity Index was used to grade the severity of chronic underlying conditions[7]. Patients who had extraintestinal NTS infection or intestinal complications, underwent surgery, developed a complication of dehydration and/or sepsis, or experienced severe reactive sequelae were regarded as complicated cases. Invasive disease was defined as isolation of *Salmonella* from blood, cerebrospinal fluid, bone or joint fluid or another sterile site, and excluded soft tissue abscesses and wound cultures. Australian Bureau of Statistics ACT population estimates for each year were used in calculations[8].

Data Analysis

Microsoft Excel (Microsoft Corp., USA) was used for descriptive analysis and Stata v. 14 (StataCorp, USA) for descriptive test statistics, and univariate and multivariate analyses. Chi square tests were used for homogeneity and trends in proportions, two sample t tests to compare means, and Wilcoxon rank sum tests for other group comparisons. Among the sub-population of hospitalised cases, risk factors for the development of (i) complications and (ii) invasive disease were independently assessed via the calculation of relative risks (RR) and adjusted relative risks (aRR), with associated 95% confidence intervals (CI), and P values using a two-tailed Fisher's exact test. General linear models were constructed using a manual

backward stepwise approach. A P value cut off of <0.20 was used to aid variable selection. For the final models, exposures with low case numbers or judged to be of lower clinical significance were also excluded. Statistical significance was reported at the p≤0.05 level.

Ethics Approval

Ethics approval was granted by the Human Research Ethics Committees of the ACT Government Health Directorate (ETHLR.12.112) and Calvary Health Care ACT (28-2013).

Results

NTS infection in the Australian Capital Territory

There were 1469 NTS notifications, with 51% (749/1469) in females. The mean age was 29.0 years (95% CI 27.9-30.1), with no significant difference between sexes. There were two age-related peaks in crude incidence. These occurred in children, particularly under 1 year of age, and in the 20 to 29 year age group (Figure 1). The majority of infections (65%) occurred in summer and autumn.

The mean crude incidence of NTS infection was 41.8 cases per 100,000 population (95% CI 33.1-50.4), with a mean crude incidence of hospitalisation of 5.9 cases per 100,000 population (95% CI 4.8-6.9). Annual crude incidence increased from 24.4 to 61.3 cases per 100,000 population and was accompanied by an increase in the number of foodborne NTS outbreaks (Figure 2). Eggs were implicated in 12 out of 22 foodborne outbreaks, while other food vehicles included chicken, pork, salad and rockmelon (personal communication ACT HPS).

Hospitalisation due to NTS infection

Fourteen percent (205/1469) of NTS cases were hospitalised. There was a non-significant decrease in the proportion of NTS cases requiring hospitalisation over time. While 16.1% (33/205) of hospitalisations were

identified as part of a recognised *Salmonella* outbreak, there was no association between outbreak status and hospitalisation.

Fifty-one percent (105/205) of admitted cases were female. The mean age of hospitalised cases of 36.5 years (95% CI, 33.0-40.1) was significantly older than non-hospitalised cases ($\overline{x}$=27.8 years, 95% CI, 26.7-28.8) (t= 5.58**,** p<0.001). Peaks in age-related crude incidence for hospitalisation were seen with extremities of age (Figure 1). Although infants under 1 year of age had the highest crude incidence for hospitalisation, it was the elderly having the highest proportion of NTS infections requiring hospitalisation (16/25 cases of those 80 years and older) (Figure 1).

Thirty percent (62/205) of hospitalised cases experienced a complication. A range of complications were documented, with acute kidney injury being the most common (Table 1). Individuals aged ≥80 years were significantly more likely to develop complications ($\chi 2 = 5.12$, $p = 0.02$). Comorbidities were present in 41% (85/205) of hospitalised cases, with peptic ulcer disease and/or proton pump inhibitor use identified in 55% (47/85). Univariate analysis identified peptic ulcer disease, chronic pulmonary disease and ischaemic heart disease (IHD) as being associated with the development of complications. However, only IHD remained as an independent risk factor in the multivariate analysis (Table 2). Multivariate analysis also identified haematological malignancy and IHD as independent risk factors for invasive NTS infection (Table 3). Male sex was associated with reduced risk of invasive disease.

The median length of stay for a NTS related admission was 4 days, with no gender based differences observed. An increased median length of stay (5 days) was shown for hospitalised cases identified with any complication (*Z*=-3.68, p=0.002) or an underlying co-morbidity (*Z*= -5.74, p=<0.001).

Three deaths occurred among persons hospitalised for NTS infection, representing 1.5% of admitted cases. All involved patients over 50 years of age, with Charlson Comorbidity Index scores of ≥8, and complications

including multi-organ dysfunction, empyema or secondary aspiration pneumonia. One case was a primary NTS bacteraemia (no history of diarrhoea and a negative stool culture).

NTS Serotypes

Serotype data was available for 99.2% (1458/1469) of notified cases, with *S*. Typhimurium accounting for 64.1% (935/1458) of typed isolates (Figure 3A). This pattern was also seen among hospitalised cases where the most common non-*S*. Typhimurium serotypes were *S*. Enteritidis (3.9%), *S*. Virchow (3.4%), *S*. Muenchen (2.4%), *S*. Saintpaul (2.4%) and *S*. Bovismorbificans (2.0%). These proportions did not differ significantly from the total NTS notifications with the exception of *S*. Muenchen which demonstrated an association with hospitalisation ($\chi 2=5.62$, $p=0.02$).

There were 23 cases with invasive disease, representing 10.7% of hospitalised cases and 1.6% of all NTS notifications. They included 21 cases of bacteraemia and single cases of pleural empyema, pancreatic abscess, and aortitis with lumbar osteomyelitis. Non-*S*. Typhimurium serotypes carried significantly increased risk for both complicated and invasive NTS infection in hospitalised patients (Figure 3B, Tables 2 and 3).

Antibiotic Resistance

Among hospitalised patients, resistance to ampicillin, trimethoprim-sulfamethoxazole and ceftriaxone was 9.9% (20/203; annual range 0-28.6%), 4.4% (9/203; annual range 0-9.1%) and 0% (0/203), respectively, with no trend noted in the resistance rate over time. Naladixic acid resistance and/or a raised ciprofloxacin minimum inhibitory concentration (>0.06mg/L) was seen in 2.5% (5/203; annual range 0-13.3%) of NTS isolates. No quinolone resistance was detected in hospitalised patients after 2009 and all resistant isolates were acquired overseas. The countries of travel were documented in 4 cases (Thailand (2 cases), Indonesia (1 case) and India (1 case)).

Discussion

Our study provides important information on the epidemiology of NTS infection in a well-defined geographic region in Australia. The average annual notification rate for NTS infection in the ACT was 41.8 notifications per 100,000 population between 2003 and 2012. In Australia it is estimated that there are 7 cases of undocumented salmonellosis for each culture-confirmed case[9] and so, while our notification rate sits within that reported for other developed countries (USA 17.6 cases per 100,000 population; New Zealand 42.8 per 100,000; Denmark 79 per 100,000)[10-12], it is expected to be a significant underestimate of the real burden of community disease. The increase in NTS notifications observed in ACT residents between 2003 and 2012 correlates with Australian data for this time period. In 2011, there were 54.3 cases per 100,000 population in Australia, a 23% increase over the previous 5 years[13]. This is in contrast with the declining incidence seen in the UK[14] and Israel[15], and the stable incidence of NTS infection reported in the USA[10] over a similar period in time.

The increase in the number of foodborne outbreaks observed in the ACT may be responsible for the increasing rate of NTS infection, although an increase in testing in the setting of well publicised foodborne outbreaks has likely also contributed to the higher NTS crude incidence. The ACT had one of the highest rates of foodborne outbreaks in Australia in 2011[13]. Outbreak associated case numbers have a more significant effect on overall disease incidence in a small population such as the ACT. The presumed cause for both the increasing disease incidence and the frequency of foodborne outbreaks in the ACT during the period of our study is eggs, a problem that has been documented nationwide[13,16].

Age-related peaks in NTS notifications were seen in infants under 1 year of age and younger adults (20-39 years). Numerous studies describe the highest rate of *Salmonella* infection occurring in children between the ages of 0 to 4 years[11-13,15,17]. The high incidence in this age group is likely to be due to highly susceptible intestinal microflora in the setting of an immature immune system[18], a greater tendency to place contaminated items into their mouths and a lower threshold for testing. The peak in NTS infection in

younger adults seen in this study has been described in other comparable settings[12] and could relate to poor food safety practices and increased consumption of high risk food after leaving the family home[19].

The 14% of NTS infections leading to hospitalisation was lower than that seen in other developed countries, where incidences of 16-20 cases per 100,000 individuals, representing 22-29% of NTS infections, are commonly reported[11,14,17]. Unlike NTS notifications in ACT residents, the rate of NTS hospitalisation did not increase over time, suggesting that there was not an increase in the severity of NTS infection. Like many other studies, ours showed that it is patients at the extremes of age that more likely to be admitted to hospital as a consequence of NTS infection, with those over 65 years of age having the highest rates of hospitalisation[2,11,17].

The ability of NTS infection to result in bacteraemia and invasive focal infection is well recognised. It is estimated that 1-5% of enteric NTS infections result in bacteraemia[3,17]. We found that 1.4% of NTS infections resulted in bacteraemia, including one case with focal infection in the aorta and lumbar spine in a 73 year old male. Population based studies report that approximately 10% of adults aged over 50 years of age with documented NTS bacteraemia have a suppurative endovascular focus of infection[20], providing a rationale for aggressive investigation and treatment of NTS bacteraemia in the older individual.

Chronic disease has been associated with extraintestinal NTS infection in other reports[11,21]. However, our finding of a significant association between IHD and invasive infection risk should be interpreted with caution. Despite remaining significant after multivariate analysis, our estimate for risk displays a degree of imprecision, reflected by the width of the confidence limits and our overall sample size. Secondly, the clinical plausibility is difficult to reconcile with an absence of published supporting data. Nevertheless the finding may warrant future consideration, with a comparison of IHD incidence between hospitalised and community NTS cases one means of further examination. We also found haematological malignancy to be associated with invasive NTS disease, consistent with numerous reports that link immunosuppressive states with extraintestinal NTS infection[4]. The finding that male sex was a protective factor for invasive

salmonellosis in our hospitalised population is unusual as when a gender difference has been noted previously it has been men that have a higher incidence[22].

The majority of cases of NTS infection are caused by a limited number of serotypes. *S*. Enteritidis is the most common serotype worldwide[23]. However, considerable geographic variation in serotype distribution exists, with *S*. Typhimurium most dominant in Australia followed by *S*. Enteritidis, *S*. Virchow and *S*. Saintpaul[13,23]. A number of uncommon serotypes have a recognized propensity for bacteraemia and other forms of invasive disease. These include *S*. Dublin and *S*. Choleraesuis in particular, but also serotypes *S*. Virchow, *S*. Heidelberg and *S*. Enteritidis[4,11,17]. In our study there were no *S*. Dublin or *S*. Choleraesuis cases but non-*S*. Typhimurium serotypes, including *S*. Enteritidis, *S*. Bovismorbificans and *S*. Virchow, showed an association with invasive disease.

Invasive and severe forms of NTS infection require antimicrobial therapy and there are concerns regarding increasing antimicrobial resistance in animal and human NTS isolates globally[5,24]. No isolates in our study demonstrated ceftriaxone resistance, whereas third generation cephalosporin resistance is seen in 3% of NTS isolates in the USA[25] and 1.4% of European isolates[26]. In addition, we did not detect an increase in ampicillin, trimethoprim-sulfamethoxazole or quinolone resistance over time. Of particular interest, we found evidence of quinolone resistance in only 2.5% of hospital NTS isolates, with no resistant isolates detected after 2009. This contrasts with the rising incidence in the USA (3.3% in 2013)[25] and high levels of quinolone resistance seen in Europe (17.6%)[26]. All of the quinolone resistance seen in our study was acquired overseas, in returned travelers from Asia, where reduced susceptibility to ciprofloxacin is seen in up to 45% of clinical NTS isolates[24]. To add to this there have now been reports of carbapenemase-producing NTS isolates[27]. Therefore, while our data are reassuring, consideration of a resistant isolate remains important when choosing empiric antibiotic therapy for a patient with a history of overseas travel.

The design of this study allowed for exclusion of non-ACT residents resulting in a more accurate picture of *Salmonella* infection and calculation of crude incidence. However, its retrospective nature means that there

was some loss of data, particularly in regards to clinical history such as travel and linkage to outbreaks. A further limitation is the exclusion of hospitalised cases with NTS infection admitted interstate or directly to private hospitals. However, we believe that these represent small numbers as most cases requiring hospitalisation in the ACT will present via a public Emergency Department and so have been included.

Conclusion

This study demonstrates an increasing incidence of NTS infection in the ACT that is potentially driven in part by an increase in foodborne outbreaks. No comparable increase in the incidence of hospitalisation was observed. Admission and complication rates were seen proportionately more in the elderly. *S*. Typhimurium was the most common serotype overall and within the hospitalised subgroup. However, non-*S*. Typhimurium serotypes and comorbidities, such as IHD and haemtological malignancy, were associated with invasive NTS infection. Antimicrobial resistance, including to quinolones, in NTS was low and did not increase. Local epidemiology is important for understanding the burden of disease and informing prevention and treatment strategies.

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Figure Legends

Figure 1. Incidence of NTS notifications and NTS hospitalisations by age per 100,000 population, in ACT residents between 2003 and 2012. The percentage of NTS infections resulting in hospitalisation by age is indicated.

Figure 2. Annual incidence of NTS notifications and hospitalisations per 100,000 population and the number of foodborne outbreaks of NTS per year, 2003 to 2012. Food vehicles linked to outbreaks included eggs (12 outbreaks), chicken (2), pork (2), fish (1), kebab (1), yum cha (1), ice cream (1), salad (1) and rockmelon (1).

Figure 3. The most common serotypes isolated from (A) total NTS notifications and (B) invasive NTS disease, in ACT residents between 2003 and 2012. The other invasive disease serotypes include single isolates of *S*. Mbandaka, *S*. Heidelberg, *S*. Corvalis, *S*. Javiana, *S*. Orientalis and *S*. Panama.

Tables

Table 1. Complications among patients hospitalised with NTS infection in the ACT, 2003-2012.

Complication[†]	**Frequency** Number (%)
Extraintestinal disease	
Bacteraemia	21 (10.2%)
Focal Infections	
Aortitis and vertebral osteomyelitis	1 (0.5%)
Pleural empyema	1 (0.5%)
Femoral graft wound infection	1 (0.5%)
Intestinal complications	
Pancreatic abscess	1 (0.5%)
Perianal abscess	3 (1.5%)
Acute pancreatitis	3 (1.5%)
Appendicitis	2 (1.0%)
Cholecystitis	1 (0.5%)
Small bowel obstruction	1 (0.5%)
Per rectal bleed requiring transfusion	1 (0.5%)
Other significant complication	
Acute kidney injury[‡]	30 (14.6%)
Septic shock	3 (1.5%)
Severe metabolic acidosis	5 (2.4%)

Multiorgan dysfunction	1 (0.5%)
Myocardial infarct	3 (1.5%)
Transient ischaemic attack	1 (0.5%)
Aspiration pneumonia	2 (1.0%)
Febrile seizure	5 (2.4%)
Salmonella-related death	3 (1.5%)
Reactive complication	
Myopericarditis	2 (1.0%)
Arthritis	1 (0.5%)
Post-infective ADEM-like illness[§]	1 (0.5%)
Unnecessary surgery[¶]	
Appendicectomy	3 (1.5%)

[†] More than 1 complication was recorded in some cases

[‡] Defined as a ≥2-fold increase in serum creatinine

[§] Acute disseminated encephalomyelitis (ADEM)

[¶] No pathological finding during surgery

Table 2. Risk factors associated with the development of a complication among persons hospitalised with NTS.

	With Factor		Without Factor		Univariate Analysis		Multivariate analysis	
Potential Risk Factor	**Total cases**	**Compli-cated cases**	**Total cases**	**Compli-cated cases**	**Risk ratio (95% CI)**	**P**	**Risk ratio (95% CI)**	**P**
Male sex	100	41	105	35	1.23 (0.86-1.76)	0.256	0.79 (0.57-1.09)	0.144
Foodborne outbreak	33	9	172	67	0.70 (0.39-1.26)	0.203	-	-
Serotype								
S. Typhimurium	132	42	73	34	0.68 (0.48-0.97)	0.036	-	-
Non-S. Typhimurium	73	34	132	42	1.46 (1.03-2.08)	0.036	1.24 (1.24-1.24)	<0.001
Age								
<16 years	53	11	152	65	0.49 (0.28-0.85)	0.004	-	-
16-64 years	115	42	90	34	0.97 (0.68-1.38)	0.853	-	-
≥65 years	37	23	168	53	1.97 (1.41-2.76)	<0.001	1.24 (0.77-1.99)	0.373
Comorbidity								
Peptic ulcer disease[†]	47	27	38	13	1.68 (1.01-2.78)	0.033	1.28 (0.83-1.99)	0.265

Ischaemic heart disease	11	10	74	30	2.24 (1.61-3.13)	0.002	2.00 (1.44-2.79)	<0.001
Chronic pulmonary disease[‡]	19	5	66	35	0.50 (0.23-1.09)	0.040	1.01 (0.65-1.58)	0.956
Diabetes mellitus	22	14	63	26	1.54 (1.00-2.37)	0.070	1.35 (0.98-1.87)	0.067
Chronic kidney disease	8	4	77	36	1.07 (0.51-2.23)	0.861	-	-
Solid tumour	7	4	78	36	1.24 (0.62-2.46)	0.577	-	-
Haematological malignancy	7	5	78	35	1.59 (0.94-2.70)	0.178	-	-

[†] Includes those with a diagnosis of peptic ulcer disease and/or were taking a proton pump inhibitor (89%, 42/47).

[‡] Includes chronic obstructive pulmonary disease and asthma.

Table 3. Risk factors associated with invasive NTS infection among persons hospitalised with NTS.

	With Factor		Without Factor		Univariate Analysis		Multivariate analysis	
Potential Risk Factor	**Total cases**	**Invasive disease**	**Total cases**	**Invasive disease**	**Risk ratio (95% CI)**	**P**	**Risk ratio (95% CI)**	**P**
Male sex	100	12	105	11	1.15 (0.53-2.48)	0.730	0.47 (0.24-0.92)	0.027
Foodborne outbreak	33	1	172	22	0.24 (0.03-1.70)	0.104	-	-
Serotype								
S. Typhimurium	132	6	73	17	0.20 (0.08-0.47)	<0.001	-	-
Non-S. Typhimurium	73	17	132	6	5.12 (2.11-12.42)	<0.001	5.46 (1.69-17.65)	0.005
Age								
<16 years	53	1	152	22	0.13 (0.02-0.94)	0.012	-	-
16-64 years	115	14	90	9	1.22 (0.55-2.68)	0.625	-	-
≥65 years	37	8	168	15	2.42 (1.11-5.29)	0.027	0.65 (0.24-1.78)	0.407
Comorbidity								
Peptic ulcer disease[†]	47	7	38	5	1.13 (0.39-3.28)	0.819	-	-

Ischaemic heart disease	11	4	74	8	3.36 (1.21-9.32)	0.023	4.18 (1.20-14.60)	0.025
Chronic pulmonary disease[‡]	19	3	66	9	1.16 (0.35-3.86)	0.812	-	-
Diabetes mellitus	22	5	63	7	2.05 (0.72-5.79)	0.178	1.83 (0.56-6.01)	0.320
Solid tumour	7	1	78	11	1.01 (0.15-6.74)	0.989	-	-
Haematological malignancy	7	3	78	9	3.71 (1.30-10.65)	0.023	6.93 (2.54-18.94)	<0.001

[†] Includes those with a recorded diagnosis of peptic ulcer disease and/or were taking a proton pump inhibitor (89%, 42/47).

[‡] Includes chronic obstructive pulmonary disease and asthma.