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Salmonella bacteriuria: an increasing entity in elderly women in the United States

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SUMMARY

Salmonellosis is a major cause of gastroenteritis in the United States and can lead to septicaemia, and other extra-intestinal illness including urinary tract infections (UTIs). To examine trends in *Salmonella* bacteriuria in the United States, surveillance data from the National *Salmonella* Surveillance System from 1980 to the end of 1999 were reviewed. Overall, 17 442 urinary *Salmonella* isolates were reported, representing 2% of all *Salmonella* isolates from a known source. This proportion increased from 2% during 1980–1984 to 4% during 1995–1999. The median age of persons from whom these isolates came was 51 years; 12 176 (70%) were women. Compared to the last national survey conducted between 1968 and 1979, the rate of *Salmonella* bacteriuria increased among women, from 2·0 per million persons in 1980 to 3·7 in 1999; the highest rate occurring in women $\geqslant$70 years. National reporting of *Salmonella* bacteriuria increased in absolute incidence and as a proportion of all *Salmonella*, especially in elderly women and may represent an increase in the incidence of *Salmonella* UTIs. Better understanding of the uropathogenicity of *Salmonella* serotypes may further clarify the mechanisms of *Salmonella* UTIs.

INTRODUCTION

Salmonellosis is a major cause of illness in the United States, resulting in gastroenteritis, septicaemia, and extra-intestinal illness including urinary tract infection (UTI). Chronic illness, immunosuppression and structural abnormalities of the urinary tract are predisposing factors for non-typhoidal *Salmonella* UTIs [1, 2].

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In a retrospective survey conducted during 1968–1979, the Centers for Disease Control and Prevention (CDC) identified 3393 urine isolates of *Salmonella* submitted to laboratories; this represented 0·63 % of all reported *Salmonella* isolates [3]. To determine recent national trends in *Salmonella* isolates from urine, we reviewed the last two decades of *Salmonella* surveillance from 1980 to the end of 1999.

MATERIALS AND METHODS

National serotype-based surveillance for *Salmonella* began in 1962 by agreement of the Council of State

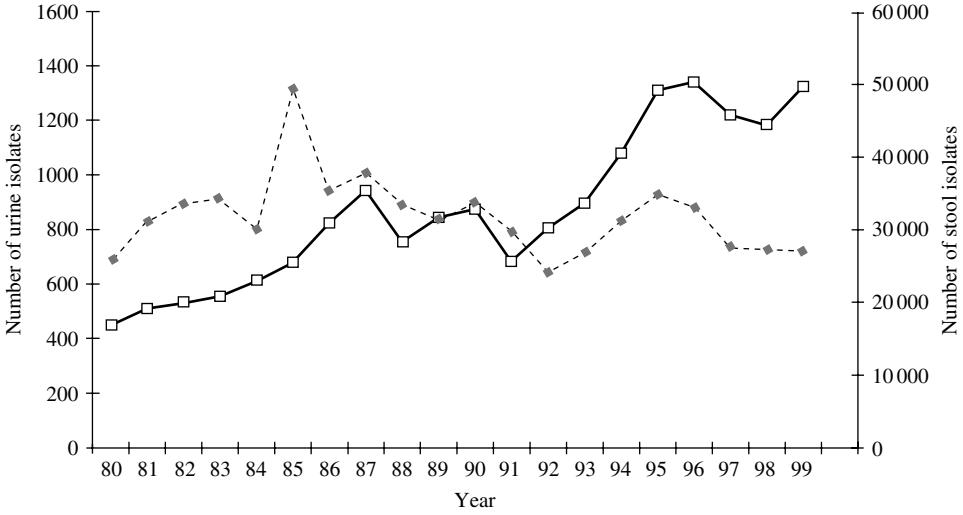

Fig. 1. Number of *Salmonella* isolates from urine (–□–) and stool (--◆--), United States, 1980–1999.

and Territorial Epidemiologists, the Association of Public Health Laboratories and CDC. The *Salmonella* surveillance system is a passive, laboratory-based system where clinical laboratories are requested or required (depending on the state) to forward clinical isolates of *Salmonella* species to their state public health department laboratory for serotyping [4]. Isolates are serotyped in the state public health laboratories according to the modified Kauffman and White scheme, using somatic (O) and flagellar (H) antigens [5]. Weekly reports of serotyped *Salmonella* isolates are then transmitted electronically to CDC from the 50 states and the District of Columbia via the Public Health Laboratory Information System (PHLIS). The report includes information on sex, age, race, county and state of residence, specimen source and serotype but no other clinical or epidemiological information. Summaries of the reported isolates are tabulated annually [6], and published periodically [4, 7]. For this study, we reviewed reported human isolates of *Salmonella* from urine, blood and stool collected from 1980 to the end of 1999. To determine if certain *Salmonella* serogroups were isolated more frequently from urine compared to stool we calculated a ratio of urine to 1000 stool isolates for serogroups accounting for at least 1% of urine or stool isolates.

Statistical analysis

We calculated age-specific isolation rates with U.S. Census Bureau data [8] using 1990 population as the denominator for the period 1980–1999. To compare the female-to-male ratios for urine and stool isolates, we used χ^2 tests; to compare median age, we used the two-sample Wilcoxon Rank-sum test. Pearson correlation coefficient was calculated to compare the ratio of urine to 1000 stool isolates with blood to 1000 stool isolates. All analysis was done using the SAS System for Windows (Release 8e; SAS Institute, Cary, NC, USA).

RESULTS

From 1980 to 1999, 17 422 urine isolates of *Salmonella* were reported to CDC, representing 2% of all *Salmonella* isolates from a known source. During the same period, blood isolates accounted for 5% and stool isolates accounted for 91% of all *Salmonella* isolates. Of the urine *Salmonella* isolates reported, information on serotype was reported for 96%, on sex for 95%, on age for 82%, and on race for 1%.

The annual number of urine isolates increased from 449 in 1980 to 1326 in 1999. Among *Salmonella* isolates from a known source, the proportion that was reported to come from urine, increased from 2% during 1980–1984 to 4% during 1995–1999. A similar increase was not seen in stool isolates reported during the same time (Fig. 1). Females of all ages had a higher incidence of *Salmonella* isolates from urine than did males (Fig. 2) but females aged $\geqslant$70 years had the highest annual incidence rate of 11 isolates per million persons. The highest incidence rate for males was in persons $\geqslant$70 years (4·5 isolates per million persons) and infants $<$1 year (4 isolates per million persons). The greatest difference in sex-specific rates of urine isolation for *Salmonella* occurred

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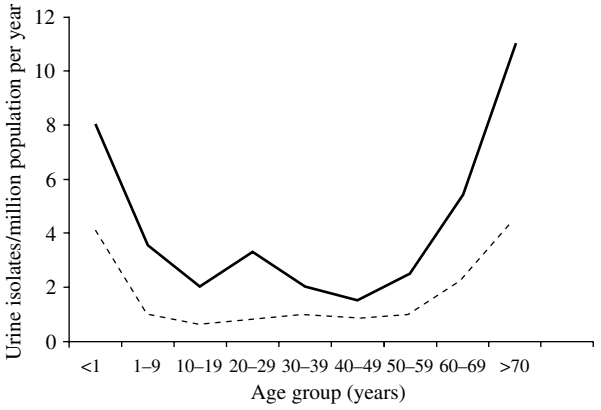

Fig. 2. Age-specific rates (per million population) of *Salmonella* isolation from urine, by sex, United States, 1980–1999. ——, Female; - - -, male.

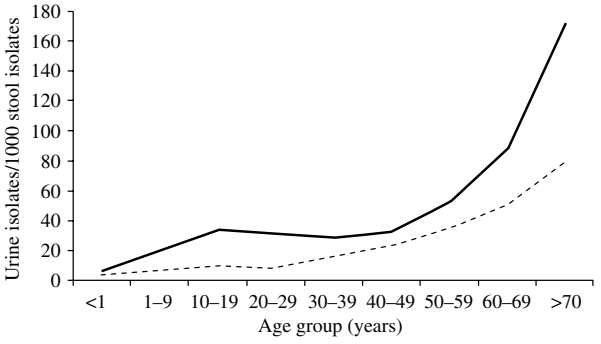

Fig. 3. Age- and sex-specific ratios of urine *Salmonella* isolates per 1000 stool isolates, United States, 1980–1999. ——, Female; - - -, male.

among those 70 years or older (11 isolates per million persons for females *vs.* 4·5 isolates per million for males).

The median age of persons from whom the urine isolates came was 51 years (range <1–106 years) and women were significantly older than men (median: 52 *vs.* 47 years; $P<0{\cdot}0001$). Of the reported urine isolates, 12176 (70%) were from females. The female-to-male ratio of urine *Salmonella* isolates was 2·8, compared to 1·0 for stool isolates and 0·76 for blood isolates. For both sexes, the ratio of urine isolates to stool isolates of *Salmonella* increased with increasing age, ranging from a ratio of 5 per 1000 isolates among persons <1 year old, to 138 per 1000 isolates among those ⩾70 years (Fig. 3). The greatest sex-specific disparity between the ratio of urine to stool isolates occurred for persons ⩾70 years. In this age group, females had a ratio of 172 urine per 1000 stool isolates, compared to males who had a ratio of 80 per 1000 stool isolates.

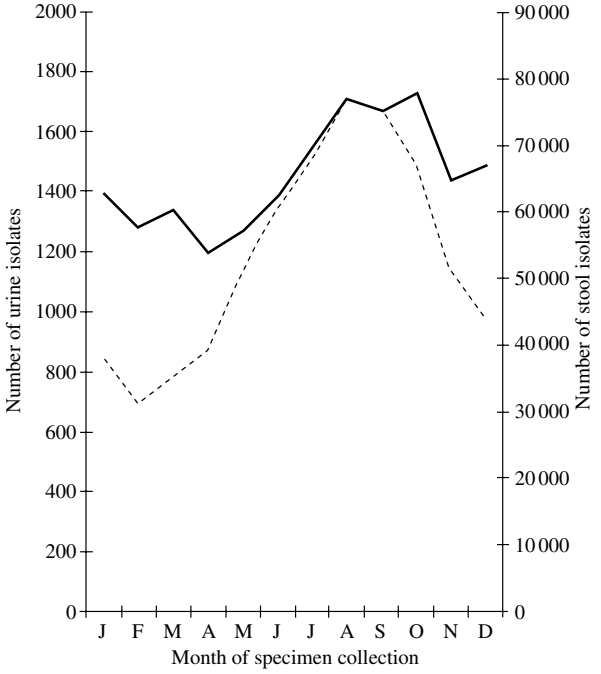

Fig. 4. Number of urine (——) and stool (- - -) *Salmonella* isolates reported, by month of specimen collection, United States, 1980–1999.

Seasonal variation in the frequency of *Salmonella* isolated from urine was more pronounced in females than males, with a peak occurring during the summer months. A similar seasonal pattern for women is seen in the frequency of *Salmonella* isolated from stool (Fig. 4).

There were 19 *Salmonella* serotypes that each accounted for at least 1% of all urine isolates (Table). The four most commonly reported *Salmonella* serotypes from urine were *S.* Typhimurium, *S.* Enteritidis, *S.* Heidelberg and *S.* Newport, which are also the most commonly reported serotypes from all specimen sources [4]. In the survey conducted between 1968 and 1979, the top four serotypes reported from urine were *S.* Typhimurium, *S.* Heidelberg, *S.* Enteritidis and *S.* Infantis. *S.* Typhi, which was reported in 5% of urine isolates in the earlier study, represented less than 1% of isolates in the present study, paralleling the decreased incidence of infection with *S.* Typhi in general [4].

Comparing serogroups of *Salmonella* accounting for at least 1% of isolates from urine and stool, the most common was group B, followed by groups C1 and D for urine isolates; the most common was group B, followed by groups D and C2 for stool isolates. Comparing ratios of urine-to-stool isolates by serotype, *S.* Tennessee, *S.* Senftenberg, *S.* Mbandaka,

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Table. *Ratios of urine and blood isolates to stool isolates for* Salmonella *serotypes responsible for ⩾1% of reported urine isolates in the United States, 1980–1999*

Serotype (group)	Number of urine isolates (%)	Number of stool isolates (%)	Number of blood isolates (%)	Ratio of urine to 1000 stool isolates	Ratio of blood to 1000 stool isolates
Typhimurium (B)	2498 (14)	179 790 (28)	5686 (16)	14	32
Enteritidis (D1)	2228 (13)	105 741 (17)	8219 (23)	21	78
Heidelberg (B)	1395 (8)	50 317 (8)	5006 (14)	28	99
Newport (C2)	798 (5)	36 422 (6)	527 (1)	22	14
Hadar (C2)	586 (3)	17 525 (3)	397 (1)	33	23
Montevideo (C1)	553 (3)	12 686 (2)	579 (2)	44	46
Infantis (C1)	535 (3)	15 045 (2)	300 (0·8)	36	20
Agona (B)	505 (3)	16 234 (3)	309 (0·8)	31	19
Oranienburg (C1)	402 (2)	8739 (1)	858 (2)	46	98
Thompson (C1)	354 (2)	10 022 (2)	242 (0·6)	35	24
Saintpaul (B)	325 (2)	9355 (2)	310 (0·8)	35	33
Muenchen (C2)	320 (2)	10 163 (2)	189 (0·5)	32	19
Javiana (D1)	292 (2)	10 262 (2)	272 (0·7)	29	27
Tennessee (C1)	232 (1)	1533 (0·2)	47 (0·1)	151	31
Senftenberg (E4)	213 (1)	2174 (0·3)	32 (0·08)	98	15
Braenderup (C1)	207 (1)	8000 (1)	146 (0·4)	26	18
Mbandaka (C1)	202 (1)	2738 (0·4)	85 (0·2)	74	31
Derby (B)	179 (1)	4557 (1)	153 (0·4)	39	34
Reading (B)	175 (1)	2802 (0·4)	180 (0·4)	63	64
All others	5625 (32)	132 879 (21)	12 841 (35)	44	97
Total	17 422 (100)	636 984 (100)	36 378 (100)	27	57

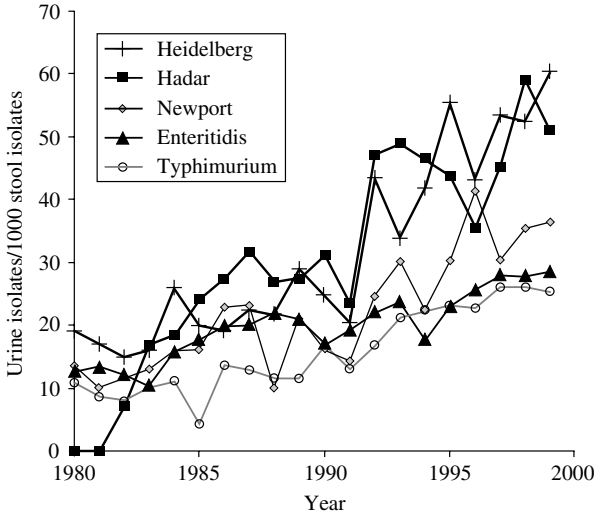

Fig. 5. Ratio of urine to 1000 stool *Salmonella* isolates, by year, for the five most common serotypes reported, United States, 1980–1999.

S. Reading, *S.* Oranienburg and *S.* Montevideo had the highest ratios, all with >50 urine isolates per 1000 stool isolates. All but *S.* Reading (group B) are serotypes in groups C1 or E. The urine-to-stool ratios of the five most common urine-associated serotypes (*S.* Typhimurium, *S.* Enteritidis, *S.* Heidelberg, *S.* Newport, and *S.* Hadar) increased during the 20-year study period (Fig. 5). We compared the ratios of urine-to-stool isolates with ratios of blood-to-stool isolates to determine if the serotypes which were commonly isolated from urine were also likely to be isolated from blood; we found no correlation, $r(19) = -0{\cdot}08$, $P = 0{\cdot}74$.

DISCUSSION

In the last two decades, national reporting of *Salmonella* isolates from urine has increased both in absolute incidence and as a proportion of all *Salmonella*. *Salmonella* isolated from urine increased from 2% of all *Salmonella* isolates during 1980–1984 to 4% during 1995–1999. Compared to the annual rate of *Salmonella* isolation from urine reported in the previous national survey (1968–1979), there has been increase among females from 2·0 per million women to 3·7 per million women and no significant change in males (from 1·0 to 1·3 per million persons). The age-adjusted rate of reported urine isolates in women has doubled since the 1970s while the rate in men has not changed significantly. In addition, the highest rate of urine isolation is now in elderly women, rather than in

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infants >1 year old, as it was in the previous study [3]. This shift may reflect increased susceptibility to UTIs in elderly women, increased virulence of uropathogenic organisms, or an increase in frequency of obtaining urine culture from elderly women compared to other age groups or from men. The observed increase in urinary *Salmonella* isolates might be explained if urine of women, particularly elderly women, are more likely to be cultured with methods that lead to faecal contamination. However, we are unaware of data suggesting a change in urine culture practice has occurred. During the 20-year study period the demographics of the United States population has changed, and may partially, but not entirely, explain some of the these trends. The proportion of persons aged ⩾65 years increased from 10·5% in 1980 to 12·4% in 2000 [8], while the proportion of persons >65 years who were female remained approximately 58%.

The age and gender distribution of reported urinary *Salmonella* isolates parallels the distribution of UTIs in general, most commonly due to organisms in the family Enterobacteriaceae [9]. For any given age, women are more likely to acquire UTIs than men, and a greater increase in UTI incidence occurs in women compared to men during reproductive years [9]. Previous studies have noted that chronic illness, immunosuppressive therapy, and structural abnormalities of the urinary tract play an important role in the pathogenesis of *Salmonella* UTIs [2, 10]. Presumed mechanisms by which the urinary tract is infected by *Salmonella* species is via an ascending route from the perineum or by haematogenous dissemination after ingestion of the organism. In this study, serotypes that had high urine-to-stool ratios were not those with high blood-to-stool ratios, suggesting that the serotypes found in urine are not arriving there via clinically significant bacteraemia. This finding is supported by a recent outbreak investigation of *S.* Havana infections in California in which a high proportion of isolates (6 out of 18; 33%) were from urine [11]. The median age of patients with *Salmonella* bacteriuria was 76 years, and three were aged ⩾80 years, this is consistent with findings in our study in which women aged ⩾70 years had the highest incidence of *Salmonella* isolated from urine. The six patients with *Salmonella* bacteriuria only reported symptoms of lower UTIs and five of those did not report significant diarrhoea. Another study involving in-patients and outpatients at private hospitals suggests that symptomatic cystitis may be a more common clinical presentation of *Salmonella* UTIs than previously thought [12]. Among the 23 patients with bacteriuria due to non-typhoidal *Salmonella* species, one had acute pyelonephritis and one had concomitant bacteraemia, while the remaining 22 had symptomatic cystitis. None had any immunosuppressive disorders and only 13% had structural abnormalities of the urinary tract [12]. These studies suggest that predisposing immunosuppression or genitourinary tract anomalies are not a prerequisite for *Salmonella* UTIs and that ascending infection rather than bacteraemia may be the more common route to establishing *Salmonella* UTIs.

We found that certain *Salmonella* serotypes had higher urine-to-stool ratios, particularly those in serogroups C1 or E. A previous national study found that three (50%) of the six serotypes with high urine-to-stool isolate ratios belonged to groups C1 or C2 [3]. Following an outbreak of *S.* Montevideo and *S.* Meleagridis infections in 1996 in which a high proportion of strains were isolated from urine, the California State Laboratory conducted a 5-year (1992–1996) retrospective review of data on approximately 23 000 isolates of *Salmonella* submitted to the laboratory for serotyping [13]. In this survey, urine isolates represented 3·4% of all reported *Salmonella* isolates and they noted that serogroups C1 and E were over-represented among urinary isolates, compared to their frequency of isolation from stool. A major outbreak of salmonellosis in California with more than 650 confirmed cases due to *S.* Montevideo (group C1) and *S.* Meleagridis (group E) probably contributed to this finding [13, 14].

The finding in the present study that *S.* Reading has a high urine-to-stool ratio but does not belong to groups C1 or E suggests that uropathogenesis may be independent of O-group characteristics, as is the case for uropathogenic *Escherichia coli* (UPEC). UPEC isolates typically belong to specific serotypes or lineages [15] and possess one or more of the four pathogenicity islands (large regions of DNA inserted into a bacterial genome, variably present, and implicated in virulence) that have been associated with urovirulence [16]. Five pathogenicity islands called *Salmonella* pathogenicity islands (SPIs), have been described for *Salmonella* [17]; however, the role, if any, of these SPIs in uropathogenesis has not been studied. Interestingly, one of the pathogenicity islands associated with *E. coli* urovirulence has recently been detected in *Salmonella* isolates belonging to subspecies IIIa, IIIb and VI, but not in subspecies I isolates [18]. Subspecies I isolates represent approximately 99% of all

human isolates [5]. Further investigation may clarify virulence traits of serotypes isolated from patients with documented *Salmonella* UTIs. Another explanation for the over-representation of certain serotypes isolated from urine compared to stool is that these serotypes may be less enteropathogenic and, therefore, may not be isolated from stool as frequently as other serotypes.

There are major limitations to these data. We could not differentiate between true UTI, asymptomatic colonization or contamination of urine with faeces during collection because we do not know whether isolates were recovered in pure culture. Therefore, we are limited to only describing trends in *Salmonella* bacteriuria rather than UTIs. In addition, clinical information on patients was not available, therefore, we could not assess the contribution of host susceptibilities to culturing *Salmonella* from urine.

In summary, we observed that *Salmonella* isolated from urine was more common in women than men, and the reported rates have doubled in women compared to rates reported before 1980, especially in the elderly [3]. Reasons for this increase are unclear. The most common serogroups isolated in urine have not changed dramatically since 1969. Some serotypes belonging to groups B, C1 and E, were more likely to be isolated from urine than stool, suggesting these serotypes to have a predilection for invading the urinary tract. Further investigation of the role of pathogenicity islands in *Salmonella* may help explain these observations.

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