

Original Report

Increasing incidence of non-typhi *Salmonella* bacteremia among children living in southern Israel

Pablo Yagupsky,⁽¹⁾ Nimrod Maimon,⁽¹⁾ and Ron Dagan⁽²⁾

Objectives: To determine if the epidemiology of *Salmonella* gastroenteritis and childhood bacteremia among the two ethnic populations (Jews and Bedouins) living in southern Israel has changed in recent years.

Methods: Retrospective review of laboratory records and medical charts of patients from whom non-typhi salmonellae were isolated from stool and blood cultures in the 1990–1995 period.

Results: The overall incidence of enteric *Salmonella* infections was 123.5 per 100 000 inhabitants and remained stable during the study period. The incidence of bacteremia among children younger than 4 years increased from 9.3 per 100 000 in the 1990–1992 period to 26.8 per 100 000 in the 1993–1995 period ($P < 0.01$). This increment was especially caused by *Salmonella virchow* and *S. enteritidis*, which were also isolated with increasing frequency from stool cultures. The Bedouin population was underrepresented among stool isolates, whereas its representation among blood isolates closely resembled the fraction of this ethnic group in the overall population of the area.

Conclusions: The incidence of enteric salmonellosis has remained stable at a high endemic level in recent years in southern Israel. The incidence of children's bacteremia has experienced a significant increase, associated with *S. virchow* and *S. enteritidis*. Differences in the utilization of medical services may explain differences in the epidemiology of *Salmonella* infections found in the two resident ethnic groups.

Key Words: bacteremia, enteric infections, epidemiology, non-typhi salmonellae

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INTRODUCTION

Despite continuous improvements in food hygiene practices, a steady increase in the incidence of gastroenteritis, bacteremia and other invasive infections caused by non-typhi members of the genus *Salmonella* has been observed since the 1970s in the USA and Europe.^{1–3} This paradox has been explained by a combination of multiple factors, including modern breeding technologies, mass food production, consumption of contaminated eggs, and the international raw food trade.^{1–5} Information on the extent and dynamics of the problem outside the Western world is scarce. A retrospective study was conducted in southern Israel to investigate possible changes in the epidemiology of enteric and extra-enteric infections caused by non-typhi salmonellae in recent years.

MATERIALS AND METHODS

Background

The Negev area, located in the southern part of Israel, is populated by two ethnic groups. The Jewish group

(population 303 000) enjoys Western living and economic standards, including sewage infrastructure and running water. The Bedouin group (population 85 000) lives in separate settlements or in semi-nomadic conditions in poverty and with overcrowding, with deficient sanitary installations, making it comparable to developing world populations.

Medical care is universally accessible and provided free of charge in 129 health clinics spread throughout the region, including Bedouin settlements and remote rural areas. Most diagnostic bacteriology services, which are identical and available in all the health clinics, are provided by a single large microbiology laboratory, located at the Soroka Medical Center, which is the only hospital in the region.

Bacteriological methods

Stool specimens were sent to the microbiology laboratory of the Soroka Medical Center fresh or in modified Stewart transport medium and seeded onto MacConkey agar and a selenite broth tube. After a 24 h incubation, the selenite broth was plated onto *Shigella*–*Salmonella* agar. Blood cultures, obtained from emergency room and hospitalized patients, were inoculated into BACTEC 660NR pediatric bottles and processed by the blood culture instrument according to the manufacturer's instructions (Becton & Dickinson Diagnostic Instrument Systems, Towson, Md, USA). Identification of salmonellae was based on typical biochemical tests, as

⁽¹⁾Clinical Microbiology Laboratory, ⁽²⁾Pediatric Infectious Disease Unit, Soroka Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

Address correspondence to: Dr. Pablo Yagupsky, Clinical Microbiology Laboratory, Soroka Medical Center, Beer-Sheva 84101, Israel. Tel: +972-76400507, Fax: +972-76403541, E-mail: yagupsky@bgumail.bgu.ac.il.

Corresponding Editorial Office: New York

recommended.⁶ Serogrouping was performed by agglutination with specific antisera (Wellcome Foundation, UK). In addition, *Salmonella* isolates were sent to the Central Salmonella Reference Laboratory in Jerusalem for subtyping.

Collection of data

The records of the microbiology laboratory for the 6-year period 1990–1995 were reviewed to identify stool and blood cultures from which non-typhi salmonellae were isolated. For the positive stool cultures, the following data were gathered from the laboratory logs: date of specimen submission, patient's name and ethnic background (Jewish or Bedouin), and serogroup and serotype to which the recovered *Salmonella* organism belonged. When more than one stool specimen was submitted from the same patient within a 1-month period, a single result was included in the study. Ages of the patients from whom stool cultures were obtained were inconsistently recorded, and so this information was not included in the data analysis. In addition, a medical chart of all pediatric patients with non-typhoid salmonellae bacteremia was reviewed, and relevant demographic, clinical and bacteriologic data, including subtyping results, were collected.

Statistical analysis

Attack rates of salmonellosis (per 100 000 persons) were computed using the average annual population for the relevant age group as the population at risk. Population figures were obtained from the bulletin of the Israel Central Bureau of Statistics. To examine whether changes have occurred in the course of the study, incidence rates were calculated separately for the 1990–1992 and 1993–1995 subperiods. Confidence limits for the rates were computed using the method described by Fleiss.⁷ To assess the relative virulence of the different *Salmonella* serotypes, the proportions of isolates of a given serotype isolated from cultures of stool or blood out of the total number of isolates of the same specimen type were calculated and compared, using the Chi-square test. The Chi-square goodness of fit test was used to assess the statistical significance of the seasonal distribution of isolates. A *P* value <0.05 was considered statistically significant.

RESULTS

During the 6-year period 1990–1995, 2796 of 93 937 (3.0%) stool cultures grew non-typhi salmonellae. The percentage of positive cultures ranged between 2.2% in 1995 to 4.4% in 1994. Four-hundred and twenty-eight (15.3%) of all positive cultures were obtained during the spring months (March–May), 937 (33.5%) during the summer (June–August), 984 (35.2%) in the fall (September–November), and 447 (16.0%) in the winter

(December–February) ($P < 0.001$). Overall, 2604 (93.1%) positive stool cultures were obtained from Jews, and only 192 (6.9%) from Bedouin patients.

The annual incidence of bacteriologically-proven enteric *Salmonella* infections for the period was 123.7 per 100 000 inhabitants, and ranged between 96.9 per 100 000 in 1995 and 155.7 per 100 000 in 1994. The annual incidences for the periods 1990–1992 and 1993–1995 were remarkably similar (Table 1).

The distribution of *Salmonella* serotypes among stool isolates showed significant changes over time (Table 2). Isolation of *S. agona* exhibited a significant increase during the second half of the surveillance period, caused by a large disease epidemic in 1994 which was traced to a popular snack contaminated with the organism.⁵ *S. virchow* and *S. enteritidis* also showed significant increases, whereas serotypes *bredeney*, *hadar*, *infantis* and DT 104 decreased during the same period.

During the same period, 61 children with non-typhi *Salmonella* bacteremia were diagnosed at the Soroka Medical Center, of whom 34 (55.7%) were males and 27 (44.3%) were females. Six (9.8%) children were diagnosed in the spring, 17 (27.9%) in the summer, 30 (49.2%) in the fall and 7 (11.5%) in the winter

Table 1. Annual incidence of *Salmonella* enteritis and bacteremia by study period and age group

	Incidence per 100 000 population		<i>P</i>
	1990–1992	1993–1995	
Enteric disease (children and adults)	123.5	123.9	NS
Bacteremia (children)			
0–4 years	9.3	26.8	<0.01
5–14 years	0.4	1.8	NS

NS, not significant.

Table 2. Percentage of the different *Salmonella* serotypes isolated from enteric infections by period

Sero- group	Serotype	Period		<i>P</i>
		1990–1992 <i>n</i> =1289 %	1993–1995 <i>n</i> =1507 %	
B	<i>agona</i>	2.5	16.4	<0.001
	<i>bredeney</i>	3.3	1.2	<0.001
	<i>typhimurium</i>	10.2	9.5	NS
	Others	6.1	3.0	<0.001
C	<i>blockley</i>	13.2	5.2	<0.001
	<i>hadar</i>	4.5	5.5	NS
	<i>infantis</i>	8.3	5.3	0.002
	<i>virchow</i>	11.0	21.2	<0.001
	Others	10.7	4.5	<0.001
D	DT 104	10.3	5.7	<0.001
	<i>enteritidis</i>	16.5	21.0	0.003
	Others	1.5	0.8	NS
Others		2.0	0.7	0.004
		100.0	100.0	

NS, not significant.

($P=0.009$). Forty-six (75.4%) bacteremic children were Jews, and 15 (24.6%) were of Bedouin ancestry. Forty-one (67.2%) children were younger than 12 months (all in the 2–12-month range), 11 (18.0%) were aged 13–24 months, 3 (4.9%) were aged 25–48 months, and 6 (9.8%) were older than 48 months. Fourteen (23.0%) children were diagnosed in the 1990–1992 period, and 47 (77.0%) between 1993 and 1995. The incidence of non-typhi *Salmonella* bacteremia in children-years during the 6-year surveillance was 7.5 per 100 000 population and showed marked age-related differences: 18.5 per 100 000 in children younger than 5 years, and 1.2 per 100 000 in the 5–14-year-old group. The incidence of bacteremia showed a significant increase over time, from 3.7 episodes per 100 000 children younger than 14 years in the 1990–1992 period, to 11.0 per 100 000 in the 1993–1995 period ($P<0.01$). This increment was especially marked for children younger than 4 years of age, among whom non-typhi salmonellae became the third most common cause of bacteremia after *Streptococcus pneumoniae* and *Staphylococcus aureus* (Table 1). This increase was observed in both ethnic population groups (data not shown).

Predisposing factors were noted in six (10.2%) children: primary immunodeficiency and chronic administration of steroids in two patients each, and burns and malnutrition in one child each. Clinical presentation included fever in all patients, but diarrhea was noted in only 32 of 53 (60.4%) children in whom the data were recorded. Twenty-six (42.6%) children were hospitalized, and 35 (57.4%) were managed as outpatients. Two children (3.4%) developed suppurative complications (septic arthritis and osteomyelitis), and one child who had severe combined immunodeficiency experienced recurrence of bacteremia caused by the same organism, 2 months later. No fatalities occurred.

Distribution of *Salmonella* serogroups among blood isolates was as follows: B was isolated in 9 of 61 (14.8%) bacteremic children, C in 30 (49.2%), and D in 22 (36.1%). Fifty-one of the 61 blood isolates were subtyped. *S. virchow* was found in 17 isolates, *S. enteritidis* in 12, and DT 104 in 8, of which 15, 11 and 5 were isolated during the second part of the study period, respectively.

Comparison of the distribution of *Salmonella* serotypes among stool and blood isolates showed significant differences. During the 6-year period, *S. virchow* was overrepresented among blood isolates ($P=0.003$), whereas *S. agona* was significantly more frequent among stool organisms ($P=0.032$).

DISCUSSION

The results of the present study show that non-typhi *Salmonella* infections constitute a common cause of gastroenteritis in southern Israel. With the exception of 1994, the incidence rate of the disease has remained stable over the years. The endemic level observed is

substantially higher than that recorded in the USA and western European countries, where 20–67 documented cases per 100 000 inhabitants have been diagnosed.^{1,2} It should be mentioned that, despite substantial improvement in the socio-economic conditions experienced by the Israeli population in recent decades, the incidence rates of other enteric infections such as shigellosis also remain much higher than those reported from other industrialized countries.⁸

Because the present study was not population-based with regard to stool cultures, the presented data on the incidence of enteric disease can only be considered a minimal estimate and may have been affected by several biases. Because of the low socio-economic and sanitary living standards prevalent among a large fraction of the Bedouin community, a much higher attack rate of enteric salmonellosis should have been expected in this group compared to the Jewish population. However, only a small number of stool isolates was derived from Bedouin patients. On the other hand, the percentage of Bedouin children among patients with *Salmonella* bacteremia closely resembled the fraction of children of this ethnic origin in the population of the area. It is speculated that the Bedouin population does not seek medical attention for uncomplicated enteric *Salmonella* infections, but attends health clinic services for more severe clinical disease. It is noticeable that a similar observation has been made regarding enteric *Shigella* infections, which show an apparent underrepresentation among the Bedouin population.⁹

The present results show that, although the incidence of enteric salmonellosis in southern Israel has remained stable in the last few years, that of bacteremia has been steadily increasing among the pediatric population of the area. This increase was especially noticeable in infants and toddlers, among whom non-typhi salmonellae currently represent one of the most common causes of pediatric bacteremia. It should be pointed out that none of the bacteremic infants was younger than 2 months of age. This finding substantially differs from the US experience, in which a peak rate in the youngest age group has been consistently found.^{3,10,11} As expected, the disease exhibited a clear seasonal pattern, and the majority of patients were diagnosed during the summer and fall months.¹¹ The clinical presentation was usually mild and consistent with that previously described in the medical literature.^{3,10,12} Affected children generally appeared only mildly ill, more than half were managed as outpatients, septic complications and recurrence were infrequent, and no fatalities occurred.

Different *Salmonella* serotypes were unequally represented among stool and blood isolates. *S. virchow* was significantly more frequent among blood organisms, whereas *S. agona* was underrepresented, suggesting that certain subspecies are more virulent than others. In previous studies, *S. heidelberg*, *S. choleraesuis*, *S. dublin* and *S. typhimurium* have been found to be associated with increased risk of invasive disease.^{1,2,11} Close

examination of the results demonstrates that the increased incidence of bacteremia observed in the late surveillance period was caused mainly by *S. virchow* and *S. enteritidis*, which showed a parallel increase in the isolation rate from stool cultures. Although the design of the study did not allow identification of the sources of human infection, it should be pointed out that these two serotypes, which were also the most common causes of *Salmonella* gastroenteritis and food poisoning country-wide, were the two most frequent serotypes isolated from poultry in Israel in recent years.¹³ Data gathered by the Central Salmonella Reference Laboratory show that *S. virchow* represented between 6.3% and 20.6% and *S. enteritidis* between 4.3% and 53.9% of all *Salmonella* serotypes from chicken sources in the 1991–1996 period. Moreover, the phage-type distribution of *S. enteritidis* isolates from patients with gastroenteritis and that of organisms isolated from chickens showed a remarkable similarity. Phage type B3 represented 44.1% of human isolates and 54.0% of chicken isolates, F3 was found in 24.8% and 9.4%, F1 in 16.3% and 8.8%, C8 in 10.1% and 7.4%, and C14 in 3.3% and 6.8%, respectively, suggesting that contaminated poultry may be an important source of human disease.

Enteric infections caused by non-typhi salmonellae continue to pose an important health threat to the population of southern Israel, and the risk of bacteremia among young children has increased in recent years. Identification of sources of human infection, education of the general public about basic food hygiene, and implementation of strict control measures in the food industry are necessary to limit the extent of this growing problem.

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