The changing panorama of bacterial enteric infections

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SUMMARY

We studied the age-specific population-based incidence of bacterial enteric infections caused by *Shigella, Salmonella* and *Campylobacter*, in Jerusalem. During 1990–2008, 32 408 cases were reported (incidence rate 232·1/100 000 per annum). The patterns of *Shigella* (47·4% of cases), *Salmonella* (34·4%) and *Campylobacter* (18·2%) infections evolved noticeably. *Campylobacter* rates increased from 15·0 to 110·8/100 000 per annum. *Salmonella* rates increased from 74·2 to 199·6/100 000 in 1995 then decreased to 39·4/100 000. *Shigella* showed an endemic/epidemic pattern ranging between 19·7 and 252·8/100 000. Most patients (75%) were aged <15 years; children aged <5 years comprised 56·4% of cases, despite accounting for only 12·9% of the population. *Campylobacter* was the predominant organism in infants aged <1 year and *Shigella* in the 1–4 years group. The hospitalization rates were: *Shigella*, 1·8%; *Campylobacter*, 2·3%; *Salmonella*, 6·9%. Infants were 2·2 times more likely to be hospitalized than children aged 1–14 years ($P = 0·001$). Household transmission occurred in 21·2% of *Shigella* cases compared with 5% in the other bacteria.

Key words: *Campylobacter*, children, enteric infections, *Salmonella*, *Shigella*.

INTRODUCTION

Acute diarrhoeal illness in early childhood is a major public health problem, responsible for a significant burden of morbidity and mortality. Three quarters of the estimated 3–4 billion annual cases in developing countries occur in children aged <5 years, with over 1·5 million deaths. This is despite improvements in hygiene and sanitary conditions, improved child nutrition and care, and progress in case management over recent decades [1–4]. Israel is considered a developed country, with Western public health standards and minimal mortality from infectious disease; nevertheless, the rate of enteric infection, paradoxically, is high [5, 6].

Incidence rates and aetiological agents of acute childhood diarrhoeal disease differ between developing and developed countries [7–10]. Rotaviruses are the leading cause of severe diarrhoea in children worldwide; with the increasing use of the novel rotavirus vaccines, bacterial pathogens will presumably play a more significant role in future [11]. The most common bacteria causing gastroenteritis in children in developed countries are *Shigella, Salmonella* and *Campylobacter* [8, 9, 12]. Many cases result from transmission in the household or in child-care facilities

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[13], and from outbreaks in deprived socioeconomic communities. No vaccines against these bacterial infections are commercially available, although various vaccine candidates are at present under development. Hence, preventive public health strategies should focus on the traditional approach of promoting appropriate personal and environmental hygiene measures [14].

The aim of our study was to investigate population-based, age-specific epidemiological trends of enteric bacterial infections of *Shigella*, *Salmonella* and *Campylobacter* in the Jerusalem district, with a special focus on disease patterns in young children aged <5 years.

METHODS

Infections caused by *Shigella*, *Salmonella* and *Campylobacter* are legally notifiable in Israel and apply both to physicians and microbiological laboratories [5]. The District Health Office communicable diseases database is compiled from these reports. Since *Escherichia coli* O157:H7 is rarely reported (<1 case/year), and *Yersinia enterocolitica* is not notifiable, these two infections were not included in the study. Data on all reported cases of these three enteric bacterial infections in Jerusalem district from 1990 to 2008 were collected, including epidemiological investigations, hospital files and laboratory reports. The variables recorded were: age, gender and ethnicity, date of disease onset, hospitalization, bacteria isolation, serogrouping and biotyping. Isolates of bacteria were sent to the national public health laboratories for determination of serogroup or biotype. Serogrouping was performed according to standard laboratory methods [15, 16].

Cases were classified according to the standard definitions, i.e. a confirmed case was a clinical case of diarrhoea with the isolation of *Shigella*/*Salmonella*/*Campylobacter* from stool [17]. We defined household transmission of disease as the occurrence of more than a single case of the same enteric pathogen in a given household within a period of 14 days.

District population and incidence rates

The district population data are provided annually by the National Population Register of the Ministry of Interior Affairs in Israel. From 1990 to 2008, Jerusalem's population increased from 578 400 to 879 700. The population is comprised essentially of two ethnic groups: Jews (70·1 %) and Arabs (29·9 %). Children aged <15 years comprised 35 %, children aged <5 years 12·9 %, and infants <1 year 2·7 % of the district's population [18]. The annual incidence rates in Jerusalem district were compared to the national rates provided by the Ministry of Health [5, 6].

Statistical analysis

The demographic, laboratory and clinical data were analysed using SPSS software [19]. Incidence rates per 100 000 population and seasonal trends were analysed with WINPEPI software [20]. Rates of the different bacteria were compared using Tukey's analysis for multiple pairwise comparisons. The Kruskal–Wallis test was used to compare medians. The rate ratio (RR), odds ratio (OR) and 95 % confidence intervals (CI) are reported. Variability in seasonality was evaluated by the Ratchet circular scan test for a 3-month peak. Continuous variables were compared by Student's t test; dichotomous variables were analysed by Pearson's χ^2 test. A P value $\leqslant 0.05$ was considered significant for all comparisons.

RESULTS

Between 1990 and 2008, 32 408 cases of enteric bacterial infection were reported in the Jerusalem district; 15 374 were *Shigella* infections (47·4 %), 11 143 *Salmonella* infections (34·4 %) and 5891 *Campylobacter* infections (18·2 %). The overall average annual incidence of enteric infection was 232·1/100 000, which was higher than the national average of 169·9/100 000 (RR 1·38, 95 % CI 1·31–1·45, $P = 0.0001$). The difference in enteric infection rates between Jerusalem and the rest of the country, which amounted to 62·2/100 000, was attributable entirely to *Shigella* (61 % of the difference) and *Salmonella* (39 %) infections; there was no difference in *Campylobacter* infection rates. Disease patterns in Jerusalem changed considerably over the years 1990–2008, with annual overall incidence rates ranging from 111·4 to 412·9/100 000 (Fig. 1). The incidence of *Campylobacter* infection increased steadily from 15 to 110·8/100 000 (RR 7·36, 95 % CI 5·92–9·18, $P = 0.0001$). The *Salmonella* incidence rate per 100 000 in 1990 was 74·2, which then rose threefold, peaking in 1995 at 199·6; following this it fell gradually to 39·4 in 2008 (RR 0·53, 95 % CI 0·46–0·61, $P = 0.0001$). In contrast, *Shigella* infections presented a sinusoidal pattern, with alternating
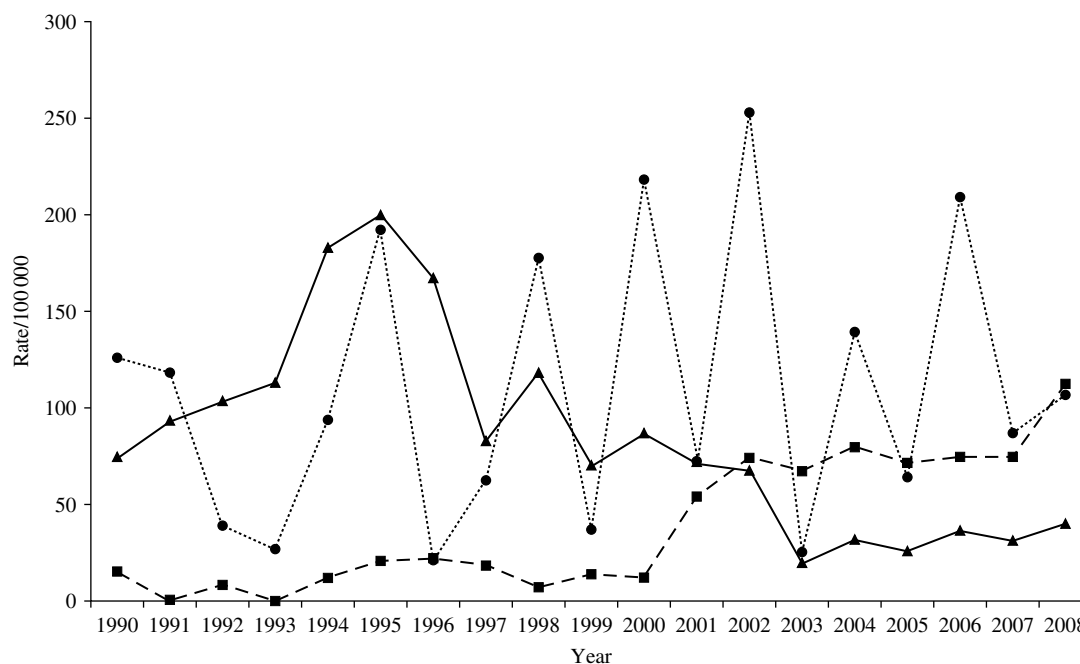
Fig. 1. Annual reported incidence rates (per 100 000) of infection with bacterial enteric pathogens [*Shigella* (··· ● ···), *Salmonella* (—▲—), *Campylobacter* (- - ■ - -)] in the Jerusalem district, Israel, 1990–2008.

endemic and epidemic years varying from 19·7/100 000 in 1996 to a peak of 252·8 in 2002 (2002 *vs.* 1996; RR 12·8, 95% CI 10·8–15·3, $P = 0·0001$).

The seasonality of the three pathogens varied considerably. While *Shigella* infections prevailed in late winter (February–April, 38·7% of cases, $P < 0·005$); *Campylobacter* prevailed in spring (May–July, 29·8% of cases, $P < 0·005$), and *Salmonella* in summer (June–August, 35·7% of cases, $P < 0·005$).

Most infections occurred in children: 75% were aged <15 years, 56·4% <5 years and 7·1% were infants aged <1 year. The overall average age was $12·3 \pm 17·3$ with median age of 4 years. Children <5 years had a markedly higher overall incidence (930·6 *vs.* 107·2; RR 8·7, 95% CI 7·9–9·5, $P = 0·0001$), as well as higher pathogen-specific incidence rates (RR 13·7 for *Shigella*, 8·3 for *Salmonella* and 4·6 for *Campylobacter*, all $P = 0·0001$) compared to persons aged ⩾5 years (Fig. 2). Peak incidences for all three pathogens were observed in the second year of life, with an overall rate of 1272·2/100 000.

The age distribution differed considerably between the three pathogens (Fig. 2), with *Shigella* being the predominant pathogen for those aged 1–14 years (62·2%) and *Campylobacter* the predominant pathogen in those aged <1 year (51·4%) and >15 years (55·3%). *Shigella* predominated in the 1–4 years age group (65·7%) followed by *Campylobacter* (22·4%)
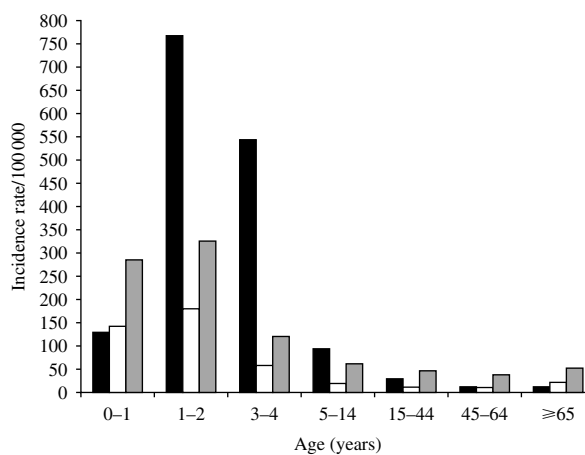

Fig 2. Age-specific reported incidence rates (per 100 000) of infection with bacterial enteric pathogens [*Shigella* (■), *Salmonella* (□), *Campylobacter* (▨)] in the Jerusalem district, Israel, 1990–2007.

and *Salmonella* (1·9%). In infants aged <1 year *Campylobacter* (51·4%) was the most common, followed by *Salmonella* (25·4%) and *Shigella* (23·2%). In infants aged <6 months *Campylobacter* predominated (58·4% of cases). However, the median age of *Campylobacter* cases (9·1 years) was significantly higher than the median ages of *Salmonella* and *Shigella* cases which were 3·7 and 3·5 years, respectively ($P = 0·0001$).

On the whole, bacterial enteric infections were more common in males: 53·4%, compared to 49·9% of males in the Jerusalem population (RR 1·07, 95% CI 1·05–1·09, $P = 0·0001$). This was particularly evident with regard to *Campylobacter* (57·3%), less so for *Salmonella* (54·1%) and least for *Shigella* (50·4%). Infants aged <1 year had a higher male/female ratio than persons aged ⩾1 year (1·4:1 *vs.* 1·1:1; OR 1·2, 95% CI 1·03–1·5, $P = 0·02$).

Overall, 11·7% ($n = 3540$) of the cases were Arab, which was significantly lower than expected based on their proportion in the district's population (29·9%) (OR 3·2, 95% CI 2·5–4·1, $P = 0·0001$). The proportion of Arab cases was also significantly lower than expected for each of the three pathogens: 17·7% of *Salmonella* cases, 18·8% of *Campylobacter* cases, and 4·5% of *Shigella* cases ($P < 0·0001$ for all the above comparisons). However, when evaluated by age, 33·2% of infant cases aged <1 year were Arab, against 10% of children aged 1–14 years (OR 4·4, 95% CI 3·6–5·5, $P = 0·0001$).

Hospitalization

The proportions hospitalized differed considerably between pathogens: 1·8% for *Shigella*, 2·3% for *Campylobacter*, and 6·9% for *Salmonella* cases ($P = 0·001$). The average age of hospitalized patients was 15·7 ± 21·8 years, and the median age 4·8 years. The overall proportion hospitalized decreased with age: <1 year (4·6%), 1–4 years (2·1%) and 5–14 years (2·3%). Infants aged <1 year were more likely to be hospitalized than children aged 1–14 years (OR 2·2, 95% CI 1·4–3·6, $P = 0·001$). Additionally, infants aged <3 months had an increased rate compared to those aged 3–12 months (12·2% *vs.* 3·9%; OR 3·4, 95% CI 1·03–10·4, $P = 0·016$). The most common indications for hospitalization of children were dehydration and electrolyte disturbances.

Household transmission

The proportion of secondary infections in the households also differed noticeably. A higher proportion of secondary cases was observed among *Shigella* cases, 21·2% against 5·45% and 5·04% for *Salmonella* and *Campylobacter*, respectively ($P < 0·001$).

Laboratory results

Most *Shigella* isolates were S. *sonnei* (95·3%); the rest were S. *flexneri* (3·7%), S. *boydei* and others (1%). S. *flexneri* was more prevalent in Arab (9%) compared to Jewish (3·4%) patients (RR 2·6, 95% CI 1·6–4·3, $P = 0·0001$). S. Enteritidis (19·9%), S. Typhimurium (11·5%), S. Virchow (11·2%) and S. Hadar (7·4%) were the commonest serotypes isolated. The hospitalization rate in S. Typhimurium cases (44·1%) was higher than any other *Salmonella* serotype (average 2·4%) (OR 32·1, 95% CI 20·7–50·2, $P = 0·0001$). Most *Campylobacter* isolates were classified as C. *jejuni* (97%).

DISCUSSION

Acute diarrhoeal disease is a leading cause of death in children aged <5 years worldwide, second only to respiratory tract infections. The global burden of acute bacterial diarrhoea is estimated at millions of children with devastating human and economic consequences [1–4, 21, 22].

We demonstrated a substantial burden of acute bacterial enteric infections in young children in Jerusalem. Children aged <1, <5 and <15 years constituted 2·7%, 12·9% and 35% of the district's population, respectively, yet they were overrepresented by contributing 7·1%, 56·4% and 75% of the cases. Children aged <5 years had a significantly higher probability of infection with *Shigella* (RR 13·7), *Salmonella* (RR 8·3) and *Campylobacter* (RR 4·6) compared to persons aged >5 years. This distribution of enteric pathogens is rather different from that in developed countries, which generally report the highest incidence rates for *Campylobacter*, followed by *Salmonella* and *Shigella* infection, respectively [9, 23, 24].

For children aged 1–4 years, *Shigella* (mainly S. *sonnei*) was the leading pathogen, accounting for 68% of bacterial enteric infections, followed by *Campylobacter* (21%) and *Salmonella* (11%). In infants, *Campylobacter* was the leading pathogen, accounting for half the cases. *Shigella* and *Salmonella* each accounted for around a quarter of the cases. *Campylobacter* was particularly predominant in infants aged <6 months, accounting for about two thirds of cases.

Bacterial enteric infections were more prevalent in males. This applied particularly to *Campylobacter* infections, to a lesser extent in *Salmonella* and negligibly in *Shigella*. The male predominance in *Campylobacter* infection in young children in the USA has been reported previously [9], and has recently been shown in a UK population to extend from birth to the

late teens [25]. The reason for this tendency is not clear.

The Jerusalem district population consists mainly of two ethnic groups – Jews and Arabs. The ethnicity distribution differed between pathogens and with the patient's age, with a higher percentage of Arab patients among infants aged <1 year. These findings may be attributed to differences in provision and utilization of health services and to the under-diagnosis and under-reporting of cases in the Arab population, requiring further surveillance and evaluation in addition to interventional programmes. The higher proportion of *S. flexneri* in Arab patients may reflect socioeconomic differences. It has been reported that *S. sonnei* predominates in developed countries while *S. flexneri* and *S. dysenteriae* prevail in developing countries [26]. Evidence of previous exposure to *Shigella* infection was significantly higher in adolescents from a low socioeconomic background than a higher one in Israel [27].

There was notable variability with regard to seasonality of the pathogens. *Shigella* infections peaked in late winter, *Campylobacter* in spring and *Salmonella* in summer. The summer and early autumn seasonality of *Salmonella* and other enteric infections has been reported previously [9]. *Campylobacter* enteritis has a variable seasonality in developed and developing countries [28]: in developed countries with a temperate climate it has been demonstrated that *Campylobacter* infections generally peak in spring [29].

Overall, during the study period *Shigella* was the leading enteric bacterial pathogen, especially in the <5 years age group. *Shigella* infections were characterized by a see-saw pattern, alternating between endemic and epidemic years (Fig. 1). In endemic years, most cases were sporadic, whereas in epidemic years outbreaks occurred in young children, largely in childcare facilities. Periodic *Shigella* outbreaks have been reported in Israel, with a predominance of *S. sonnei* and a characteristic peak in wintertime [5, 6]. Outbreaks such as these, arising in distinct communities such as ultra-orthodox Jewish communities in the USA or in public settings (e.g. child day-care facilities), have also been described elsewhere [14, 30–32]. The apparent biennial–triennial pattern of *S. sonnei* outbreaks suggest that a pool of susceptibles must accumulate before an outbreak occurs. The peak incidence rates were observed in children aged 1–4 years, especially in those in their second year of life which is the regular age of entry to day-care centres in Israel. Infection before age 6 months was rare,

possibly indicating passively acquired immunity. The higher incidence in young children has been attributed to poor hygiene practices in addition to the low infectious dose for *Shigella* [1, 8, 9, 23]. Indeed, household secondary infection was four times higher with *Shigella* infections than with *Salmonella* or *Campylobacter*.

The incidence of *Salmonella* infection increased in the early 1990s and then declined after 2000. The epidemiology of salmonellosis in Israel resembles the global trends, and after three decades of rising, the incidence began to decline [33]. The recent decrease may be a result of improved food safety practices. However, the decline may be temporary, as changes in the incidence of *Salmonella* infections tend to evolve rapidly [33–35]. *Salmonella* incidence (particularly *S.* Typhimurium) has decreased over the last decade in the USA [24], and of all salmonellosis in the European Union by an average of 27% from the peak year of 1997 to 2001, and watchful surveillance is essential [34]. We found a significantly higher rate of hospitalization in *Salmonella* patients, especially those with *S.* Typhimurium, probably due to the severity of clinical symptoms. The rising rates of antimicrobial resistance worldwide are of major concern in non-typhoid *Salmonella* [33].

Campylobacter enteritis rates increased steadily from 1990 in Jerusalem, stabilized for several years, and then rose significantly, so that by 2008 it became the leading cause of diagnosed bacterial enteric infection. *Campylobacter* infects all age groups; in developing countries early childhood infection is common, reflecting exposure to contaminated water, food or direct animal contact with farm animals [26]. *Campylobacter jejuni* is the leading known bacterial cause of diarrhoea in developed countries such as Canada [36] and the USA [24] and is the second commonest known cause of travellers' diarrhoea after *E. coli*.

The communicable diseases surveillance system of the Jerusalem District Health Office enabled us to assess temporal trends of specific pathogens and to characterize cases according to demographic variables. However, the number of reported cases is probably an underestimate because of asymptomatic infections, under-diagnosis and under-reporting, mainly of mild disease cases. The gap between reported and expected cases among the Arab population supports this conjecture. The actual disease incidence is probably several times higher. The estimated ratio of reported to actual cases of bacterial

enteric infection has been studied in several community settings. They reportedly can range from 1:8 (for *Salmonella* and *Campylobacter*) in a UK survey of GP reporting practices [37] to as much as 1:50 in Canada [38]. The bacterial enteric infection rate in the Jerusalem district was 36% higher than the national average [5] and about six times higher than that reported in the USA [24, 39]. The difference between sub-populations had been described previously [27] and requires additional evaluation.

Israel's public health achievements rank with those of other developed countries, yet the burden of enteric disease, particularly in children, is more reminiscent of less advanced societies. The explanation probably lies largely in Israel's socioeconomic structure. A very high percentage of women are in the workforce, and maternity leave following birth is only 12 weeks. Consequently, children are placed in various child-care facilities from a young age – a situation that is known to be conducive to transmission of communicable diseases, particularly respiratory and enteric. This population-based study verified a high disease burden, particularly in young children. In the absence of a reliable vaccine, prevention depends primarily on appropriate personal and environmental hygiene measures taken by children and their caretakers.

The increasing use of effective rotavirus vaccines may induce a shift in the aetiology of childhood diarrhoea towards enteric bacteria, hence it seems prudent to collect surveillance-based data on bacterial pathogens. Our study indeed revealed significant changes in the patterns of bacterial enteric disease, which are important in our understanding of these diseases.

DECLARATION OF INTEREST

None.

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