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Geographical variations in *Salmonella* incidence in Israel 1997–2006: the effect of rural residency

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SUMMARY

The overall incidence and serotype distribution of non-typhoid *Salmonella* (NTS) may vary between different geographical localities. To investigate possible regional differences and the effect of demographic factors, we studied 15 865 episodes of laboratory-confirmed NTS infection in Israel. Using Poisson models we found significant variation in the average annual incidence rate of NTS in 15 administrative sub-districts, which was inversely associated with the percent of rural residency (incidence rate ratio 0·75, 95% confidence interval 0·65–0·86, $P<0·001$). Variation was also found in the relative incidence of the most prominent serotypes (Enteritidis, Virchow, Typhimurium, Hadar, Infantis), which was affected by rural residency, the percent of non-Jewish population in the sub-district, and the percent of population aged $\geqslant 55$ years in the sub-district. Rural residency had a major effect on the epidemiology of salmonellosis in Israel. Future research is required to understand whether decreased incidence in rural areas is an under-detection bias or reflects true differences in NTS illnesses.

Key words: Epidemiology, geographical information systems, *Salmonella*.

INTRODUCTION

Non-typhoid *Salmonella* (NTS) is a leading cause of foodborne infections worldwide and a major challenge to healthcare authorities [1–3]. In the USA, NTS is a major contributor to hospitalization and death due to foodborne infections [1, 4]. Increasing resistance to antibiotics, including quinolones and β-lactams, is another important global concern [5, 6]. In most patients, NTS infection presents as a self-limited gastroenteritis, lasting 3–7 days. In 5–8% of patients, however, the infection may become invasive and extend beyond the gastrointestinal tract [7, 8]. Overall mortality rates in developed countries are less than 1% [4, 9], but are higher in the African continent [10]. Mortality has been associated with invasive disease, patient's age, state of immune suppression, the infecting serotype, and geographical location [1, 7, 9].

The sources of NTS infection are mostly food-borne, mainly from food of animal origin, including poultry and eggs, beef, and dairy products [7].

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Roughly 10% of illnesses are the result of direct animal contact, including reptiles, amphibian pets and farm animals [6, 11, 12]. Fresh produce, as well as microwavable ready-to-eat foods, are increasingly recognized as the cause of large-scale outbreaks and raise issues regarding the safety of our food chain [13–16]. World Health Organization reports have revealed significant variations in the incidence and serotype distribution between countries and geographical localities [17]. Similarly, geographical information system (GIS)-based maps have been used to demonstrate considerable diversity in the overall incidence and serotype distribution in European countries [18]. Several studies showed differences in the spatial distribution of NTS infection within even smaller geographical localities such as states or counties [19–22]. However, there is still little understanding as to the source of such differences. Identifying demographic risk factors may be a useful tool in controlling the *Salmonella* epidemic, both locally and globally.

The burden of NTS infection in Israel is substantial. Despite a trend of declining incidence over the last two decades, rates are still high compared to those reported in the USA and many European countries [3, 23–25]. NTS infection in Israel is associated with a 0·6% 30-day mortality rate and curtailed long-term survival [26].

In order to identify environmental factors that may influence the burden of NTS infection in Israel, we investigated regional variations in the incidence and species distribution of NTS infections and their association with geographical and demographic characteristics.

METHODS

Data collection

Salmonellosis is a reportable disease in Israel. All microbiology laboratories countrywide passively submit human *Salmonella* isolates from all sources to the Ministry of Health's *Salmonella* Reference Laboratory at the Government Central Laboratories in Jerusalem, where final serological identification is performed according to the Kauffmann–White scheme [27]. Data on episodes of NTS infection for 1997–2006 were retrieved from the Government Central Laboratories' records and included date and source of NTS isolation and results of serotype identification.

During the study period, 180 different NTS serotypes from human sources were received and identified in the *Salmonella* Reference Laboratory. Five serotypes, Enteritidis, Typhimurium, Virchow, Hadar and Infantis, were responsible for 69% of infection episodes [26]. These top five serotypes are the focus of our study.

Patients' identification data were matched, by special permission, with the Ministry of Interior's registry to obtain demographic data including age, sex and home address as described previously [26]. For each patient, isolates of the same serotype from the same year were counted only once. Street addresses were geo-coded onto GIS maps. ArcGIS software version 10 (Environmental Systems Research Institute, USA) was used together with geomaps of Israel (MAPA, Israel). Israel is divided into six administrative districts and 15 sub-districts. Geomaps of the sub-districts were used to present the incidence rates in a visual manner.

Demographic characteristics of the sub-districts, including population size and nationality, age distribution, population density and rural/urban characteristics of the settlements were obtained from the Israeli Central Bureau of Statistics (http://www1.cbs.gov.il/reader/shnatonenew_site.htm).

Statistical methods

The average annual incidence rate of the total top five NTS serotypes in each sub-district, as well as the average annual incidence rate of the different serotypes were calculated for each year of the study period (1997–2006). Sensitivity analysis of the incidence rate pattern for the 15 sub-districts for two 5-year periods, 1997–2001 and 2002–2006, yielded the same pattern as that found for the overall 10-year study period.

A univariate Poisson model was used to compare the average annual incidence rate of the five top NTS serotypes and of Enteritidis alone (dependent variable) between the various sub-districts (independent variables). The sub-district with the highest population density (Tel Aviv) was used as reference.

A multivariate Poisson model was used to compare the frequency of the different NTS serotypes in each sub-district, across all sub-districts. The dependent variable was the average annual incidence rate of NTS serotypes and the independent variables were the sub-district and the interaction between *Salmonella* serotypes and the sub-district. Enteritidis, the most frequent serotype, was used as reference.

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Univariate and multivariate Poisson models were used to study the association between the average annual incidence rate of *Salmonella* (dependent variable) and the following demographic characteristics of the sub-districts (independent variables): percent of rural residency, percent of non-Jewish population, and percentages of specific age groups.

A multivariate Poisson model was used to study the effects of the demographic characteristics on the incidence rate ratio (IRR) of the non-Enteritidis NTS serotypes (four serotypes) *vs*. the Enteritidis serotype. Thus, for each Enteritidis–non-Enteritis serotype pair, a model was built in which the incidence rate was the dependent variable and the independent variables were as follows: an indicator for the serotype (e.g., 1 = Typhimurium, 0 = Enteritidis); the interaction between the serotype and the demographic characteristic (e.g. serotype × percent of rural residency), and a categorical variable for the sub-district.

According to the model, the IRR of a non-Enteritidis *vs*. Entertains pair estimated using the coefficient of the serotype indicator might depend on the demographic characteristic (estimated using the coefficient of the interaction, e.g. serotype × percent of rural residency).

Each effect was expressed as an IRR and 95% confidence interval (CI) and the models were adjusted for over-dispersion. Analyses were performed using SAS software version 9.2 (SAS Institute Inc., USA).

Ethical considerations

The study was approved by the local ethics committee at Assaf Harofeh Medical Center and measures were taken to maintain patients' confidentiality.

RESULTS

The study included a total of 15 865 patients with verified demographic data of which 9479 (59·75%) were aged <5 years, and 1733 (10·92%) were aged ⩾55 years. The average annual incidence rates of the total top five NTS serotypes and of the individual serotypes differed among the 15 sub-districts (Fig. 1, Table 1). The highest incidence rate for the total top five NTS serotypes was found in the Petah Tiqwa sub-district of the Central district (35·67/100 000 population) and the lowest was in the Kinneret sub-district of the Northern district (7·96/100 000 population). Compared with the Tel Aviv sub-district, the IRR of the total top five NTS serotypes was significantly higher in two sub-districts (Petah Tiqwa, Jerusalem) and significantly lower in five sub-districts (Kinneret, Golan, Zefat, Yizre'el, Hadera) located in the northern part of Israel (Fig. 2). A similar pattern was found for the incidence of the Enteritidis serotype, the most prevalent among the top five NTS serotypes, when examined alone (Fig. 2).

Indeed, Enteritidis was the most common NTS serotype in all 15 sub-districts, followed by serotypes Virchow, Typhimurium, Hadar and Infantis (Table 1). This order was maintained in 11 of the 15 sub-districts, while in three sub-districts (Hadera, Golan, Be'er Sheva) Typhimurium ranked second and Virchow ranked third. In one sub-district (Kinneret) Typhimurium ranked first, Virchow ranked second and Enteritidis ranked third (Table 1). When the frequencies of the non-Enteritidis serotypes were compared to that of Enteritidis, the incidence rates of all four non-Enteritidis serotypes were significantly lower than the incidence rate for Enteritidis in nine sub-districts (Fig. 3). In the remaining sub-districts (Golan, Zefat, Kinneret, Yizre'el, Akko, Hadera), all located in the northern part of Israel, the pattern was less uniform. In these sub-districts the incidence rate of Virchow, Typhimurium and Hadar did not usually differ significantly from that of Enteritidis. Serotype Infantis had a significantly lower incidence rate in five of the six sub-districts.

Demographic characteristics differed considerably among the 15 sub-districts of Israel (Table 1). Ranges for population density and percent of rural residency were 30·7–6788·0/km^2 and 0·4–37·5%, respectively; the range for the non-Jewish population was 0·2–62·7%; and the ranges for age groups <5 years and ⩾55 years were 6·7–13·0% and 18·2–35·9%, respectively.

A high negative correlation was found between the percent of rural residency and population density (Pearson's $r = -0{\cdot}89$, $P < 0{\cdot}0001$, log-linear relationship) and so in further analyses we refer only to the percent of rural residency.

The associations between the above-mentioned demographic characteristics of the sub-districts and the average annual incidence rates of the top five NTS serotypes was initially evaluated using a univariate Poisson model. We found a significant inverse association with the percent of rural residency (crude IRR 0·75, 95% CI 0·65–0·86, $P < 0{\cdot}001$) and a non-significant association with the other demographic characteristics. Since we found medium to high

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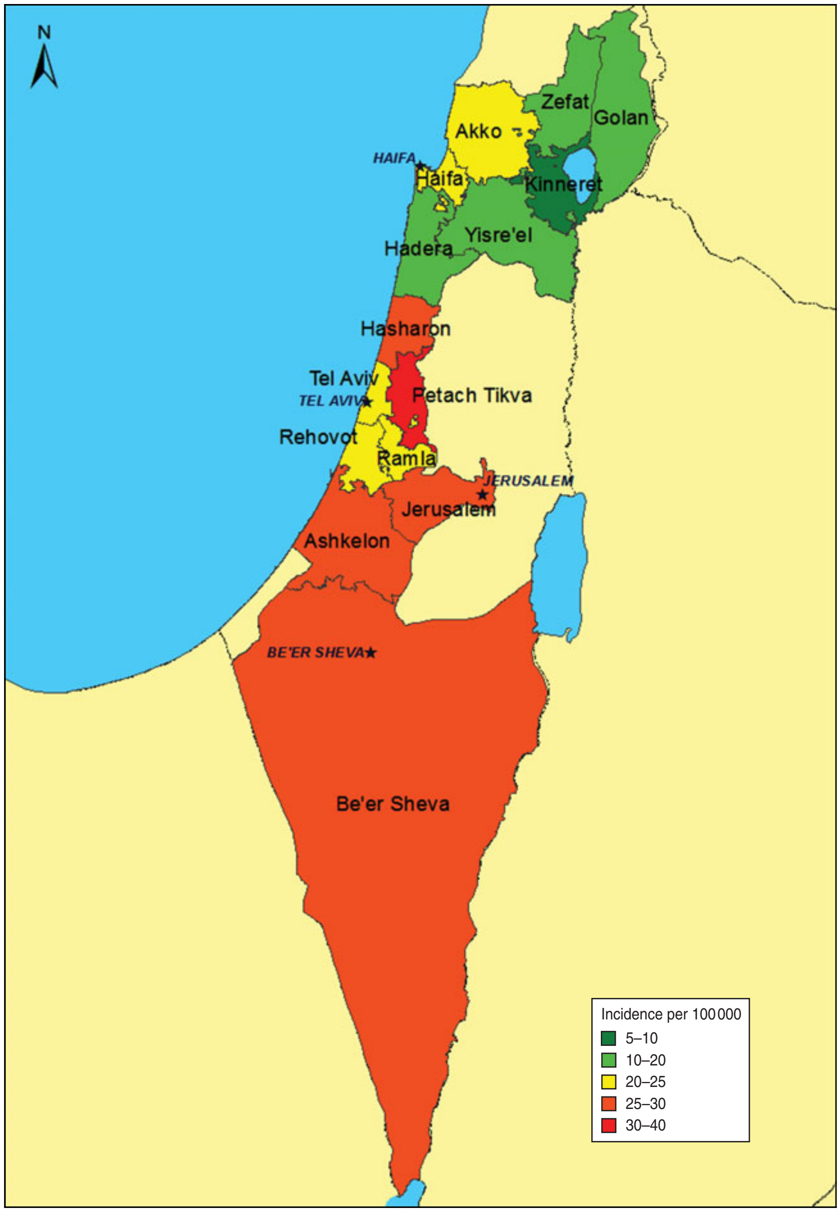

Fig. 1. Average annual incidence (per 100 000 population) of the total top five *Salmonella* serotypes in 15 sub-districts, Israel 1997–2006.

bivariate correlations between the demographic characteristics in the sub-districts, we were unable to build multivariate models that included all characteristics simultaneously as independent variables.

Table 2 presents results of the Poisson models for the dependence of the relative incidence rate of each non-Enteritidis serotype compared with Enteritidis on the demographic characteristics of each of the sub-districts.

The relative incidence rates of serotypes Typhimurium and Infantis compared to Enteritidis were significantly dependent on rural residency ($P=0{\cdot}001$ and $P=0{\cdot}052$, respectively) while that of serotype Hadar was borderline significantly dependent ($P=0{\cdot}131$). The relative incidence rates of serotypes Typhimurium, Hadar and Infantis were significantly dependent on the percent of non-Jewish population ($P=0{\cdot}006$, $P=0{\cdot}036$, $P=0{\cdot}044$, respectively) in a positive way and significantly dependent on the proportion of population aged $\geqslant 55$ years ($P=0{\cdot}016$, $P=0{\cdot}217$, $P=0{\cdot}210$, respectively) in a negative way. The relative incidence rate of serotype Virchow did not depend significantly on any of the demographic characteristics of the sub-districts.

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Table 1. *NTS incidence and demographic characterization of 15 sub-districts, Israel 1997–2006*

District/sub-district	Average annual incidence/100 000						Demographic characteristics*				
	Ent	Vir	Typ	Had	Inf	Top5	Pop den/km²	% Rural settle	% Non-Jew	% Age ⩽5 yr	% Age ⩾55 yr
Northern district											
Golan SD	3·38	1·13	3·1	2·25	0·56	10·43	30·66	37·45	54·91	10·87	18·18
Zefat SD	3·59	2·28	2·17	1·63	1·2	10·87	138·75	29·65	10·03	10·47	26·14
Kinneret SD	1·72	1·83	2·58	1·08	0·75	7·96	176·14	26·96	30·3	10·08	23·62
Yizre'el SD	6·13	5·06	4·13	2·86	1·42	19·6	334·52	15·58	51·4	11·67	22·43
Akko SD	6·08	5·73	4·7	3·97	1·92	22·4	519·96	8·66	62·65	11·87	20·85
Haifa district											
Hadera SD	5·6	4·43	4·73	3·76	1·17	19·69	528·18	8·29	43·13	11·95	22·67
Haifa SD	8·94	5·59	3·79	3·45	1·63	23·4	1814·86	1·97	9·38	6·73	37·08
Central district											
Sharon SD	11·62	6·86	5·89	3·4	2·12	29·88	949·09	14·3	20·62	9·96	28·55
Petah Tiqwa SD	14·25	8·12	6·49	4·99	1·81	35·67	1791·78	4·59	4·78	9·17	30·52
Ramla SD	8·31	5·38	4·68	3·59	1·62	23·57	687·41	12·61	10·89	11·61	23·02
Rehovot SD	8·75	5·78	4·27	3·42	1·51	23·73	1411·04	4·94	0·17	8·25	30·94
Tel Aviv†	9·16	5·66	4·52	3·68	1·58	24·61	6788·01	0·38	1·26	7·64	35·94
Jerusalem†	12·95	6·08	5·04	3·23	1·96	29·25	1192·27	3·54	28·58	12·98	22·54
Southern district											
Ashqelon SD	10·27	6·74	5·5	4·48	1·78	28·76	324·71	10·88	0·18	9·63	29·71
Be'er Sheva SD	9·71	5·47	6·32	3·45	1·55	26·49	39·19	15·48	23·64	12·75	23·28

* Data presented are for 2001 in the middle of study period 1997–2006.

† Both a district and a sub-district.

SD, Sub-district; Ent, Enteritidis; Vir, Virchow; Typ, Typhimurium; Had, Hadar; Inf, Infantis; Top5, top five serotypes; Pop den, population density; Rural settle, % of population living in rural settlements; Non-Jew, non-Jewish population; Age ⩽5 yr, age group ⩽5 years; Age ⩾55 yr, age group ⩾55 years.

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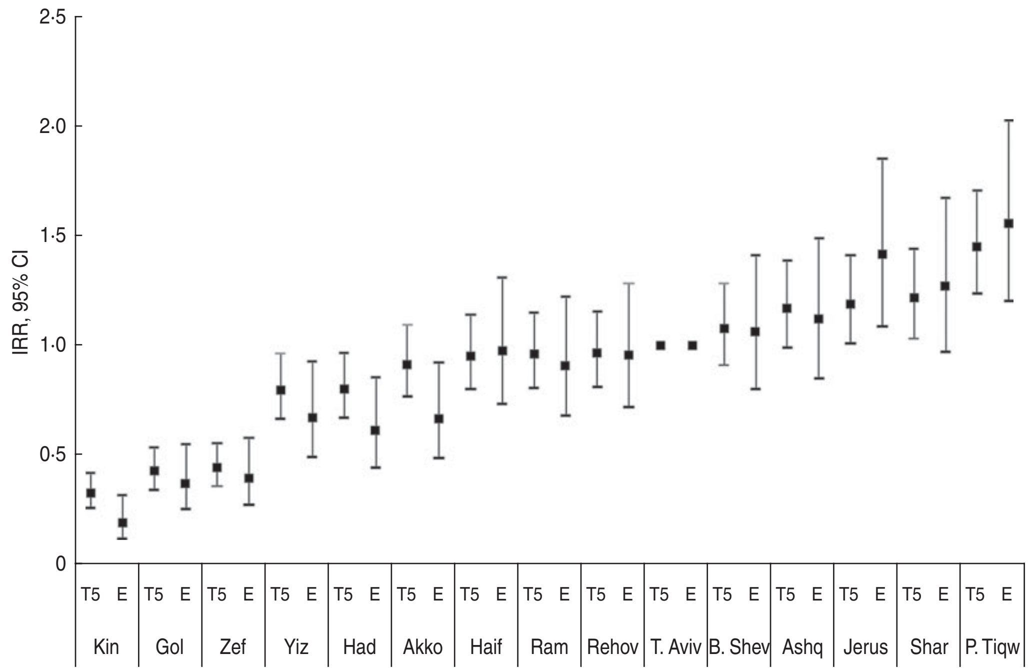

Fig. 2. Incidence rate ratio (IRR) and 95% confidence interval (CI) of the total top five *Salmonella* serotypes (T5) and serotype Enteritidis (E) in 15 sub-districts, Israel 1997–2006. Reference: Tel Aviv sub-district with the highest population density. Sub-districts are arranged in order of IRR magnitude. Kin, Kinneret; Gol, Golan; Zef, Zefat; Yiz, Yizre'el; Had, Hadera; Haif, Haifa; Ram, Ramla; Rehov, Rehovot; T. Aviv, Tel Aviv; B. Shev, Be'er Sheva; Ashq, Ashqelon; Jerus, Jerusalem; Shar, Sharon; P. Tiqw, Petah Tiqwa.

The relative incidence rates of all four non-Enteritidis serotypes were not significantly dependent on the proportion of population in the <5 years age group in the sub-districts.

DISCUSSION

Our study demonstrated significant variations in the incidence rates of NTS illnesses throughout Israel, which were negatively associated with the percent of rural residency. The lowest incidence rates were found in northern Israel where the proportion of rural residency is the highest.

Israel is a small country with substantial demographic variety in its districts and sub-districts. About half of the Israeli population lives in central Israel, while most of the rural settlements are concentrated in the five northern sub-districts. The sub-district of Tel Aviv, located in the centre of Israel, constitutes a huge urban metropolitan area. In terms of nationality, about 75% of the Israeli population is Jewish; the largest non-Jewish population is located in the northern sub-districts, followed by Be'er Sheva, Israel's southernmost sub-district (http://www.old.health.gov.il/download/pages/briut_sofi.pdf).

Previous studies that examined the effect of urban *vs.* rural residency on the incidence of *Salmonella* infection found conflicting results. While a Scottish study suggested that the incidence of *Salmonella* Typhimurium DT104 was higher in rural areas [22], a study conducted in Ontario, Canada, using the ArcGis system and Poisson regression models, found significantly higher rates of this pathogen in counties with a high degree of urbanization [21]. Studies from Michigan, USA showed a similar incidence of NTS in both rural and urban counties [19, 20].

How does the degree of urbanization affect *Salmonella* incidence rates? There are several possible explanations. First, it is highly likely that the lower incidence in rural areas is false, reflecting the lower availability of healthcare facilities rather than the true incidence of infected persons. In the present study, the incidence rate is based on the number of culture-confirmed infections, which in turn relies on patients seeking medical care and the vigilance of physicians in submitting stool cultures from patients with diarrhoeal illnesses [28]. A recent publication by the Israel Ministry of Health reveals disturbing inequalities in the distribution of community healthcare services in rural compared to urban areas. The

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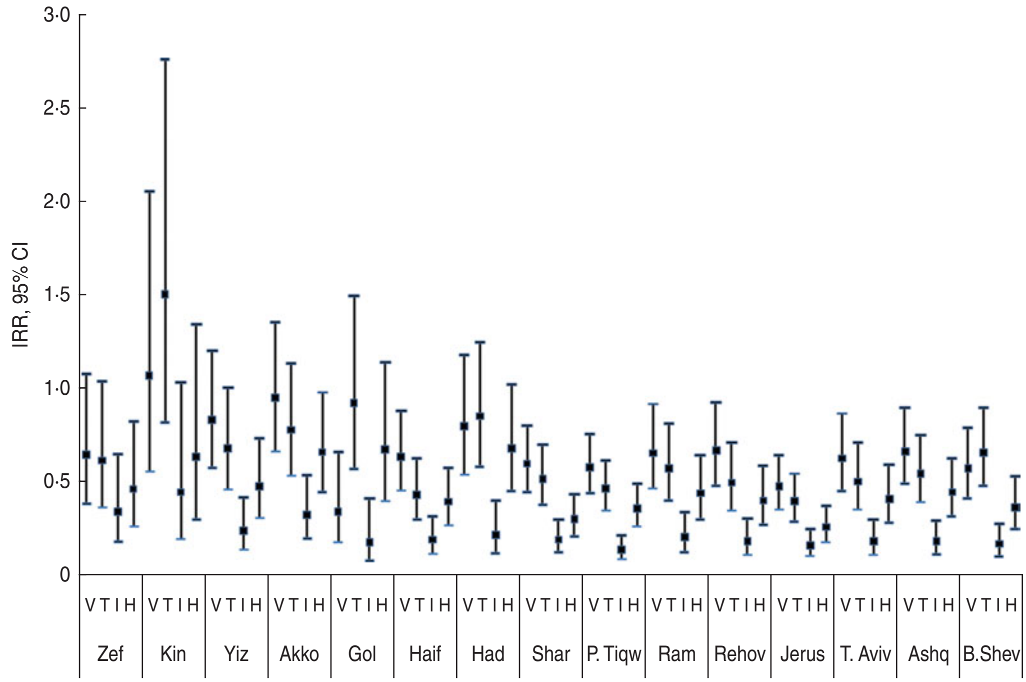

Fig. 3. Incidence rate ratio (IRR) and 95% confidence interval (CI) of non-Enteritidis *Salmonella* serotype compared to serotype Enteritidis in 15 sub-districts, Israel 1997–2006. Reference: serotype Enteritidis. Sub-districts are arranged from North to South. V, Serotype Virchow; T, serotype Typhimurium; I, serotype Infantis; H, serotype Hadar; Zef, Zefat; Kin, Kinneret; Yiz, Yizre'el; Gol, Golan; Haif, Haifa; Had, Hadera; Shar, Sharon; P. Tiqw, Petah Tiqwa; Ram, Ramla; Rehov, Rehovot; Jerus, Jerusalem; T. Aviv, Tel Aviv; Ashq, Ashqelon; B. Shev, Be'er Sheva.

availability of doctors and primary-care clinics is lower in rural communities, particularly so in northern and southern Israel (http://www.old.health.gov.il/download/pages/briut_sofi.pdf). Notably, a study conducted in southern Israel showed that distance from the 'big city' has a negative effect on the number of clinic visits made [29].

Second, inhabitants of rural areas may be more likely to purchase their food products from small, local businesses rather than large supermarket chains. In addition, eating out may be less commonly practised in rural communities. Eating chicken prepared outside the home was found to be a risk factor for *Salmonella* Enteritidis infection in the USA [30] and a recent meta-analysis found that chicken consumed at restaurants was a major risk factor for salmonellosis [31].

Variations in the incidence of *Salmonella* and other foodborne illnesses have also been associated with socioeconomic status. Lower socioeconomic status may negatively affect healthcare-seeking behaviour, thus creating a bias towards lower *Salmonella* detection in persons in this group [32]. On the other hand, individuals of higher socioeconomic status are more likely to exhibit risky food consumption practices (eating pink hamburgers, eating undercooked eggs, eating raw oysters, drinking raw milk) and food-handling habits (not washing hands with soap after handling raw meat or chicken and not washing the cutting surface with soap/bleach after using it for cutting raw meat or chicken), increasing the number of reported foodborne illnesses in this group [33]. The above may provide insight into our results, which show that the lowest incidence of NTS infection is found in the northern district, as this district also has the lowest average income and the highest rate of unemployment in Israel (http://www.old.health.gov.il/download/pages/briut_sofi.pdf).

The study also revealed variations in the relative incidence of the individual top five NTS serotypes in the 15 sub-districts of Israel where relative frequencies of non-Enteritidis serotypes were higher in the northern sub-districts. Higher incidence rates of non-Enteritidis serotypes (except for Virchow) compared to serotype Enteritidis were significantly affected by the degree of urbanization, the percentage of non-Jewish population, and the percentage of adults aged

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Table 2. *The association between the incidence rate of non-Enteritidis compared to Enteritidis NTS serotypes and the demographic characterization of 15 Israeli sub-districts*

	Serotype Typhimurium		Serotype Hadar		Serotype Infantis		Serotype Virchow	
Demographic variables	IRR (95% CI)	*P* value	IRR (95% CI)	*P* value	IRR (95% CI)	*P* value	IRR (95% CI)	*P* value
Percent of population living in rural settlements*	1·24 (1·09–1·42)	0·001	1·13 (0·96–1·34)	0·131	1·17 (1·00–1·36)	0·052	1·00 (0·87–1·15)	0·967
Percent of non-Jewish population*	1·09 (1·03–1·16)	0·006	1·07 (1·01–1·15)	0·036	1·07 (1·00–1·15)	0·044	1·03 (0·98–1·09)	0·217
Percent of population in the ⩾55 years age group*	0·74 (0·58–0·99)	0·016	0·84 (0·64–1·11)	0·217	0·84 (0·64–1·10)	0·241	0·97 (0·78–1·20)	0·784
Percent population in the ⩽5 years age group*	1·61 (0·76–3·45)	0·216	1·09 (0·50–2·41)	0·823	1·24 (0·57–2·70)	0·582	0·97 (0·55–1·73)	0·931

IRR, Incidence rate ratio; CI, confidence interval.

* Per 10% increase.

⩾55 years. Ethnicity and religion may also play an important role in people's food consumption and preparation and even food-purchasing habits, as exemplified by a recent Israeli consumers research by Oz Almog, which noted that the Israeli Arabic population tends to shop in local shopping centres and is therefore less likely to purchase food in the country-wide supermarket chains (http://www.peopleil.org/ details.aspx?itemID=7821&searchMode=0&index=1). The incidence of NTS serotypes is also known to differ in the various age groups in Israel [34]. About one quarter of the elderly Israeli population (aged ⩾65 years) live alone, and are relatively less affluent compared to the general population [35]. This may also affect food purchasing and dietary habits. For example, elderly people who live alone may prefer ready-to-eat foods, and those with lower incomes may purchase poorer quality food products. Understanding the specific food sources of the various NTS serotypes may shed more light on this issue.

One of the limitations of this study is that it relies on passive reporting to the National *Salmonella* Reference Center. Hence, possible reporting differences among the sub-districts may have a considerable effect on the findings of our study. To explore this possible bias, we examined reporting rates of enteropathogens (*Salmonella, Shigella, Campylobacter*) by the Sentinel Laboratory Network, which was established in 1997 by the Israeli Center for Disease Control (ICDC) and which covers about 30% of the Israeli population [36]. Laboratories in the network passively submit *Salmonella* isolates to the National *Salmonella* Reference Center, while actively reporting salmonellosis episodes to the ICDC. Compared to the active reporting, the passive submission rate of isolates was 96·5% and there were no significant differences between the various areas covered by the Sentinel Network [37].

In summary, urban residency was found to have a major effect on the epidemiology of salmonellosis in Israel. Differences in the relative distribution of *Salmonella* serotypes were also affected by ethnicity and population's age. Future ecological research should focus on the patterns of health-seeking behaviours and habits related to food consumption and handling that may explain these variations. In particular, more research is required to understand whether these differences reflect true variability in *Salmonella* illnesses or stem merely from detection bias.

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DECLARATION OF INTEREST

None.

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