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Recent trends in the epidemiology of shigellosis in Israel

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SUMMARY

We provide an update on the epidemiology of shigellosis in Israel using data generated by a sentinel laboratory-based surveillance network for the period 1998–2012. The average annual incidence of culture-proven shigellosis was 97/100 000. We estimated that each case of shigellosis accounted for 25 cases in the community indicating the high burden of disease. Orthodox Jewish communities, living in highly crowded conditions and with a high number of children aged <5 years were the epicentre of country-wide biennial propagated epidemics of *S. sonnei* shigellosis. *S. flexneri* was the leading *Shigella* serogroup in Israeli Arabs. *S. flexneri* 2a and *S. flexneri* 6 alternated as the most common serotypes. Both *S. sonnei* and *S. flexneri* isolates showed high rates of resistance to ampicillin and trimethoprim/sulfamethoxazole and very low rates of resistance to quinolones and third-generation cephalosporins. Shigellosis due to *S. sonnei* conferred 81% (95% confidence interval 69–89) protection against the homologous *Shigella* serotype when epidemic exposure re-occurred 2 years later. These data are of value in the process of *Shigella* vaccine development.

Key words: Antibiotic resistance, epidemics, host (in infections), *Shigella*, surveillance system.

INTRODUCTION

Shigellosis is endemic throughout the world and is hyperendemic in developing countries. In the late 1990s, the annual number of shigellosis episodes was estimated at 163·2 million in developing countries (with around 1 million deaths) and 1·5 million in industrialized countries [1, 2]. More recent estimates of the global burden of shigellosis report a similar extent of morbidity but a significantly lower mortality due to lower case-fatality rates [3]. Clinical manifestation of shigellosis can vary from moderate diarrhoea to severe dysentery. Children with dysentery from

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developing countries have an increased risk for persistent diarrhoea, nutritional faltering, and death [4–7]. Four *Shigella* serogroups: *S. dysenteriae* (known to have 13 serotypes), *S. flexneri* (16 serotypes), *S. boydii* (20 serotypes), and *S. sonnei* (one serotype), are the aetiological agents of shigellosis. *Shigella* is also an important aetiological agent of diarrhoea in travellers and in soldiers deployed to endemic regions [4, 8]. Shigellae are highly contagious with infectious doses of as low as 10–100 viable bacterial cells [9]. Transmission occurs via the faecal–oral route, usually from person-to-person contact or by intake of contaminated food or drinking water [4]. Significant fly-borne transmission of *Shigella* has also been documented [10].

Despite the improved socioeconomic conditions, Israel has remained a highly endemic area for shigellosis [11, 12]. It has been shown that children aged 1–4 years and soldiers serving in field units are at increased risk of developing shigellosis [11, 12].

The present report provides an update on the burden and epidemiology of shigellosis in Israel, describes the recent cyclic pattern of occurrence of epidemics of shigellosis, and comments on and points out host- and agent-related characteristics of the disease. These data are important for designing intervention programmes to reduce the burden of the disease.

METHODS

Shigellosis is a notifiable disease in Israel. Reports on culture-proven cases of shigellosis are submitted by bacteriological laboratories throughout the country to the corresponding public health districts and then collated at the Department of Epidemiology of the Ministry of Health. This passive surveillance system which was established at the beginning of the 1950s provides long-term assessment of the trends in the incidence of the disease in Israel. However, it lacks information on the *Shigella* serogroup and serotype for each case and demographic data on the cases are incomplete [13].

An additional, active surveillance system for bacterial enteric diseases (shigellosis, salmonellosis, campylobacteriosis), based on sentinel community and hospital microbiological laboratories located throughout Israel, was established in 1997. Data on the isolation of the enteropathogens including *Shigella* at the sentinel laboratory, demographic information related to patients and characterization of isolates at the National Reference Centers of the Ministry of Health, are collated at the Israel Center for Disease Control (ICDC) (Fig. 1) The population served by the five community laboratories represents 31·0% of the total Israeli population and its structure is almost identical to that of the total Israeli population according to gender and age groups. There is a slight overrepresentation of the Israeli Arab subpopulation, 25·7% *vs.* 20.5% in the general population. Israeli Jews and Israeli Arabs are citizens of the State of Israel residing in Israel at the time of the study.

Fig. 1. Community sentinel laboratories included in the study and their location on the map of Israel. Clalit Health Maintenance Organization (HMO) laboratories in Afula (A) and Haifa (H) representing the North of the country; Clalit HMO laboratory of Soroka Medical Centre in Beer Sheva (S) serving the population in the South; Meuheded HMO laboratory in Jerusalem (M) and Maccabi HMO laboratory of Ramat Gan/Mahoz Dan (D) serving the population in the centre of Israel. The National Reference Centres of the Ministry of Health and the Israel Centre for Diseases Control are located in Jerusalem and Ramat Gan, respectively.

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Isolation and identification of *Shigella* and serogrouping were performed at the sentinel clinical microbiological laboratories using similar routine microbiological procedures. Identification of *Shigella* serogroup was confirmed at the *Shigella* Reference Laboratory of the Israel Ministry of Health. This was followed by the definition of serotypes using monovalent antisera (Denka Seiken, Japan). Susceptibility to antimicrobial agents was determined in all *S. flexneri* and in a systematic sample of *S. sonnei* isolated during 2000–2008. This was done at the *Shigella* National Reference Laboratory of the Ministry of Health using the Kirby–Bauer disk diffusion method [14], on Muller–Hinton agar (Difco, BD Bioscience, USA) following the guidelines of the Clinical and Laboratory Standards Institute [15]. Commercially manufactured discs (Oxoid, UK) containing six antimicrobial agents were used: 10 μg ampicillin (AMP), 25 μg trimethoprim-sulphamethoxazole (SXT), 30 μg nalidixic acid (NAL), 30 μg chloramphenicol (CHL), 30 μg ceftriaxone (CRO), and 30 μg tetracycline (TET). Multi-drug resistance (MDR) was defined as resistance to three or more antimicrobial agents.

A case of shigellosis was defined as a subject with a positive stool culture for *Shigella* spp. A case of shigellosis was counted only once when *Shigella* of the same serotype was isolated from stool specimens submitted during the acute and convalescent stages of the diarrhoeal episode (within 1 month after the first isolation).

For the computation of incidence rates, the sizes of the catchment populations of the different sentinel laboratories were calculated based on data received from the Central Bureau of Statistics and the Health Maintenance Organization (HMO) to which the laboratories belonged.

Adjusted incidence rates were calculated based on data from population and physician surveys and from HMO databases used to determine the gaps in the various surveillance steps and the reciprocal multipliers for calculation of the diarrhoeal disease burden in childhood in Israel [16], and the approach previously described to determine the burden of shigellosis in Thailand and salmonellosis in the USA, respectively [2, 17]. The multipliers for each surveillance step were the inverse of the proportion of subjects responding positively [2]. The overall multiplier was the product of the multipliers for each surveillance step. Based on the previous report [16] the proportion of subjects complying with the various surveillance steps were: 38·8% in the 0–17 years age group (we estimated only 30% for all age groups) who had a diarrhoeal disease and visited a physician; 24% were referred by the physician to provide a stool specimen (75% of whom provided a stool specimen); 70% sensitivity of the stool culture for detection of *Shigella* spp. [17, 18]; and 100% reporting from sentinel laboratories to ICDC on *Shigella* isolates. The respective multipliers were: 3·3 (or 1:0·3), 4·2, 1·3, 1·4 and 1. The overall multiplier was 25·2.

We examined the extent of protection conferred by *S. sonnei* shigellosis contracted in one outbreak against the onset of homologous repeat disease during the outbreak occurring 2 years later. To this end, we determined in each new outbreak the attack rate of *S. sonnei* shigellosis in subjects who were reported as culture-proven cases of *S. sonnei* shigellosis in the previous outbreak (by cross-checking the identifiers of the culture-proven cases in the two outbreaks) and in the rest of the children for whom there was no report on *S. sonnei* shigellosis in the previous outbreak. We then calculated the relative risk of repeat disease for each outbreak and overall, and estimated the extent of protection conferred by homologous culture-proven disease according to the formula:

$$1 - \text{relative risk of repeat } S.\ sonnei \text{ shigellosis} \times 100.$$

We restricted this analysis to children aged 0–4 years belonging to the catchment population of laboratory M in Jerusalem. As a rule, the denominators in the second outbreak included only children aged <4 years.

To exemplify in numbers for the outbreak in 2006: four repeat cases of *S. sonnei* from 405 *S. sonnei* cases identified in 2004 (attack rate 9·9/1000); 578 cases of *S. sonnei* shigellosis in 11 838 children for whom there was no report on *S. sonnei* shigellosis in 2004 (attack rate 48·8/1000). The relative risk and protective efficacy yielded by these figures were 0·2 [95% confidence interval (CI) 0·08–0·54] and 79·8% (95% CI 46·0–92·4), respectively.

Analysis of data was performed using SPSS v. 21 (IBM Corp., USA). In addition, WINPEPI Computer Programs for Epidemiologists [19] was used to calculate incidence rates/100 000 Pearson's χ^2 *P* values and 95% confidence intervals.

RESULTS

Figure 2 depicts data generated by the passive surveillance system showing that in the population of Israel the average incidence of culture proven-cases of

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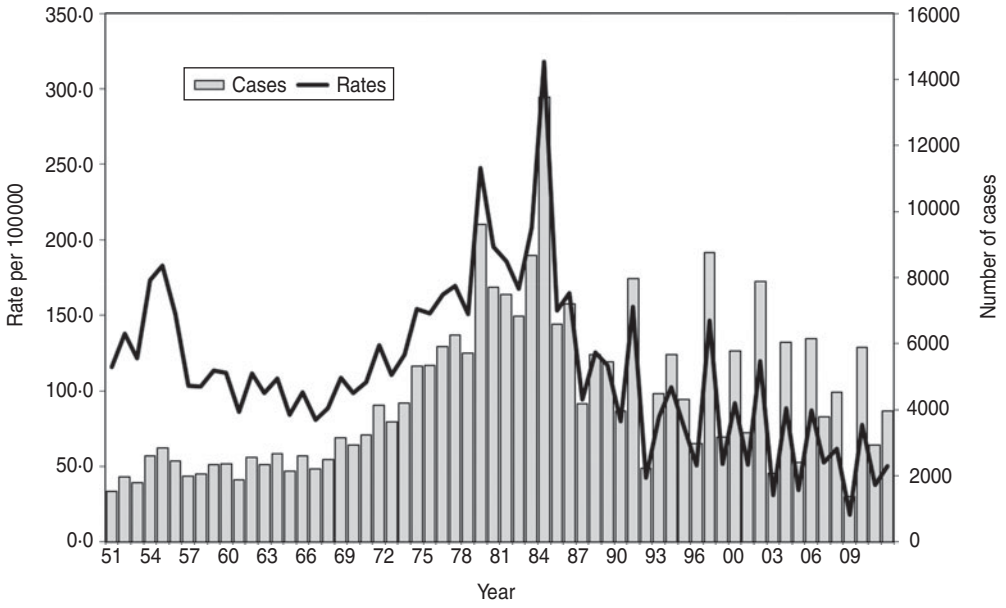

Fig. 2. Total cases and incidence rates of shigellosis in Israel based on passive reporting on culture-proven cases of disease by microbiological laboratories and physicians, 1951–2012 [13].

shigellosis is around 70–100 cases/100 000 per year [13]. After being relatively stable until around 1974, the incidence of shigellosis gradually increased to a peak in 1985 associated with a large waterborne epidemic of *S. sonnei* shigellosis in the Haifa region [20]. This was followed by an overall decline until the beginning of the 1990s and by a change in the pattern of disease occurrence later on characterized by peaks in the incidence of shigellosis occurring every 2–3 years (Fig. 2).

The incidence rates of shigellosis for the overall population served by the five community sentinel laboratories between 1998 and 2012 followed a clear cyclic pattern and ranged from 89–178 to 25–83 cases/100 000 in the years of high and low incidence of shigellosis, respectively. Out of 30 337 *Shigella* isolates at the sentinel community laboratories 85·3% were *S. sonnei* and 11·3%, 2·5% and 0·7% were *S. flexneri, S. boydii* and *S. dysenteriae*, respectively. The incidence rates of *S. sonnei* shigellosis in the epidemic years were significantly higher than those in the consecutive non-epidemic years (Table 1). In the Jewish population, 93·7% ($n = 24\,808$) of the new cases of shigellosis were *S. sonnei* shigellosis following the cyclic pattern of peaks of morbidity (Fig. 3). By contrast, in the Israeli Arab population, 50·3% of the new cases of shigellosis ($n = 4084$) were caused by *S. flexneri*, 34·4% by *S. sonnei*, 12·2% by *S. boydii*, and 3·0% by *S. dysenteriae* (Fig. 4).

Overall, the average annual incidence of shigellosis was 97/100 000 throughout the 15 years of surveillance. It was higher in the Jewish population compared to the Arab population (105/100 000 *vs.* 55/100 000 respectively; $P < 0{\cdot}001$).

The age-specific incidence rates were the highest in the 0–4 years age group with values ranging from 569–939 to 139–496 cases/100 000 in the years of high and low incidence of shigellosis, respectively (Fig. 5). Throughout the 15 years of surveillance, the 0–4 years age group had the highest incidence rates of shigellosis in both the Jewish (an average of 721/100 000 mostly due to *S. sonnei*) and Arab (an average of 248/100 000) populations. Within the 0–4 years age group and in Jews, the lowest incidence was found in the first year of life and the highest in the third. However, for Arabs the highest incidence was in the second year followed by the first year of life. The incidence of shigellosis was significantly higher in Arabs (287/100 000) compared to Jews (165/100 000) ($P < 0{\cdot}001$) in the first year of life while in all other age groups the incidence was significantly higher in Jewish children compared to Arab children.

In the 0–4 years age group, the female/male risk ratio was 0·88 and 0·81 for Jews and Arabs, respectively ($P < 0{\cdot}001$ in both populations), and significantly >1 in the 15–24, 25–34, 35–44, 45–54 and 55–64 years age groups (Table 2).

The adjusted average incidence of shigellosis in the community for the whole Israeli population was

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Table 1. *Incidence rates and rate ratios of* Shigella sonnei *shigellosis in epidemic and non-epidemic years in the population served by the sentinel laboratories*

Year	*n*	*N*	Incidence rate (per100 000)	95% CI for incidence	RR	95% CI
1998	2785	1 801 465	154·6	148·9–160·4	3·63	3·37–3·92
1999	1054	1 848 835	57·0	53·6–60·6	1·34	1·22–1·47
2000	2128	1 896 996	112·2	107·5–117·0	2·64	2·44–2·85
2001	1177	1 941 465	60·6	57·2–64·2	1·42	1·31–1·56
2002	2607	1 984 140	131·4	126·4–136·5	3·09	2·86–3·33
2003	916	2 028 854	45·1	42·2–48·2	1·06	0·97–1·16
2004	2467	2 068 619	119·3	114·6–124·1	2·8	2·6–3·03
2005	896	2 105 112	42·6	39·9–45·5	*	–
2006	2666	2 144 199	124·3	119·7–129·1	2·92	2·71–3·15
2007	1480	2 218 865	66·7	63·4–70·2	1·57	1·44–1·71
2008	2000	2 261 184	88·4	84·6–92·4	2·08	1·92–2·25
2009	428	2 319 778	18·5	16·7–20·3	0·43	0·39–0·49
2010	2309	2 360 617	97·8	93·9–101·9	2·3	2·13–2·49
2011	929	2 407 829	38·6	36·14–41·14	0·91	0·83–0·99
2012	2046	2 455 985	83·3	79·74–86·99	1·957	1·809–2·119

RR, Rate ratio; CI, confidence interval.
* Reference category = 2005.

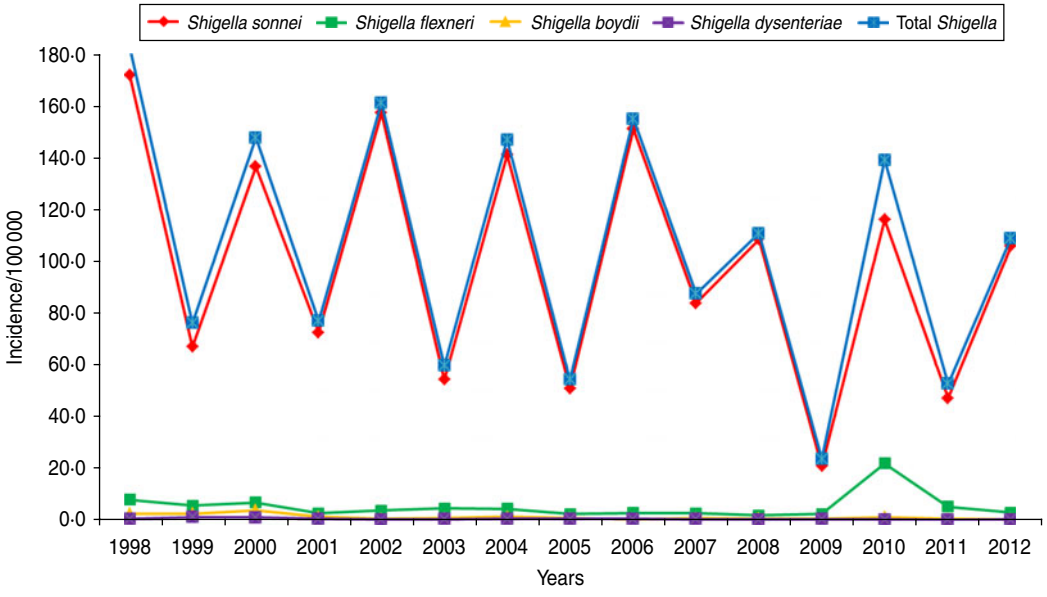

Fig. 3 [*colour online*]. Incidence of shigellosis by *Shigella* serogroup in the Jewish population served by the sentinel laboratories.

2425/100 000 per year during 1998–2012 after using the multiplier of 25 to control for estimated gaps in the surveillance steps (see also Methods section).

Characteristics of *S. sonnei* shigellosis

The incidence of *S. sonnei* increased constantly from January to July with a significant drop in April and reached its peak in July. The earliest and steepest increase in incidence of *S. sonnei* in the epidemic years occurred in winter, in the M and D laboratories, representing the Jerusalem and Central districts (Fig. 1). This was usually followed by a significant increase in the number of isolates in laboratory S covering the South of Israel. The M and D laboratories serve the Jewish Orthodox religious neighbourhoods

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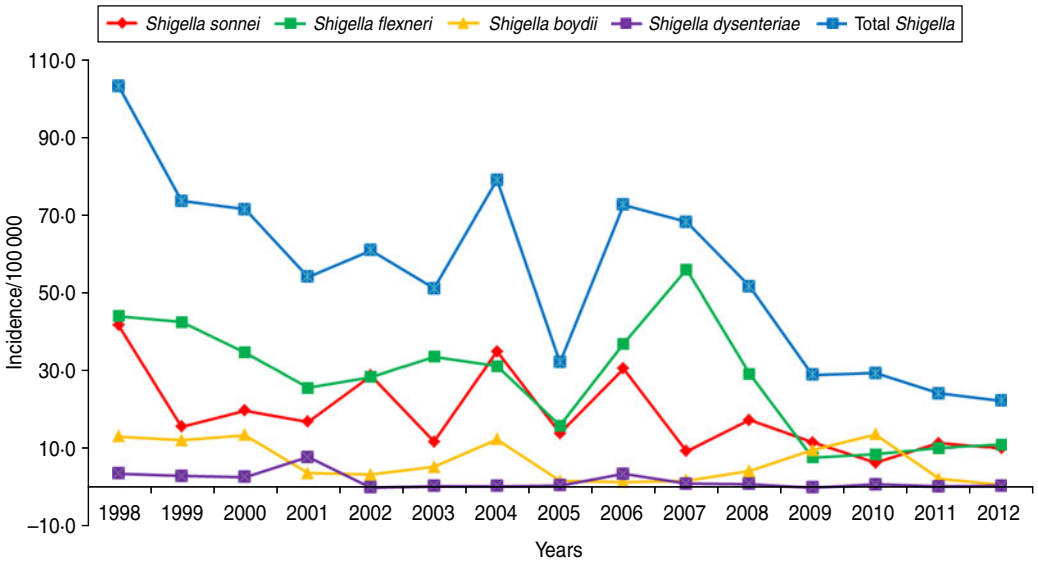

Fig. 4 [*colour online*]. Incidence of shigellosis by *Shigella* serogroup in the Arab population served by the sentinel laboratories.

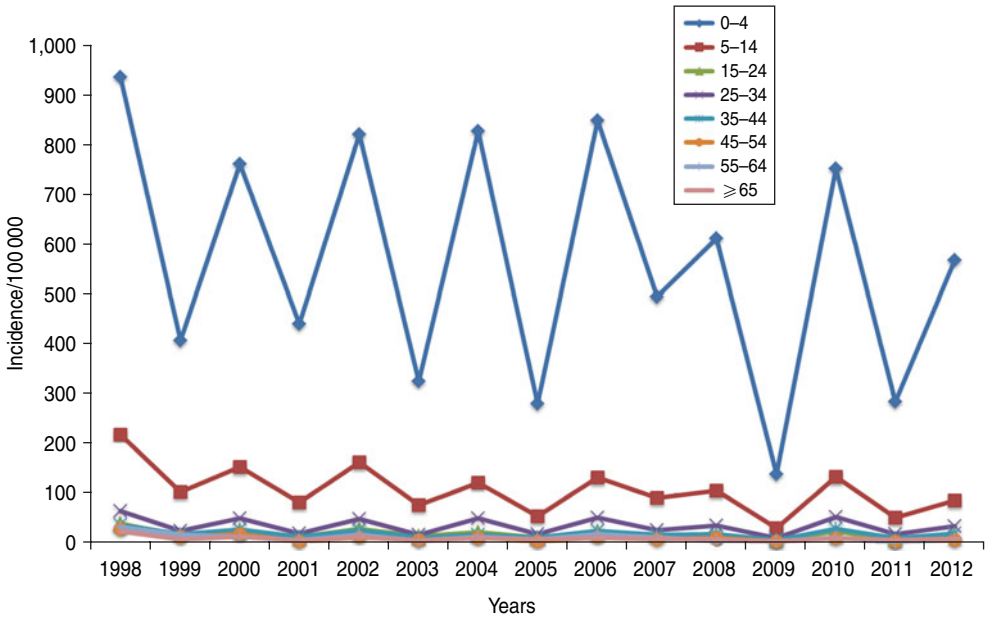

Fig. 5 [*colour online*]. Incidence of shigellosis in the various age groups of the general population served by the sentinel laboratories.

of Jerusalem and Bnei Brak, respectively, inhabited by families with a large number of children living in crowded conditions.

The average serotype-specific protective efficacy conferred by *S. sonnei* infection for a 2-year period was 81·8% (95% CI 69·9–89·0), derived from calculated protective efficacies of 87·3% (95% CI 60·6–95·9) in the 2002 outbreak, 95·4% (95% CI 67·4–99·4) in the 2004 outbreak, 79·8% (95% CI 46·0–92·4) in the 2006 outbreak and 51·3% (95% CI 46·0–92·4) in the 2008 outbreak.

After 8 years of almost 100% resistance of *S. sonnei* to trimethoprim/sulfamethoxazole, a significant decrease to 80% occurred, as in the case of resistance to tetracycline, which dropped from 80% in 2000 to 10–20% between 2002 and 2008 (Fig. 6). *S. sonnei* isolates showed a consistent resistance rate of 80% to ampicillin while that to nalidixic acid, chloranphenicol

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Table 2. *Average incidence of shigellosis for 1998–2012 in the population served by the sentinel laboratories by age, sex and ethnicity*

Age group (yr)	Jews								Arabs							
	Males			Females					Males			Females				
	%	*n*	Avg. annual incidence/ 100000	%	*n*	Avg. annual incidence/ 100000	Rate ratio	*P*	%	*n*	Avg. annual incidence/ 100000	%	*n*	Avg. annual incidence/ 100000	Rate ratio	*P*
0–4	53·1	8465	751	46·9	7462	662	0·88	<0·01	55·2	1577	270	44·8	1282	220	0·81	<0·01
5–14	50·2	2686	132	49·8	2660	131	0·99	0·722	53·7	454	45	46·3	392	39	0·86	0·033
15–24	36·2	289	15	63·8	509	26	1·76	<0·01	42·0	47	7	58·0	65	9	1·38	0·089
25–34	30·9	423	25	69·1	947	55	2·24	<0·01	39·6	44	8	60·4	67	12	1·52	0·029
35–44	32·9	202	14	67·1	412	29	2·04	<0·01	27·4	17	4	72·6	45	10	2·65	<0·01
45–54	34·1	91	7	65·9	176	13	1·93	<0·01	43·2	16	6	56·8	21	8	1·31	0·411
55–64	29·7	63	6	70·3	149	14	2·37	<0·01	32·3	10	6	67·7	21	13	2·10	0·048
⩾65	44·4	99	8	55·6	124	10	1·25	0·094	39·1	9	7	60·9	14	11	1·56	0·297
Total	49·8	12318	103	50·2	12439	104	1·01	0·442	53·3	2174	56	46·7	1907	49	0·88	<0·01

and ceftriaxone did not exceed 5% and 1%, respectively, since 2002 (Fig. 6).

Characteristics of *S. flexneri* shigellosis

The incidence of *S. flexneri* shigellosis showed a constant summer increase, from April to August, with its peak in July. Sixty-three percent of *S. flexneri* were isolated from Arab patients, mostly in the 0–4 years age group. *S. flexneri* 2a and *S. flexneri* 6 alternated as being the two most common serotypes during the 15 years of surveillance accounting for ~71% of the isolates. *S. flexneri* 1b was the third most frequently isolated serotype. In 2010 an outbreak of *S. flexneri* 6 occurred in the Orthodox Jewish community in Jerusalem and its surroundings. Thirty-five percent ($n=416$) of all *S. flexneri* 6 isolates were isolated in 2010.

The resistance rate of *S. flexneri* ($n=2173$) to ampicillin, tetracycline, trimethoprim/sulfamethoxazole and chloramphenicol ranged mostly between 60% and 80% from 2000 to 2008 with some significant annual fluctuations (Fig. 7). There was a significant decrease in the resistance rate to trimethoprim/sulfamethoxazole which reached 40% in 2007 and 2008. The resistance rate to nalidixic acid and ceftriaxone did not exceed 5% and 1%, respectively.

Of *S. sonnei* and *S. flexneri* isolates 12·1% and 72·9%, respectively, were multidrug resistant (resistant to three or more antimicrobial agents).

DISCUSSION

The sentinel laboratory-based active surveillance network for shigellosis was established in 1998 as an add-on to the passive surveillance system of notifiable infectious diseases (including shigellosis) instituted in Israel at the beginning of the 1950s. It provides comprehensive information on demographic variables related to subjects from whom *Shigella* sp. was isolated and also the complete serological characterization of the *Shigella* isolates.

S. sonnei was responsible for more than 85% of the cases of shigellosis in Israel during 1998–2012. *S. flexneri* was the second most prevalent *Shigella* serogroup (11·3%). In 1993 *S. sonnei* and *S. flexneri* accounted for 77% and 19%, respectively, of *Shigella* isolates characterized at the Ministry of Health *Shigella* Reference laboratory [12]. Interestingly, during 1998–2012, *S. sonnei* was identified in 93·7% of the new *Shigella* isolates in the Jewish population

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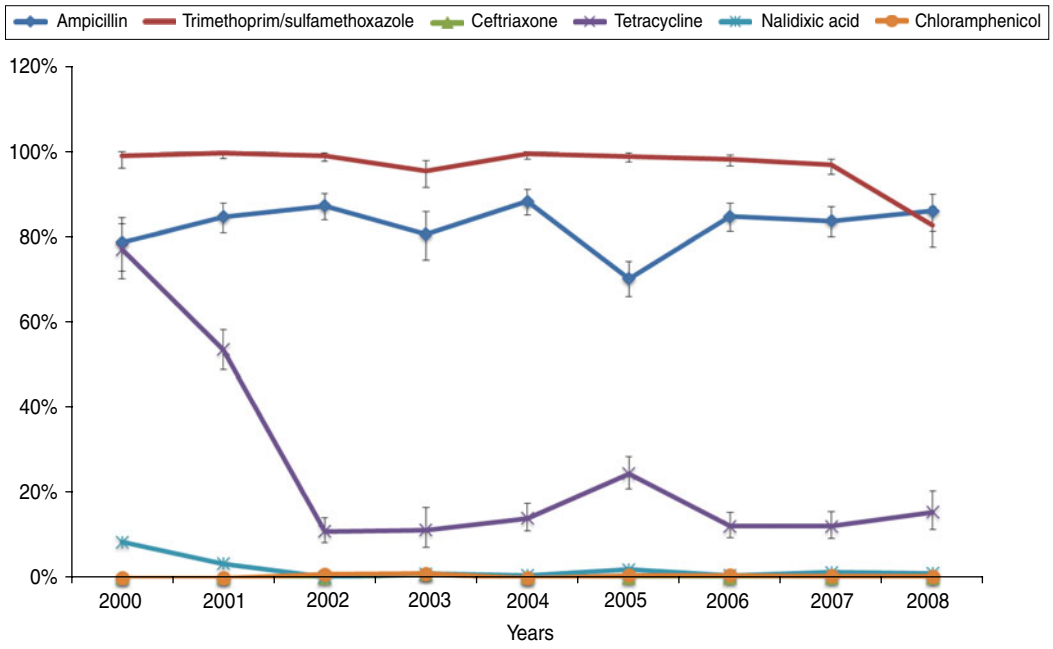

Fig. 6 [*colour online*]. Resistance pattern of *S. sonnei* isolates ($n = 3642$) to six antimicrobial agents during 2000–2008.

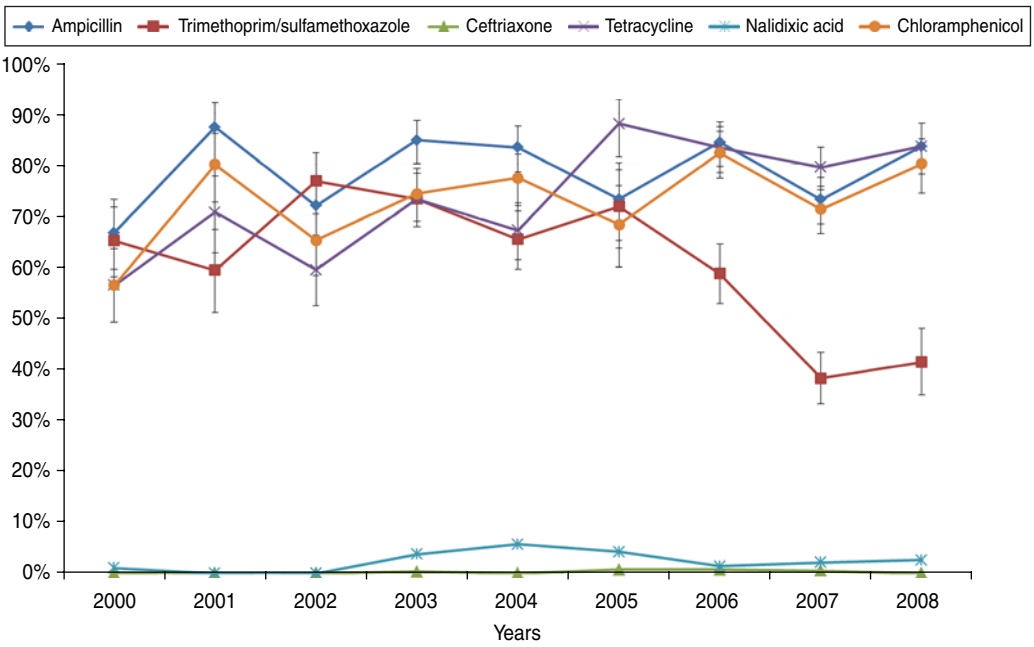

Fig. 7 [*colour online*]. Resistance pattern of *S. flexneri* isolates ($n = 2173$) to six antimicrobial agents during 2000–2008.

and in only 34·4% of the *Shigella* isolates in Israeli Arabs where *S. flexneri* was the leading serogroup accounting for 50·3% of the *Shigella* isolates. The increase in the predominance of the relative importance of *S. sonnei* compared to *S. flexneri* and the other *Shigella* serogroups (*S. boydii, S. dysenteriae*) is a trend characteristic to developed countries [18, 21, 22], while *S. flexneri* remains the leading *Shigella* serogroup in developing countries or in subpopulations of lower socioeconomic level, living in rural areas and with lower levels of sanitation [18, 23, 24]. The serotypes *S. flexneri* 2a and *S. flexneri* 6 alternated as being the two most common serotypes during the 15 years of surveillance as also reported from many

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other countries [25] and supporting the inclusion of both serotypes (or respective O polysaccharides) in candidate multivalent *Shigella* vaccines [25].

S. sonnei was associated with the occurrence of country-wide epidemics of *S. sonnei* shigellosis in Israel every 2 years. The clearest cyclic pattern and the highest incidence of disease were found in the 0–4 years age group and in the catchment area of M and D laboratories, which provide microbiological laboratory services to the Jewish Orthodox religious neighbourhoods of Jerusalem and Bnei Brak, inhabited by families with a large number of children living in crowded conditions. A lower level of exposure of an infant compared to a toddler, to person-to-person, foodborne transmission and transmission by fomites of *Shigella*, and on the other hand, a potential protective level of *S. sonnei* antibodies of maternal origin could explain the lowest incidence of shigellosis in the first year of life. Toddlers, already mobile, are at a high risk of being in contact with faecal material while they are in transition from the stage of using diapers to the stage when they are completely trained to use the toilet for defecation. Inadequate hand-washing, diapering practices and a high toddler–toilet ratio have been associated with *S. sonnei* transmission in daycare centres or in households [26–30]. In addition, child-to-child transmission, caregivers who both prepare meals and change diapers [30] or just various fomites at the daycare centres or at home can serve as vehicles and augment the transmission of *Shigella* [29, 30]. It has been shown that attendance at a daycare centre or a pre-school setting were the main risk factors for primary cases in affected households in an outbreak of *S. sonnei* shigellosis in similar Jewish Orthodox communities in New York [29, 31]. Conditions of crowding and a younger age of the primary case, strongly support secondary transmission in households augmenting the outbreak [31].

Interestingly, in Israeli Arabs the highest incidence of shigellosis (mostly caused by *S. flexneri*) was in the second year of life followed by the first year, suggesting that significant exposure to *Shigella* occurs earlier after birth in Arab children compared to Jewish children.

Similar differences between Israeli Arabs and Jews were described for the age-specific incidence of hepatitis A, another faeco-orally transmitted disease [32]. This finding, as well as the leading role of *S. flexneri* in the aetiology of shigellosis, can be related to lower environmental and socioeconomic conditions and living predominantly in a rural environment in Arab children compared to Jewish children, which may offer a wider range of modes of transmission of *Shigella* early in life.

The increase in the number of new cases of *S. sonnei* shigellosis usually started in the winter months, possibly enhanced by more intimate contact in households and daycare centres during the time spent in indoor activities and peaked in July after a consistent drop in April. April is usually the month of the Passover vacation which may break temporarily the chain of person-to-person propagation of *S. sonnei* when children are absent from daycare centres, kindergartens and schools. *S. flexneri* had a consistent summer increase and much lower number of isolates during the rest of the year suggesting potential involvement of multiple modes of transmission enhanced by the higher summer temperatures.

We assume that females in the 15–44 and 45–64 years age groups with 50–100% excess of shigellosis compared to males comprise mothers, grandmothers or caregivers who had a much higher risk of exposure to *Shigella* while taking care of sick children. Similar age- and sex-related patterns of infection have been reported previously from other laboratory-based surveillance networks [21, 33]. Previous observational and experimental studies in humans reported findings on serotype-specific immunity following *Shigella* natural infection [22, 34, 35]. In this study we were able to quantify the extent of protective efficacy conferred by naturally acquired *S. sonnei* shigellosis (around 80%) against the homologous *Shigella* serotype when epidemic exposure re-occurred 2 years later. We have shown that serum IgG anti-*Shigella* lipopolysaccharide (LPS) antibodies, which are elicited by natural infection, are strongly associated with protection against homologous disease [36, 37]. We assume that there is an association between the cyclic peaks of morbidity due to *S. sonnei* and changes in the level of natural immunity to the organism acquired by the affected population. An outbreak of shigellosis occurring in children in the 0–4 years age group will be followed by an increase in the level of natural immunity to the homologous *Shigella* organism (*S. sonnei*) which will also provide the level of herd immunity sufficient to prevent the onset of a new epidemic. After 1 or 2 years, waning in the level of anti-LPS antibodies together with the intake of a new cohort of naive newborns will lead to a decrease in the level of heard immunity below a critical level. Under high and continuous risk of exposure to *Shigella* in children aged 0–4 years, living in crowded

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conditions, this will allow the renewal epidemic transmission of *S. sonnei*.

There were similarities and also differences between the antibiotic resistance patterns of the two leading *Shigella* serogroups in Israel during 2000–2008. Both *S. sonnei* and *S. flexneri* isolates showed high rates of resistance to commonly used antimicrobial agents such as ampicillin and trimethoprim/sulfamethoxazole. These resistance rates are similar to or higher than those reported in Israel in the mid-1990s [38, 39] and in other countries more recently [40, 41]. On the other hand, both *S. sonnei* and *S. flexneri* displayed very low rates of resistance to quinolones (nalidixic acid) and third-generation cephalosporins (ceftriaxone) as also found in a series of studies conducted globally [40–44] with the exception of some of the Asian countries where resistance to these antibiotics has significantly increased [18, 24, 44]. Resistance of *S. sonnei* to tetracycline fell markedly from 2000 to 2002 and remained low thereafter. Similar differences between *S. sonnei* and *S. flexneri* in percent of resistance to tetracycline and chloramphenicol found in our study were also detected in the FoodNet sites in the USA between 2000 and 2010 [41].

The present study has some limitations. We are dealing with the tip of the iceberg in respect of the actual burden of shigellosis in the community. To have a culture-proven case of shigellosis means that the patient must seek medical care first, the physician must order a stool culture, a stool specimen must be obtained and submitted to the laboratory for culture and the laboratory has to isolate the organism. On the one hand, data on culture-proven cases in community laboratories could select for moderate to severe cases of shigellosis compared to those who would not visit a community clinic. On the other hand, we did not include *Shigella* isolates from hospitalized patients since we did not have a denominator for them to calculate incidence rates. In this case we could have lost the most severe cases of shigellosis requiring direct hospitalization. There might be also a differential utilization of medical services and health-seeking behaviour in respect to diarrhoeal diseases in the Jewish and Arab subpopulations possibly leading to a differential underestimation of the burden of shigellosis in Israeli Arabs. We determined an estimated multiplier of 25 to close the gaps in the surveillance steps and estimated the adjusted average incidence of shigellosis in the community for the whole Israeli population at 2425/100 000 per year during 1998–2012. Applying this figure to the population of Israel (8 012 400 inhabitants as of 31 March 2013) we reached the estimate of 194 300 outpatient cases of shigellosis per year. Assuming an additional 10% of inpatient cases, the approximate total average number of new cases of shigellosis per year will be 213 730 which represents an impressive burden especially when referring to the epidemic years.

With regard to the estimates of protection, it might be possible that the number of repeat *S. sonnei* shigellosis identified in a new outbreak in children who suffered from the disease in the first outbreak, 2 years previously, might be lower than expected thus overestimating the protective efficacy conferred by natural *S. sonnei* infection. This could be due to potential lower exposure since these children will be 2 years older (but still in the 0–4 years age group), to a lower chance that they and their parents will seek care, being already experienced with the diseases from the previous episode, or perhaps just having a milder repeat disease as a result of potential partial protection thus reducing the chance that they would be identified.

CONCLUSIONS

The sentinel laboratory-based surveillance network led to the identification of the cyclic occurrence of *S. sonnei* epidemics in Israel. The burden of shigellosis is high. Intervention programmes including promotion of personal hygiene with special emphasis on hand washing are needed to prevent the transmission of shigellae when the first clusters of disease occur. Immunization of children in the 1–4 years age group with an efficacious *S. sonnei* vaccine when such a vaccine is available should be considered as the means to interrupt the cycles of morbidity and significantly reduce the burden of shigellosis in Israel.

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DECLARATION OF INTEREST

None.

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