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Burden and risk factors of *Shigella sonnei* shigellosis among children aged 0–59 months in hyperendemic communities in Israel

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ABSTRACT

Objectives: Ultraorthodox Jewish populations living in towns with good sanitary infrastructure but with conditions of crowding have been the epicenter of *Shigella sonnei* shigellosis outbreaks. In this study, the incidence and risk factors of *S. sonnei* shigellosis in children living in an ultraorthodox community were determined.
Methods: Data for the years 2000–2013 for all reported culture-proven *S. sonnei* shigellosis cases in children aged 0–59 months in the city of Elad were compared with data for the rest of the sub-district. Environmental factors obtained through parental interviews were evaluated for 78 incident cases of *S. sonnei* shigellosis and 141 community controls, matched by age, sex, and neighborhood. Conditional logistic regression models were performed.
Results: Cyclic epidemics of *S. sonnei* shigellosis occurred every 2 years. The mean annual incidence was 10.0 per 1000 children in Elad (95% confidence interval 7.9–12.6) vs. 3.8 per 1000 children (95% confidence interval 3.3–4.4) in the sub-district ($p < 0.001$). Concurrent diarrheal disease in family members, having the same person in the daycare center responsible for food handling and changing diapers, and more rooms and sinks in the center, were positively associated with *S. sonnei* shigellosis, while children's hand-washing before meals was inversely associated.
Conclusions: The burden of *S. sonnei* shigellosis in ultraorthodox communities is high. Enhanced hygiene interventions are required for epidemic control.

Introduction

Shigellosis is common worldwide and hyperendemic in developing countries, with approximately 250 million cases annually (Khalil et al., 2018). About 13% of all diarrheal disease deaths are attributed to *Shigella*, which translates to 212 438 deaths in all age groups globally (Khalil et al., 2018). Around two million shigellosis cases occur annually in industrialized countries (Khalil et al., 2018; Pires et al., 2015), where the main risk groups are toddlers in crowded settings and daycare centers (Garrett et al., 2006; Mohle-Boetani et al., 1995; Sobel et al., 2004), travelers to endemic regions (Porter et al., 2017; Zboromyrska et al., 2014), and soldiers serving under field conditions (Cohen et al., 2001; Hyams et al., 1991).

Shigella flexneri is the most commonly isolated *Shigella* species in low-income countries (Livio et al., 2014). *Shigella sonnei* predominates as the cause of shigellosis in high-income countries (Gupta et al., 2004; Vinh et al., 2009; von Seidlein et al., 2006). In addition, an emerging trend has been documented in which *S. sonnei* has replaced *S. flexneri* as the leading cause of shigellosis in countries undergoing economic development and improvements in sanitation and water quality (Vinh et al., 2009; Levine et al., 2007; Thompson et al., 2014).

Israel, a high-income country, is endemic for shigellosis, with an annual incidence rate of culture-proven shigellosis of 0.97 per 1000 people (Cohen et al., 2014), which is about 10–20 times higher than in the USA (Gupta et al., 2004). *S. sonnei* is responsible for more than 85% of the cases of shigellosis in Israel (nearly 95% in the

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Jewish population), while *S. flexneri* is most common among Bedouins in southern Israel. The low inoculum required to cause shigellosis (DuPont et al., 1989) facilitates *Shigella* transmission by various routes. In industrialized countries where a good level of sanitation exists, the risk factors for shigellosis are mostly those that increase the chance of person-to-person and fomite-borne transmission of *Shigella* in households and daycare centers (Mohle-Boetani et al., 1995; De Schrijver et al., 2011). Interventions based on enhanced hand-washing have been found to be inversely related to shigellosis (Curtis and Cairncross, 2003).

Ultraorthodox Jewish communities, characterized by crowding and a high number of young children, have been the epicenter of the countrywide biennial propagated epidemics of *S. sonnei* shigellosis occurring in Israel during the last 15 years (Cohen et al., 2014). The aims of this study were to determine the incidence of *S. sonnei* shigellosis in a high-risk Jewish ultraorthodox town that is consistently affected by the biennial propagated outbreaks of *S. sonnei* shigellosis, and to identify environment-related risk factors for the disease in young children.

Materials and methods

Study population and design

The study population comprised children aged 0–59 months from ultraorthodox Jewish communities in Israel. Access to health care in Israel is high due to universal health insurance provided to all citizens. Fertility rates, household crowding, and poverty rates are higher in the ultraorthodox communities, while the median age and family income are lower compared to the general population (Israel Central Bureau of Statistics, 2016; Gurovich and Eilat, 2004). This study was conducted in the ultraorthodox town 'Elad', located in the center of Israel. In 2009, Elad had 33 900 residents and the annual population growth rate was 5.8%. Socio-demographic characteristics of the population of Elad compared to those of the sub-district population are presented in the Supplementary material (Table S1).

The incidence proportions of *S. sonnei* shigellosis during 2000–2013 among children aged 0–59 months were determined in a descriptive study. Data on the number of culture-proven cases of *S. sonnei* shigellosis were obtained through a laboratory sentinel surveillance system and from passive reports to the health sub-district office (Israel Center for Diseases Control and Division of Epidemiology Public Health Services, Ministry of Health Notifiable Infectious Diseases in Israel, 2012). Shigellosis is a notifiable disease; thus all laboratories, physicians, hospitals, clinics, etc., are required to report cases to the Ministry of Health, through the health sub-district office. All reports on shigellosis were validated against all *Shigella* documented isolates from all microbiology laboratories serving the city of Elad and the rest of the sub-district, thus ensuring 100% completeness of data on culture-proven *Shigella* isolates.

Identifying risk factors for *S. sonnei* shigellosis was conducted in a case–control study. Consecutive *S. sonnei* shigellosis cases occurring during 2010 and 2012 in Elad were identified through a laboratory sentinel surveillance system (Israel Center for Diseases Control and Division of Epidemiology Public Health Services, Ministry of Health Notifiable Infectious Diseases in Israel, 2012). During the study period, all shigellosis cases in Elad were caused by *S. sonnei*. Only one child from the same household was included. For each case, one or two randomly selected community controls identified through the national population registry were enrolled within 2 weeks of the case illness. Control children had not had diarrhea within the 2 weeks before the interview and were matched to cases by age ($\pm$6 months), sex, and neighborhood. Since the incidence of shigellosis is highest in children aged 2–4 years, it was assumed that the majority of cases would be in this age group; therefore, matching for age was planned at 6-month age intervals.

Telephone interviews with parents (mostly mothers) were conducted to collect data on parental age, education, and employment, the number of siblings, household crowding, drinking water sources, breastfeeding, hygiene practices, sharing pacifiers/feeding bottles between siblings, and attending daily facilities (nursery for children aged less than 3 years, kindergarten for older children, or staying at home). The question regarding child hand-washing before meals was not applicable for infants. When relevant, mothers were asked about the environmental characteristics and hygiene practices at the nursery or kindergarten (Supplementary material, Table S2). The face and content validity of the questionnaire were assessed. A pilot study ($n = 20$) evaluated and confirmed the utility and feasibility of the telephone interview.

The socio-demographic profile of the study sample was comparable to the population in Elad. For example, 92.9% of the population in Elad comprised people born in Israel, compared to 92.5% of the participants' fathers in this study. According to the population census in Israel (Israel Central Bureau of Statistics, 2017), the average number of persons living in a household in Elad in 2008 was 5.1, compared to 6.0 in the study sample; 15.2% of men aged $\geq$15 years had an academic degree compared to 17.1% of the fathers in the study sample. Of men and women aged $\geq$15 years, 53.6% and 70.6%, respectively, were employed, compared to 53.0% and 69.0% in the study sample. During the study period, 35%, 22%, and 20% of all *S. sonnei* cases were 2, 3, and 4 years old, respectively, compared to 33%, 23%, and 19% of the cases in the present study. These data suggest that the study sample was representative of the source/target population.

Laboratory methods

The isolation and identification of *Shigella* and sero-grouping were performed at the sentinel clinical microbiology laboratories by stool culture using similar routine microbiological procedures. The identification of S. *sonnei* was confirmed at the *Shigella* reference laboratory of the Ministry of Health.

Statistical methods

Incidence proportions

Annual incidence proportions for *S. sonnei* shigellosis per 1000 children were calculated by dividing the number of reported cases of culture-proven *S. sonnei* shigellosis by the number of residents aged 0–59 months in Elad and the rest of the district, using the Central Bureau of Statistics population estimates (Israel Central Bureau of Statistics, 2016). The 95% confidence intervals (CI) for the incidence proportions were calculated using the Wilson score method (Newcombe, 1998). The difference in the incidence proportion between Elad and the rest of the sub-district was assessed using the Chi-square test. The epidemic years (2000, 2002, 2004, 2006, 2008, 2010, and 2012) were defined based on significant peaks in disease incidence compared to the previous or subsequent year.

Risk factor analysis

Differences between cases and controls in socio-demographic, household, and daycare center characteristics were examined using matched conditional logistic regression models. The variables included in the multivariable models were selected according to the a priori hypotheses (e.g., hygiene practices affect the risk of shigellosis). Independent variables that were associated with case–control status, with $p < 0.2$ in the bivariate analysis, were considered in the multivariable analysis, assuming that one variable per ~10 cases could be included. One multivariable model included all the children and assessed associations of child and household characteristics with *S. sonnei* shigellosis. Another model included only the children who attended nursery/kindergarten, and assessed associations of characteristics of these facilities with the case–control status. Correlations between independent variables were assessed using Phi correlation coefficients for binary variables and Spearman's rank correlation coefficient for ordinal variables. Unadjusted (OR) and adjusted odds ratios (aOR) and 95% CI were obtained from these models. A *p*-value of <0.05 was considered statistically significant. For some questions on the features of the nursery/kindergarten, parents replied 'I do not know'. These were treated as missing values for which multiple imputation was used (Sterne et al., 2009). The analyses were performed using IBM SPSS version 25 software (IBM Corp., Armonk, NY, USA).

Sample size calculation

The sample size of the case–control study was determined using the following assumptions: a prevalence of 50% of one of the exposure variables (e.g., a family member with diarrhea) in the control group and an OR = 3, type 1 error = 0.05, power 80%, and two controls per case. Using these assumptions, the minimum sample size was 50 cases and 100 controls. A total of 78 cases and 141 controls were enrolled. The cases included in the study represented 35% of the *S. sonnei* shigellosis cases reported in 2010 and 2012.

Table 1
Socio-demographic characteristics of cases and controls.[a]

Variable	Cases ($n = 78$)	Controls ($n = 141$)	*p*-Value
Sex, male	32 (41)	57 (40)	1.0
Age (months)			0.17
0–11	1 (1)	2 (1)	
12–23	13 (17)	12 (9)	
24–35	26 (33)	47 (33)	
36–59	38 (49)	80 (57)	
Maternal age (years), mean (SD)	31.3 (4.4)	32.1 (5.0)	0.17
Paternal age (years), mean (SD)	33.3 (4.6)	34.0 (5.7)	0.2
Maternal education, academic[b]	29 (38)	39 (29)	0.4
Paternal education, academic[b]	15 (20)	21 (16)	0.6
Maternal employment[b]	52 (67)	97 (70)	0.6
Paternal employment[b]	43 (55)	71 (51)	0.6
Family income, above the average[b]	21 (28)	25 (21)	1.0
Density index, mean (SD)[c]	1.6 (0.4)	1.7 (0.5)	0.04
Number children aged 0–5 years, 3+[d]	28 (36)	59 (43)	0.3
The child receives tap water[b]	54 (69)	92 (76)	0.3

SD, standard deviation.
[a] Data are absolute numbers with percentages in parentheses, unless specified otherwise. *p*-Value from matched conditional logistic regression models. Information was missing on the following variables: maternal age (one case, three controls), paternal age (one case, four controls), maternal education (two cases, seven controls), paternal education (one control), family income (three cases, 24 controls), siblings aged 0–5 years (five controls), tap water (20 controls), and household density (two controls).
[b] Yes vs. no.
[c] Household density index calculated as the number of persons living in the household divided by the number of rooms in the household.
[d] Three or more vs. 0–2 children.

Results

Incidence of S. sonnei *shigellosis*

Between 2000 and 2013, 1010 cases of *S. sonnei* shigellosis among children aged 0–59 months were reported for Elad and 2644 for the rest of the sub-district. The corresponding mean annual incidence proportions were 10.0 per 1000 (95% CI 7.9–12.6) and 3.8 per 1000 (95% CI 3.3–4.4) (Chi-square = 51.8 $p < 0.001$). The incidence of *S. sonnei* shigellosis followed a cyclic pattern with epidemics every 2 years (Figure 1); peaks were observed in the years 2000, 2002, 2004, 2006, 2008, 2010, and 2012, which were considered epidemic years. In Elad, the increases in the incidence between the non-epidemic years and epidemic years were prominent and they decreased significantly in each subsequent non-epidemic year, except for the difference between 2007 and 2008. In the rest of the sub-district, significant differences were also observed between epidemic and non-epidemic years.

Risk factors for S. sonnei *shigellosis*

Overall, 218 children of mean age 38.7 months (standard deviation 14.3 months) were enrolled. The cases ($n = 78$) and controls ($n = 141$) had similar socio-demographic and household characteristics (Table 1).

The cases had a 3-fold increased likelihood ($p = 0.003$) of concurrently having one family member with diarrhea and an

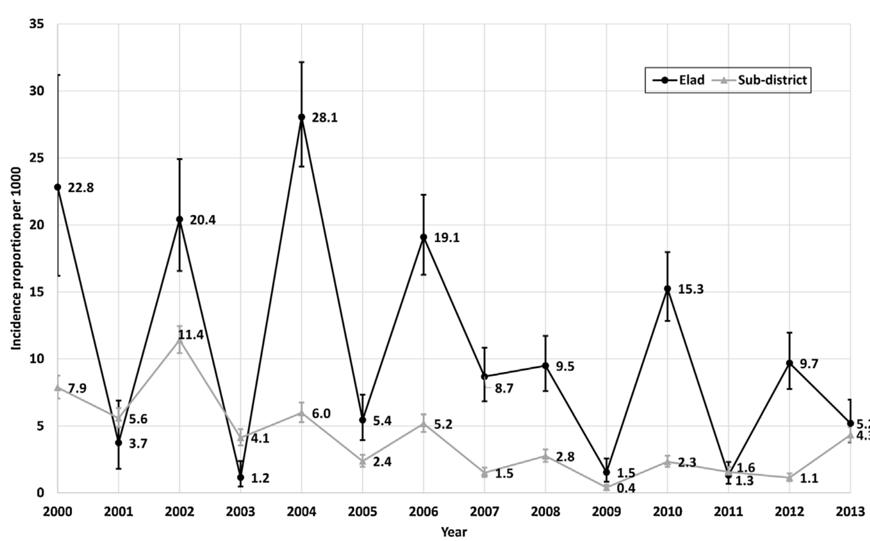

Figure 1. Incidence proportion per 1000 (95% confidence interval) of *Shigella sonnei* shigellosis among children aged 0–59 months, for Elad and the rest of the sub-district—Israel, 2000–2013.

Table 2
Environmental conditions of cases and controls.[a]

Variable	Cases (n = 78)	Controls (n = 141)	Matched OR (95% CI)	p-Value
Breastfeeding[b]	66 (86)	121 (86)	0.83 (0.36–1.90)	0.6
Antibiotic use in the week before symptoms[b]	3 (4)	17 (13)	0.21 (0.05–0.96)	0.045
History of visiting physician due to diarrhea[b]	39 (51)	44 (31)	2.32 (1.25–4.30)	0.007
Number of family members with diarrhea				<0.001
1 (versus none)	22 (28)	26 (18)	3.41 (1.52–7.67)	0.003
2+ (versus none)	25 (32)	6 (4)	11.28 (4.14–30.7)	<0.001
Other children share the child's bottle[b]	43 (55)	93 (66)	0.64 (0.35–1.17)	0.14
Other children share the child's pacifier[b]	60 (77)	117 (82)	0.67 (0.31–1.46)	0.3
Mother's spoon-sharing habits[b]	31 (40)	69 (49)	0.66 (0.37–1.18)	0.16
Boiling bottlers/nipples for child feeding[b]	26 (49)	40 (63)	0.61 (0.25–1.47)	0.2
Child hand-washing before meals[c]	61 (82)	129 (94)	0.26 (0.09–0.76)	0.014
Parents' hand-washing before preparing food[b]	72 (92)	135 (96)	0.34 (0.08–1.43)	0.14
Cleaning the house every day[b]	18 (23)	43 (31)	0.72 (0.38–1.38)	0.3

OR, odds ratio; CI, confidence interval.
[a] Data are absolute numbers with percentages in parentheses, unless specified otherwise. p-Value from matched conditional logistic regression models. Information was missing on the following variables: breastfeeding (one case, one control), antibiotic use in the week before symptoms (one case, five controls), history of visiting physician due to diarrhea (one case, two controls), cleaning the house every day (one control), child hand-washing before meals (five cases, five controls), and parents hand-washing before preparing food (one control).
[b] Yes vs. no in all comparisons except for the number of family members with diarrhea, for which the reference groups were defined as not concurrently having a family member with diarrhea.
[c] The question was not applicable for infants and was treated as a missing value in the analysis.

11-fold increased likelihood of having two or more family members with diarrhea ($p < 0.001$). A history of physician visits due to diarrhea (not related to the current episode) was positively and significantly associated with *S. sonnei* shigellosis. A significant inverse association was found between antibiotic use in the week before illness and *S. sonnei* shigellosis. Parental report that their child washes hands before meals was also inversely associated with *S. sonnei* shigellosis. No significant differences between cases and controls were found regarding other independent variables (Table 2).

A multivariable model showed that compared to children whose parents reported no concurrent diarrhea in the family, children having one family member with diarrhea had a 5-fold (95% CI 1.65–16.4) increased likelihood of *S. sonnei* shigellosis and a 14-fold (95% CI 3.82–52.24) increased likelihood if they had two or more family members with diarrhea. Child hand-washing before meals was associated with an 84% lower risk of *S. sonnei* shigellosis (aOR 0.16, 95% CI 0.04–0.69) (Table 3). Antibiotic use before illness and a history of attending a physician due to diarrheal disease were not significant in this model, neither were other household characteristics and hygiene characteristics.

Environmental characteristics of the nursery/kindergarten

Sixty-eight cases (87%) and 124 controls (88%) attended a nursery or kindergarten. Information on some of the environmental conditions of the nursery/kindergarten was missing, since parents did not always know these details (Supplementary material, Table S3), therefore multiple imputation was performed.

The likelihood of attending a nursery vs. kindergarten was higher among cases than controls: OR 3.12 (95% CI 1.25–7.79). Having at least one sink in every room/facility and using pacifiers were positively associated with *S. sonnei* shigellosis: OR 2.66 (95% 0.97–7.30). No significant differences between the groups were found regarding other environmental characteristics of the nursery/kindergartens (Table 4). Similar results were obtained when using the original dataset without multiple imputation (Supplementary material, Table S3), therefore the complete-case dataset was used in the multivariable analysis.

The type of facility (nursery vs. kindergarten) was significantly correlated with age (Spearman's correlation coefficient 0.64, $p < 0.001$). Facility type was also correlated with the variable 'having the same person in the daycare center responsible for food handling and changing diapers' (Phi correlation coefficient 0.50, $p < 0.001$). Therefore, only this variable was assessed in the multivariable model. This model showed that having the same person responsible for both food handling and changing diapers of children increased the risk of *S. sonnei* shigellosis (aOR 2.93, 95% CI 0.83–10.35), but the difference was not significant ($p = 0.09$). Having two rooms or more vs. one room at the facility increased the disease risk by 2.50-fold (95% CI 1.05–5.96) ($p = 0.04$), as did

Table 3
Multivariable conditional logistic regression analysis of household-related correlates of *Shigella sonnei* shigellosis.

Variable	Adjusted OR (95% CI)[a]	p-Value
Number of family members with diarrhea	df = 2	<0.001
1 (reference = none)	5.21 (1.61–16.43)	0.005
≥2 (reference = none)	14.14 (3.82–52.24)	<0.001
Child hand-washing before meals (reference = no)[b]	0.16 (0.04–0.69)	0.014
Antibiotic treatment before illness (reference = no)	0.40 (0.07–2.23)	0.2
History of a visiting physician due to diarrhea (reference = no)	1.33 (0.56–3.15)	0.5
Other children share the child's bottle (reference = no)	0.66 (0.30–1.45)	0.3
Other children share the child's pacifier (reference = no)	0.47 (0.13–1.64)	0.2

OR, odds ratio; CI, confidence interval.
[a] Adjusted the variables in the table. Another model was run and included the variables mother's spoon-sharing habits and parents' hand-washing before preparing food. Significant associations were not shown for these variables with *S. sonnei* shigellosis ($p = 0.9$ and $p = 0.6$, respectively), thus they were excluded from the model.
[b] The question was not applicable for infants and was treated as a missing value in the analysis.

Table 4
Environmental characteristics of the nursery/kindergarten for the cases and controls.[a]

	Cases ($n = 68$)	Controls ($n = 124$)	Matched OR (95% CI)	p-Value
Facility				
Nursery	32 (47)	33 (27)	3.12 (1.25–7.79)	0.014
Kindergarten	36 (53)	91 (73)	Reference	
Daily hours spent at the facility[b]				0.3
4–5	37 (54)	70 (57)	Reference	
6–7	7 (11)	22 (18)	0.53 (0.19–1.44)	0.2
8–10	24 (35)	31 (25)	1.18 (0.55–2.51)	0.6
10 o'clock meal[b]				
Receives at the facility	27 (40)	30 (24)	1.65 (0.79–3.45)	0.17
Brings from home	41 (60)	93 (76)	Reference	
At the end of the day[b]				
Going home	55 (81)	103 (84)	Reference	0.4
Another framework/facility	13 (19)	20 (16)	1.39 (0.60–3.19)	
Eating lunch[b]				
At home	38 (56)	86 (71)	Reference	0.17
Outside home	30 (44)	36 (30)	1.63 (0.80–3.31)	
Arrival at facility[b]				
Private car	62 (94)	111 (91)	1.44 (0.45–4.57)	0.5
Organized transportation	4 (6)	11 (9)	Reference	
Number of children at the facility				0.7
1–14	19 (28)	24 (20)	Reference	
15–20	16 (23)	35 (29)	0.73 (0.29–1.89)	0.5
≥21	33 (49)	64 (52)	0.67 (0.26–1.67)	0.3
Number of rooms at the facility				
1	30 (44)	70 (57)	Reference	
≥2	38 (56)	54 (43)	2.00 (0.95–4.22)	0.066
Number of bathrooms at the facility				
1–2	45 (66)	85 (69)	Reference	
≥3	23 (34)	39 (31)	1.05 (0.52–2.09)	0.8
At least one sink in every room[c]	57 (84)	89 (71)	2.66 (0.97–7.30)	0.05
At least one diaper changing table per room[c]	38 (56)	57 (46)	1.99 (0.42–9.24)	0.3
Hand dryers near sinks[c]	9 (13)	18 (14)	1.10 (0.39–3.10)	0.8
Pots for children[c]	15 (22)	22 (18)	1.36 (0.34–5.35)	0.6
Closed trash cans for dirty diapers[c]	40 (59)	65 (52)	1.27 (0.51–3.16)	0.5
Use of diapering equipment[c]	46 (67)	77 (62)	1.30 (0.15–11.02)	0.7
Laundry of defecated clothes at the facility[c]	10 (15)	18 (15)	1.05 (0.30–3.63)	0.9
Use of personal pacifiers[c]	45 (66)	63 (51)	2.40 (1.01–5.70)	0.04
Permission to bring food from home[c]	56 (82)	111 (89)	0.69 (0.25–1.86)	0.4
Using disposable kitchenware[c]	14 (20)	35 (28)	0.62 (0.22–1.72)	0.3
Same person for changing diapers and food preparation[c]	43 (64)	50 (40)	2.59 (0.64–10.41)	0.15
Demand to take child with diarrhea home[c]	55 (81)	107 (86)	0.75 (0.24–2.34)	0.6
Refuse to accept child with diarrhea[c]	56 (82)	111 (89)	0.60 (0.20–1.81)	0.3
Not sending child with diarrhea to the facility[c]	8 (12)	10 (8)	1.23 (0.41–3.62)	0.7

OR, odds ratio; CI, confidence interval.
[a] For children attending a nursery/kindergarten. Data are absolute numbers with percentages in parentheses, unless specified otherwise. p-Value from conditional logistic regression models.
[b] Missing information for daily hours spent at the facility (one control), 10 o'clock meal (one control), at the end of the day (one control), eating lunch (two controls), arrival at facility (two controls, two cases).
[c] Comparison between yes vs. no.

having a sink in every room at the facility (aOR 2.95, 95% CI 1.00–8.90) ($p = 0.05$). Another model showed aOR 2.70 (95% CI 1.00–7.49) for being in a nursery vs. kindergarten.

Discussion

This study investigated the incidence and risk factors of *S. sonnei* shigellosis in a Jewish ultraorthodox community consistently affected by the biennial propagated outbreaks of *S. sonnei* shigellosis. The mean incidence of *S. sonnei* shigellosis in this town was high, especially compared to the rest of the sub-district. Since a passive surveillance system was used, the estimated incidence of *S. sonnei* shigellosis is only the tip of the iceberg in regard to the burden of shigellosis. A single case of culture-proven shigellosis implies that the patient had sought medical care, a stool culture was ordered, a stool specimen was submitted to the laboratory, the laboratory successfully isolated the microorganism, and a notification was sent to the Ministry of Health. We have previously estimated a multiplier of 25 to close these gaps (Cohen et al., 2014). Applying this multiplier to the present study yields an overall annual incidence of *S. sonnei* shigellosis of 250.4 per 1000 children aged 0–59 months in Elad.

It is assumed that the cyclic peaks of *S. sonnei* shigellosis affect the population's natural immunity level to the organism and vice versa. Natural exposure to *S. sonnei* through massive shigellosis epidemics likely increases natural immunity levels to the homologous *Shigella* organism (*S. sonnei*); these are probably mediated, at least in part, by serum IgG antibodies to *S. sonnei* lipopolysaccharide (LPS) (Cohen et al., 1988, 1991). Herd immunity may also be sufficient to temporarily reduce the circulation of the bacterium in the community and prevent the onset of a new epidemic in the subsequent year. The influx of new and large cohorts of susceptible newborns, together with a waning level of anti-LPS antibodies in older children, could lead to a decrease in the herd immunity below a critical level, and thus enable renewed epidemic transmission of *S. sonnei* in the community. A similar phenomenon has been observed in other ultraorthodox Jewish communities in Israel and abroad (Cohen et al., 2014; De Schrijver et al., 2011); this also resembles the cyclic measles epidemics before the introduction of mass measles vaccination.

Important environmental correlates of *S. sonnei* shigellosis were identified in the setting described: concurrent diarrhea of individuals in the household (likely caused by *Shigella*), characteristics of daycare facilities, and a protective effect of children's hand-washing.

It was found that having family members with diarrhea significantly increased the risk of *S. sonnei* shigellosis, likely leading to a high secondary attack rate (Mohle-Boetani et al., 1995).

In the current study, hand-washing performed by the children before meals was found to be protective against *S. sonnei* shigellosis. This important observation indicates that *S. sonnei* shigellosis can be prevented by promoting hand-washing, which should be persuaded in such risk groups. This observation is in line with findings from a meta-analysis, which showed that hand-washing reduced the risk of shigellosis by 59% (Curtis and Cairncross, 2003).

The risk factors of secondary transmission of *S. sonnei* shigellosis in households were studied within an outbreak occurring in the Jewish orthodox community of Antwerp in 2008 (De Schrijver et al., 2011). Having more than three children in the household and having children younger than 12 years who assisted their parents in caring for young siblings significantly increased the risk of secondary transmission (De Schrijver et al., 2011).

A study from the USA that compared daycare centers with and without cases of shigellosis showed that 47–92% of shigellosis cases were attributable to daycare centers (Mohle-Boetani et al., 1995). An important risk factor for shigellosis in daycare centers was the practice of having the same staff members both preparing meals and changing diapers (Mohle-Boetani et al., 1995). The present study also found that having the same person in the daycare facility responsible for both food handling and changing diapers was associated with a 2.9-times higher likelihood of shigellosis, although the association was not statistically significant ($p = 0.09$). A study of secondary transmission of *S. sonnei* shigellosis in Cincinnati, Ohio, identified the following risk factors: exposure of children to soiled diapers, employing volunteers to diaper infants, and compromised hand-washing practices. The attack rate was the highest in mixed classrooms with both toilet-trained and diapered children (Shane et al., 2003).

This study has limitations. It is likely that the incidence of *S. sonnei* shigellosis was underestimated, since passive surveillance was used. The case–control study relied on parental reports including hygiene practices. Information was missing on some environmental conditions of the kindergarten/nursery; however, this was similar among cases and controls. This study also has strengths, including the multi-year incidence data for both Elad and the rest of the sub-district, which were determined in the same manner. Moreover, the sample selected for the case–control study was representative of the source/target population of Elad city.

In conclusion, a high burden of *S. sonnei* shigellosis in ultraorthodox communities was demonstrated. Education programs to increase parental awareness of household cleaning and personal hygiene after the onset of diarrhea in a family member could prevent further transmission of *Shigella*. A new generation of promising conjugate and other *Shigella* vaccines is in clinical development (Ashkenazi and Cohen, 2013; Mani et al., 2016). *S. sonnei* candidate vaccines could be tested in these settings, and safe and efficacious ones could be used routinely once licensed.

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Ethical approval

The study was approved by the Ethics Committee of Tel Aviv University. Oral informed consent over the phone was obtained from the children's parents.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2019.02.031.

References

Ashkenazi S, Cohen D. An update on vaccines against *Shigella*. Ther Adv Vaccines 2013;1:113–23.

Cohen D, Green MS, Block C, Rouach T, Ofek I. Serum antibodies to lipopolysaccharide and natural immunity to shigellosis in an Israeli military population. J Infect Dis 1988;157:1068–71.

Cohen D, Green MS, Block C, Slepon R, Ofek I. Prospective study of the association between serum antibodies to lipopolysaccharide O antigen and the attack rate of shigellosis. J Clin Microbiol 1991;29:386–9.

Cohen D, Sela T, Slepon R, Yavzori M, Ambar R, Orr N, et al. Prospective cohort studies of shigellosis during military field training. Eur J Clin Microbiol Infect Dis 2001;20:123–6.

Cohen D, Bassal R, Goren S, Rouach T, Taran D, Schemberg B, et al. Recent trends in the epidemiology of shigellosis in Israel. Epidemiol Infect 2014;142:2583–94.

Curtis V, Cairncross S. Effect of washing hands with soap on diarrhoea risk in the community: a systematic review. Lancet Infect Dis 2003;3:275–81.

De Schrijver K, Bertrand S, Gutierrez Garitano I, Van den Branden D, Van Schaeren J. Outbreak of *Shigella sonnei* infections in the Orthodox Jewish community of Antwerp, Belgium, April to August 2008. Euro Surveill 2011;16.

DuPont HL, Levine MM, Hornick RB, Formal SB. Inoculum size in shigellosis and implications for expected mode of transmission. J Infect Dis 1989;159:1126–8.

Garrett V, Bornschlegel K, Lange D, Reddy V, Kornstein L, Kornblum J, et al. A recurring outbreak of *Shigella sonnei* among traditionally observant Jewish children in New York City: the risks of daycare and household transmission. Epidemiol Infect 2006;134:1231–6.

Gupta A, Polyak CS, Bishop RD, Sobel J, Mintz ED. Laboratory-confirmed shigellosis in the United States, 1989–2002: epidemiologic trends and patterns. Clin Infect Dis 2004;38:1372–7.

Gurovich NC-K, Eilat. Ultra-orthodox Jews: geographic distribution and demographic, social and economic characteristics of the ultra-orthodox population in Israel, 1996–2001. Central Bureau of Statistics; 2004.

Hyams KC, Bourgeois AL, Merrell BR, Rozmajzl P, Escamilla J, Thornton SA, et al. Diarrheal disease during Operation Desert Shield. N Engl J Med 1991;325:1423–8.

Israel Center for Diseases Control and Division of Epidemiology Public Health Services, Ministry of Health Notifiable Infectious Diseases in Israel. 60 years of surveillance 1951–2010; 2012.

Israel Central Bureau of Statistics. Israel abstracts 2015; 2015. http://www.cbs.gov.il/reader/shnaton/shnatone_new.htm.http://wwwcbsgovil/reader/shnaton/shnatone_newhtm.

Israel Central Bureau of Statistics. Elad; 2017. https://www.cbs.gov.il/he/Settlements/Pages/%D7%99%D7%99%D7%A9%D7%95%D7%91%D7%99%D7%9D/%D7%90%D7%9C%D7%A2%D7%93.aspx. [Accessed February 2019].

Khalil IA, Troeger C, Blacker BF, Rao PC, Brown A, Atherly DE, et al. Morbidity and mortality due to shigella and enterotoxigenic *Escherichia coli* diarrhoea: the Global Burden of Disease Study 1990–2016. Lancet Infect Dis 2018;18(11):1229–40, doi:http://dx.doi.org/10.1016/S1473-3099(18)30475-4.

Levine MM, Kotloff KL, Barry EM, Pasetti MF, Sztein MB. Clinical trials of *Shigella* vaccines: two steps forward and one step back on a long, hard road. Nat Rev Microbiol 2007;5:540–53.
Livio S, Strockbine NA, Panchalingam S, Tennant SM, Barry EM, Marohn ME, et al. *Shigella* isolates from the global enteric multicenter study inform vaccine development. Clin Infect Dis 2014;59:933–41.
Mani S, Wierzba T, Walker RI. Status of vaccine research and development for *Shigella*. Vaccine 2016;34:2887–94.
Mohle-Boetani JC, Stapleton M, Finger R, Bean NH, Poundstone J, Blake PA, et al. Communitywide shigellosis: control of an outbreak and risk factors in child day-care centers. Am J Public Health 1995;85:812–6.
Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998;17:857–72.
Pires SM, Fischer-Walker CL, Lanata CF, Devleesschauwer B, Hall AJ, Kirk MD, et al. Aetiology-specific estimates of the global and regional incidence and mortality of diarrhoeal diseases commonly transmitted through food. PLoS One 2015;10: e0142927.
Porter CK, Olson S, Hall A, Riddle MS. Travelers' diarrhea: an update on the incidence, etiology, and risk in military deployments and similar travel populations. Mil Med 2017;182:4–10.
Shane AL, Tucker NA, Crump JA, Mintz ED, Painter JA. Sharing *Shigella* risk factors for a multicommunity outbreak of shigellosis. Arch Pediatr Adolesc Med 2003;157:601–3.
Sobel J, Gomes TA, Ramos RT, Hoekstra M, Rodrigue D, Rassi V, et al. Pathogen-specific risk factors and protective factors for acute diarrheal illness in children aged 12–59 months in Sao Paulo, Brazil. Clin Infect Dis 2004;38:1545–51.
Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338.
Thompson CN, Anders KL, Nhi le TQ, Tuyen HT, Van Minh P, Tu le TP, et al. A cohort study to define the age-specific incidence and risk factors of *Shigella* diarrhoeal infections in Vietnamese children: a study protocol. BMC Public Health 2014;14:1289.
von Seidlein L, Kim DR, Ali M, Lee H, Wang X, Thiem VD, et al. A multicentre study of *Shigella* diarrhoea in six Asian countries: disease burden, clinical manifestations, and microbiology. PLoS Med 2006;3:e353.
Vinh H, Nhu NT, Nga TV, Duy PT, Campbell JI, Hoang NV, et al. A changing picture of shigellosis in southern Vietnam: shifting species dominance, antimicrobial susceptibility and clinical presentation. BMC Infect Dis 2009;9:204.
Zboromyrska Y, Hurtado JC, Salvador P, Alvarez-Martinez MJ, Valls ME, Mas J, et al. Aetiology of traveller's diarrhoea: evaluation of a multiplex PCR tool to detect different enteropathogens. Clin Microbiol Infect 2014;20:O753–9.