Epidemiologic Surveillance in Israel of *Cryptosporidium*, a Unique Waterborne Notifiable Pathogen, and Public Health Policy

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ABSTRACT: **Background:** *Cryptosporidium* is a major threat to water supplies worldwide. Various biases and obstacles in case identification are recognized. In Israel, Cryptosporidiosis was included among notifiable diseases in 2001 to determine the burden of parasite-inflicted morbidity and to justify budgeting a central drinking water filtration plant.

Objective: To summarize the epidemiologic features of 14 years of *Cryptosporidium* surveillance and to assess the effects of advanced water purification treatment on the burden of disease.

Methods: From 2001 to 2014, a passive surveillance system was used. Cases were identified based on microscopic detection in stool samples. Confirmed cases were reported electronically to the Israeli Ministry of Health. Overall rates as well as age, gender, ethnicity and specific annual incidence were calculated per 100,000 population in five age groups: 0–4, 5–14, 15–44, 45–64, › 65 years.

Results: A total of 522 *Cryptosporidium* cases were reported in all six public health districts. More cases were detected among Jews and among males, and mainly in young children, with a seasonal peak during summer. The Haifa sub-district reported 69% of the cases. Most were linked to an outbreak from the summer of 2008, which was attributed to recreational swimming pool activity. Cases decreased after installation of a central filtration plant in 2007.

Conclusions: As drinking water in Israel is treated to maximal international standards, the rationale for further inclusion of *Cryptosporidium* among mandatory notifiable diseases should be reconsidered. Future surveillance efforts should focus on timely detection of outbreaks using molecular high-throughput testing.

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KEY WORDS: *Cryptosporidium*, health policy, notifiable diseases, waterborne hazard, water purification

Supply of safe and clean drinking water is defined as an elemental human right, recognized in international law, and one of the cornerstones of public health [1]. The waterborne protozoa *Cryptosporidium* is a worldwide major threat to water supplies, in developed and developing countries alike [2,3,4]. *Cryptosporidium*, first reported in 1976 as a human pathogen, causes diarrheal disease in sporadic and epidemic patterns and has been recognized as a common cause of diarrhea in otherwise healthy children [4], as well as in immunocompromised people [5,6], and in malnourished children in the least developed countries [6,7]. Extremely high infectivity [2] and resistance to routine chlorine disinfection [8] facilitates outbreaks and challenges control efforts [8,9]. Differentiating *Cryptosporidium* from other non-bloody diarrheal diseases is based on stool sample analysis. The clinical and laboratory diagnostic process and case-finding is highly prone to numerous pitfalls at all levels, often resulting in under-diagnosis and under-reporting [3,10]. Microscopy is a time-honored diagnostic method, necessitating high technical and visual expertise. Detection is facilitated by recently introduced antigen detection and molecular advanced methods [11,12].

Emergence of *Cryptosporidium* massive outbreaks originating in drinking water supply facilities in the 1990s underlined the necessity of close monitoring by health authorities and of water quality standards and regulations [2,9]. Consequently, the disease is notifiable in most developed countries, although actual burden worldwide is unknown, due to under-reporting [4,6,11]. In Israel, surveillance and monitoring of over 200 mandatory notifiable significant infectious diseases is performed under the Public Health Ordinance (1940) from 6 public health district authorities, further divided to 15 sub-districts [13,14]. Surveillance is passive, based on regular reporting of disease data by physicians and laboratories, without active search for cases. Traditionally, *Cryptosporidium* was not considered a threat to public health in Israel and its inclusion as a notifiable disease in 2001 was based on unusual reasoning. The Ministry of Treasury requested an estimation of the waterborne parasite burden of disease to justify budgeting a US$150 million central water filtration plant for treatment and purification of the surface water carried from the Sea of Galilee via the national water conduit and pooled in the Eshkol central storage reservoir prior to supplying the entire country via a closed piping system.

Concurrently, toward the end of the 20th century, the perspective of expected water quality in the developed world evolved, as major outbreaks heralded demands for water treatment policy improvements [2,9]. In addition, since 2000, water regulations in Israel have been set to the highest international standards. Thus, although assessment of the parasite waterborne burden of disease initially included budgeting of the costly water filtration processes, eventually, due to pressure by the Ministry of Health, the public, and academics, the Eshkol water filtration plant was budgeted and completed by 2007, independently of waterborne diseases data, which had not yet been collated. Yet, as notification of *Cryptosporidium* remained mandatory, a unique opportunity to analyze the data before and after the intervention emerged.

Recreational water is an additional *Cryptosporidium*-associated major waterborne hazard [15-19]. Swimming pools have been recognized as a major source of outbreaks, even when apparently well maintained [17,20]. *Cryptosporidium* is the most common cause of swimming pools outbreaks [11,19] due to the great resistance to chlorine [8] and difficult elimination by filtration. To the best of our knowledge, no studies of other possible modes of transmission, such as foodborne, person-to-person, or transmission from domestic animals have been conducted in Israel [3].

The aim of our study was to summarize the epidemiologic features of 14 years of population-based *Cryptosporidium* surveillance and to assess the effect of advanced water treatment on the burden of disease in Israel.

PATIENTS AND METHODS

EPIDEMIOLOGICAL INVESTIGATIONS

A passive surveillance system was used during the period of our study (2001–2014). Cases were identified based on detection in stool samples. Testing was conducted at specific physician requests. All laboratories used a modified Ziehl-Neelsen microscope, and relied on expertise of highly skilled experienced technicians. Laboratory-confirmed cases were reported electronically to the Ministry of Health via the district health bureaus, including patient's name and identification number,

Table 1. Cryptosporidium cases reported by districts public health bureaus 2001–2014

		Haifa		North					Jerusalem	Center				Tel Aviv	South	
Year	Total number of cases	Haifa (% of total in Haifa district; % of total in Haifa sub-district, 153)	Hadera	Acco	Afula	Safed	Galilee	Nazareth	Jerusalem	Sharon district	Petah Tikva	Ramla	Rehovot	Tel Aviv	Beer Sheva	Ashkelon
2001	21	21 (100;100)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2002	16	16 (100;100)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2003	10	8 (80;80)	0	1	0	0	0	0	0	0	0	1	0	0	0	0
2004	41	35 (85.4;85.4)	0	3	0	0	0	0	0	2	0	0	1	0	0	0
2005	42	34 (81;81)	0	1	0	1	0	0	0	5	0	0	1	0	0	0
2006	68	57 (86.8;83.8)	1	4	4	1	0	0	0	0	0	0	0	1	0	0
2007	16	14 (87.5;87.5)	0	1	0	0	0	0	0	0	0	0	1	0	0	0
2008	177	153 (90.4;86.4)	7	11	2	2	0	0	0	0	0	0	0	1	0	1
2009	7	5 (85.7;71.4)	1	1	0	0	0	0	0	0	0	0	0	0	0	0
2010	30	11 (40.0;36.7)	1	1	0	0	0	0	0	0	0	6	1	6	3	0
2011	25	1 (28.0;4.0)	6	0	0	0	0	0	1	1	0	3	0	6	6	1
2012	48	4 (8.3;8.3)	0	1	0	0	0	0	0	1	0	6	5	23	5	3
2013	9	0 (0;0)	0	0	0	0	0	0	1	0	0	5	0	2	1	0
2014	12	0 (0;0)	0	2	0	1	0	0	1	0	3	1	0	2	1	1
Total	522	359	16	26	6	6	0	0	3	9	3	22	9	41	16	6

date of positive test, referring physician, healthcare provider, place of residence, age, gender, ethnicity, and religion. Official population data from the Central Bureau of Statistics were used to calculate rates by year, reporting districts, age, gender, and ethnicity. Five age groups were defined: 0–4, 5–14, 15–44, 45–64, > 65 years. Overall and age, gender, ethnicity, and specific annual incidence rates were calculated per 100,000 population.

GEOGRAPHIC INFORMATION SYSTEM MAPPING OF OUTBREAK CASES

Cases of *Cryptosporidium* that were determined in 2008 in the Haifa district during a summer outbreak were retrospectively mapped using a geographic information system (GIS), and including personal details of all cases, names, addresses, ages, and health care providers. Home addresses were geo-coded, converted into X,Y coordinates, and positioned on maps provided by the Central Bureau of Statistics. ArcGIS 9.xTM software (ESRI, USA) was used.

RESULTS

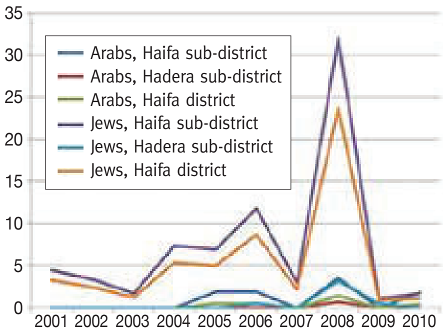
Only 522 *Cryptosporidium* cases were reported from 2001 to 2014 [Table 1]. The Haifa sub-district reported 359/522 (69%) of all cases, all but five before 2011 [Table1, Figure 1]. A large local cluster was observed in a Haifa sub-district in 2008 (153 cases). Only a small number of solitary or almost solitary cases were reported from 2010 to 2014. From 2013 to 2014 there were no cases in the Haifa district and only 21 cases in the rest of Israel. As the Haifa district, and specifically the Haifa sub-district, was the main and most steady and stable source of notification, the following analyses are based on those reports.

More cases of *Cryptosporidium* were detected among Jews than Arabs [Figure 1A]. Incidence among males was higher than among females across all sub-districts and ethnicities. The average male to female ratio was 2.1 ± 1.3, 0–4 years unimodal age peaking was shown in the Haifa district, remarkebly noticeable also during the 2008 outbreak [Figure 1B]. Rates of diagnosis in 2008 were 175/100,000 for children aged 0–4 years, 19.9/100,000 for ages 5–14, 1.4/100,000 for ages 15–44, and no cases older than this age. The number of cases increased in July, peaked in August–September, and extended until October–December [Figure 1C]. Almost no cases were reported from January to June. This seasonal distribution was also prominent during 2008 outbreak.

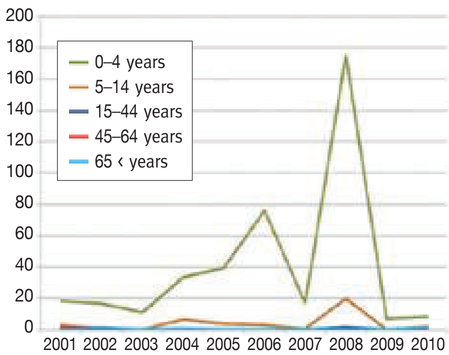
GIS mapping [Figure 2] demonstrated clustering in suburbs of the city of Haifa. Most cases were patients of six local pediatricians. Figure 3 presents annual numbers of cases from the Haifa district, including and excluding the year 2008. For demonstration purposes, all the cases from 2008 were excluded for the illustration, as it was not possible to calculate exactly how many cases were attributed to a presumed swimming pool outbreak and how many were sporadic. The

Figure 1. Annual incidence rates of *Cryptosporidium* per 100,000 population

[A] Annual incidence rates of *Cryptosporidium* per 100,000 population, by ethnic groups and by Haifa and Hadera sub-districts, in Haifa district, 2001–2010



[B] Annual incidence rates of *Cryptosporidium* per 100,000 population, by age groups in Haifa district, 2001–2010



[C] Annual incidence rates of *Cryptosporidium* cases, by date, of laboratory positive sample, Haifa district, 2001–2010 (n=364 cases)

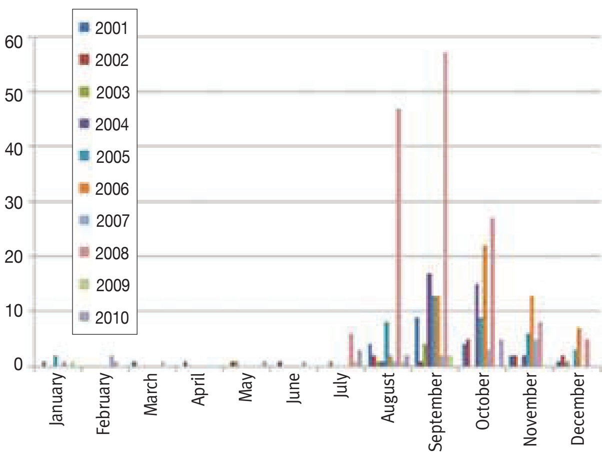
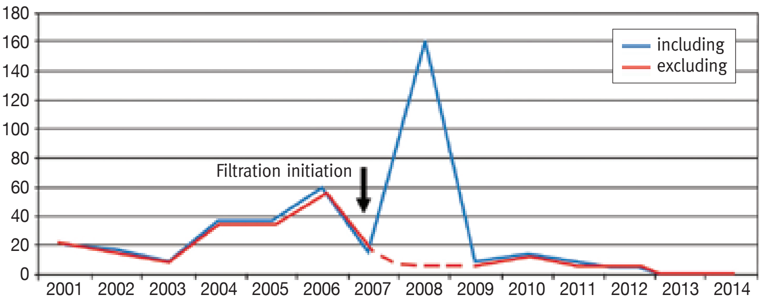


Figure 2. Distribution of *Cryptoporidium* cases shown using GIS mapping, from July to December 2008, city of Haifa and suburbs. Symbols represent patients referred by six pediatricians

Figure 3. Annual Cryptosporidium cases in Haifa district, 2001–2004, including and excluding 200 cases (including 2008) n=375



decline from 2006 in 2007 is statistically significant (OR = 4.07, P = 0.0000). During the 6 years period before filtration treatments were installed (2001–2006) [Table 1], there were 171 cases in the Haifa district (mean 28.5 cases/year) compared with the period 2009–2014, when there were only 21 cases (mean 3.5 cases/year). The significant decline coincides with initiation of surface water filtration, officially launched in mid-2007, but partially operable earlier.

DISCUSSION

This case study of *Cryptosporidium* surveillance was initiated to assess the implications of a major public health intervention, namely the installation of a water treatment plant in the Eshkol national central water reservoir. Reliability of data collected among subpopulations regarding actual burden of disease for this specific pathogen during 2001–2014 was shown to be influenced by biases and artifacts. Our observation that most surveillance data clustered in a single region (the Haifa sub-district) is striking, but not uncommon for the *Cryptosporidium* pathogen, as reflected in the medical literature from Europe. The United Kingdome reports higher rates to The European Surveillance System (TESSy) than do other European countries [10]. Those rate discrepancies are partially due to different approaches to *Cryptosporidium* ascertainment and reporting, and do not totally reflect genuine rate variations [10]. Similarly, we hypothesize that the variation between sub-districts reported is largely due to referral and detection biases, rather than differences in actual incidence. Primary practitioners differ in awareness and request of specific analyses [Figure 3], and as the diagnostic methods used were technician-dependent, it is possible that some laboratories were better skilled.

Our data showed ethnic and regional differences in detection rates. These differences may be explained by disparities in health behavior and referral patterns, and deserves further research. In this context it is noteworthy that *Cryptosporidium* seroprevalence was found to be in the same range among the Jewish and Arab populations [3]. Morbidity peaks within the young male age group were consistent across all subpopulations, sub-districts, and ethnicities, supporting a genuine high rate. Prominent infliction of children younger than 4 years is also reported in global surveillance programs [16]. Less established hygiene protocols and lack of pre-existing immunity renders this subpopulation more susceptible and symptomatic. Selection bias with preference of the pediatric age group may contribute as well. Seasonality with clustering of cases during summer and autumn is clearly demonstrated, similar to findings in other countries [11,16] and presumably due to vacation travel and swimming pool use.

Missed cryptosporidiosis outbreaks are a common phenomenon worldwide [10] as was the unrecognized and timely investigated 2008 clustering. Based on a literature search, epidemiologic features, and water monitoring, we hypothesize that this outbreak originated in a recreational water source. It is well established worldwide that drinking water quality regulations led to decreased *Cryptosporidium* incidence and drinking-water outbreaks [9,16,17] and that former biannual peaks, occurring spring and autumn, were replaced by a single peak in late summer and early autumn [4], which was attributed to recreational swimming pool activity, in a pattern similar to our observed 2008 single peak. Summertime swimming pool outbreaks are demographically characterized by younger age, while outbreaks associated with drinking water affect all age groups with excess cases typically concentrated in adults [10]. However, seasonal timing is not necessarily during the summer [9]. Additional support is derived from monitoring records in the Haifa sub-district with no evidence of drinking water contamination. In contrast, evidence gathered from swimming pool monitoring in the Haifa district has shown that in 2008 contamination events were a few fold higher than previous and following years. Sanitary conditions in pools in Haifa district generally improved during 2007–2014, with the exception of 2008.

A GIS-based approach enables investigation of geographical and temporal patterning of presumed outbreaks [Figure 2]. The clustering of cases in the suburbs of Haifa may reflect a local swimming pool outbreak and amplification via community-wide transmission [11]. Referral bias seems to be a contributing factor, as predominantly 6 of 60 pediatricians practicing in the sub-district were appointed as health providers of most confirmed cases.

The strategy used to monitor most notifiable diseases is passive surveillance. Inherent disadvantages jeopardize accurate completeness and timeliness of data [13,14]. The active surveillance approach provides a more complete reporting of health events, but its major disadvantage is high use of expensive resources. Syndromic surveillance is a recently developed approach addressing modern surveillance challenges and global needs to rapidly detect and contain public health threats and emergencies. Syndromic surveillance uses existing health-related information and can signal and alert a sufficient probability of an outbreak risk. Currently, use is still limited to highly prioritized diseases due to its reliance on an established specific infrastructure. In the United Kingdom, in which *Cryptosporidium* is prioritized, this approach has been applied [20,21]. In Israel, syndromic surveillance is implemented for monitoring high-prioritized specific conditions, mainly acute flaccid paralysis and influenza. It is beyond the scope of our study to further discuss novel surveillance approaches in detail.

Within the existing passive surveillance network, reporting improvements should be implemented at all levels. Although clinicians could be educated to change practices, the key to better diagnosis and case definition is focused at the laboratory level**.** During the period of our retrospective study, molecular methods and genotyping were not undertaken. Upgraded diagnostic methods [11,22,23] enable case definitions that are not dependent on subjective laboratory technician skills. Molecular methods are increasingly implemented for *Cryptosporidium* isolate characterization [12,23], enabling outbreak detection and investigation as well as source tracking [6,11,22,23]. Multiplex molecular assays for routine combinations of pathogens are already being used in numerous countries, including Israel [12,23,24]. Those techniques enable high throughput screening of many samples with increased sensitivity and short turnaround times, which are essential in modern large microbiology laboratories, and can shed light on routine epidemiologic surveillance and investigation of future outbreaks [12,23,24].

A major strength of our study is the long-term surveillance of *Cryptosporidium* incidence, starting 6 years before the water filtration intervention and continuing 7 years after. The population-based surveillance enables sub-group analysis [11,16]. Furthermore, excellent monitoring data and documentation of drinking water and swimming pools was available. The inherent insensitivity of passive surveillance is a universal limitation [10,11]. Despite mandatory guidelines issued by the Ministry of Health [13], under-reporting and under-estimation of actual incidence of *Cryptosporidium* disease is likely [14]. Nevertheless, we were able to demonstrate that during over a decade of surveillance, a decline of *Cryptosporidium* morbidity followed the introduction of central water filtration. Recreational water has maintained its role as a source for waterborne infections and outbreaks, even when regulations are clear and enforced [18,19].

CONCLUSIONS

The primary reason for introduction of *Cryptosporidium* as a mandatory notifiable disease was to create a database for considerations of cost effectiveness regarding drinking water filtration. From a public health viewpoint, it was highly justified that authorities took all measures to bring the water quality to the highest level, without the prerequisite of the surveillance of waterborne diseases outcome. As water is being treated to maximal international standards, the rationale for further inclusion of *Cryptosporidium* among mandatory notifiable diseases should be reconsidered. Future efforts should focus on timely detection of outbreaks. Surveillance and monitoring should rely on more sophisticated contemporary approaches, and on molecular high throughput testing.

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Capsule

Targeting cancer transmission in devils

The population of Tasmanian devils has been dropping rapidly, leading to their designation as endangered species. The species has been succumbing to a transmissible cancer called devil facial tumor disease. In a perspective, **Patchett and Woods** discussed the emerging ideas about how this disease has evolved to be transmitted between individuals. Recent findings demonstrate how these tumors evade the host immune system, revealing potential strategies for therapeutic intervention.

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Capsule

Stress-glucocorticoid–TSC22D3 axis compromises therapy-induced antitumor immunity

Psychological distress has long been suspected to influence cancer incidence and mortality. It remains largely unknown whether and how stress affects the efficacy of anticancer therapies. **Yang** et al. observed that social defeat caused anxiety-like behaviors in mice and dampened therapeutic responses against carcinogen-induced neoplasias and transplantable tumors. Stress elevated plasma corticosterone and upregulated the expression of glucocorticoid-inducible factor *Tsc22d3*, which blocked type I interferon (IFN) responses in dendritic cell (DC) and IFN-γ^+ T cell activation. Similarly, close correlations were discovered among plasma cortisol levels, *TSC22D3* expression in circulating leukocytes and negative mood in patients with cancer. In murine models, exogenous glucocorticoid injection, or enforced expression of *Tsc22d3* in DC was sufficient to abolish therapeutic control of tumors. Administration of a glucocorticoid receptor antagonist or DC-specific *Tsc22d3* deletion reversed the negative impact of stress or glucocorticoid supplementation on therapeutic outcomes. Altogether, these results indicate that stress-induced glucocorticoid surge and *Tsc22d3* upregulation can subvert therapy-induced anticancer immunosurveillance.

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