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An autochthonous case of cystic echinococcosis in Finland, 2015

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We report a case of pulmonary cystic echinococcosis in a child from eastern Finland with no history of travelling abroad. The cyst was surgically removed and the organism molecularly identified as *Echinococcus canadensis* genotype G10. This parasite is maintained in eastern Finland in a sylvatic life cycle involving wolves and moose; in the present case, the infection was presumably transmitted by hunting dogs.

In Fennoscandia (Finland, Norway and Sweden) and parts of western central Europe, cystic echinococcosis (CE) or hydatidosis is a rare disease seen in immigrants or other people who have resided in endemic countries. Here we present an unexpected autochthonous case of pulmonary CE in a Finnish child.

Case description

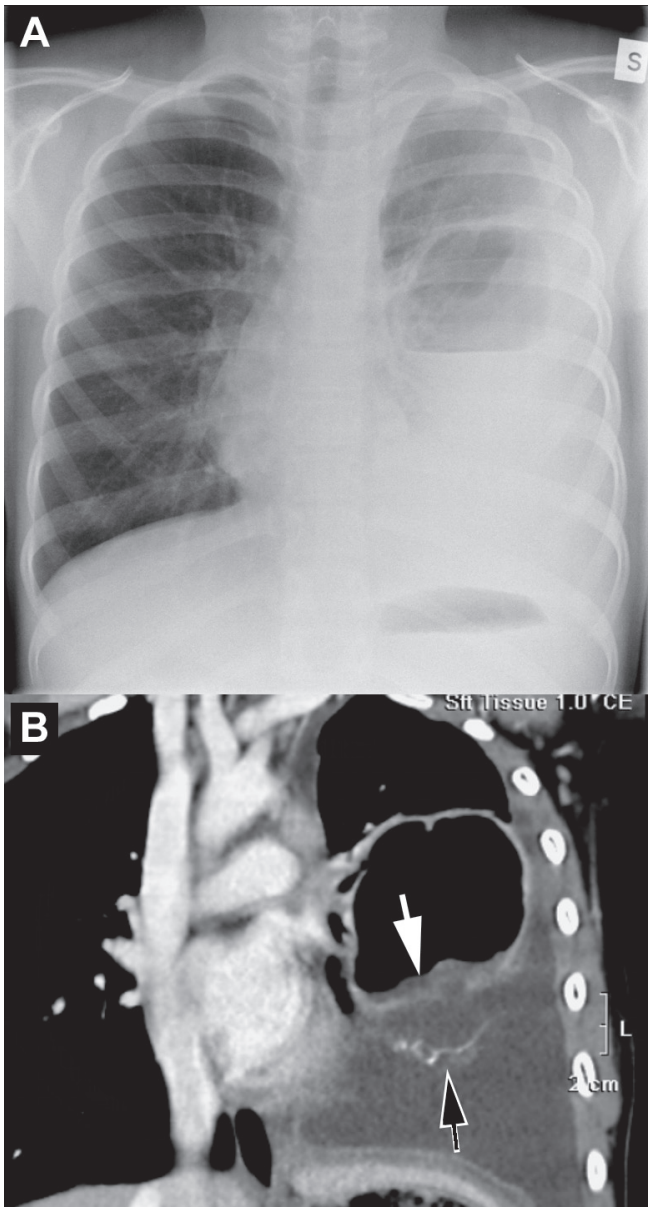
At the end of February 2015, an eight-year-old previously healthy child from eastern Finland had sudden abdominal pain and developed a vigorous generalised urticarial rash without other abnormal findings. The child had never travelled abroad. A week later, the child was admitted to hospital because of fever (38.5 °C) and a persistent cough. Upon admission, the patient was pale and their breath sounds were decreased over the left side of the chest. A chest X-ray revealed a large cavity, partially filled with fluid (Figure 1A). The ultrasound showed a considerable avocado-sized hollow (13.5 x 9 cm) with multiple lobulation. Consistent with these findings and an elevated C-reactive protein (58 mg/L; norm: <3 mg/L), and high normal leukocyte count (12.9 x 10^9/L; norm: 4.5-13.5 x 10^9/L), a lung abscess with parapneumonic empyema was set as the principal diagnosis. Elevation of the serum eosinophil leucocytes (4.7 x 10^9/L; norm: 0.1–0.4 x 10^9/L) was also observed.

Despite empirical treatment with intravenous cefuroxime (100 mg/kg/day divided in three doses) and clindamycin (40 mg/kg/day divided in three doses), the fever and cough persisted and the radiological findings did not resolve within a week. Computed tomography (CT) of the thorax on day 5 after admission revealed a pleural effusion and an empyema in the lower lobe of the left lung, and an abscess suspicion in the upper lobe (Figure 1B). A left-sided thoracotomy was performed on day 7 after admission. An empyema was detected and debridement of the pleural cavity and decortication was carried out. The suspected abscess cavity was opened and partially resected. Clinically, it proved to be a cystic structure with connection to small bronchi. This bronchocystic fistula was closed with sutures.

On the first postoperative day, the direct microscopic examination of calcofluor white-stained fragments of cyst wall and cyst content showed plenty of hooks and protoscolices, typical of *Echinococcus*. Hooks were detected also in Gram (Figure 2) and Ziehl-Neelsen stained samples. After this finding, albendazole treatment (10–15 mg/kg/day divided in two doses) was started. Because of the obvious CE, a re-thoracotomy was performed on the second postoperative day. The cyst was close to the hilar structures and thus the upper lobe of the left lung had to be removed.

Figure 1

Chest X-ray and computed tomography, autochthonous cystic echinococcosis case in a child, east Finland, March 2015



A: Chest X-ray showing pleural effusion and a large cyst with air-fluid level in the upper lobe of the left lung. The cyst wall is thick and slightly irregular.

B: Coronal reconstruction image from contrast-enhanced computed tomography showing the cyst and pleural effusion. The cyst wall is enhanced; the collapsed endocyst is indicated by the white arrow and the small calcifications are indicated by the black arrow.

PCR for *Echinococcus* (partial mitochondrial cytochrome *c* subunit I gene [1]) was positive in specimens taken during the first thoracotomy from both the cyst and pleural empyema, indicating either spontaneous or intraoperative spillage of the cyst content into the pleural cavity. Sequencing revealed 100% identity with *Echinococcus canadensis* genotype G10 previously isolated in cervids from Finland [2].

Postoperatively, the lung function recovered slowly. A thorax and abdomen CT and an abdominal ultrasound did not reveal signs of hydatid cysts in the liver or other parts of the body. The findings in brain magnetic resonance imaging (MRI) were also normal. A serum sample taken six weeks after the first operation was strongly positive for IgG antibodies against *E. granulosus* by ELISA and IHA (Swiss Tropical and Public Health Institute, Basel, Switzerland). The tests are based on material of *E. granulosus* sensu stricto (s.s.) genotype G1 of sheep originating in Sardinia (Bruno Gottstein, University of Bern). Albendazole treatment was continued postoperatively for a total of three months.

Investigation of close family members and dogs owned by the family

The patient's parents and two siblings were examined for *Echinococcus* infection. Chest X-rays and abdominal ultrasound results proved normal and serological tests were negative. The family lives in the countryside and has three dogs, which are used mostly for fowling. There was no history of feeding dogs with raw cervid viscera. The dogs were regularly dewormed, but not with anthelmintics effective against *Echinococcus*. Before treatment with praziquantel, faecal samples were collected from the dogs. Mitochondrial DNA was extracted directly from the faecal material [3] because the small size of the samples did not allow isolation of parasite eggs. A fragment of mitochondrial ribosomal DNA of the *E. granulosus* sensu lato (s.l.) complex [4] was detected by PCR in all the samples, but the short unspecific sequence did not reveal the exact species. Control specimens taken one month after deworming were PCR-negative.

Background

The most important aetiological agents of human CE are *E. granulosus* s.s. and *E. canadensis*, both of which were formerly included in the species complex of *E. granulosus* s.l [5]. Canids are the definitive hosts of these parasites, and various ungulates serve as intermediate hosts [6].

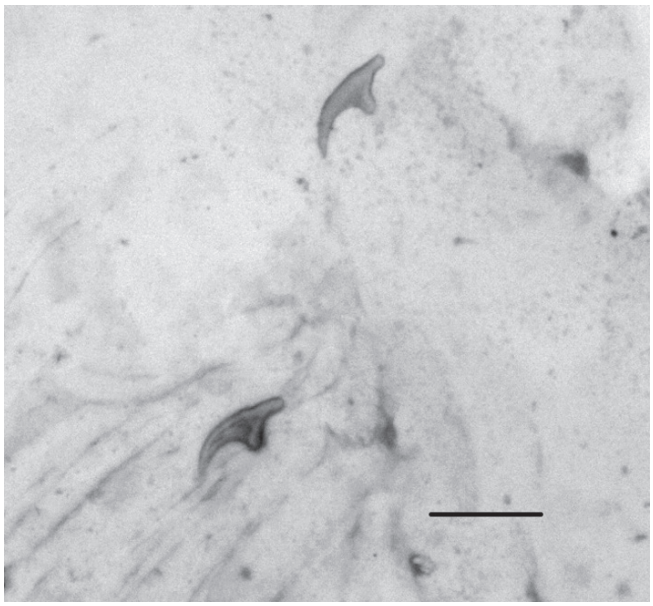
CE is found worldwide, prevailing in many endemic areas, typically in pastoral communities where people have close contact with dogs [6]. In the northern Fennoscandia, endemic human CE occurred in the reindeer herding area until the second half of the last century [7]. In Finland, the last published autochthonous case was diagnosed in 1963, in Sweden in 1967, and in Norway in 1977 [8]. Human infections derived from a synanthropic cycle involving dogs and reindeer, which broke up due to changes in traditional reindeer husbandry including decline of herding dogs [7,8]. A sylvatic wolf–moose cycle still exists in Finland, but it has not been linked to human infections [7].

Discussion

Since our patient had never travelled abroad, a parasite infection was not initially considered in the differential diagnostics. In endemic areas with high prevalence of

Figure 2

Gram stain of the cyst wall showing two *Echinococcus* hooks, autochthonous cystic echinococcosis case in a child, east Finland, March 2015



Scale bar 30 µm.

clinical cases (e.g. in the Middle East or parts of Africa) the eosinophilia, generalised urticaria and pulmonary involvement would be expected to raise a suspicion of CE. The incidental finding of *Echinococcus* hooks in smears obtained for both mycological and bacterial staining highlights the importance of direct microscopic examination in this case.

The growth rate of hydatid cysts is slow (max. 13 cm per year, but usually much less) [9,10], depending on location, causative species and probably also patient's age [9,11,12]. In the present case, the cyst had presumably been growing for at least one year and eventually constricted the lower lobe, thus predisposing to a secondary pulmonary infection. During this process, a fistula had ruptured and the cyst had been partially drained into the bronchial tree causing a persistent cough. Cyst leakage and exposure to echinococcal antigens probably account for the abdominal pain and urticarial rash.

Based on ultrasound, CT and clinical findings, the present case can be classified as CE4l according to the classification of the World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE) [9,13]. In the classification, '4' refers to an inactive stage (with degenerative contents and calcification in the present case) and 'l' to a large size [13]. Most cysts of this type are not fertile [13], but in this case protoscolices were present, indicating fertility.

Surgery still remains the main therapeutic option in pulmonary CE [6]. Here the cyst was not fully removed in the initial operation, since the parasitic aetiology was recognised only after microscopic examination. Due to the large size and difficult location of the cyst, the patient was re-operated and a lobectomy was performed for complete eradication of the parasite, and to avoid relapses and bacterial infections. An optimal length of postoperative albendazole treatment has not been established [9]. However, considering the formation of the fistula and the spilling during the initial operation, a prolonged course of albendazole was considered warranted. Furthermore, follow-up visits including serology are planned every three to six months over the first year and, thereafter, once a year by serology and MRI at least for five years if no clinical symptoms or findings develop.

According to reports from Alaska and Canada, 'sylvatic' (transmitted in wildlife) CE attributed to *E. canadensis* is more benign than classic 'pastoral' CE predominantly caused by *E. granulosus* s.s. in sheep-raising countries [11,14-16]. Relative mildness was also typical of endemic CE which occurred in the reindeer herding area of Fennoscandia [8]. The sylvatic form of CE is characterised by pulmonary involvement of relatively small hydatids with thinner laminated membrane (endocyst), and spontaneous cure because of cyst rupture into bronchi [11,14,15,17]. Patients are mostly asymptomatic and complications uncommon [11,14,15]. Percutaneous aspiration and drainage have been successfully accomplished for therapeutic and diagnostic purposes [12,15,17]. Anaphylaxis and secondary seeding have been extremely rare even in spontaneously ruptured cases [11,14,18]. Thus, in contrast to the global guidelines [6], in endemic cases in Alaska and Canada surgery is limited to symptomatic, infected or rapidly growing cysts [11,12,14-17]. Consistent with the clinical picture of our patient, children are more frequently symptomatic and prone to complications (e.g. bacterial secondary infections) from a cyst rupture, probably because the cysts occupy a large proportion of the lung volume, and the small calibre of bronchi prevents expectoration of parasite remnants [12].

The causative agents of sylvatic CE in the old clinical reports presumably represented the same genotypes (G8 and G10) that occur across the circumpolar north today. So far, G10 has been recorded only in three human cases: the first in southern Mongolia in 2011, the second in north-western Sakha Republic, Russia in 2013, and the most recent one in north-eastern China in 2015 [19-21]. All cases were treated surgically but the clinical course was not presented. The genotype G8 has been reported only once; the patient was operated in southeastern Alaska in 1999 [18,22]. The case, with multiple cysts disseminated in the peritoneal cavity, was atypical as sylvatic CE [18]. It is not known whether these different genotypes of *E. canadensis* correlate with differences in the clinical presentation of sylvatic CE.

The case presented here most likely originated in the sylvatic cycle via dogs. Given the slow growth of the larval stage and short lifespan of adult parasites, it is unclear whether the cyst in the patient was attributed to the infection detected in the dogs of the patient's family. Although fed only with commercial dog foods, the dogs may have eaten raw viscera, e.g. during hunting, unnoticed by the owner.

Cervid offals are usually discarded at the shooting site. Even though wild scavengers operate rapidly, potentially infected offals are easily available during the moose hunting season for hunting dogs and others roaming freely in the woods. To prevent transmission, raw unfrozen or uncooked cervid viscera are not to be given to dogs, and cestocidic medication is to be regularly administered to hunting dogs before and after the hunting season [7,23]. Although sylvatic human CE is rare and sporadic, veterinary authorities should inform hunters and dog owners about these precautions and the potential risk of CE in areas where *E. canadensis* occurs in wildlife. In Europe, this includes Finland, the Baltic countries and Russia [7], and probably also some other countries which belong to the distribution range of wolves.

Conflict of interest

None declared.

Authors' contributions

Drafting the manuscript: SH, AL; commenting on and revising the manuscript: AK, MA, TH, JK, JH, EB, KV, ET, TH-K, AO; attending physicians: SH, MA, TH, JH, EB, KV; consulting specialists: AK, TH-K; microbiological diagnosis: JK; genetic identification: AL; radiological interpretation: ET; veterinary diagnostics: AO.

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Louse-borne relapsing fever (*Borrelia recurrentis*) diagnosed in 15 refugees from northeast Africa: epidemiology and preventive control measures, Bavaria, Germany, July to October 2015

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We report 15 imported louse-borne relapsing fever (LBRF) cases in refugees in Bavaria, Germany. One patient died. Epidemiological findings confirmed that all were young males from the Horn of Africa (12 from Somalia), who had similar migration routes converging in Sudan continuing through Libya and Italy. The majority likely acquired their infection during migration. Healthcare workers should be aware of LBRF in refugees passing through north Africa to ensure correct treatment and preventive measures.

From July 2015 until October 2015, Louse-borne relapsing fever (LBRF) was diagnosed in 15 refugees originating from the Horn of Africa and arriving in Bavaria, southern Germany, presenting with fever. The main travel route included Sudan, Libya and Italy. In this rapid communication, microbiological confirmation, simple first-line epidemiologic assessment and preventive control measures in relation to these cases are described.

Case investigation

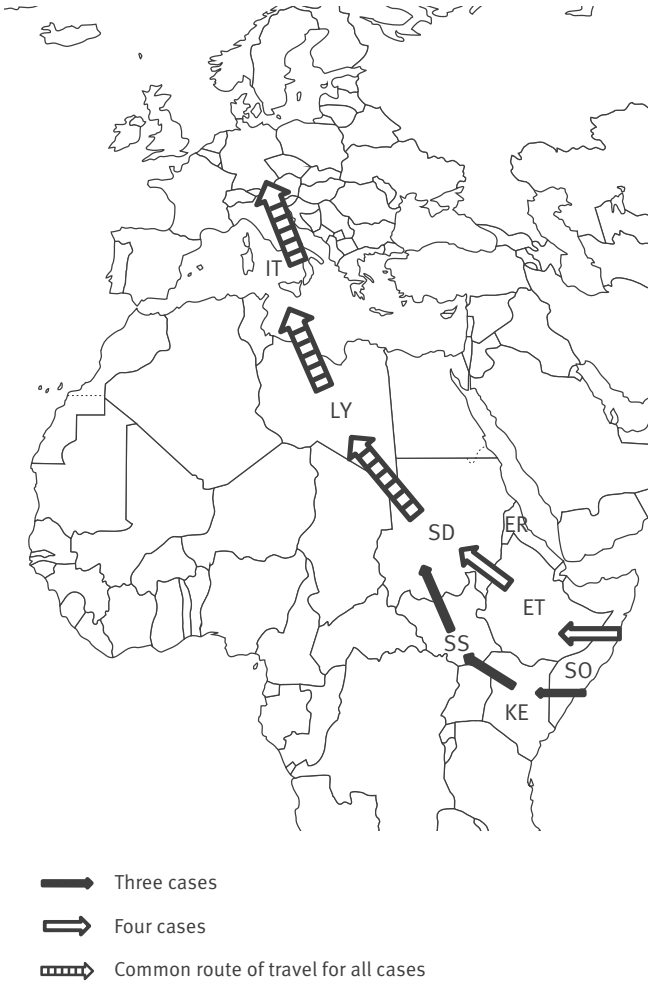
In all cases, a preliminary diagnosis was established by clinicians based on clinical symptoms and visible spirochetes in Giemsa stained blood films The German National Reference Centre (NRC) for Borrelia in Oberschleißheim was contacted directly by clinicians for confirmation. Microbiological confirmation of LBRF from EDTA blood included: Dark field microscopy (Leitz Dialux 20 microscope, Leitz, Germany, objective 40, occular 10) and PCR targeting 16S rRNA, *flab,* and *glpQ* followed by sequencing [1-3].

Blood samples were used for in vitro cultures in modified Kelly-Pettenkofer (MKP) medium [4]. A case was regarded as confirmed when sequencing revealed *B. recurrentis*.

Because of a potentially high public health relevance, i.e. establishment of local foci of louse-borne transmission in refugee facilities, treating hospitals and spill over to the local population, epidemiological data to establish preventive measures are of utmost importance. Therefore a standardised questionnaire for case investigations and interviews was developed, distributed and evaluated by the Bavarian Task-Force Infectiology and International Health Regulations. Interviews were performed by public health physicians of local public health agencies as part of the official investigation of infectious diseases of public health concern according to the German federal law, and with the help of an interpreter. The interviews were performed in a hospital setting and by taking into consideration potential emotional and psychological trauma of refugees. Anonymised data were used for further analysis. When interviewing was not possible, information was retrieved from medical records, if available. A leaflet informing about clinical presentation, epidemiology, diagnostics as well as preventive control measures, was developed and sent to clinicians and public health authorities to raise general awareness.

Figure 1

Travel routes of cases of imported louse-borne relapsing fever in refugees from northeast Africa to Bavaria, Germany, July–September 2015 (n=7[a])



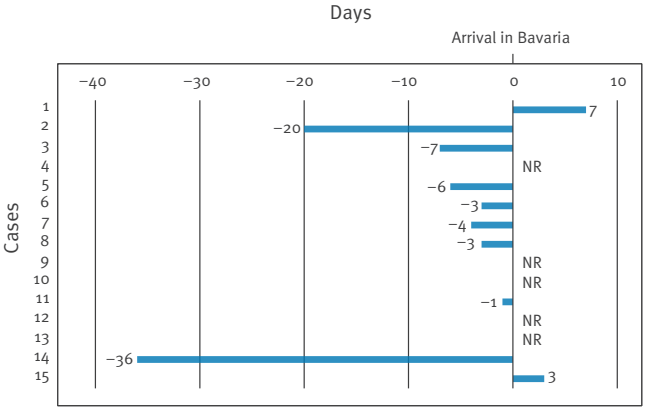
Map obtained from d-maps (http://www.d-maps.com/carte.php?num_car=18215&lang=en).

[a] Comprehensive information on migration routes was available for seven of the 15 cases.

ER: Eritrea; ET: Ethiopia; IT: Italy; KE: Kenya; LY: Libya; SD: Sudan; SO: Somalia; SS: South Sudan.

Figure 2

Duration from onset of symptoms to and since arrival in Bavaria for cases of imported louse-borne relapsing fever in refugees from northeast Africa to Bavaria, Germany, July–October 2015 (n=15)



Negative numbers represent an onset of symptoms before arrival in Bavaria whereas positive numbers represent an onset of symptoms after arrival in Bavaria.

NR: not reported.

Results of the investigations

Of the 15 suspected LBRF cases submitted to the NRC, 14 were confirmed as being caused by *B. recurrentis*. In one case, spirochetes were visible on Giemsa stained blood films, but insufficient material was provided for molecular diagnosis. However, the epidemiological data suggest LBRF. Details of diagnostic results are shown in Table 1.

Table 2 gives an overview of basic epidemiological information including disease onset and travel history.

All 15 cases were males with a median age of 20 years (range 15 to 33 years) and all originated from northeast Africa: 12 from Somalia, two from Eritrea and one from Ethiopia.

Information about migration route was available from 12 patients (Table 2). A comprehensive migration route was indicated by seven patients, all from Somalia: From Somalia via Ethiopia to Sudan (n=4) or via Kenya, South Sudan to Sudan (n=3), all went further to Libya and then via Italy and transit through Austria to Bavaria (Figure 1).

Four patients reported a stay in Italy between two and 14 days, respectively. Six patients reported changing of clothes upon arrival in a refugee camp in Italy. Five patients reported a longer stay in Libya (ranging from 17 days to nine months). Three of them reported to have been exposed to very poor, overcrowded living conditions during transit in Libya. They also reported of fellow refugees with pruritus and infestation with lice. Travel duration of individuals ranged from eight weeks to one year. In eight of the 10 patients with available information, onset of symptoms was before arrival in Munich. Only two reported onset of symptoms after arrival (Figure 2). Nine refugees reported that they had already been accommodated in a refugee facility in Bavaria, four were directly hospitalised upon arrival in Munich, and for two patients information was not specified. Duration of stay in a refugee

Table 3 gives an overview over reported symptoms. All patients were hospitalised and received antibiotic treatment with doxycyline. One of the 15 patients died of multi-organ failure after initiation of antibiotic therapy despite intensive care treatment. Although Jarisch-Herxheimer reaction was not systematically

Table 1

Diagnostic results of cases of imported louse-borne relapsing fever in refugees from northeast Africa to Bavaria, Germany, July–October 2015 (n=15)

Case	Microscopy		Sequencing		
	Darkfield	Giemsa	*16S rDNA*	*glpQ*	*flab*
1[a]	Positive	Positive	Positive	Positive	Positive
2	Negative	Positive	Positive	Positive	Positive
3[a]	Positive	Positive	Positive	Positive	Positive
4[a]	Positive	Positive	Positive	Positive	Positive
5[a]	Positive	Positive	Positive	Positive	Negative
6	NA	Positive	NP	NP	NP
7[a]	Positive	Positive	Positive	Positive	Positive
8	Negative	Positive	Positive	Negative	Positive
9	Negative	Positive	Positive	Positive	Negative
10	Negative	Positive	Positive	IP	Positive
11	Positive	Positive	Positive	Positive	Positive
12	Positive	Positive	Positive	Positive	Positive
13[a]	Positive	Positive	Positive	Positive	Positive
14	Positive	Positive	Positive	IP	Positive
15	Positive	Positive	Positive	Positive	Positive

[a] Successful cultivation.
IP: in process; NA: not available; NP: no material provided.

Table 2

Descriptive epidemiological information on cases of imported louse-borne relapsing fever in refugees from northeast Africa to Bavaria, Germany, July–October 2015 (n=15)

Characteristic	Number of cases
Sex	
Male	15
Age (years)	
15–20	8
20–25	4
25–33	3
Country of origin	
Somalia	12
Eritrea	2
Ethiopia	1
Migration route	
SO-KE-SS-SD-LY-IT	3
SO-ET-SD-LY-IT	4
SO-unknown-SD-LY-IT	1
From SO via LY	3
From ER via LY and IT	1
NR	3
Travel duration	
1–2 months	1
2–5 months	6
5 months–1 year	1
NR	7
Onset of symptoms	
Before arrival in Bavaria	8
After arrival in Bavaria	2
NR	5
Stay in a refugee facility in Bavaria	
Yes	9
No	4
NR	2

ER: Eritrea; ET: Ethiopia; IT: Italy; KE: Kenya; LY: Libya; NR: not reported; SD: Sudan; SO: Somalia; SS: South Sudan.

investigated, all 10 patients with available information were reported to have had Jarisch-Herxheimer reaction to antibiotic treatment.

Discussion

Historically, LBRF was observed as large outbreaks affecting millions of people during wars, civil unrest or under extreme poverty [5,6]. Notably, mortality can still be high, above 30% for untreated cases and 2% to 6% for those receiving appropriate treatment [7]. Endemic areas of LBRF were known to exist in northeast Africa in Ethiopia and in neighbouring countries, including Eritrea, Somalia and Southern Sudan, and are suspected in the Peruvian Andes and the Himalayas [5,8-10]. However, according to recent research, it is believed that endemic LBRF hot spots only persist in Ethiopia, occasionally spilling to neighbouring countries [7,11,12].

In Germany, only three cases of imported LBRF were reported since 1999 [13-15]. Imported LBRF among refugees from endemic areas entering the European Union (EU) is not unexpected considering the massive increase in migration of refugees from northeast Africa [16,17]. According to official data, Eritrea is one of the main countries of origin of refugees in Bavaria (652 in January–June 2015) [18]. In Germany, 3,284 refugees from Somalia were seeking asylum in 2015 until the month of August [19].

Our data suggest that young male refugees originating from the Horn of Africa may be at particular risk of acquiring LBRF. Accordingly, imported LBRF was found in three young male refugees from Eritrea only recently in Switzerland and the Netherlands [20,21].

Onset of symptoms in the eight of 10 patients with available information in our series was just before or shortly after arrival in Bavaria. None of them reported recurring fever episodes. Hence, we assume an early stage of disease in them. Considering a mean incubation period of four to eight days (range 2 to 15 days) [22] and a duration of migration ranging from eight weeks to one year, infection in these eight patients has most likely been acquired towards the end of their journeys, hence in Libya or Italy. The patients could only provide rough estimates of the exact travel duration and accordingly very limited information on when they entered or left transit countries. Therefore, the exact place of infection remains unclear. However, especially

Table 3

Reported symptoms and outcome in louse-borne relapsing fever in refugees from northeast Africa to Bavaria, Germany, July– October 2015

Case	Symptoms at the beginning of the journey	Fever › 38 °C	Recurring fever	Severe malaise	Headache Myalgia	Other symptoms	Infestation with lice	Pruritus/ skin lesions	Hospitalisation	Recovery
1	No	No	No	NR	NR	No	No	NR	Yes	Yes
2	NR	Yes	NR	NR	NR	NR	NR	NR	Yes [f]	NR
3	NR	Yes	NR	NR	NR	NR	NR	NR	Yes [f]	NR
4	No	Yes	Several episodes	NR	No	Yes[a]	Yes[b]	No	ICU	Yes
5	No	Yes	No	Yes	Yes	Yes[c]	No	Yes	Yes	Yes
6	No	Yes	No	Yes	Yes	No	No	No	Yes	Yes
7	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes
8	No	Yes	No	Yes	Yes	No	NR	No	Yes	Yes
9	NR	Yes	NR	NR	NR	NR	NR	NR	Yes [f]	NR
10	NR	Yes	NR	NR	NR	NR	NR	NR	Yes [f]	NR
11	NR	Yes	NR	Yes	NR	Yes [c,d]	Yes	Yes	Yes	Yes
12	NR	Yes	NR	Yes	NR	No	NR	Yes	Yes	Yes
13	NR	Yes	NR	NR	NR	NR	NR	NR	Yes	No[e]
14	NR	Yes	No	Yes	yes	No	Yes	No	Yes	Yes
15	NR	Yes	No	Yes	yes	Yes[c]	No	Yes	Yes	Yes

ICU: intensive care unit; NR: not reported.

[a] Abdominal pain.

[b] Infestation was not reported, but seen at hospital admission.

[c] Jaundice.

[d] Vomiting.

[e] Patient died.

[f] Lost to follow-up.

for five cases who reported onset of symptoms within days before or shortly after arrival, an infection not only in Libya but also in Italy or while crossing the Mediterranean Sea is possible. Two patients reported an onset of symptoms 20 and 36 days, respectively, before arrival in Germany. The patient with the longer duration of symptoms reported that he had travelled through Ethiopia. For the two patients and those with insufficient information regarding the travel route, an infection while travelling through the known endemic hot spot Ethiopia or Sudan could not be ruled out. However, considering incubation time, onset of symptoms, travel duration and the fact that six patients did report no symptoms when leaving their country of origin, we assume that LBRF was acquired later, at places along migration routes with established endemic LBRF foci.

We are aware that the data retrieved during interviews are limited by recall bias and language problems. In particular, the lack of exact data on duration of the journeys remains problematic when estimating the probable place of infection. Indeed, we conclude that LBRF has already been introduced in places along migration routes, most likely in Libya, on refugee boats crossing the Mediterranean Sea and perhaps in Italy. Looking at specified migration routes, the introduction of LBRF to these places is possible by refugees who acquired the disease in Ethiopia.

Interestingly, not a single LBRF infection was found in refugees originating from other African regions though their migration routes partially overlap [23].

The current assessment provides no evidence that transmission occurred while the individuals were in Bavaria. However, public health measures were implemented to prevent further transmission, since nine of the 15 refugees already stayed in a refugee facility in Bavaria before they were diagnosed. As primary preventive public health measure, basic hygiene was recommended which includes changing, washing and drying of clothes and bedding at ≥ 60 °C on a regular basis for infected individuals and close contacts [24]. Additionally, active contact tracing of cases in terms of symptoms, infestation with body lice and assessment of living conditions was recommended as a further precaution. Furthermore, it was recommended to actively offer washing of clothes upon arrival, especially, but not limited to refugees from endemic areas. As the detection of infestation with lice might generally not be very reliable (in our assessment only reported in four patients) these preventive measures have become pivotal [22,24].

To raise awareness in the medical and public health communities, public health authorities and physicians throughout Bavaria have been informed about clinical symptoms and general epidemiology of LBRF. Leaflets describing LBRF and recommended public health measures were distributed nationally. Public health institutions in Libya and Italy were already informed by the Robert-Koch-Institute (RKI) (personal communication, Dr H Wilking, RKI, September 2015) as well as further organisations such as the World Health Organization (WHO) and Médecins Sans Frontières (MSF).

Conclusions

Young male refugees originating from the Horn of Africa seem to be at major risk for acquiring LBRF. LBRF most likely was not acquired in their countries of origin but on migration routes, most likely in Libya or Italy. No evidence for transmission of LBRF infections in Bavaria was found. However meaningful preventive control measures were implemented. The findings of our investigation should be strengthened by further epidemiological studies and followed by a pan-European prevention strategy.

Conflict of interest

None declared.

Authors' contributions

Wrote the manuscript: MH, VF, AR; performed epidemiological analysis: MH, AR, FP; interviewed the patients: JZ; performed laboratory investigation: GM, VF, AW; revised the manuscript: KS, WH, TL, AS, GM; cared for the patients: MS, LB, UB, WG, KH.

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Research article

Change in incidence of clinic visits for all-cause and rotavirus gastroenteritis in young children following the introduction of universal rotavirus vaccination in Israel

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Both rotavirus vaccines RotaTeq and Rotarix were efficacious against severe rotavirus gastroenteritis in clinical trials; yet real-world data on the effect of rotavirus vaccines on mild to moderate disease are limited. We used a large computerised database of Maccabi Health Services Health Maintenance Organisation (HMO), the second largest HMO in Israel covering 25% of the Israeli population, to compare the incidence of acute gastroenteritis (AGE) clinic visits in community settings (n = 302,445) before (2005–10) and after (2011–13) the introduction of universal rotavirus immunisation in Israel. We retrieved laboratory results of rotavirus antigen tests (n = 18,133) and using a weighted analysis, we estimated the impact of rotavirus immunisation on the disease burden of rotavirus AGE clinic visits. Following the introduction of universal rotavirus immunisation, the typical winter peaks of rotavirus AGE were substantially lower and significant reductions of 14.8% (95% confidence interval (CI): 13.5–16.1) in all-cause AGE clinic visits and of 59.7% (95% CI: 59.8–62.6) in rotavirus AGE clinic visits were observed. The decrease was observed in all age groups, but it was greater in children aged 0 to 23 months than those aged 24 to 59 months. Continued rotavirus laboratory surveillance is warranted to monitor the sustainability of these changes.

Introduction

Rotavirus is the leading cause of severe acute gastroenteritis (AGE) in young children worldwide [1-3], accounting for 15 to 35% of AGE outpatient visits, 25 to 55% of severe AGE cases requiring hospitalisation, and 5% of the global mortality in children under five years [3,4]. The majority of deaths caused by rotavirus occur in developing countries [1,3,4], while in industrialised countries, rotavirus gastroenteritis is associated with high healthcare costs [5,6] as well as non-medical costs [7].

The new rotavirus vaccines RotaTeq (Merck) and Rotarix (GlaxoSmithKline) have shown an efficacy of 85 to 98% against severe rotavirus gastroenteritis in trials conducted in the Americas and Europe [8,9], and were introduced into routine vaccination programmes in the United States, Latin American countries, Australia [10-12] and few European countries [13,14]. Post-marketing studies have shown that rotavirus vaccines are highly effective (>80%) in preventing hospitalisations for rotavirus gastroenteritis [12,15-18] in high and middle income countries, although a lower effectiveness was reported in some settings [12]. In these countries, significant reductions (49–89%) in rotavirus gastroenteritis hospitalisations of children younger than five years were documented in the period after introduction of rotavirus vaccination compared with the pre-vaccination era [12]. Furthermore, fatality from diarrhoeal diseases in young children declined substantially in Mexico [19] and Brazil [20] following the introduction of rotavirus vaccination.

Severe rotavirus disease resulting in hospitalisations and deaths comprises only the tip of the iceberg of the rotavirus disease burden [3]. Only limited evidence, mainly from the United States [21,22], exists on the impact of rotavirus vaccination on mild to moderate gastroenteritis in community and outpatients settings.

In a previous study, we found that rotavirus was the leading cause of AGE hospitalisations in the pre-vaccination period (2007–08), accounting for 39% of all gastroenteritis hospitalisations among children under the age of five years in northern Israel, with typical winter

Table 1

Incidence of clinic visits due to acute gastroenteritis in children aged 0–59 months, Maccabi Health Services, Israel, 2005–14 (n = 302,445)

		All			Male			Female		
Year	Age (months)	Visits	Population	IR/100 (95% CI)	Visits	Population	IR/100 (95% CI)	Visits	Population	IR/100 (95% CI)
2005	0–59	27,728	182,647	15.2 (15.0–15.4)	15,455	94,659	16.3 (16.1–16.6)	12,273	87,988	14.0 (13.7–14.2)
	0–23	18,313	72,119	25.4 (25.1–25.7)	10,121	37,308	27.1 (26.7–27.6)	8,192	34,811	23.5 (23.1–24.0)
	24–59	9,415	110,528	8.5 (8.4–8.7)	5,334	57,351	9.3 (9.1–9.5)	4,081	53,177	7.7 (7.5–7.9)
2006	0–59	37,664	182,473	20.6 (20.5–20.8)	20,822	94,484	22.0 (21.7–22.3)	16,842	87,989	19.1 (18.9–19.4)
	0–23	24,503	70,778	34.6 (34.3–35.0)	13,518	36,640	36.9 (36.4–37.4)	10,985	34,138	32.2 (31.7–32.7)
	24–59	13,161	111,695	11.8 (11.6–12.0)	7,304	57,844	12.6 (12.4–12.9)	5,857	53,851	10.9 (10.6–11.1)
2007	0–59	32,271	182,732	17.7 (17.5–17.8)	17,787	94,444	18.8 (18.6–19.1)	14,484	88,288	16.4 (16.2–16.7)
	0–23	21,213	70,419	30.1 (29.8–30.5)	11,708	36,394	32.2 (31.7–32.7)	9,505	34,025	27.9 (27.5–28.4)
	24–59	11,058	112,313	9.9 (9.7–10.0)	6,079	58,050	10.5 (10.2–10.7)	4,979	54,263	9.2 (8.9–9.4)
2008	0–59	36,634	184,461	19.9 (19.7–20.0)	20,025	95,273	21.0 (20.8–21.3)	16,609	89,188	18.6 (18.4–18.9)
	0–23	24,223	72,452	33.4 (33.1–33.8)	13,165	37,324	35.3 (34.8–35.8)	11,058	35,128	31.5 (31.0–32.0)
	24–59	12,411	112,009	11.1 (10.9–11.3)	6,860	57,949	11.8 (11.6–12.1)	5,551	54,060	10.3 (10.0–10.5)
2009	0–59	27,581	187,141	14.7 (14.6–14.9)	15,104	96,250	15.7 (15.5–15.9)	12,477	90,891	13.7 (13.5–14.0)
	0–23	18,992	74,487	25.5 (25.2–25.8)	10,385	38,050	27.3 (26.9–27.7)	8,607	36,437	23.6 (23.2–24.0)
	24–59	8,589	112,654	7.6 (7.5–7.8)	4,719	58,200	8.1 (7.9–8.3)	3,870	54,454	7.1 (6.9–7.3)
2010	0–59	40,964	192,762	21.3 (21.1–21.4)	22,363	99,154	22.6 (22.3–22.8)	18,601	93,608	19.9 (19.6–20.1)
	0–23	25,980	78,021	33.3 (33.0–33.6)	14,187	40,078	35.4 (34.9–35.9)	11,793	37,943	31.1 (30.6–31.6)
	24–59	14,984	114,741	13.1 (12.9–13.3)	8,176	59,076	13.8 (13.6–14.1)	6,808	55,665	12.2 (12.0–12.5)
2011	0–59	27,922	195,670	14.3 (14.1–14.4)	15,527	100,409	15.2 (15.0–15.4)	12,647	95,261	13.3 (13.1–13.5)
	0–23	17,886	78,886	22.7 (22.4–23.0)	9,644	40,591	23.8 (23.4–24.2)	8,242	38,295	21.5 (21.1–21.9)
	24–59	10,036	116,784	8.6 (8.4–8.8)	5,631	59,818	9.4 (9.2–9.7)	4,405	56,966	7.7 (7.5–8.0)
2012	0–59	30,753	195,012	15.8 (15.6–15.9)	16,709	99,961	16.7 (16.5–17.0)	14,044	95,051	14.8 (14.6–15.0)
	0–23	19,215	76,127	25.2 (24.9–25.6)	10,440	39,023	26.8 (26.3–27.2)	8,775	37,104	23.7 (23.2–24.1)
	24–59	11,538	118,885	9.7 (9.5–9.9)	6,269	60,938	10.3 (10.1–10.5)	5,269	57,947	9.1 (8.9–9.3)
2013	0–59	32,266	194,608	16.6 (16.4–16.8)	17,729	99,951	17.7 (17.5–18.0)	14,537	94,657	15.4 (15.1–15.6)
	0–23	20,764	75,713	27.4 (27.1–27.7)	11,522	38,997	29.6 (29.1–30.0)	9,242	36,716	25.2 (24.7–25.6)
	24–59	11,502	118,895	9.7 (9.5–9.8)	6,207	60,954	10.2 (10.0–10.4)	5,295	57,941	9.1 (8.9–9.4)
2014[a]	0–59	8,662	194,281	[a]	4,570	99,916	[a]	4,092	94,365	[a]

CI: confidence intervals; IR: incidence rate.

[a] Data up to 16 May 2014, therefore the incidence rate was not calculated for 2014.

seasonality and peak incidence around December [23]. In mid-2007, both RotaTeq and Rotarix were licensed in Israel and parents could purchase the vaccine through the Health Maintenance Organisation (HMO) with partial reimbursement [24]. In December 2010, the Ministry of Health included three doses of RotaTeq in the childhood national immunisation programme (NIP) at ages 2, 4, and 6 months.

We aimed to estimate the impact of the universal rotavirus immunisation programme on the burden of mild to moderate AGE in children younger than five years by comparing the incidence and seasonality of clinic visits for all-cause AGE and for rotavirus AGE in community settings before (2005–10) and after (2011–13) the inclusion of universal rotavirus vaccination.

Methods

Study population and design

A retrospective study was conducted using the computerised database of Maccabi Health Services (MHS), a health maintenance organisation (HMO) with 2 million members in Israel, covering one quarter of the Israeli population. All Israeli citizens have health insurance according to the National Health Insurance Law introduced in 1995, consequently all citizens have access to healthcare. Included in the study population were all children younger than five years and insured in the MHS HMO during the study period from 1 January 2005 through 16 May 2014. The total number of children ranged from 182,473 to 195,670 in those years. Access

Table 2

Incidence of clinic visits due to all-cause acute gastroenteritis before (2005–10) and after (2011–13) introduction of universal rotavirus vaccination, by age group, Maccabi Health Services, Israel (n = 64,121)

	Before universal vaccination (2005–10)			Universal vaccination era (2011–13)			Reduction	
Age (months)	Visits/year	Population	IR/100 (95% CI)	Visits/ year	Population	IR/100 (95% CI)	Risk difference per 100 (95% CI)	RR reduction (95% CI)
0–11	8,967	35,495	25.3 (24.8–25.7)	7,639	37,572	20.3 (19.9–20.7)	4.9 (4.3–5.5)	19.5 (17.1–21.9)
12–23	13,237	37,551	35.3 (34.8–35.7)	11,649	39,337	29.6 (29.2–30.1)	5.6 (5.0–6.3)	16.0 (14.1–17.9)
24–35	6,511	37,669	17.3 (16.9–17.7)	5,989	39,611	15.1 (14.8–15.5)	2.2 (1.6–2.7)	12.5 (9.5–15.5)
36–47	3,594	37,390	9.6 (9.3–9.9)	3,613	39,610	9.1 (8.8–9.4)	0.5 (0.1–0.9)	5.1 (0.8–9.4)
48–59	1,498	37,265	4.0 (3.8–4.2)	1,423	38,967	3.6 (3.5–3.8)	0.4 (0.1–0.6)	9.2 (2.4–15.9)
0–59	33,807	185,369	18.2 (18.1–18.4)	30,314	195,097	15.5 (15.4–15.7)	2.7 (2.5–2.9)	14.8 (13.5–16.1)

CI: confidence intervals; IR: incidence rate; RR: relative risk.

Table 3

Estimated burden of clinic visits for all-cause and rotavirus acute gastroenteritis, children aged 0–59 months, Maccabi Health Services database, Israel, 2005–13 (n = 293,783)

Year/period	AGE visits	RV tests	% tests performed among visits	% RV-positive	Estimated RV AGE [a]	Estimated incidence rate per 100 of RV AGE (95% CI)
2005	27,728	992	3.6	22.5	5,333	2.9
2006	37,664	1,649	4.4	25.7	8,356	4.6
2007	32,271	1,757	5.4	24.3	6,603	3.6
2008	36,634	2,207	6.0	19.2	5,988	3.2
2009	27,581	1,779	6.5	13.3	3,379	1.8
2010	40,964	2,814	6.9	19.6	7,409	3.8
2011	27,922	1,858	6.7	13.9	3,857	2.0
2012	30,753	2,170	7.1	5.3	1,665	0.9
2013	32,266	2,305	7.1	7.0	2,340	1.2
Annual average in the pre-vaccination period 2005–10	33,807	1,866	5.5	20.7	6,179	3.3 (3.25–3.4)
Annual average in the universal vaccination era 2011–13	30,314	2,111	7.0	8.7	2,621	1.34 (1.29–1.40)
Absolute reduction in the annual average between pre- and post-vaccination period	3,493	[b]	[b]	12.0	3,557	1.98 (1.89–2.08)
Average annual reduction between pre- and post-vaccination period [c]	10.3%	[b]	[b]	57.9	57.6	59.7 (59.8–62.6)

AGE: acute gastroenteritis; CI: confidence intervals; RV: rotavirus.

[a] Estimated by weighted analysis using the inverse of the sampling fraction as the weights, assigned separately in each sex and age group by month and year.

[b] No reduction in rotavirus testing was found after the introduction of universal rotavirus immunisation; on the contrary, there were 245 tests more in 2011-13 than in 2005-10, corresponding to a 13.0% increase in rotavirus testing.

[c] Calculated as: [(Annual average in 2005–10 – annual average 2011–13) / annual average in 2005–10]*100.

Table 4

Average annual clinic visits due to rotavirus acute gastroenteritis before (2005–10) and after (2011–13) introduction of universal rotavirus vaccination, by age, Maccabi Health Services, Israel

Age (months)	Before universal rotavirus vaccination (2005–10)			Universal rotavirus vaccination era (2011–13)			Reduction	
	Estimated RV AGE[a]	Population	Estimated annual IR of RV AGE per 100 (95% CI)	Estimated RV AGE[a]	Population	Estimated annual IR of RV AGE per 100 (95% CI)	Absolute reduction in IR per 100 (95% CI)	% reduction In IR (95% CI)
0–11	1,588	35,495	4.5 (4.3–4.7)	340	37,572	0.9 (0.8–1.0)	3.6 (3.3–3.8)	79.8 (74.6–85.0)
12–23	3,049	37,551	8.1 (7.8–8.4)	1,290	39,337	3.3 (3.1–3.5)	4.8 (4.5–5.2)	59.6 (55.6–63.7)
24–59	1,542	112,324	1.37 (1.33–1.44)	991	118,188	0.83 (0.78–0.89)	0.53 (0.44–0.62)	38.9 (32.7–45.2)

AGE: acute gastroenteritis; CI: confidence intervals; IR: incidence rate; RV: rotavirus.

[a] Estimated by weighted analysis.

to care such as visits to clinics is similar in the four HMOs in Israel; patients do not pay for these services, which are included in the 'national basket health services', irrespective of HMO. Furthermore, the primary care clinics are widespread across the country, the hospitals are public and access to these hospitals is similar among the four HMOs. In addition, access to vaccines included in the NIP is universal and vaccines are given through widespread maternal and child health clinics, mostly operated by the Ministry of Health.

Data on visits to clinics in community settings were retrieved from the MHS database using the International Statistical Classification of Diseases version 9 (ICD-9) codes of acute gastroenteritis and suspected or proven gastroenteritis [25]. We also collected data on the patient's age, sex and date of visit, which was used to define week, month, calendar year and study period with respect to the introduction of RotaTeq into the NIP. Only upon request from the physician, the community microbiological laboratories examine stool specimens obtained from AGE patients for *Shigella*, *Salmonella*, *Campylobacter*, protozoa or viruses including rotavirus. Rotavirus gastroenteritis is not a notifiable disease in Israel, therefore we used the MHS database. We included data on those laboratory tests for rotavirus antigen that were performed within seven days of the clinic visit.

Data analysis

The annual age-specific incidence rates of AGE (per 100 capita) and their 95% confidence intervals (CIs) were calculated for each study period. Laboratory results on rotavirus testing were available only for a sample of 6% all AGE clinic visits, therefore we employed weighted analysis to estimate the number of clinic visits due to rotavirus AGE in children aged 0 to 59 months in MHS. The weights were defined separately for sex and age group, in each month and year, as the inverse of the sampling fraction in each of these strata; the sampling fraction was considered as the total number of rotavirus tests divided by the total number of AGE clinic visits in the same stratum. The weights were assigned separately for male and female children in each age group (0–11, 12–23 and 24–59 months) in each month and year (January 2005 through May 2014), i.e. in 678 different strata, because rotavirus testing differed by age, sex and period. Using data available for full calendar years (1 January 2005 to 31 December 2013), we calculated the absolute and relative change (in percentages) for the following parameters: number of AGE, number of rotavirus-positive tests, proportion of rotavirus-positive tests, and incidence rate (per 100) of rotavirus-related AGE visits.

We analysed seasonality in the period before universal vaccination and in the universal immunisation era by Pocock's harmonic analysis [26], using weekly counts of AGE clinic visits. In this analysis we used data on clinic visits that occurred from 1 January 2005 through 31 December 2013.

Ethical considerations

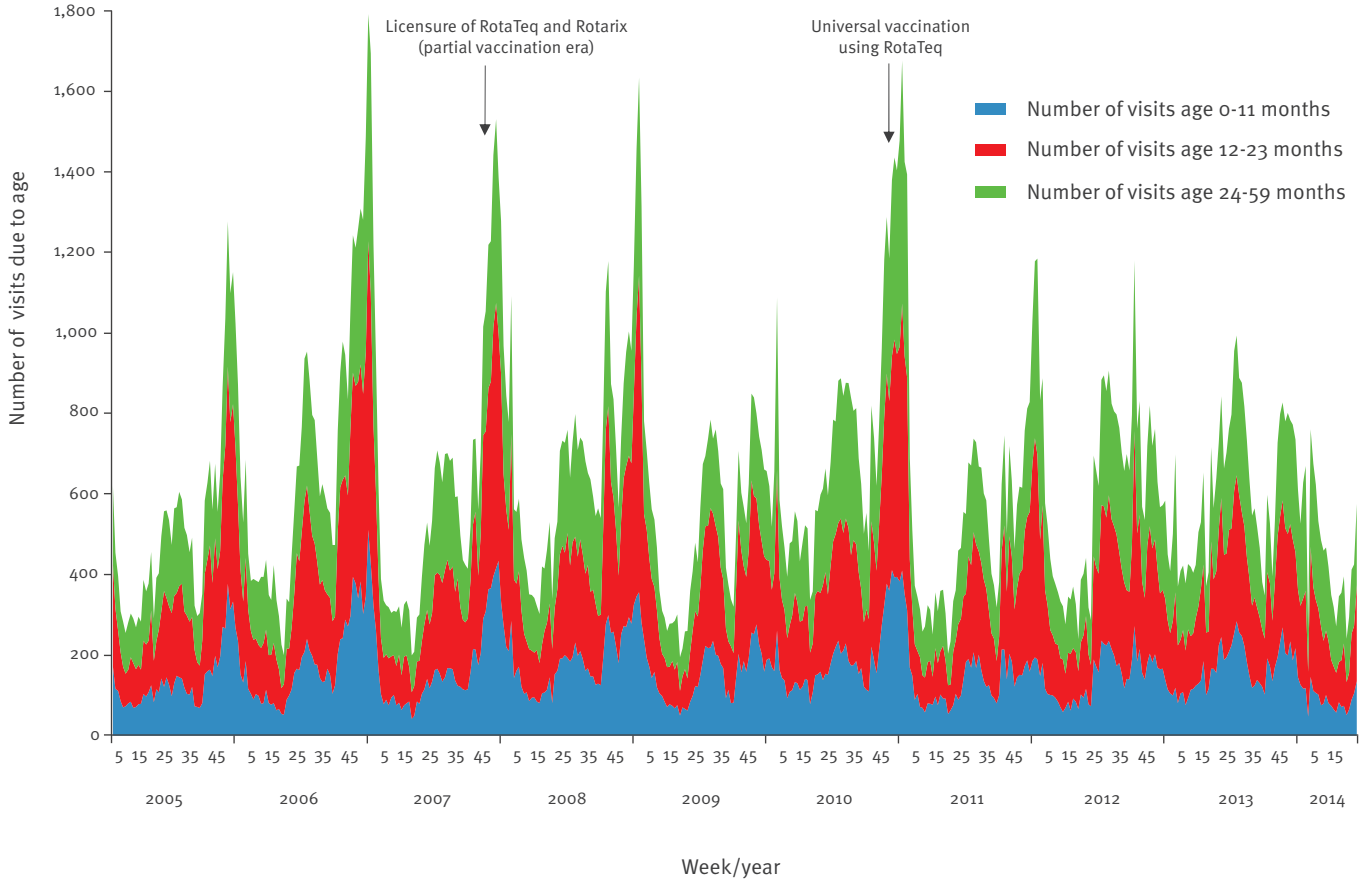
The study protocol was approved by the Institution Review Board of Asuta Medical Center. All data were anonymous and no personal identifying information was available for the study investigators. The study was given an exempt from informed consent given its nature of using historical anonymous data.

Results

During the study period, a total of 302,445 visits to clinics in the community setting due to AGE were documented. Of these, 54.8% were male and 45.2% were female children. The mean age of the patients was 21.1 months (standard deviation: 12.7; range 0–59). There were yearly fluctuations in the incidence rate of AGE clinic visits, which were evident in both sexes and in stratification by age (Table 1). These fluctuations were more obvious before the introduction of rotavirus vaccines to the NIP than in the period with universal vaccination (2011–13). Overall, the annual incidence of visits

Figure 1

Number of weekly clinic visits due to acute gastroenteritis, by age group, Maccabi Health Services, Israel, 2005–14 (n = 302,445)



AGE: acute gastroenteritis.

to a physician due to AGE followed a downward trend in the period with universal vaccination, ranging from 14.3 to 16.6 (mean: 15.5) per 100 compared with the period from 2005 to 2010 (range: 14.7–21.3; mean 18.2 per 100 (Table 1).

A significant relative reduction of 14.8% and an absolute risk reduction of 2.7 per 100 in the annual average incidence of AGE clinic visits (Table 2) were found following the introduction of universal rotavirus immunisation. This decline was greater in children aged 0–11 and 12–23 months than in the older groups (Table 2). The magnitude of the change was similar in both sexes (data not shown).

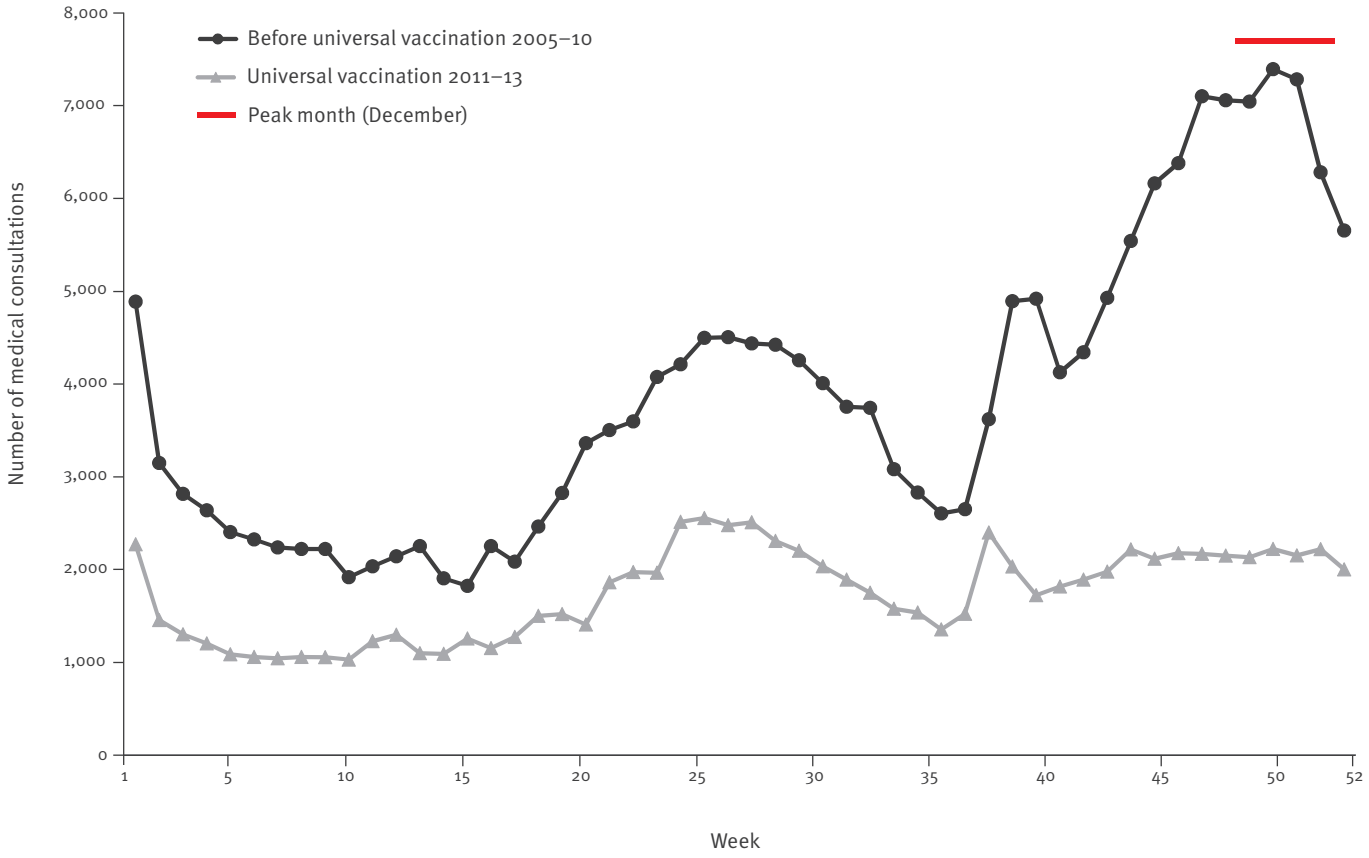
During the period from 1 January 2005 through 16 May 2014, 18,133 tests for the detection of rotavirus antigen were performed within seven days of the AGE clinic visit. Of those, 2,910 (16.0%) were positive and 15,223 (84.0%) were negative. Rotavirus testing differed by age, sex and period. Infants (0–11 months) and toddlers (12–23 months) were more likely to be tested (odds ratio (OR) = 2.07 and 1.82, respectively; $p<0.001$) than children aged 24–59 months, testing was performed slightly more often in male than female children (OR = 1.08; $p<0.001$), in the post- vs pre-vaccination era (OR = 1.31; $p<0.001$), and month-to-month variation was also observed.

In the weighted analysis, using the information on clinic visits attributed to laboratory-confirmed rotavirus AGE from 1 January 2005 till 31 December 2013, we estimated a yearly average of 6,179 rotavirus AGE clinic visits (incidence rate: 3.3 per 100) in the pre-vaccination period compared with 2,621 (incidence rate: 1.34 per 100) in the universal immunisation era, which corresponds to a reduction of 57.6% in the absolute number and 59.7% in the incidence rate of rotavirus AGE clinic visits) in MHS (Table 3). There was a gradient in the reduction with age: 79.8%, 59.6% and 38.9% in the age groups 0–11, 12–23 and 24–59 months, respectively (Table 4).

Between 2005 and 2010, there was a clear bimodal seasonality with peaks in spring/summer (warm) and winter (cold) (Figure 1). Except for 2009, the peaks in winter were twice as high as those in summer. This difference between the summer and winter peaks was not apparent in the post-vaccination period.

Figure 2

Seasonality of weekly clinic visits (aggregated counts) due to acute gastroenteritis in children aged 0–59 months, before and after universal rotavirus vaccination, Maccabi Health Services, Israel, 2005–13 (n = 293,761)



While the timing of the summer peaks were not altered after the introduction of rotavirus immunisation, the winter peaks in the period from 2011 to 2014 occurred earlier (Figure 1). Whereas in the pre-vaccination period, the yearly peak was in December, this changed with the introduction of universal vaccination (Figure 2). In 2011, the winter peak was still observed around December, but this was not evident in 2012 and 2013 (Figures 1 and Figure 3).

Test for seasonality was significant ($p<0.001$) both in the period before universal immunisation and in the universal vaccination period. Nonetheless, following the introduction of universal rotavirus immunisation, there was a decrease in the average number of weekly AGE clinic visits (from 648 to 583) as well as in the seasonal variation (from 70.9% to 57.3%), while the non-seasonal and random variation increased from 28.4% to 41.3%, and the standardised ratio of seasonal to random variation consequently decreased from 1.72 to 0.74. Rotavirus positivity followed typical winter seasonality (Figure 3) that coincided with the winter peaks of clinic visits for all-cause AGE (Figure 1, Figure 2 and Figure 3). The percentage of rotavirus-positive samples decreased after the introduction of universal rotavirus vaccination (Figure 3 and Table 3).

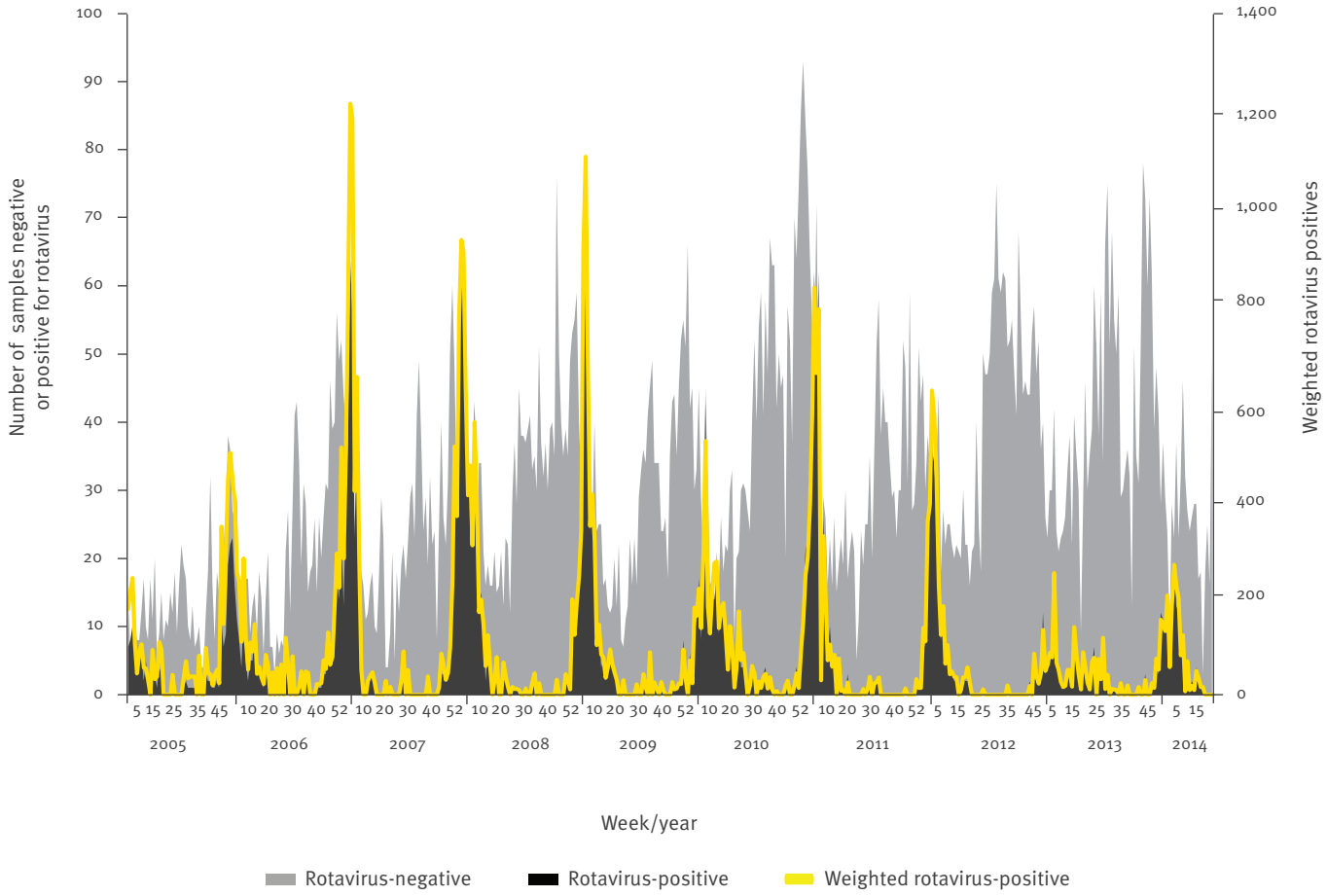
Discussion

In this large population study, we examined the impact of the universal rotavirus immunisation programme using RotaTeq on the burden of mild to moderate AGE and on rotavirus AGE associated with visits to primary care clinics among children younger than five years.

We found that introducing RotaTeq to the NIP in Israel was followed by an impressive reduction (59.7%) in incidence rate of mild to moderate rotavirus AGE associated with clinic visits (from 3.3 to 1.3 per 100) and a more modest (14.8%) decline in clinic visits due to all-cause AGE (from 18.2 to 15.5 per 100) in the paediatric population of MHS. The decrease was most notable in children aged 0 to 23 months, but a reduction was also documented in older children. Rotarix and RotaTeq were licensed in Israel in mid-2007, became available on the market towards the end of 2007 and were administered in the HMO primary care clinics for an approximate fee of ca EUR 88 (ca USD 100) [24]. Parents who purchased rotavirus vaccine received partial reimbursement by their HMO. Therefore, the reduction in rotavirus AGE clinic visits in the older groups could be attributed to partial rotavirus vaccination between 2008 and 2010, to herd protection conferred by universal rotavirus immunisation of infants or to both. Herd immunity due to rotavirus immunisation was described in

Figure 3

Rotavirus antigen test results in stools of patients who visited clinics for acute gastroenteritis, by week and year, Maccabi Health Services, Israel, 2005–14 (n = 18,133)



other studies that mostly focused on hospitalisations (reviewed by Patel et al. [12]). The remarkable reduction in clinic visits for rotavirus AGE is probably the result of the high effectiveness of rotavirus vaccines in Israel [15,24], good matching between the predominant circulating rotavirus genotypes and the vaccine strains [15,23], and high vaccination coverage of ca 80% for three doses. Our findings provide evidence that universal rotavirus immunisation can have a broad impact on reducing the burden of less severe disease in a developed country. So far, the introduction of universal rotavirus immunisation has been slow in middle- and high-income countries, including in the European region [13,14]. The barriers for implementing universal rotavirus immunisation in many European countries, which have been reviewed recently, include low awareness of the disease burden, perception of unfavourable cost-effectiveness and scepticism regarding the potential benefit of universal vaccination [13,14]. Our findings demonstrate a substantial reduction in the rotavirus gastroenteritis burden which was achieved only after the implementation of universal vaccination policy coupled with high immunisation coverage. Such evidence argues against some of the above barriers.

Healthcare utilisation resulting from all-cause diarrhoea was suggested as a possible data source to monitor the impact of rotavirus immunisation on disease burden [27,28]. Yet this can be a useful instrument only in settings with good historical medical records. Using healthcare utilisation practices without laboratory information may widely underestimate the true impact of the vaccine. Under these circumstances, the role of existing sentinel laboratory surveillance networks [29,30] becomes crucial.

Before the introduction of universal rotavirus vaccination, there was a clear bimodal seasonality of clinic visits for all-cause AGE, with summer and winter peaks, while clinic visits for rotavirus AGE occurred predominantly in the winter. Following the introduction of RotaTeq to the NIP, the summer peaks remained unaffected while the winter peaks were substantially lower. The change in the winter peaks of AGE clinic visits and rotavirus-positive samples were similar, thus it is plausible to attribute the changes in the all-cause AGE winter peaks to rotavirus immunisation.

Our study may have some limitations. First we considered AGE clinic visits as mild to moderate disease; however, it is possible that a small percentage of

the patients presented with severe illness and were referred to hospital by their primary care physician. Since disease severity is dynamic, it can be expected that a fraction of the patients who presented with mild disease later developed severe disease and may have been hospitalised. However, it is well documented that only a small fraction (up to 3%) of rotavirus gastroenteritides are severe enough to lead to a hospitalisation [3]. Indeed, we have estimated the incidence of rotavirus gastroenteritis hospitalisations in children under the age of five years in the pre-vaccination period in Israel at ca 5.7 per 1,000. Applying this figure to the MHS paediatric population shows that up to 3.1% of clinic visits could have been severe cases which may have resulted in hospitalisations. These data support the assumption that the majority of cases included in our study had mild to moderate gastroenteritis. Moreover, the majority of children who visited a clinic for AGE were not tested for rotavirus. However, knowing the total number of AGE clinic visits and retrieving data on rotavirus antigen testing, which was performed in ca 7% of all clinic visits, allowed us to conduct a weighted analysis to estimate the impact of rotavirus immunisation on rotavirus AGE clinic visits. It is worth mentioning that we characterised the factors that were significantly associated with rotavirus testing (age, sex, month and year of clinic visit) and that all were taken into account in the weighting procedure. Lastly, the period before universal rotavirus immunisation included three years (2008–10) of partial immunisation in which the uptake of the vaccine was fair (ca 50% in MHS) [24]. Therefore the current study is likely to underestimate vaccine impact.

The strengths of our study include the use of a computerised HMO database which includes a large representative sample of ca 25% of the Israeli population. Information in this database is gathered as part of routine clinical care of MHS members. We included data that were gathered over a nine-year period on over 0.3 million recorded clinic visits. This enabled us to detect the true impact of the universal rotavirus immunisation programme on the primary care setting. All laboratory tests in MHS are performed in one central laboratory (Mega Laboratory) and to our knowledge, the rotavirus testing method did not change during the time covered in this study.

Conclusion

Universal rotavirus vaccination in Israel was followed by a considerable decline in rotavirus AGE clinic visits and, to a lesser extent, in all-cause AGE clinic visits in children younger than five years. The decrease was greatest in children under the age of two years but was also evident in older children, possibly resulting from herd protection and/or partial rotavirus immunisation of the older cohorts during the pre-universal rotavirus immunisation era. Using data on healthcare utilisation may widely underestimate the true impact of the vaccine and may not be valuable in the long term, especially given the altered rotavirus seasonality after inclusion of universal rotavirus immunisation. Therefore, continued laboratory-based surveillance for rotavirus is warranted. These results have implications for global public health and policy making.

Conflict of interest

None declared.

Authors' contributions

K.M, D.C, G.C and V.S planned the study. G.C and V.S, collected the data. K.M, D.C, S.G, T.Z and E.A analysed the data. K.M, D.C and G.C wrote the first draft of the manuscript. All authors contributed the interpretation of the results and finalising the manuscript. K.M and G.C have equal contribution as first authors.

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IMI launches new call for proposals

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On 6 October, the Innovative Medicines Initiative (IMI) launched its 6th call for proposals. The IMI calls give researchers the opportunity to participate in partnerships between the public and private sectors aimed at developing the medicines of the future.

The latest IMI call includes the following topics:

- Development of Quantitative System Toxicology (QST) approaches to improve the understanding of the safety of new medicines

- Establishing impact of respiratory syncytial virus (RSV) infection, resultant disease and public health approach to reducing the consequences

Topics under the new Big Data for Better Outcomes programme:

- Real World Outcomes Across the Alzheimer's disease (AD) Spectrum (ROADS) to Better Care

- Development of an outcomes-focused platform to empower policy makers and clinicians to optimise care for patients with haematological malignancies

The deadline for submitting short proposals under the call is 12 January 2016.

The IMI is a partnership of the European Union (EU) and the European pharmaceutical industry. The IMI budget, half of which comes from the EU, is EUR 3.276 billion for 2014 to 2024.

The full text of the topics and details of how to apply can be found on the IMI website: http://www.imi.europa.eu/content/stage-1-17