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Humidifier-associated paediatric Legionnaires' disease, Israel, February 2012

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We report a fatal case of community-acquired Legionnaires' disease in an infant aged under six months. Epidemiological and microbiological investigations suggested that a free-standing cold water humidifier using domestic tap water contaminated with *Legionella pneumophila* serogroup 1 served as a vehicle for infection. These findings were corroborated by sequence-based typing (SBT). Humidifier-associated Legionnaires' disease can be prevented by appropriate control measures. This case also illustrates the emerging role of SBT in the investigation of legionellosis.

Case report

In February 2012, an infant under six months of age with an unremarkable gestational and perinatal history was admitted to hospital due to high fever, cough, wheezing, vomiting, gastrointestinal symptoms and loss of appetite of several days' duration. For six weeks before admission, the patient had been treated with inhaled salbutamol and corticosteroids for repeated episodes of shortness of breath and wheezing. Room air humidification had also been advised. Upon admission, the infant was alert and respiratory distress was evident. A lower respiratory tract infection was suspected and a chest X-ray showed bilateral infiltrates. Despite combined standard antimicrobial, corticosteroid and oxygen therapy, the lung infiltrates progressed over the following days and mechanical ventilation was required due to respiratory failure. Antimicrobial therapy was switched to intravenous ceftriaxone and clindamycin and oral azithromycin. Initial tests for bacterial respiratory pathogens were negative; however, on the fifth day in hospital, a urinary antigen test was positive for *Legionella pneumophila* serogroup (sg) 1. A sputum culture and sputum polymerase chain reaction (PCR) test (Seeplex PneumoBacter ACE detection, Seegene, South Korea) obtained that day were both

positive for *L. pneumophila* sg.1. Sputum PCR was also positive for respiratory syncytial virus (RSV). Following diagnosis of Legionnaires' disease (LD), antimicrobial treatment was extended but the patient's condition continued to deteriorate and extracorporeal membrane oxygenation therapy was needed. Despite maximal intensive care and appropriate antimicrobial therapy, the patient succumbed two weeks following admission.

Background

Human *L. pneumophila* infection (legionellosis) typically presents as a self-limiting influenza-like illness (Pontiac fever) or as pneumonia with systemic manifestations (LD) [1]. LD most commonly affects the elderly or individuals with typical risk factors [1]. Paediatric LD is uncommon and accounts for 0.43% of European cases [2]. Most paediatric infections involve immunocompromised children, commonly in a nosocomial setting, while community-acquired infection in an otherwise healthy child is rarely reported [3]. We describe here a fatal case of community-acquired paediatric LD that involved a distinct source of transmission and discuss its public health implications.

Epidemiological investigation

An investigation was carried out, as mandated in all cases of LD, by the regional public health office and the infectious disease and microbiology departments of the hospital where the patient had been admitted. No typical risk factors for LD or possible nosocomial source of infection could be determined. The patient's parents were questioned about possible exposure to water aerosols at home or outdoors and consequently the use of a free-standing cold water humidifier at the patient's home became evident. The humidifier had not been regularly cleaned and had been filled with tap water that had not been pre-boiled or frequently changed.

The investigation did not reveal any epidemiologically linked cases in the patient's household or in the hospital. However, an additional case of paediatric LD (Case 8) had been diagnosed at the same hospital, several weeks before the current case (Table). The finding of two paediatric cases triggered a retrospective review of national surveillance data at the Ministry of Health (January 2010 to July 2012). Seven additional cases (≤ 24 months of age) were identified (Table), none of whom were linked to the current case. Eight of the nine cases were male, seven were likely to have been nosocomial, six had underlying risk factors and the case fatality rate was 33% ($n=3$). Respiratory coinfection was documented in six of the cases. The use of cold water humidifiers was reported for five of the seven cases for whom this information was available.

Microbiological Investigation

Microbiological samples were obtained from several sites of the cold and hot water system at the patient's household. *L. pneumophila* was identified and colony-forming units (cfu) enumerated according to standard methods and phenotypically characterised using the Dresden panel of monoclonal antibodies [4]. Genotype was determined according to the standardised sequence-based typing (SBT) method developed by the former European Working Group for *Legionella* Infections (EWGLI) [5,6] and sequence types (STs) were assigned using the SBT quality tool [7].

The strain recovered from the patient's sputum was identified as *L. pneumophila* sg.1 monoclonal antibody (mAb) subgroup OLDA/Oxford, which typically accounts for almost a third of environmental isolates but only 3.6% of clinical cases [8]. Of seven domestic environmental samples obtained, two grew *L. pneumophila* sg.1: one from the water system was mAb subgroup Allentown/France (300 cfu/L) and one from the humidifier residual water was initially classified as mAb subgroup Philadelphia (30,000 cfu/L).

Initial genotyping revealed that the clinical strain was ST₁, whereas the strain derived from the water system was ST₄₀. It was not possible to obtain the ST of the humidifier-derived strain because of suboptimal sequence quality. When Bionumerics v6.1 (Applied Maths, Belgium) was used to analyse the sequences obtained from the humidifier-derived strain, several double peaks were evident, suggesting the possible presence of mixed STs in the humidifier water, which, in retrospect, gave rise to a false mAb subgroup result, erroneously implicating the presence of the Philadelphia strain in that sample. Following meticulous subculturing and colony picking, both the OLDA/Oxford ST₁ and Allentown/France ST₄₀ strains were isolated and identified in the humidifier sample, thus providing a link between humidifier water contamination and clinical infection.

The original DNA extract used for PCR-based diagnosis was re-tested post-mortem. An additional untested

sputum sample that had been frozen was also tested and was culture-negative. Both samples were positive for *L. pneumophila* based on a quantitative PCR assay that targets the *mip* gene (cycle threshold values of 18 and 21, respectively, indicating a high level of the gene target in the tested samples) [9]. Both samples were also tested by direct nested SBT [10]: both were ST₁.

Public health and control measures

After elucidating the role of free-standing cold water humidifiers as possible vehicles for LD, the identified risk was communicated by the Public Health Services to healthcare professionals as well as to the public via national media (television news and Internet). The Public Health Services issued guidance to the public regarding the regular maintenance of domestic water systems and the safe and appropriate use of cold water humidifiers. This included the mandatory use of sterile or chilled pre-boiled water with daily water changes, and regular weekly and seasonal instrument cleaning.

Additionally, the Public Health Services have approached the Standards Institution of Israel and new regulations mandating hazard labelling of cold water humidifiers and inclusion of package inserts with user manuals aimed at legionellosis prevention are being set up.

Discussion

As paediatric LD is highly unusual, especially in the first months of life, it may be easily missed by clinicians [3]. Paediatric LD may be either community acquired (e.g. neonatal LD following water birth [11]) or hospital acquired, and may be associated with respiratory coinfection [12,13]. In our case report and case series, such coinfection chiefly involved RSV or adenovirus. In the case reported here, *L. pneumophila* was most likely transmitted at home via the proliferation of the pathogen in stagnant water within a cold water humidifier followed by the generation of *Legionella*-contaminated aerosols by this device. The isolation of *L. pneumophila* sg.1 strains with an identical ST from both the humidifier in the patient's home and respiratory specimens has implicated the humidifier as the source of infection and suggest that humidifiers may serve as competent vehicles for community-acquired LD. The role of humidifiers in additional paediatric LD cases in Israel is intriguing (Table) and should be investigated prospectively.

Viral or bacterial coinfections, as described above, have been reported in LD [12-14]. In the current case, and perhaps in others in our series, respiratory coinfection may have played a role in contracting LD. Specifically, we hypothesise that the prolonged episode of respiratory infection caused by RSV in the current case, who lacked typical underlying risk factors for LD, facilitated *Legionella* infection, by frequent use of the humidifier as well as increased susceptibility to the infection through alteration of local immunity and an enhanced inflammatory response.

TABLE

Paediatric cases of Legionnaires' disease, Israel, January 2010–July 2012 (n=9)

Case number	Year	Age group (months)	Outcome	Risk factors	Setting	Intensive care	Diagnostic method	Coinfection	Environmental findings	History of cold water humidifier use
1	2010	19–24	Alive	Chronic lung disease	Nosocomial	No	Urinary Ag	RSV	sg.1, sg.3	Yes
2	2010	7–12	Alive	None	Community	No	Urinary Ag	Adenovirus	None	Yes
3	2011	7–12	Death ^a	Immunocompromised	Nosocomial	Yes	Urinary Ag	None	sg.3	Unknown
4	2011	1–6	Alive	Surgery	Nosocomial ^b	No	Urinary Ag, PCR	None	None	Yes
5	2011	19–24	Alive	Immunocompromised	Nosocomial ^b	Yes	Urinary Ag, PCR	None	None	No
6	2012	13–18	Alive	Immunocompromised, surgery	Nosocomial	Yes	Urinary Ag	RSV	sg.3	Yes
7	2012	7–12	Death ^a	Immunocompromised	Nosocomial	No	PCR	<i>Streptococcus pneumoniae</i>	sg.3	No
8	2012	1–6	Alive	None	Nosocomial ^b	No	Urinary Ag	RSV and adenovirus	No data	Unknown
9 Current case	2012	1–6	Death ^a	None	Community	Yes	Urinary Ag, culture, PCR	RSV	sg.1	Yes

Ag: antigen; PCR: polymerase chain reaction; RSV: respiratory syncytial virus; sg: serogroup.

^a Attributed to Legionnaires' disease.^b Most likely nosocomial but epidemiological investigation inconclusive.

In 2008, humidifiers were implicated as a possible vehicle of LD in a cluster in a nursery in Cyprus: 11 neonates fell ill and the case fatality rate was 27% [14]. According to the preliminary report, possibly more than one strain of *L. pneumophila* was implicated [15]. It is noteworthy that evidence supporting a clear association between LD and humidifier use in that nursery has not been published to date; to the best of our knowledge, our report is the first to confirm this potential source of infection.

Newly manufactured devices with water sonication may improve humidification efficiency but may also generate potentially contaminated aerosols. This may explain the accumulation of humidifier-associated LD in recent years, as is evident from our report and the cluster in Cyprus. In light of the increased availability of new-generation humidifiers, enhanced vigilance and a low index of suspicion should be exercised. Education of healthcare professionals, parents and caregivers regarding correct device use is crucial. Bearing in mind that humidifier-associated LD has been recognised in different countries and settings, these control measures should be complemented by appropriate public health actions, such as national or international regulations that mandate hazard labelling of cold water humidifiers. Lastly, the role of humidifiers in the transmission of *Legionella* should be prospectively studied.

This case also illustrates the challenges associated with linking clinical and environmental *Legionella* isolates, in light of recognised limitations of culture-based methods. Thus SBT emerges as a powerful tool not only for delineating the molecular epidemiology of legionellosis, but also for outbreak investigation.

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The Hajj: updated health hazards and current recommendations for 2012

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This year the Hajj will take place during 24–29 October. Recent outbreaks of Ebola haemorrhagic fever in Uganda and the Democratic Republic of the Congo, cholera in Sierra Leone, and infections associated with a novel coronavirus in Saudi Arabia and Qatar required review of the health recommendations of the 2012 Hajj. Current guidelines foresee mandatory vaccination with quadrivalent meningococcal vaccine for all pilgrims, and yellow fever and poliomyelitis vaccine for pilgrims from high-risk countries. Influenza vaccine is strongly recommended.

The annual Hajj is one of the greatest assemblies of humankind on earth. Each year, three million Muslims attend the Hajj in Mecca, Saudi Arabia. Of these, 1.8 million non-Saudi Arabians usually come from overseas countries and 89% (1.6 millions) of them arrive by air [1]. Pilgrims come from more than 180 countries worldwide and about 45,000 pilgrims each year arrive to Saudi Arabia from the European Union [2].

Preventive measures during the Hajj

Saudi Arabia provides free healthcare to all pilgrims during the Hajj. For the 2012 Hajj, which will take place on 24–29 October 2012, the country has prepared 25 hospitals, 4,427 beds including 500 critical care beds and 550 emergency care beds. In addition, there are 141 healthcare centres in the vicinity of the Hajj area with 20,000 specialised healthcare workers. The planning for the Hajj relies on the coordinated efforts of 24 supervisory committees [2]. The Hajj preventive medicine committee oversees all public health and preventative matters during the Hajj. A large number of public health officers regulate ports of entry for all pilgrims to ensure compliance with the requirements of the Saudi Arabian Ministry of Health. Public health teams are located in various areas of the Hajj, including 21 mobile teams. At each of the 18 hubs at King Abdulaziz International Airport Hajj terminal in Jeddah, two clinical examination rooms and a large holding area are dedicated to assess arriving pilgrims, check their immunisation status, and administer the recommended prophylactic medicines [2]. The public health

teams and teams at the ports of entry report back to the command centre on nine communicable diseases using electronic and manual surveillance systems. These diseases are influenza, influenza-like illness, meningococcal disease, food poisoning, viral haemorrhagic fevers, yellow fever, cholera, poliomyelitis, and plague [2].

Pre- and post-Hajj travel advice

The Hajj is a unique event with possible impact on international public health. Healthcare practitioners around the world must be attentive to the potential risks of disease transmission during the Hajj. They must recommend appropriate strategies for the prevention and control of communicable diseases before, during and after the completion of the Hajj. The current international collaboration in planning vaccination campaigns, developing visa quotas, arranging rapid repatriation, and managing health hazards at the Hajj are crucial steps in this process. The Saudi Arabian Ministry of Health publishes the Hajj requirements for each Hajj season. This year's Hajj recommendations have recently been published [3].

Recent outbreaks of Ebola haemorrhagic fever in Uganda and the Democratic Republic of the Congo (DRC), cholera in Sierra Leone, and infections associated with a novel coronavirus in Saudi Arabia and Qatar required review of the health recommendations of the 2012 Hajj. We present here the changes and additions made in the recommendations for these diseases. For completeness, we also summarise the existing recommendations [3,4].

Meningococcal disease

The risk of the occurrence of meningococcal outbreaks is a real concern during the Hajj seasons. This risk is related to the high carriage rates with one study from Mecca reporting carriage rate as high as 80% [5]. Due to the previous occurrence of meningococcal outbreaks, the bivalent A and C meningococcal vaccine became a requirement for the attendance of the Hajj in 1986. Two large outbreaks caused by meningococcal

serogroup W135 in 2000 and 2001 [6-8] resulted in an extension of the previous requirement to include serogroups Y and W135, and the quadrivalent (A, C, Y, W135) meningococcal polysaccharide vaccine was included as a requirement for a Hajj visa in May 2001 [9]. In addition, visitors arriving from countries in the African meningitis belt receive chemoprophylaxis with ciprofloxacin tablets (500 mg) at the port of entry to lower the rate of meningococcal carriage. It is estimated that about 400,000 to 460,000 pilgrims receive the recommended doses at the port of entry in Saudi Arabia. Compliance with meningococcal vaccination among arriving international pilgrims exceeded 97% in 2011 [1].

Yellow fever

In accordance with the International Health Regulations 2005, all travellers arriving from countries identified by the World Health Organization (WHO) as areas at risk of yellow fever must present a valid yellow fever vaccination certificate showing that the person was vaccinated at least 10 days previously and not more than 10 years before arrival at the border. In the absence of such a certificate, the individual will be placed under strict surveillance for six days from the date of vaccination or the last date of potential exposure to infection, whichever is earlier. Health offices at entry points will be responsible for notifying the appropriate Director General of Health Affairs in the region or governorate about the temporary place of residence of the visitor. Aircrafts, ships and other means of transportation arriving from countries affected by yellow fever are requested to submit a certificate indicating that it applied disinfection in accordance with methods recommended by the WHO.

Risks of respiratory tract infections

Acute upper respiratory tract infections (URTIs) are the most common disease during Hajj. There are many factors promoting the spread of respiratory pathogens, including close contact among pilgrims, shared sleeping tents and dense air pollution [2]. The pathogens causing URTIs among pilgrims are respiratory syncytial virus (RSV), parainfluenza virus, influenza virus and adenovirus [10]. The rates of different types of respiratory virus infections are as follows: influenza (9.8%), parainfluenza (7.4%), adenovirus (5.4%) and RSV (1.4%) [11]. Because of overcrowding and the fact that many Muslims come from countries where tuberculosis (TB) is endemic, pulmonary tuberculosis was a leading cause of hospitalisation in patients with community-acquired pneumonia [12]. The estimated risk of tuberculosis acquisition during the Hajj is thought to be around 10%, based on the use of pre-visit and post-visit QuantiFERON TB assay test [13]. In another community-based survey of the epidemiology of tuberculosis in Saudi Arabia, positive tests using purified tuberculin antigens were more frequent in Saudi Arabians living in the Holy cities hosting pilgrims compared to other cities in Saudi Arabia [14]. The development of strategies to reduce the transmission of TB during the Hajj

is a challenge for which no evidence-based approved measures are available to date. The Saudi Arabian Ministry of Health continues to recommend wearing face mask in crowded places and changing them frequently to minimise transmission of respiratory infections. Controlling tuberculosis transmission in mass gatherings is an area that needs urgent research studies. [14].

Novel coronavirus infection

Of particular interest is the recent report of two cases of acute respiratory failure associated with a novel coronavirus. Both patients were previously healthy adults. The cases occurred a few months before the 2012 Muslim Hajj season. The first case of infection with the novel coronavirus was identified in a Saudi Arabian national, who died in June 2012 [15,16]. The second case was a patient from Qatar who was transferred to a hospital in London, United Kingdom in early September 2012 [17]. Available data to date do not support human-to-human transmission of this novel coronavirus, and zoonotic transmission is highly suspected. In the second case of this novel coronavirus infection, none of the 64 close contacts developed severe disease, 13 of them (20%) reported mild respiratory symptoms, and the novel coronavirus was not detected in 10 symptomatic contacts who were tested [17].

The WHO does not recommend any travel restrictions to or from Saudi Arabia. The current case definitions from the WHO [18] and from the Saudi Arabian Ministry of Health can be found on the WHO website (http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/index.html) and in Table 1, respectively. The practice of good hand hygiene and cough etiquette was associated with less respiratory illness among United States travellers to the 2009 Hajj [19]. It is recommended that pilgrims continue to practice proper hand hygiene, protective behaviours and cough etiquette to further decrease the occurrence of respiratory diseases.

Food-borne diseases and cholera

Diarrhoeal illnesses during mass gathering including Hajj are a potential health hazard. Many factors may contribute to this problem including: inadequate standards of food hygiene, shortage of water, the presence asymptomatic carriers of pathogenic bacteria, and the preparation of large numbers of meals poorly stored by pilgrims. There are only few studies describing the incidence and aetiology of traveller's diarrhoea during the Hajj. In one study, diarrhoea was the third most common cause (6.7%) of hospitalisation [20]. Another study describes an outbreak of diarrhoeal illness in a small number of soldiers during the Hajj season [21]. As a precautionary measure the Saudi Arabian Ministry of Health strongly enforces that pilgrims are not allowed to bring fresh food into Saudi Arabia. Only properly canned or sealed food or food stored in containers with easy access for inspection is allowed in

TABLE 1

Severe respiratory disease associated with novel coronavirus: case definition by the Saudi Arabian Ministry of Health

	Clinical definition	Epidemiological criteria	Laboratory data
Suspected case	A person requiring hospitalisation with community-acquired acute respiratory syndrome Symptoms include: fever (≥ 38 °C) and cough, with confirmed lower airway involvement (clinical and radiological evidence of pneumonia) not explained by any other infection or other aetiology.	None	
Confirmed case	As for suspected case	None	A person with laboratory-confirmed infection with the novel coronavirus

small quantities, sufficient for one person for the duration of their trip.

Cholera is another risk during the Hajj, especially in light of the continued occurrence of outbreaks in different countries. As of 20 September 2012, a total of 19,283 cases, including 276 (1.4%) deaths have been reported in the ongoing cholera outbreak in Sierra Leone since the beginning of the year [22]. The highest numbers of cases occurred in the Western area of the country where the capital city of Freetown is located. In addition, the WHO reported a sharp increase in the number of cholera cases in July in the DRC and many other countries [23]. The Ministry of Health of Saudi Arabia has updated its public health staff at all ports of entry for pilgrims, to be observant of all pilgrims coming from areas where cholera has been reported by WHO, and to maintain a high level of vigilance for any signs and symptoms of diarrhoea, and to continue surveillance at their camps and initiate quarantine and contact tracing once a case is suspected. Emphasis is being placed on early detection of cases and timely provision of treatment at all Hajj premises, once pilgrims have passed the ports of entry while incubating the disease.

Poliomyelitis

Poliomyelitis is still predominant in certain countries around the world. The attendance of visitors from these countries to the Hajj may pose a health risk for other visitors. All travellers arriving from polio-endemic countries and re-established transmission countries, namely Afghanistan, Angola, Chad, the DRC, Nigeria and Pakistan, regardless of age and vaccination status, should receive one dose of oral poliovirus vaccine (OPV). Proof of OPV vaccination at least six weeks prior departure is required to apply for entry visa for Saudi Arabia. These travellers will also receive one dose of OPV at borders points on arrival in Saudi Arabia. The same requirements are valid for travellers

from recently endemic countries at high risk of reimportation of poliovirus, i.e. India (Table 2).

Polio cases secondary to wild poliovirus importation or to circulating vaccine-derived poliovirus in the past 12 months have been reported in the following countries: China, Central African Republic, Côte d'Ivoire, Kenya, Mali, Niger, Somalia and Yemen [4]. All visitors aged under 15 years travelling to Saudi Arabia from these countries should be vaccinated against poliomyelitis with the OPV or inactivated poliovirus vaccine (IPV). Proof of OPV or IPV vaccination six weeks prior to application is required for entry visa. Irrespective of previous immunisation history, all visitors under 15 years arriving in Saudi Arabia will also receive one dose of OPV at border points (Table 2).

Ebola outbreaks

Two large outbreaks of Ebola have been reported by the Ministries of Health of Uganda and the DRC. In Uganda, a total of 24 probable and confirmed cases were reported during the outbreak. Eleven of these 24 cases have been laboratory-confirmed by the Uganda Virus Research Institute in Entebbe. A total of 17 deaths were reported in this outbreak. The last confirmed case was admitted on 3 August 2012 and discharged from hospital on 24 August 2012 [24,25]. This is twice the maximum incubation period (21 days) for Ebola proposed by the WHO during Ebola outbreak response operations. In the DRC, 46 cases (14 laboratory-confirmed, 32 probable) of Ebola haemorrhagic fever were reported until 15 September 2012. Of these, 19 have been fatal (six confirmed, 13 probable). The cases occurred in two health zones of Isiro and Viadana in Haut-Uélé district in Province Orientale. Additionally, 26 suspected cases have been reported and are being investigated.

The two Ebola outbreaks are not epidemiologically linked and have been caused by two different Ebola subtypes: Ebola subtype Sudan in Uganda, and Ebola

TABLE 2

Saudi Arabian health requirements and recommendations for entry visas for the Hajj seasons in 2012

	Countries or areas at risk	Requirement
Yellow fever	<p>Africa:</p> <p>Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Cote d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Gabon, Guinea, Guinea-Bissau, Gambia, Ghana, Kenya, Liberia, Mali, Mauritania, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, Sudan, South Sudan, Togo and Uganda</p> <p>South and Central America:</p> <p>Argentina, Venezuela, Brazil, Colombia, Ecuador, French Guiana, Guyana, Panama, Paraguay, Peru, Bolivia, Suriname, and Trinidad and Tobago</p>	<p>A valid yellow fever vaccination certificate (at least 10 days previously and less than 10 years before arrival). In the absence of such a certificate, the individual will be placed under strict surveillance for six days from the last date of potential exposure to infection.</p>
Meningococcal meningitis	<p>a) Visitors from all countries</p> <p>b) Visitors from the African meningitis belt:</p> <p>Benin, Burkina Faso, Cameroon, Chad, Central African Republic, Côte d'Ivoire, Eritrea, Ethiopia, Gambia, Guinea, Guinea-Bissau, Mali, Niger, Nigeria, Senegal and Sudan</p> <p>c) Local pilgrims and the Hajj workers</p>	<p>a) Certificate of vaccination with the quadrivalent (ACYW135) vaccine issued not more than three years previously and at least 10 days before arrival in Saudi Arabia</p> <p>b) ACYW135 vaccine (as above)</p> <p>AND</p> <p>ciprofloxacin 500 mg chemoprophylaxis administered at the port of entry</p> <p>c) Vaccination with quadrivalent (ACYW135) vaccine is required for:</p> <ul style="list-style-type: none"> - all citizens and residents of Medina and Mecca (not vaccinated during the past three years) - all citizens and residents undertaking the Hajj - all Hajj workers (not vaccinated in the past three years) - any individual working at entry points or in direct contact with pilgrims in Saudi Arabia
Poliomyelitis	<p>a) Arriving from polio-endemic countries and re-established transmission countries:</p> <p>Afghanistan, Angola, Chad, the Democratic Republic of Congo, India, Nigeria and Pakistan</p> <p>b) Recently endemic countries at high risk of re-importation of poliovirus:</p> <p>India, Cameroon, Central African Republic, Cote d'Ivoire, Kenya, Mali, Niger, Somalia and Yemen</p>	<p>a) All travellers should receive one dose of OPV at least six weeks prior to departure and will receive one dose of OPV at the border on arrival to Saudi Arabia.</p> <p>b) All visitors under 15 years of age should receive one dose of oral polio vaccine (OPV) at least six weeks prior to departure and will receive one dose of OPV at the border on arrival to Saudi Arabia.</p>
Seasonal influenza	All	The Ministry of Health of Saudi Arabia recommends that all pilgrims be vaccinated against seasonal influenza

OPV: oral polio vaccine.

subtype Bundibugyo in DRC. To avoid global spread of the disease, the Saudi Arabian Ministry of Health decided to exclude pilgrims from these two countries for this Hajj season. This restriction is based on the careful review and deliberation of the national committee on communicable disease prevention who felt that it cannot be excluded that new cases may emerge, and on the fact that the risk of disease transmission is thought to be high with potential catastrophic consequences if occurring during the Hajj, as the disease has a high mortality rate and no therapeutic interventions are available.

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Surveillance of travel-associated gastrointestinal infections in Norway, 2009–2010: are they all actually imported?

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The Norwegian Surveillance System for Communicable Diseases (MSIS) includes variables related to travel for clinicians to fill when notifying travel-associated infections. We measured the completeness and validated the travel-history information for salmonellosis, campylobacteriosis, giardiasis and shigellosis reported in 2009–2010. Of all 8,978 selected infections in MSIS, 8,122 (91%) were reported with place of infection of which 5,236 (65%) were notified as acquired abroad, including 5,017 with symptoms. Of these, 2,972 (59%) notifications had information on both date of arrival in Norway and date of symptom onset, so time between travel and illness onset could be assessed. Taking in account the incubation period, of the 1,435 infections reported as travel-associated and for which symptom onset occurred after return to Norway, 1,404 (98%) would have indeed been acquired abroad. We found a high level of completeness for the variable ‘*place of infection*’. Our evaluation suggests that the validity of this information is high. However, incomplete data in the variables ‘*return date to Norway*’ and ‘*date of symptoms onset*’, only allowed assessment of the biological plausibility of being infected abroad for 59% of the cases. We encourage clinicians to report more complete travel information. High quality information on travel-associated gastrointestinal infections is crucial for understanding trends in domestic and imported cases and evaluating implemented control measures.

Background

Increased harmonisation in preventing foodborne infections at the European level and an increase in international travel in recent years has led to the need for better knowledge on the epidemiology of travel-associated infections in Europe. To this effect, the European Centre for Disease Prevention and Control (ECDC) gathers surveillance data including data from the European Travel Medicine Network EuroTravNet [1,2] that is linked to the worldwide surveillance network on travel-associated morbidity GeoSentinel [3].

Already existing national surveillance systems may also provide information on travel-associated infectious diseases. The Norwegian Surveillance System for Communicable Diseases (MSIS) includes several variables on travel history that should be filled in by clinicians when reporting notifiable diseases. This information is notified to the European Surveillance System (TESSy), and is presented in yearly surveillance reports [4].

Travel-associated gastrointestinal infections in Europe and Norway: current situation

Information provided by the EuroTravNet network in 2008 states that gastrointestinal infections are the most frequently notified travel-associated infections in Europe (33%) [5].

In 2009, European Union (EU) and European Economic Area/European Free Trade Association (EEA/EFTA) countries notified 201,605 campylobacteriosis, 109,885 salmonellosis, 7,261 shigellosis, and 16,574 giardiasis confirmed cases to ECDC. The proportion of cases with travel-history information was 72,440 (65.9%) for salmonellosis, 2,583 (35.6%) for shigellosis and 5,371 (32.4%) for giardiasis. There was no data on travel-history information for campylobacter in 2009, but in 2008, of the 193,554 confirmed cases reported, 132,677 had information on travel-history (68.5%). Of those with known travel history, the proportion that was travel-associated varied from 8% of campylobacteriosis cases to 62% of shigellosis cases [6,7].

In Norway, most cases of gastrointestinal infections notified to MSIS in 2010 were reported as travel associated, ranging from approximately 50% of campylobacteriosis cases to around 83% of shigellosis cases [8].

The challenge when notifying gastrointestinal travel-associated infections

Clinicians seeing patients returning from international trips play a critical role in recognising and notifying

travel-associated public health risks [2]. The importance of taking a travel history to establish the possibility of imported infection was highlighted almost 30 years ago by the classical publication ‘*Unde Venis?*’ (‘*Where do you come from?*’) [9]. However, published studies conclude that there is still insufficient and inadequate travel history recording, which may directly have an impact on public health [10].

The lack of standardised case definitions for travel-associated infections makes the reporting and comparison of rates between countries difficult. In Europe, there is no general agreement on how to define a travel-associated infection. Information on travel-associated infections compiled at the international level, such as through TESSy, originates from multiple sources. Data from diverse European countries may therefore not be directly comparable due to differences in surveillance and national definitions. Additionally, guidelines for classifying ‘travel-associated’ cases versus ‘domestic’ cases may not exist at the country level. In Norway, for example, there are no strict criteria for defining a case with gastrointestinal infection as travel-associated. This is determined by the reporting clinician, based on time of symptom onset, place of travel, return date and incubation period of the disease. The endemic level of the infection in Norway is also taken into account when clinicians report a case as travel-associated or domestic. Since the endemic level of most notifiable gastrointestinal infections is very low in Norway, clinicians may report a case as travel associated without taking into account the incubation period for that specific infection in relation to when the patient returned to Norway from a high-endemic country.

In order to evaluate the quality of the travel-associated information on gastrointestinal infections available in MSIS, we measured the completeness of the travel-associated variables of gastrointestinal infections notified (specifically salmonellosis, campylobacteriosis, giardiasis and shigellosis) in MSIS during 2009–2010. We also validated the information about place of infection, Norway/abroad, by looking at the reported time between travel and time of symptom onset compared to the expected incubation period of the disease.

Methods

We considered ‘*travel-associated gastrointestinal infection cases*’ to be any registered cases of salmonellosis, campylobacteriosis, giardiasis and shigellosis in MSIS where the variable ‘*place of infection*’ was a country other than Norway. To be included in our study, a case’s symptom onset date had to be between January 2009 and December 2010.

In Norway, clinicians report notifiable diseases using a paper form. When reporting, the clinician should state whether the patient acquired the disease in Norway or abroad. If the disease is reported as acquired abroad, the country visited and the date of arrival in Norway should be specified. Once the notification is filled-in,

TABLE 1

Variables related to gastrointestinal infections extracted from the Norwegian Surveillance System for Communicable Diseases, Norway, 2009–2010

Variable	Definition
Diagnosis	Salmonellosis, campylobacteriosis, giardiasis, shigellosis
Microorganism	Species, subspecies
Place of infection	Abroad /Norway
Return date to Norway	Date of arrival to Norway after travel
Date of onset of symptoms	Date of symptom onset

it is sent by post to the Norwegian Institute of Public Health (NIPH) where it is entered into MSIS.

Variables related to diagnosis, microorganism, place of infection, date of return to Norway after travel, and date of symptom onset were extracted from MSIS (Table 1).

To measure the completeness of the data on travel-associated infections we analysed the variables ‘*place of infection*’, ‘*return date to Norway*’ and ‘*date of onset of symptoms*’ for all cases of salmonellosis, campylobacteriosis, shigellosis and giardiasis notified to MSIS during the study period. For *Salmonella* infections we also did separate analyses for *S. Typhimurium* and *S. Enteritidis* as the endemic levels of these serovars are known to be very different within Norway.

Further analyses included only cases reported as having acquired infection abroad.

In order to validate the information, we used the variables ‘*date of onset of symptoms*’ and ‘*return date to Norway*’ to measure the time between travel and illness onset. We excluded all cases registered as asymptomatic (diagnosed, for example, as a result of a routine screening), since they would not have a recorded date of symptom onset. We then selected the cases where the variables ‘*date of onset of symptoms*’ and ‘*return date to Norway*’ were complete and studied the distribution of cases’ dates of symptom onset around the return date to Norway after travel.

For those cases with symptom onset after arrival in Norway, we compared the number of days between the return date to Norway and the date of symptom onset to the incubation period described in the literature for each infection, to assess the plausibility of the case having been infected while travelling. As reference, we used two thresholds for each infection, the most common incubation period and the maximum incubation period (Table 2) [11,12].

TABLE 2

Reported incubation periods for gastrointestinal diseases considered in this study, surveillance of travel-associated gastrointestinal infections, Norway, 2009–2010

Disease	Most common incubation period (in days) ^a	Maximum incubation period (in days) ^a
Campylobacteriosis	≤ 5	≤ 10
Salmonellosis	≤ 3	≤ 16
Giardiasis	≤ 10	≤ 25
Shigellosis	≤ 4	≤ 7

^a According to [11,12].

In addition to estimating infection abroad by incubation period, we also used seven days following return from travel as a cut off, as has been used in other studies [13].

Results

A total of 8,978 *Campylobacter*, *Salmonella*, *Giardia* and *Shigella* infections were notified in MSIS during the period 2009–2010. The most frequent was campylobacteriosis (5,522 cases, 61.5%), followed by salmonellosis (2,600 cases, 29%), giardiasis (567 cases, 6.3%) and shigellosis (289 cases, 3.2%). Among salmonellosis, the most frequent *Salmonella* serovar reported was *S. Enteritidis* (1,136 cases, 43.7%), followed by *S. Typhimurium* (348 cases, 13.4%) and the monophasic variant (mv) of *S. Typhimurium* (172 cases, 6.6%) (Table 3).

Completeness of the variable ‘place of infection’

Of all 8,978 gastrointestinal infections, 8,122 (90.5%) had information on place of infection, of which 5,236 (64.5%) were notified as contracted abroad.

Campylobacteriosis was the most frequent travel-associated gastrointestinal infection reported (2,730 cases, 52.1% of all travel-associated gastrointestinal infections) followed by salmonellosis (1,873 cases, 35.8%), giardiasis (435 cases, 8.3%) and shigellosis (198 cases, 3.8%).

Information on place of infection was most frequently missing for giardiasis (64 cases, 11.3%) and salmonellosis (272 cases, 10.5%). Among salmonellosis cases, *S. Typhimurium* (excluding the monophasic variant) was the serovar for which place of infection was most frequently unknown (50 cases, 14.4% of all *S. Typhimurium* cases (n=348)) (Table 3).

Completeness of ‘return date to Norway’ and ‘date of onset of symptoms’

Overall, 3,167 (63.1%) of all travel-associated symptomatic cases (n=5,017) had registered a ‘return date to Norway’ after a trip. The completeness of this variable

by infection ranged from 51.2% for giardiasis (126/246) to 68.8% for salmonellosis caused by *S. Typhimurium* (108/157) (Table 4). The variable ‘date of onset of symptoms’ was completed for 4,291 (85.5%) of all travel-associated symptomatic cases, ranging by disease from 61.8% for giardiasis (152/246) to 87.3% for salmonellosis due to *S. Enteritidis* (806/923) (Table 4).

A total of 2,972 (59.2%) of travel associated symptomatic cases had both variables ‘date of arrival in Norway’ and ‘date of onset of symptoms’ completed, ranging by disease from 43.1% for giardiasis (106/246) to 65.6% for salmonellosis due to *S. Typhimurium* (103/157) (Table 4).

Plausibility of having been infected while travelling: time of symptom onset after travel and incubation period

The Figure illustrates the date of symptoms onset in relation to return date to Norway for cases reported as travel-associated. Overall, 1,435/2,972 (48.3%) reported onset of symptoms on the day of return or after return to Norway (Table 5).

In total, 2,893 (97.3%) of the 2,972 cases reported as travel associated indicated onset of symptoms during the stay abroad or within seven days of return to Norway (Figure, Table 6), varying by disease from 91.5% for cases with giardiasis (97/106) to 98.2% for cases with salmonellosis due to *S. Enteritidis* (546/556). Ten cases (four cases of campylobacteriosis, two cases of salmonellosis and four cases of giardiasis) reported symptom onset date as more than one month after return to Norway. Three cases (one case of campylobacteriosis and two cases of salmonellosis) developed symptoms more than one year after return to Norway (Table 6).

The 1,435 cases reported as travel-associated, whose symptom onset occurred after returning to Norway are shown in Table 7. Cases are classified according to time between travel and symptom onset, relative to the respective infections’ incubation periods described in the literature. The most common incubation periods as well as the maximum incubation periods for each infection are taken into account. In light of the most common incubation periods, a total of 1,263 (88 %) of the 1,435 cases had onset of illness in Norway compatible with infection acquisition abroad. When maximum incubation periods were considered the number of cases with plausible infection abroad increased to 1,404 (97.8%).

With regard to particular infections, between 79.9% salmonellosis cases (446 of 558) and 94% campylobacteriosis cases (739 of 786) developed symptoms after return to Norway within the most common incubation period described in the literature and between 89.4% giardiasis (42 of 47) and 98.6% salmonellosis cases (550 of 558) within the maximum incubation period described.

TABLE 3

Selected gastrointestinal infections registered in the Norwegian Surveillance System for Communicable Diseases by place of infection, Norway, 2009–2010 (n=8,978)

Place of infection	Campylobacteriosis		Salmonellosis				Shigellosis	Giardiasis	Total
	n (%)	All salmonellas n (%)	S. Enteritidis n (%)	S. Typhimurium n (%)	S. Typhimurium mv n (%)	Other n (%)			
Norway	2,295 (41.6)	455 (17.50)	100 (8.8)	141 (40.5)	47 (27.3)	167 (17.7)	68 (23.5)	68 (12.0)	2,886 (32.2)
Abroad	2,730 (49.4)	1,873 (72.0)	926 (81.5)	157 (45.1)	108 (62.8)	682 (72.3)	198 (68.5)	435 (76.7)	5,236 (58.3)
Unknown	497 (9.0)	272 (10.5)	110 (9.7)	50 (14.4)	17 (9.8)	95 (10.1)	23 (8.0)	64 (11.3)	856 (9.5)
Total	5,522 (100)	2,600 (100)	1,136 (100)	348 (100)	172 (100)	944 (100)	289 (100)	567 (100)	8,978 (100)

Mv: monophasic variant; S.: *Salmonella*.**TABLE 4**

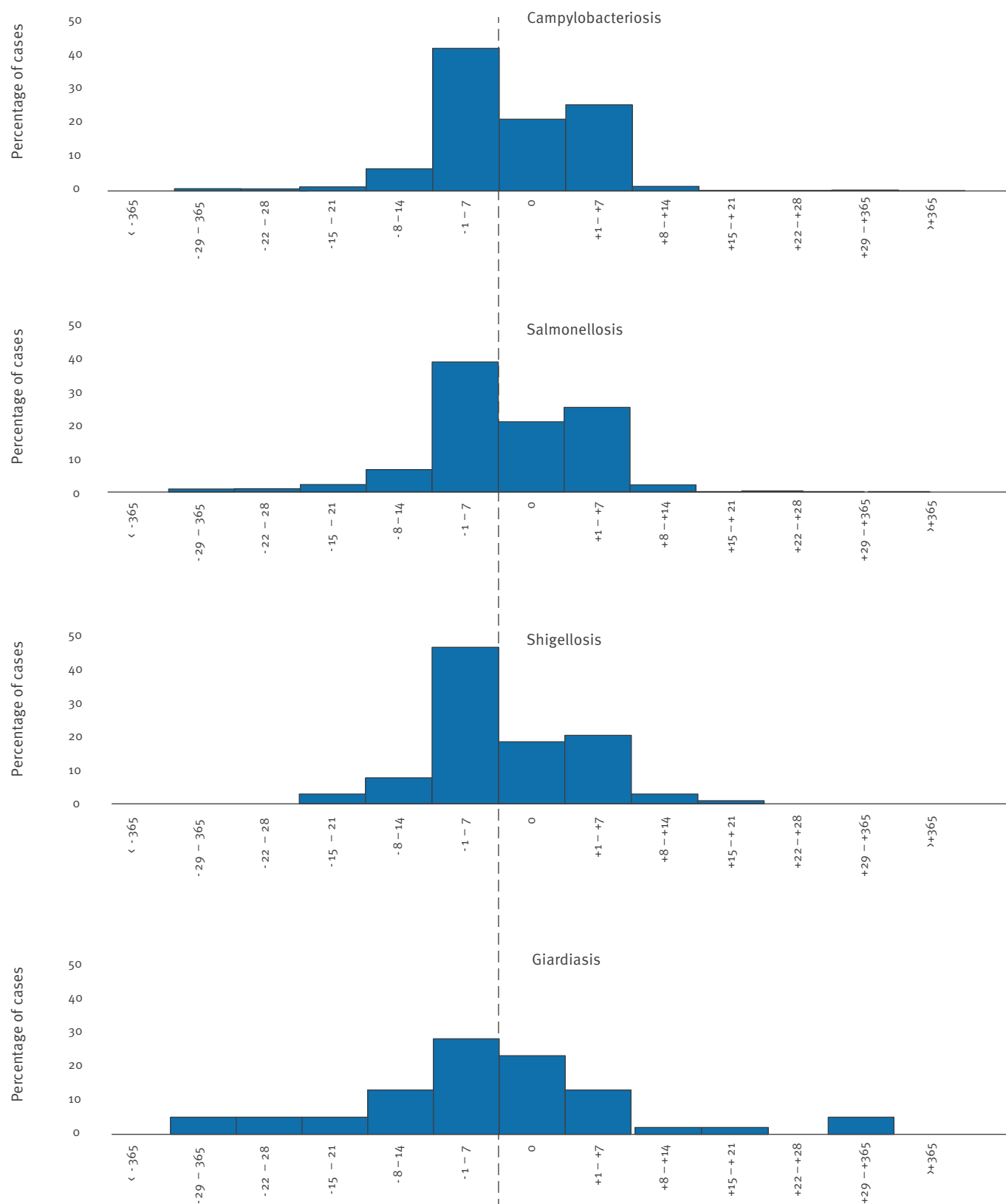
Completeness of variables for selected travel-associated gastrointestinal infections registered in the Norwegian Surveillance System for Communicable Diseases, Norway, 2009–2010 (n=5,236)

Type of infection	Reported travel-associated cases n	Reported symptomatic travel-associated cases n	Completeness of variables for symptomatic travel-associated cases		
			With reported 'return date to Norway' n (%) ^a	With reported 'date of onset of symptoms' n (%) ^a	With reported 'return date to Norway' and 'date of onset of symptoms' n (%) ^a
Campylobacteriosis	2,730	2,713	1,700 (62.7)	2,362 (87.1)	1,616 (59.6)
Salmonellosis					
All salmonellas	1,873	1,863	1,222 (65.6)	1,613 (86.6)	1,143 (61.4)
S. Enteritidis	926	923	600 (65.0)	806 (87.3)	556 (60.2)
S. Typhimurium	157	157	108 (68.8)	135 (86.0)	103 (65.6)
S. Typhimurium mv	108	108	70 (64.8)	94 (87.0)	68 (63.0)
Other	682	675	444 (65.8)	578 (85.6)	416 (61.6)
Shigellosis	198	195	119 (61.0)	164 (84.1)	107 (54.9)
Giardiasis	435	246	126 (51.2)	152 (61.8)	106 (43.1)
Total	5,236	5,017	3,167 (63.1)	4,291 (85.5)	2,972 (59.2)

Mv: monophasic variant; S.: *Salmonella*.^a The percentage is calculated relative to the respective total reported symptomatic travel-associated cases.

FIGURE

Distribution of travel-associated cases of gastrointestinal infection reported to the Norwegian Surveillance System for Communicable Diseases by date of symptom onset relative to travel-return date to Norway, 2009–2010 (n=2,972)



Interval of days of symptom onset before (-) or after (+) return date to Norway (o).

TABLE 5

Travel-associated cases with symptom onset before travel-return to Norway among travel-associated cases with known travel-return and symptom onset dates registered in the Norwegian Surveillance System for Communicable Diseases, by gastrointestinal infection, Norway, 2009–2010 (n=2,972)

Type of infection	Symptom onset before travel return to Norway	Total travel-associated cases
	n (%)	n (%)
Campylobacteriosis	830 (51.4)	1,616 (100)
Salmonellosis		
All salmonellas	585 (51.2)	1,143 (100)
S. Enteritidis	268 (48.2)	556 (100)
S. Typhimurium	49 (47.6)	103 (100)
S. Typhimurium mv	30 (44.1)	68 (100)
Other	238 (57.2)	416 (100)
Shigellosis	63 (58.9)	107 (100)
Giardiasis	59 (55.7)	106 (100)
Total	1,537 (51.7)	2,972 (100)

Mv: monophasic variant; S.: *Salmonella*.

Fourteen campylobacteriosis cases (1.8%), eight salmonellosis cases (1.4%), five giardiasis cases (10.6%) and four of 44 shigellosis cases (9.1%) would have had symptom onset outside the maximum incubation period range defined in the literature, if the infections had been acquired abroad.

Discussion

The results of the evaluation of the travel information reported in MSIS indicate a high level of completeness with regards to the variable ‘*place of infection*’. Approximately 90% of gastrointestinal infections notified to MSIS were reported with known origin. Compared to studies published in other Scandinavian countries, such as Sweden, the level of completeness found in MSIS is higher for campylobacteriosis [14], but lower for shigellosis [15] and salmonellosis [16]. The reported level of completeness found in our study is also higher than the level of completeness reported by a Canadian study [17].

The validity of the travel information of those cases reported as travel associated is also high according to our assessment on time of illness onset related to the time of travel. The time of illness onset after travel for the majority of cases fell within the maximum incubation period reported in the literature and indicates good judgement among clinicians when reporting. This information supports the assertion that most gastrointestinal infections notified in Norway are travel associated. The low endemic level is considered to be caused

by low endemic levels of the pathogens causing the diseases considered in this study in the food chain in Norway and historical low level of imports of animals and animal products in Norway [18]. Of note is the high proportion of notified travel-associated infections with symptom onset on the day of return to Norway or the prior week. This might be explained by patients who got infected shortly before returning to Norway first sought medical attention at arrival because of persisting symptoms.

Shigellosis and giardiasis were the infections most frequently classified as travel associated although illness onset occurred after the common incubation period after return to Norway. 11% of travel-associated reported giardiasis cases and 9% of shigellosis cases did not occur within a plausible incubation period. The fact that the endemic level of these two diseases in Norway is low may lead clinicians to code them as travel-associated without taking into account the incubation-period of the disease. The endemic level of different serovars of salmonellosis may also play a role in clinicians’ judgement when reporting. None of *S. Typhimurium* cases notified appeared to be misclassified. However, three *S. Enteritidis* cases reported as travel-associated had illness onset after the maximum incubation period after returning from abroad. Epidemiology of these two *Salmonella* serovars in Norway are very different: *S. Typhimurium* is the most common serovar that causes domestic salmonellosis in Norway and in addition to *S. diarizonae* the only serovar existing in Norwegian animals [19], while most *S. Enteritidis* cases are acquired abroad [8]. Therefore, clinicians might classify a *S. Enteritidis* case as travel-associated with less consideration of the number of days since return to Norway. Three cases reported as travel-associated had a date of onset of symptoms more than one year after return from travel abroad. We think this is probably due to data entry errors of the dates rather than inaccuracy when reporting. It is also important to bear in mind that despite the biological plausibility of the calculated incubation period, it does not ensure that the infection occurred abroad as the source is not verified.

We only managed to assess the biological plausibility of the travel history in 59% of all cases reported as travel-associated as these were the only notifications with both variables ‘*return date to Norway*’ and ‘*date of onset of symptoms*’ completed. Giardiasis was by far the infection in which information regarding these variables was most frequently missing. The complex clinical course of giardiasis, which can be intermittent and chronic, might have contributed to the low completeness [20]. Having been able to better assess the biological plausibility for this pathogen would have been useful, since the endemic level of this parasite in Norway is not very well described [21].

Surveillance of travel-associated gastrointestinal infections in Europe could benefit from improved

TABLE 6

Days between arrival in Norway and symptom onset, travel-associated gastrointestinal infections registered in the Norwegian Surveillance System for Communicable Diseases, Norway, 2009–2010 (n=2,972)

Disease	Date of symptom onset after travel return to Norway				Total n (%)
	≤7 days	8–30 days	31–365 days	>365 days	
	n (%)	n (%)	n (%)	n (%)	
Campylobacteriosis	1,585 (98.1)	26 (1.6)	4 (0.2)	1 (0.1)	1,616 (100)
Salmonellosis					
All salmonellas	1,108 (96.9)	31 (2.7)	2 (0.2)	2 (0.2)	1,143 (100)
S. Enteritidis	546 (98.2)	8 (1.4)	1 (0.2)	1 (0.2)	556 (100)
S. Typhimurium	98 (95.1)	5 (4.9)	0 (0)	0 (0)	103 (100)
S. Typhimurium mv	65 (95.6)	3 (4.4)	0 (0)	0 (0)	68 (100)
Other	399 (95.9)	15 (3.6)	1 (0.2)	1 (0.2)	416 (100)
Shigellosis	103 (96.3)	4 (3.7)	0 (0)	0 (0)	107 (100)
Giardiasis	97 (91.5)	5 (4.7)	4 (3.8)	0 (0)	106 (100)
Total	2,893 (97.3)	66 (2.2)	10 (0.3)	3 (0.1)	2,972 (100)

Mv: monophasic variant; S.: *Salmonella*.

Arrival in Norway (day=0).

TABLE 7

Repartition, by incubation period, of travel-associated cases of gastrointestinal infection with symptom onset after travel return registered in the Norwegian Surveillance System for Communicable Diseases, Norway, 2009–2010 (n=1,435)

Disease/microorganism	Cases n (%) by incubation period			Total n (%)
	Within the commonly reported incubation period ^a	Within the maximum incubation period ^a	Outside the maximum incubation period ^a	
Campylobacteriosis	739 (94.0)	772 (98.2)	14 (1.8)	786 (100)
Salmonellosis				
All salmonellas	446 (79.9)	550 (98.6)	8 (1.4)	558 (100)
S. Enteritidis	241 (83.7)	285 (99.0)	3 (1.0)	288 (100)
S. Typhimurium	41 (75.9)	54 (100)	0 (0)	54 (100)
S. Typhimurium mv	25 (65.8)	37 (97.4)	1 (2.6)	38 (100)
Other	139 (78.1)	174 (97.8)	4 (2.2)	178 (100)
Shigellosis	39 (88.6)	40 (90.9)	4 (9.1)	44 (100)
Giardiasis	39 (83.0)	42 (89.4)	5 (10.6)	47 (100)
Total	1,263 (88.0)	1,404 (97.8)	31 (2.2)	1,435 (100)

Mv: monophasic variant.

^a According to [11,12].

notification criteria for travel-associated infections. This might simplify reporting duties for clinicians, leading to an increase in reporting completeness. In addition, it may facilitate the comparison of the information sent by different European countries to TESSy, allowing better monitoring of specific infections in particular countries. Having high quality information available can be useful not only for providing specific advice to travellers before a trip to a specific destination, but

also for better diagnosis and management of returning travellers. In terms of public health, a correct notification of microorganism and place of infection can allow the rapid identification and response to outbreaks of potential international concern. Information about place of infection is also important in order to be able to evaluate national and European control programs implemented in the food chain to prevent foodborne gastrointestinal infections.

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