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Middle East respiratory syndrome coronavirus (MERS-CoV) infections in two returning travellers in the Netherlands, May 2014

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Two patients, returning to the Netherlands from pilgrimage in Medina and Mecca, Kingdom of Saudi Arabia, were diagnosed with Middle East respiratory syndrome coronavirus (MERS-CoV) infection in May 2014. The source and mode of transmission have not yet been determined. Hospital-acquired infection and community-acquired infection are both possible.

On 13 May 2014, a Dutch patient, returning to the Netherlands from pilgrimage in Medina and Mecca, Kingdom of Saudia Arabia, was diagnosed with Middle East respiratory syndrome coronavirus (MERS-CoV) infection, followed by diagnosis of a second patient, belonging to the same tour group, the day after. Here we describe the two cases and the public health response. The case definition that is used in the Netherlands is outlined in the Box.

Case 1

A 70 year-old male patient with cardiovascular comorbidities and diabetes mellitus was diagnosed with MERS-CoV infection on 13 May. He had been in Medina since 26 April, together with a group of 30 other travellers. During the whole journey, he shared the hotel rooms with his adult son and another family member (see below). On 29 April, while still in good health, he accompanied his son to two hospitals (Hospitals 1 and 2), both in Medina, as the son had a minor health problem unrelated to MERS CoV. He spent 45 minutes in the waiting room, reportedly among many coughing people in Hospital 1. On 1 May, he experienced diarrhoea, nausea and anorexia and felt feverish, but had no respiratory complaints. The diarrhoea remitted after loperamide treatment. On 4 May, the group of travellers, including the patient, continued to Mecca. On 5 May, he was seen at Hospital 3 for malaise, again diarrhoea, anorexia. On 7 May, he was physically examined at Hospital 4 and dismissed after three hours of observation and intravenous cefuroxime. During the flight home to the Netherlands, on 10 May, the patient's condition deteriorated: on arrival, he visited a Dutch hospital, presenting with cough and dyspnoea. Apart from a temperature of 38.2 °C (after paracetamol 37.3 °C, both measured in the ear), the physical examination was normal. Laboratory results showed a mild leuco- and lymphopenia, a C-reactive protein level of 72 mg/L (norm: 0–8 mg/L) and slightly elevated levels of troponin T (0.034 µg/L; norm: ‹0.014 µg/L) and creatinine (123 µmol/L; norm: 65–115 µmol/L). In 2012, the patient had had a tropinin T level of 0.010, with a stable and mild pre-existing chronic kidney disease with a creatinine level of 113–136 µmol/L. He was admitted to the cardiology ward with possible cardiovascular disease and isolation precautions were taken because of an unspecified infection. Reassessment of his chest X-ray the next day revealed an infiltrate. On 13 May, MERS-CoV infection was confirmed. Lung examination then revealed extensive crepitations and a chest-X-ray showed bilateral infiltrates. Myocarditis was ruled out by magnetic resonance imaging of the heart. He is currently recovering.

Box

Middle East respiratory syndrome coronavirus (MERS-CoV) case definition and definition of contacts used in the Netherlands

Suspected case

Patient with a severe acute respiratory tract infection with:
– fever (≥38 °C)[a,b] and respiratory symptoms

AND

– an infiltrate on an X-ray of the lungs, or acute respiratory distress syndrome

AND

– travel history to an area[c] with notified MERS-CoV (<14 days before the onset of symptoms)

OR

a patient who has been in contact with a confirmed symptomatic MERS-CoV case (<14 days before onset of symptoms)

OR

a patient who is part of a cluster of two or more epidemiologically linked cases with an unknown causal agent for whom admission to an intensive-care unit is necessary, within a period of 14 days, irrespective of travel history.

Confirmed case

A person with laboratory-confirmation of MERS-CoV infection (positive PCR, with or without confirmation by sequencing).

Close contact

– face-to-face contact (>15 minutes) within a household or other closed setting

OR

– a healthcare worker, providing clinical or personal care to a confirmed, symptomatic case or who was in the same room as a patient during an aerosol-generating procedure and who did not wear adequate personal protection

– flight contact (seated in the same row or three rows in front of/behind a confirmed case.

Protected hospital contact

A healthcare worker, providing clinical or personal care to a confirmed, symptomatic case or who was in the same room as a patient during an aerosol-generating procedure and who did wear adequate personal protection.

Contacts were requested to measure their temperature twice daily and report any episode of fever, cough, dyspnoea or diarrhoea for a period of 14 days post exposure. Close contacts were approached on a daily basis by the regional public health service. Protected hospital contacts were expected to report health complaints without having daily follow-up. Throat and serum samples of all contacts were examined on days 7 and 14 (molecular testing) and 7 and 21 (serology) post exposure.

[a] Or a feverish feeling in elderly people, as they do not always develop fever.

[b] An immunocompromised patient with a severe infection of any origin, who meets the epidemiological criteria, i.e. contact with a MERS-CoV confirmed case or stay in area with MERS-CoV notified cases, both <14 days before onset of symptoms.

[c] Since 1 April 2013, the Middle East, especially Jordan, Saudi Arabia, Qatar and the United Arab Emirates.

Case 2

During contact investigations, the 73 year-old sister of the patient (with cardiovascular co-morbidities, chronic kidney disease and diabetes mellitus) was found to be symptomatic and was diagnosed with MERS-CoV infection late in the night of 14 May. She had shared the hotel rooms during the entire trip with Case 1 and his adult son and developed symptoms on 5 May, having diarrhoea, feeling feverish (not measured, slight cough and slight dyspnoea. She had not sought medical care in Saudia Arabia. During a routine check-up by a general practitioner in the Netherlands on 12 May, she did not have a fever, but a slight cough and extensive crepitations of both lungs. The general practitioner considered MERS-CoV infection, because of the recent travel history, but did not arrange for diagnostic tests to be carried out as the patient did not meet the definition of a suspected case (no fever, no acute respiratory distress syndrome). Following contact tracing for Case 1, samples were taken from her and she was diagnosed with MERS-CoV infection. Following the diagnosis, she was admitted to hospital on 15 May where a chest X-ray showed bilateral infiltrates. She is currently recovering.

The travel route and a timeline of events for the two cases are shown (Figures 1 and 2).

Laboratory findings

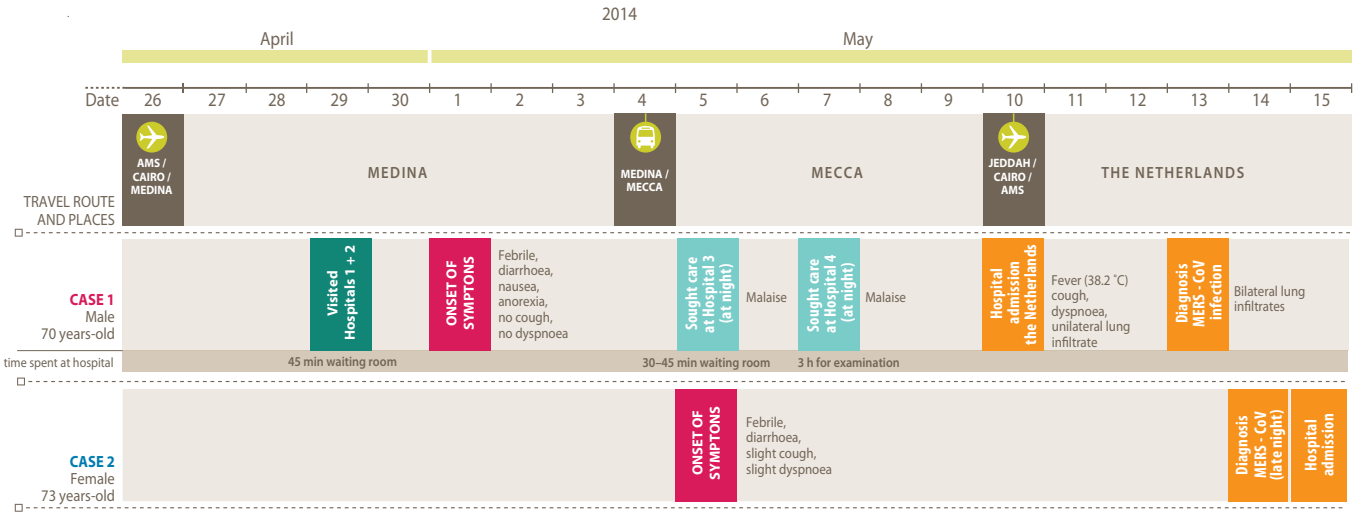
Diagnosis of MERS-CoV infection was done using an internally controlled real-time reverse transcription (RT)-PCR using nucleic acid extracts from throat swabs and published upE, N-gene and ORF1A primers [1,2] according to International Organization for Standardization (ISO) guidelines (ISO 15189:2003) [3]. The results were independently confirmed in two laboratories, Erasmus MC in Rotterdam and the National Institute for Public Health and the Environment (RIVM) in Bilthoven, the Netherlands [4]. During extensive follow-up sampling, MERS-CoV RNA was detected in throat swabs, serum and stools from both cases (Table). Case 2 had detectable MERS-CoV RNA in a throat swab, but not in a nose swab (data not shown), both collected on day 0 (date of diagnosis). Follow-up of the patients is still ongoing.

Throat swabs of both cases tested on day 0 (the day MERS-CoV was diagnosed) were negative by real-time RT-PCR for 15 other respiratory viruses (influenza A and B virus, respiratory syncytial virus types A and B, human metapneumovirus, HCoV-OC43, -229E, -NL63, rhinovirus, parainfluenza type 1, 2, 3, 4, adenovirus and bocavirus) as described elsewhere [5].

To characterise the virus strain, partial genome sequencing was done as described by Haagmans et al. [2]. Sequence analysis was carried out directly from clinical specimens (respiratory samples) of both cases, yielding in total 4 kb of genome sequence for Case 1 and 2.4 kb for Case 2 (GenBank accession numbers KJ858495-KJ858500). The sequences were nearly identical (one nucleotide difference) and were distinct from

Figure 1

Timeline of events for two MERS-CoV patients returning to the Netherlands from Saudi Arabia, May 2014



MERS-CoV: Middle East respiratory syndrome coronavirus.

recently published sequences from a hospital cluster in Jeddah, Saudi Arabia] [6]. However, the sequences clustered with that from a recently diagnosed traveller returning to the United States (US) from Saudi Arabia [7] (Figure 2).

Visits while in Saudi Arabia

The group of 31 people travelled together in Saudi Arabia, used private transport, went on a joint trip to several mosques around Medina and spent the other days individually performing religious rituals in different mosques, visiting local markets and eating in different establishments. On 3 May, 12 members of the group (not including the two cases) visited Wadi-e-Jinn near Medina and came across a dromedary camel herd with a few farmers who created a temporary shelter. All 12 drank raw dromedary milk, offered to them by the farmer. The group did not take any animal products back for Cases 1 and 2.

Contact investigations

A total of 78 close contacts were identified (among which were the travel group, relatives and flight contacts) and monitored as described in the Box. All healthcare workers were well protected. The number of flight contacts was limited (n=18) due to the fact that both cases were seated together on the last row in the plane. All flight contacts were Dutch residents. The monitoring period has come to an end for 70 close contacts and will be finalised by 29 May for the last group (n=8). No additional cases of MERS-CoV infection have been found during this period. All molecular (throat swabs) and serological samples taken from the contacts have been negative for MERS-CoV so far. The testing will be completed by mid-June.

Background

MERS-CoV was first recognised in 2012, when it caused severe pneumonia in a patient from Saudi Arabia [8]. Since then, cases have been notified from several countries in the Arabian peninsula, with occasional exportation through infected travellers [9]. The exact epidemiology of the infection remains to be determined, but contact with animals, particularly dromedary camels, as well as contact with patients with MERS-CoV infection are risk exposures [10,11] A recent upsurge in the number of primary cases in the community in the Kingdom of Saudi Arabia, possibly associated with the weaning season in dromedary cases, has been amplified by person-to-person transmission due to poor hospital hygiene measures in some hospitals in the Kingdom of Saudi Arabia [10,11].

Discussion

There are several options for the possible source of the infection of the two Dutch cases: Case 1 could have been infected during the hospital visit of his child on 29 April, after which he infected Case 2. Alternatively, both could have been exposed to a common, as yet unknown, source in Medina. Thirdly, each case could have been infected through different sources (hospital/community), though this seems unlikely, as the (partial) virus sequence of both cases was nearly identical. The resemblance in strain sequence between the Dutch cases and the case from the US is remarkable as the cases did not visit the same places in the Kingdom of Saudi Arabia. Exchange of information between the US Centers for Disease Control and Prevention and Dutch experts did not reveal any clues about mutual exposure of the Dutch and US cases. The current, limited scientific information does not support any conclusion on

the meaning of this genetic resemblance, knowing that multiple lineages of the virus can be found in camels and people [2,12]. Continued vigilance in evaluation of contacts of imported cases, including molecular testing and serology, will hopefully lead to better insights.

The public health response to these two imported cases was in line with the procedures put in place in the Netherlands [4,13]. Healthcare professionals in the Netherlands have been made aware of MERS-CoV since its emergence in 2012. MERS-CoV laboratory testing protocols have been implemented, including 24-hour availability of parallel testing in two separate laboratories if suspected cases are identified. These preparations facilitated the rapid follow-up and diagnosis of Case 2.

A national outbreak investigation team was formed of clinicians, medical virologists, public health specialists, epidemiologists, staff members from the national response unit and a press officer. This team convened in a nearly daily teleconference to (i) share new developments regarding the cases, their laboratory follow-up and case histories; (ii) to perform a structured assessment of the public health risks for the contacts; (iii) perform risk classification of contacts; (iv) issue guidelines for follow-up; (v) provide information to professionals and the media; and (vi) monitor progression of the response [13].

Immediately after the diagnosis was confirmed in Case 1, on 14 May, a press release was issued, followed by regular updates to emphasise the control measures designed to prevent secondary transmission. The World Health Organization was notified according to the International Health Regulations (IHR) by the National Focal Point, and international warnings were issued through the European Union Early Warning and Response System. The IHR Focal Point of the Kingdom of Saudi Arabia was notified as well.

Finally, updated guidelines for case finding, laboratory diagnosis, contact investigation and monitoring and infection control were revised and disseminated to the health professionals in the Netherlands using an electronic alerting system.

MERS-CoV outbreak investigation team of the Netherlands (in alphabetical order)

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Table

Real-time reverse transcription-PCR results from two MERS-CoV patients returning to the Netherlands from Saudi Arabia, May 2014

Day of sampling[a]	Throat swab[b]	Serum[b]	Faeces[b]	Urine[b]
Case 1				
D0	31.3/31.5	–	–	–
D4	29.6/27.2	34.0/30.3	–	ND/ND
D5	34.6/34.2	33.6/31.0	34.6/33.5	–
D6	33.5/31.6	33.7/31.7	–	ND/ND
D7	ND/ND	35.9/33.4	ND/ND	ND/ND
D8	ND/ND	38.3/35.8	ND/ND	ND/ND
D9	37.8/34.9	ND/37.6	–	ND/ND
Case 2				
D0	34.5/32.5	–	ND/ND	–
D1	–	35.5/33.6	38.8/ND	–
D2	–	34.6/36.4	ND/ND	–
D3	–	37.4/38.6	ND/38.4	ND/ND
D4	–	37.8/36.7	38.7/ND	ND/ND
D5	–	36.0/38.3	–	ND/ND

Dashes show where no samples were available.

MERS-CoV: Middle East respiratory syndrome coronavirus; ND: not detected.

[a] Time of sampling starts from the date of diagnosis (D0).

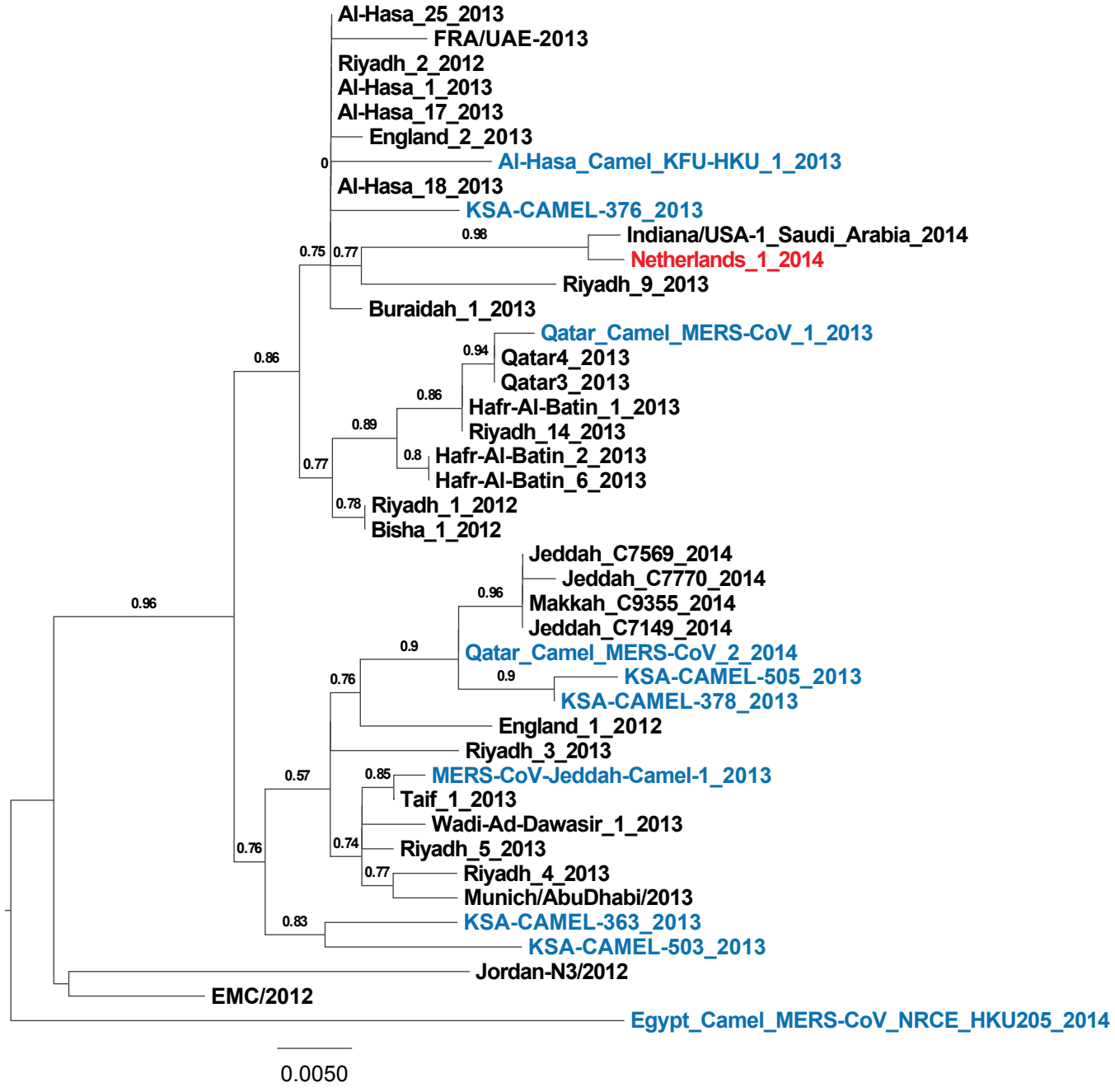
[b] Threshold cycle (Ct) values of MERS-CoV upE PCR/Ct values of N-gene reverse transcription-PCR.

Conflict of interest

None declared.

Figure 2

Phylogenetic analysis of a MERS-CoV sequence from Case 1 returning to the Netherlands from Saudi Arabia, May 2014



MERS-CoV: Middle East respiratory syndrome coronavirus.

PhyML phylogenetic tree based on 4 kb nucleotide sequence, drawn with Seaview 4 software using the GTR model. Values at branches show the result of the approximate likelihood ratio; values <0.70 are not shown. The scale bar indicates nucleotide substitutions per site.

MERS-CoV isolates from dromedary camels are shown in blue and the human MERS-CoV isolate from the Netherlands is shown in red.

Authors' contributions

All authors contributed to gathering and analysis of the information. Marleen Kraaij -Dirkzwager, Aura Timen and Marion Koopmans drafted and revised the manuscript based on all authors contributions.

References

1. Corman VM, Eckerle I, Bleicker T, Zaki A, Landt O, Eschbach-Bludau M, et al. Detection of a novel human coronavirus by real-time reverse-transcription polymerase chain reaction. Euro Surveill. 2012 Sep 27;17(39):pii=20285.
2. Haagmans BL, Al Dhahiry SH, Reusken CB, Raj VS, Galiano M, Myers R, et al. Middle East respiratory syndrome coronavirus in dromedary camels: an outbreak investigation. Lancet Infect

Dis. 2014;14(2):140-5.
http://dx.doi.org/10.1016/S1473-3099(13)70690-X

3. International Organization for Standardization (ISO). ISO 15189:2003. ISO 15189:2003. Medical laboratories -- particular requirements for quality and competence. Geneva: ISO. [Accessed 28 May 2014]. Available from: http://www.iso.org/iso/catalogue_detail?csnumber=26301
4. van Asten L, van der Lubben M, van den Wijngaard C, van Pelt W, Verheij R, Jacobi A, et al. Strengthening the diagnostic capacity to detect Bio Safety Level 3 organisms in unusual respiratory viral outbreaks, J Clin Virol. 2009;45(3):185-90. http://dx.doi.org/10.1016/j.jcv.2009.05.024
5. Hoek RA, Paats MS, Pas SD, Bakker M, Hoogsteden HC, Boucher CA, et al. Incidence of viral respiratory pathogens causing exacerbations in adult cystic fibrosis patients. Scand J Infect Dis. 2013;45(1):65-9. http://dx.doi.org/10.3109/00365548.2012.708942
6. Universitätsklinikum Bonn, Institut für Virologie. Preliminary sequences from patients in KSA, April 2014 (MERS-COV sequences from patients, KSA, April 2014). Bonn: Universitätsklinikum Bonn, Institut für Virologie. [Accessed 28 May 2014]. Available from: http://www.virology-bonn.de/index.php?id=46
7. Bialek SR, Allen D, Alvarado-Ramy F, Arthur R, Balajee A, Bell D, et al. First confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in the United States, updated information on the epidemiology of MERS-CoV infection, and guidance for the public, clinicians, and public health authorities — May 2014. MMWR Morb Mortal Wkly Rep. 2014;63(19):431-6.
8. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. 2012, Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 367(19):1814-20. http://dx.doi.org/10.1056/NEJMoa1211721
9. World Health Organization (WHO). Middle East respiratory syndrome coronavirus (MERS-CoV) – update. 16 May 2014. Geneva: WHO; May 2014. Available from: http://www.who.int/csr/don/2014_05_16_mers/en/
10. European Centre for Disease Prevention and Control (ECDC). Updated rapid risk assessment. Severe respiratory disease associated with Middle East respiratory syndrome coronavirus (MERS-CoV), Ninth update, 24 April 2014. Stockholm: ECDC; Apr 2014. Available from: http://www.ecdc.europa.eu/en/publications/Publications/Middle-East-respiratory-syndrome-coronavirus-risk-assessment-25-April-2014.pdf
11. World Health Organization (WHO). WHO risk assessment: Middle East respiratory syndrome coronavirus (MERS-CoV). 24 April 2014. Geneva: WHO; Apr 2014. Available from: http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_RA_20140424.pdf?ua=1
12. Alagaili AN, Briese T, Mishra N, Kapoor V, Sameroff SC, Burbelo PD, et al. Middle East respiratory syndrome coronavirus infection in dromedary camels in Saudi Arabia. MBio. 2014;5(2):e00884-14. Erratum in: MBio. 2014;5(2):e01002-14. Burbelo, Peter D [added]. http://dx.doi.org/10.1128/mBio.00884-14
13. Timen A, Koopmans MP, Vossen AC, van Doornum GJ, Günther S, van den Berkmortel F, et al. Response to imported case of Marburg hemorrhagic fever, the Netherland. Emerg Infect Dis. 2009;15(8):1171-5. http://dx.doi.org/10.3201/eid1508.090015

Suspected new wave of muscular sarcocystosis in travellers returning from Tioman Island, Malaysia, May 2014

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In May 2014, six patients presented in Germany with a *Sarcocystis*-associated febrile myositis syndrome after returning from Tioman Island, Malaysia. During two earlier waves of infections, in 2011 and 2012, about 100 travellers returning to various European countries from the island were affected. While the first two waves were associated with travel to Tioman Island mostly during the summer months, this current series of infections is associated with travel in early spring, possibly indicating an upcoming new epidemic.

Here we report the clinical and laboratory findings of a new, third wave of *Sarcocystis*-associated febrile myositis syndrome in travellers returning to Germany from Tioman Island, Malaysia, in spring 2014.

Case series

Six previously healthy German patients, aged 15–44 years were seen in early May 2014 in travel clinics in Tübingen, Saarbrücken and Munich, with a febrile myositis syndrome after travel. The patients (three female, three male) complained of current or very recent episodes of fever of up to 40 °C, headache and myalgia. All had returned at the end of March to the end of April from Tioman Island, Malaysia. Laboratory investigations revealed eosinophilia in all but one and elevated muscle enzyme levels in half of the patients (Table). There were no clinically relevant electrocardiogram abnormalities but mild splenomegaly was seen in some. Serological tests for trichinellosis, toxoplasmosis and dengue virus infection were negative in all patients. Tests for chikungunya virus antibodies were not carried out for one patient, but negative in all others. All patients had stayed in the north-west of Tioman Island and developed symptoms 1–18 days (mean: 10) after leaving the island. Their travel history, including locality of lodging on the island, estimated incubation time (a few days to three weeks), clinical picture and laboratory results were consistent with the *Sarcocystis*-associated febrile myositis syndrome seen in travellers returning to various European countries from Tioman Island in 2011 and 2012 [1-4]. No such series of infections were seen in 2013.

Patients 1–3

In three patients who sought medical attention 1–6 days after first onset of fever, headache and slight myalgia (i.e. in the early, rather non-specific phase of clinical disease) and who had no elevated creatine kinase (CK) levels, therapy with trimethoprim/sulfamethoxazole (cotrimoxazole) (2 × 960 mg/day) [4] was started within a few days. All three improved clinically but developed higher eosinophilia after 7–20 days, yet there was no elevation of CK level.

Patients 4–5

A couple presented in a later phase of the disease. One patient was currently asymptomatic with moderate CK elevation 23 days after a previous short-lived febrile episode. The other had fever and severe myalgia plus high eosinophilia and CK elevation 28 days after onset of a short-lived episode with high fever, headaches and night sweats. Both showed a further increase of eosinophil counts (maximum count of 500/µl and 5,260/µl, respectively) after the start of cotrimoxazole treatment. The previously symptom-free patient developed moderate myalgia together with increasing CK levels thereafter; the other had to be started on high-dose steroids four days later (prednisolone starting dose 100 mg/day) because of intensifying severe myalgia.

Patient 6

The patient with the longest interval (43 days) since onset of first symptoms (fever, headache, myalgia) was treated with steroids (prednisolone starting dose 40 mg/day).

Administration of steroids resulted in rapid clinical improvement in both patients (Patients 5 and 6), similar to observations during the first two waves of

Table

Characteristics of patients returning from Tioman Island, Malaysia, with *Sarcocystis*-associated febrile myositis syndrome, May 2014 (n=6)

Characteristic	Patient number						Norm
	1	2	3	4	5	6	
Sex	M	F	M	F	M	F	–
Days from departure from Tioman Island, Malaysia, until symptom onset	9	12	7	18	13	1	–
Myalgia (yes/no)	yes	yes	yes	yes	yes	yes	–
Maximum pain (score 0=none to 10=maximum)	2	4	4	6	9.5	8	–
Arthralgia (yes/no)	yes	yes	yes	no	no	yes	–
Headache (yes/no)	yes	yes	yes	yes	yes	yes	–
Neck pain (yes/no)	no	yes	yes	no	yes	yes	–
Body temperature (°C)	No data	38	38	38	40	40	–
Laboratory tests							
Creatine kinase (U/L)	138	80	133	159	207	450	<170 males; <145 females
Creatine kinase MB fraction (U/L)	21	15	14	22	35	9	<25 or <6% of total creatine kinase
Cardiac troponin (troponin I/ troponin T, µg/L)	<0.014	<0.014	<0.014	Negative	Negative	Not done	<0.4
Lactate dehydrogenase (U/L)	326	342	383	201	324	307	<240
Aspartate amino transferase (U/L)	49	56	46	18	39	23	<50 males; <35 females
Eosinophil count per µl	430	620	260	170	4,490	1,150	<350
Eosinophils (%)	9	8	4	8	41	12	<7
Spleen length (cm)	13.2	9.2	13.0	No data	12.1	12.5	<11
Treatment	Co-trimoxazole[a]	Co-trimoxazole[a]	Co-trimoxazole[a]	Co-trimoxazole[a]	Cotrimoxazole[a] plus prednisolone	Prednisolone	–
Days from symptom onset to start of treatment	6	3	8	23	28	43	–

F: female; M: male.

[a] Trimethoprim/sulfamethoxazole.

Sarcocystis-associated febrile myositis syndrome in travellers returning from Tioman Island in 2011 and 2012 [3,4].

In the current cluster, no muscle biopsies were taken and the presumptive diagnosis was based on the travel history, symptoms and blood test results of increasing eosinophil count and CK level and the exclusion of other infectious causes.

Background

Sarcocystosis is a cosmopolitan zoonotic disease that is caused by intracellular apicomplexan/coccidian parasites of the genus *Sarcocystis*, with more than 120 recognised species [5]. These protozoal parasites are maintained in a two-host life cycle involving a carnivore predator final host and its 'prey' as intermediate host, such as snake–rodent or human–cattle relationships, for example. In the intermediate host, invasive muscular sarcocystosis develops after infective *Sarcocystis* oocysts shed in faeces of an infected final host are ingested. Sporozoites are released from the oocysts, which invade muscular tissue of the intermediate host after several cycles of replication. In the myocytes, tube- or sac-like sarcocysts are eventually formed, which contain numerous single-celled bradyzoites. When the intermediate host falls prey to a carnivore or omnivore, the bradyzoites can complete their life cycle sexually in the intestine of the final host. Humans are final hosts for two *Sarcocystis* species, *S. hominis* and *S. suihominis*, which cause non-invasive self-limiting diarrhoeal symptoms [5]. However, humans can serve as accidental intermediate hosts after incidental ingestion of food faecally contaminated with oocysts for a presumed number of several *Sarcocystis* species, among them *S. nesbitti*, [6,7] and develop the invasive muscular form. Invasive muscular sarcocystosis causes fever and myalgia, but not diarrhoea, in contrast to the intestinal form.

Already in 1991, sarcocystosis was regarded as a possible emerging food-borne zoonosis in Malaysia, as high human seroprevalence [8] and high positive autopsy rates [9] were found. In 1993, the first cluster of patients with symptomatic muscular sarcocystosis was seen in United States service personnel in rural Malaysia [10]. In 2011 and 2012, in a two-wave outbreak, the largest series of symptomatic muscular sarcocystosis in humans worldwide was noted in travellers returning to Europe from Tioman Island, Malaysia [1-4]. The course of disease was typically biphasic, with a prodromal stage of one week characterised by fever, myalgia and headache, followed by a two-week asymptomatic period and later by a long-lasting feverish episode with severe myalgia with eosinophilia and CK level elevation [4]. An environmental survey for *Sarcocystis* oocysts conducted in November 2011 on Tioman Island could not detect the source of infection [11].

Definitive diagnosis is achieved after muscle biopsy with histological demonstration of typical sarcocysts or by molecular methods [3,6]. However, despite severe myalgia, parasite density in the muscle is apparently low and sarcocysts have thus been detected in a few patients only [3,4,6,10]. |

Conclusions

This cluster of travellers with a febrile myositis syndrome returning from Tioman Island indicates the beginning of a third wave of a presumably *Sarcocystis*-associated invasive illness. In the first two waves, in 2011 and 2012, patients acquired the disease mainly in the summer months (July to October) [1-4]. In contrast, symptom onset in patients of this current new cluster took place in spring, possibly indicating a larger upcoming epidemic in returning travellers in the summer months of this year.

The source of the infection on the island has not been determined so far, but is obviously persisting or re-emerging. The nearly simultaneous outbreak of invasive sarcocystosis among Malaysian students and teachers on a different Malaysian island, Pangkor [6], is intriguing. The snake-associated *S. nesbitti* [6,7,12] was molecularly determined to be the causative agent on Pangkor. The quest for the *Sarcocystis* species involved, the source of infection and the animal reservoir on Tioman Island is currently ongoing. It remains to be determined whether environmental factors, such as climate change or increasing reptile populations (i.e. possible final hosts) [13], play a role in this disease (re-) emergence.

Physicians should be aware of this unusual re-emerging outbreak and pre-travel advice should be given regarding individual prevention measures, such as the consumption of cooked food, well-peeled fruit and pre-packed or boiled/filtered water only. Treatment with cotrimoxazole may be a therapeutic approach in the early phase of disease to prevent muscle invasion, whereas steroids seem effective to treat severe myalgia/myositis in the later phase.

Conflict of interest

None declared.

Authors' contributions

Wrote the manuscript: DT, AS, AL, FvS, JS, GS; performed laboratory or epidemiological investigations: DT, BM; performed data analysis: DT, AS, AL, FvS, JS, GS; performed patient examinations: JS, GS, AL, FvS.

References

1. Centers for Disease Control and Prevention (CDC). Notes from the field: acute muscular sarcocystosis among returning travelers - Tioman Island, Malaysia, 2011.MMWR Morb Mortal Wkly Rep. 2012;61(2):37-8.
2. Esposito DH, Freedman DO, Neumayr A, Parola P. Ongoing outbreak of an acute muscular Sarcocystis-like illness among travellers returning from Tioman Island, Malaysia, 2011-2012. Euro Surveill. 2012;17(45):pii=20310.
3. Tappe D, Ernestus K, Rauthe S, Schoen C, Frosch M, Müller A, Stich A. Initial patient cluster and first positive biopsy findings in an outbreak of acute muscular Sarcocystis-like infection in travelers returning from Tioman island, Peninsular Malaysia, in 2011. J Clin Microbiol. 2013;51(2):725-6. http://dx.doi.org/10.1128/JCM.03063-12
4. Slesak G, Tappe D, Keller C, Cramer J, Güthoff W, Zanger P, et al. [Muscular sarcocystosis after travel to Malaysia: a case series from Germany]. Dtsch Med Wochenschr. 2014;139(19):990-5. German. http://dx.doi.org/10.1055/s-0034-1370004
5. Fayer R. Sarcocystis spp. in human infections. Clin Microbiol Rev. 2004;17(4):894-902. http://dx.doi.org/10.1128/CMR.17.4.894-902.2004
6. Abubakar S, Teoh BT, Sam SS, Chang LY, Johari J, Hooi PS, et al. Outbreak of human infection with Sarcocystis nesbitti, Malaysia, 2012. Emerg Infect Dis. 2013;19(12):1989-91. http://dx.doi.org/10.3201/eid1912.120530
7. Lau YL, Chang PY, Tan CT, Fong MY, Mahmud R, Wong KT. Sarcocystis nesbitti infection in human skeletal muscle: possible transmission from snakes. Am J Trop Med Hyg. 2014;90(2):361-4. http://dx.doi.org/10.4269/ajtmh.12-0678
8. Kan SP, Pathmanathan R. Review of sarcocystosis in Malaysia. Southeast Asian J Trop Med Public Health. 1991;22 Suppl:129-34.
9. Wong KT, Pathmanathan R. High prevalence of human skeletal muscle sarcocystosis in south-east Asia. Trans R Soc Trop Med Hyg. 1992;86(6):631-2. http://dx.doi.org/10.1016/0035-9203(92)90161-5
10. Arness MK, Brown JD, Dubey JP, Neafie RC, Granstrom DE. An outbreak of acute eosinophilic myositis attributed to human Sarcocystis parasitism. Am J Trop Med Hyg. 1999;61(4):548-53.
11. Husna Maizura AM, Khebir V, Chong CK, Azman Shah AM, Azri A, Lokman Hakim S. Surveillance for sarcocystosis in Tioman Island, Malaysia. Malaysian Journal of Public Health Medicine. 2012. 12(2).
12. Tian M, Chen Y, Wu L, Rosenthal BM, Liu X, He Y, et al. Phylogenetic analysis of Sarcocystis nesbitti (Coccidia: Sarcocystidae) suggests a snake as its probable definitive host. Vet Parasitol. 2012;183(3-4):373-6. http://dx.doi.org/10.1016/j.vetpar.2011.07.034
13. Tappe D, Abdullah S, Heo CC, Kannan Kutty M, Latif B. Human and animal invasive muscular sarcocystosis in Malaysia--recent cases, review and hypotheses. Trop Biomed. 2013;30(3):355-66.

Transfusion-transmitted hepatitis E in Germany, 2013

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The reported IgG seroprevalence against hepatitis E virus (HEV) in German blood donations is 6.8%, and HEV RNA detected in 0.08%, but documented evidence for HEV transmission is lacking. We identified two donations from a single donor containing 120 IU HEV RNA/mL plasma and 490 IU/mL. An infectious dose of 7,056 IU HEV RNA was transmitted via apheresis platelets to an immunosuppressed patient who developed chronic HEV. Further, transmission was probable in an immunocompetent child.

Hepatitis E virus (HEV) infection was diagnosed in December 2013 in Germany. Retrospective analysis identified the event as the first transfusion-associated hepatitis E virus (HEV) infection in the country. Here, we report baseline virological data on the case.

Case description

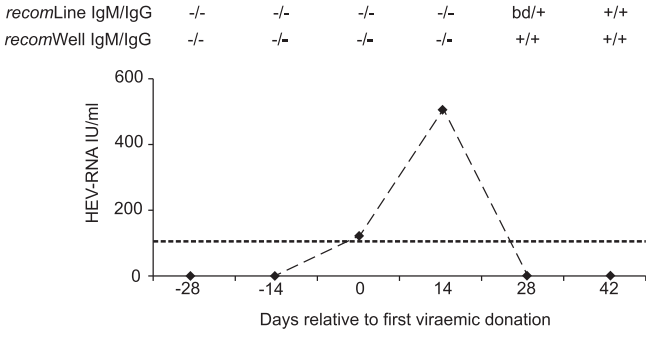
The patient (recipient 1), an immunocompromised man in his 40s, was positive for anti-HEV IgM and IgG using a recomLine HEV assay (Mikrogen, Munich, Germany), and HEV RNA was detected by real-time RT-PCR (Altona Diagnostics, Hamburg, Germany). Retrospective analysis showed that he had been chronically infected with HEV since 24 July 2013, when HEV RNA was detected for the first time. When reviewing the medical charts it was noticed that the patient had received apheresis platelets from a single donor on 4 July 2013.

A lookback procedure was initiated and two viraemic donations of this donor were identified. The donor was a man in his 40s and asymptomatic around the time of the blood donations. He donated blood regularly every 14 days. The first viraemic donation (donation 1, day 0) was from 1 July 2013 and contained 120 IU HEV RNA/mL plasma, and the second donation (donation 2, day 14) was from 15 July 2013 and contained 495 IU HEV RNA/mL plasma (Figure 1). This corresponds to an infectious dose of 7,056–8,892 IU HEV RNA in a total volume of 196–247 mL apheresis platelets transfused for donation 1 (assuming a residual plasma volume of 0.33 mL per 1 mL apheresis platelets). For donation 2, an infectious dose of 30,888–37,273 IU HEV RNA was calculated. Real-time RT-PCR results were confirmed using a nested RT-PCR protocol [1]. All other donations (n=4) of this donor before and after donations 1 and 2 tested negative by real-time RT-PCR and by nested RT-PCR (Figure 1).

The HEV nucleotide sequence of a 242 bp fragment of the ORF1 region was amplified and sequenced from donations 1 and 2 and from recipient 1 [1]. Phylogenetic analysis showed that the samples clustered together and were closely related to HEV genotype 3f, which is prevalent in Germany (Figure 2). The nearly complete nucleotide sequence (6,688 nt, GenBank accession number KJ873911) of the HEV isolate from recipient 1 was determined and compared to sequences from

Figure 1

Hepatitis E virus RNA concentration and serology results in an asymptomatic blood donor, Germany, 2013

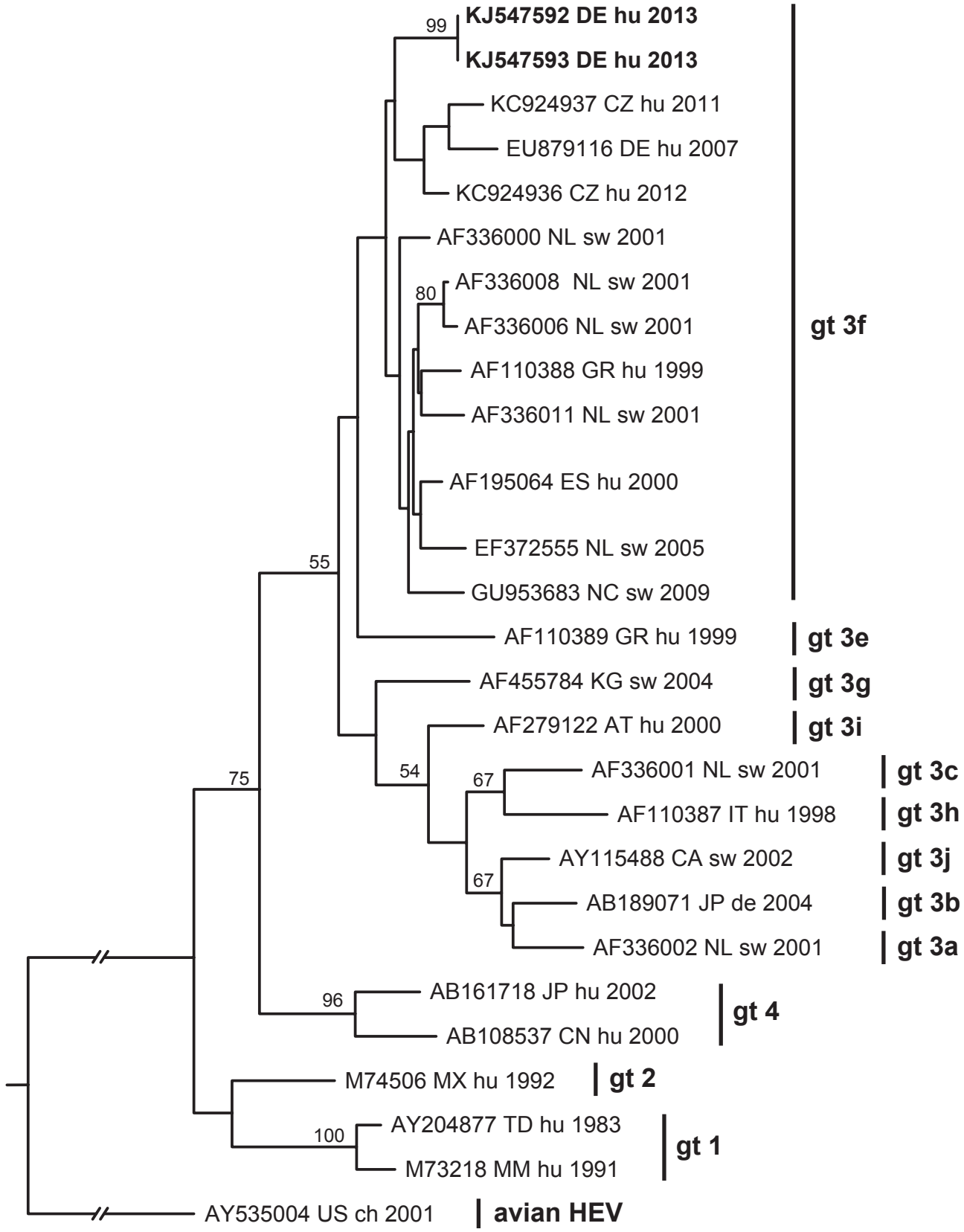


HEV: hepatitis E virus; IU: international units.

Viral RNA concentration is given on the y-axis in IU/mL as indicated by diamonds. The thin broken line indicates the limit of detection of real-time RT-PCR (Altona Diagnostics). Symbol – denotes a negative result as measured by recomLine or recomWell assay, symbol + denotes a positive result, bd indicates borderline result.

Figure 2

Rooted maximum likelihood phylogenetic consensus tree for ORF1 nucleotide sequences of selected hepatitis E virus isolates



AT: Austria; CA: Canada; ch: chicken isolate; CN: China; CZ: Czech Republic; DE: Germany; ES: Spain; GR: Greece; gt: genotype; hu: human; IT: Italy; JP: Japan; KG: Kyrgyzstan; MM: Myanmar; MX: Mexico; NC: New Caledonia; NL: Netherlands; sw: swine; TD: Chad; US: United States.

The sequences of the presented cases (KJ547592 and KJ547593, bold) cluster in subgenotype 3f. The selected sequences represent the nearest homologues in GenBank and typical members of genotype 1, 2 and 4 [15]. An avian hepatitis E virus sequence was used as an outgroup. Numbers at the nodes indicate bootstrap values of greater than 50%. Sequences are denoted by GenBank identification number, country, International Organization for Standardization country code, source, and year of isolation (or publication).

Table

Characteristics and outcome of recipients of hepatitis E virus-positive donations, Germany, 2013 (n=5)

	Transfusion recipients				HEV status		
	Transfused infectious dose HEV RNA	Recipient, sex and age	Immuno-compromised	Outcome	HEV status determined, time after transfusion	HEV PCR	Anti-HEV IgG status
Blood products from donation 1							
Apheresis platelets (196 mL)	7,056 IU	#1, male 47 years	Yes	Chronic HEV infection	6 months	Positive	Positive
Apheresis platelets (247 mL)	8,892 IU	#2, male 6 years	No	Probable HEV infection	8 months	Negative	Positive
Apheresis platelets (243 mL)	8,748 IU	#3, female 70 years	Yes	Died, sepsis	NA	NA	NA
Blood products from donation 2							
Apheresis platelets (208 mL)	30,888 IU	#4, male 71 years	Yes	No HEV infection	5 months	Negative	Negative
Apheresis platelets (251 mL)	37,273 IU	#5, male 71 years	No	Died, arrhythmia	NA	NA	NA
Apheresis platelets (249 mL)	36,976 IU	#5, male 71 years	No	Died, arrhythmia	NA	NA	NA

HEV: hepatitis E virus; NA= Not applicable.

donation 2 (4,251 nt, KJ873912). The nucleotide sequences were 100% identical proving transfusion-associated transmission.

In donation 1 and 2, anti-HEV IgG and IgM were not detected using two different serological HEV assays (recomLine HEV and recomWell HEV, Mikrogen, Munich, Germany). Seroconversion of the donor was observed 14 days after donation 2 (Figure 1). Levels of alanine aminotransferase, aspartate aminotransferase, bilirubin and gamma-glutamyl transferase were within normal range from days –28 to 42 relative to the first HEV RNA-positive donation. Detailed anamnestic exploration of possible risk factors for HEV infection (e.g. occupational exposure to pigs) remained inconclusive and the travel history was negative.

Another four recipients were identified, who had received apheresis platelets from donations 1 or 2 (Table). An immunocompetent child with a history of congenital heart disease tested positive for anti-HEV IgG and borderline for anti-HEV IgM (recomLine HEV and recomWell HEV) in a single sample eight months after receiving apheresis platelets from donation 1. Real-time RT-PCR from this sample was negative (Table). Clinical symptoms suggestive of acute HEV infection were not reported. The available samples from the remaining recipients were all negative for HEV markers (Table). Two patients died for reasons other than HEV infection.

Discussion

HEV recently emerged as a transfusion-transmissible pathogen, with reports from France, the United Kingdom, and Japan [2-4]. In Europe, the vast majority of autochthonous HEV infections are caused by HEV genotype 3 (gt-3) and are linked to the consumption of contaminated food. In general, HEV gt-3 infection remains asymptomatic or presents as mild self-limited acute hepatitis [5]. HEV IgG seroprevalence in Europe ranges from 17% in Germany to 26% in France among the general population, indicating widespread contact with HEV [6,7]. A HEV IgG seroprevalence of 6.8% was determined among German blood donors in 2011, and HEV RNA was detected in 0.08% of donations [8,9]. Juhl et al. reported an HEV IgG incidence in donors of 0.35% per year [9]. A total of 7.4 million blood products were administered in Germany in 2013, and between 1,600 and 5,900 HEV RNA-positive blood donations could be occurring in Germany per year [8,10]. In the Netherlands, one HEV-positive donation per day was reported, which implies that transmission by transfusion could be a likely event in both countries [11].

An estimated 30–40% of blood products in Germany were transfused to immunocompromised patients and these patients are at risk of developing chronic HEV gt-3 infection with increased mortality [5]. Sequence analysis of HEV strains from the Czech Republic, Germany and the Netherlands showed close homology indicating a geographically confined circulation [8]. This is supported by the high degree of sequence identity of our and recent Czech and Dutch sequences. Zoonotic transmission from pigs to humans seems to be the major mode of infection, but occupational exposure to pigs was not reported in our case [6].

Two important observations were made in this study. Firstly, we could show that the infectious dose required for HEV infection seems to be low, i.e. HEV RNA

concentrations close to the limit of detection of the real-time RT-PCR. Low levels of HEV RNA in asymptomatic donors have already been reported but without evidence for transmission [8,9]. Interestingly, Juhl et al. speculated that viraemia of around 125 IU/mL in the presence of anti-HEV IgM was not sufficient for transfusion-associated infection [9]. However, it is not clear if HEV antibodies can prevent infection. A recent study showed that infectious HEV could be propagated in cell culture in the presence of HEV-specific antibodies, suggesting that they do not efficiently reduce virus infectivity [12]. In addition, a clinical study demonstrated that anti-HEV IgG did not uniformly protect against reinfection [13].

Secondly, the duration of viraemia in our asymptomatic donor did not exceed 45 days, based on the time interval between the last and the first HEV RNA-negative donation. The interval of 14 days between first and last HEV RNA-positive donation was even shorter than the 27 to 58 days reported by Slot et al., but could be due to the shorter sampling interval in our study [11]. From our and previously published data it is obvious that highly sensitive methods would be required if screening for HEV RNA were to be considered for blood products.

The second HEV transfusion-associated transmission possibly occurred in a child. However, we were not able to definitely prove transmission since only one sample was available. In light of the very low HEV seroprevalence among children in Germany it seems probable that this child was infected by donation 1 [14]. It remains unclear why transfusion of donation 2 with a fourfold higher HEV RNA concentration did not result in infection, but this could be related to host factors.

To conclude, we could demonstrate that transmission of HEV by asymptomatic donors with low-level viraemia is possible. Current German guidelines in transfusion medicine do not recommend testing for HEV. Importantly, with regard to the possible severe consequences of transfusion-associated transmission of HEV, especially in immunocompromised patients, the necessity of screening for HEV RNA needs to be discussed in countries with a high HEV prevalence. However, more data regarding the HEV disease burden due to blood transfusions are needed before recommendations can be made.

Conflict of interest

None declared

Authors' contributions

DH, HH, MP wrote the manuscript. DB, PH, ES, RT took part in the clinical management of the patient. MU, TC, FE, RH, CSH took part in the look-back procedure. JJW, MP collaborated in molecular biology techniques. OK, SM, RU collaborated on the public health investigation. All authors participated in the investigation. All authors read and approved the final manuscript.

References

1. Schlauder GG, Dawson GJ, Erker JC, Kwo PY, Knigge MF, Smalley DL, et al. The sequence and phylogenetic analysis of a novel hepatitis E virus isolated from a patient with acute hepatitis reported in the United States. J Gen Virol. 1998;79(Pt 3):447-56.
2. Boxall E, Herborn A, Kochethu G, Pratt G, Adams D, Ijaz S, et al. Transfusion-transmitted hepatitis E in a 'nonhyperendemic' country. Transfus Med. 2006;16(2):79-83. http://dx.doi.org/10.1111/j.1365-3148.2006.00652.x
3. Matsubayashi K, Kang JH, Sakata H, Takahashi K, Shindo M, Kato M, et al. A case of transfusion-transmitted hepatitis E caused by blood from a donor infected with hepatitis E virus via zoonotic food-borne route. Transfusion. 2008;48(7):1368-75. http://dx.doi.org/10.1111/j.1537-2995.2008.01722.x
4. Colson P, Coze C, Gallian P, Henry M, De Micco P, Tamalet C. Transfusion-associated hepatitis E, France. Emerg Infect Dis. 2007;13(4):648-9. http://dx.doi.org/10.3201/eid1304.061387
5. Kamar N, Bendall R, Legrand-Abravanel F, Xia NS, Ijaz S, Izopet J, et al. Hepatitis E. Lancet. 2012;379(9835):2477-88. http://dx.doi.org/10.1016/S0140-6736(11)61849-7
6. Faber MS, Wenzel JJ, Jilg W, Thamm M, Hohle M, Stark K. Hepatitis E virus seroprevalence among adults, Germany. Emerg Infect Dis. 2012;18(10):1654-7. http://dx.doi.org/10.3201/eid1810.111756
7. Chaussade H, Rigaud E, Allix A, Carpentier A, Touze A, Delzescaux D, et al. Hepatitis E virus seroprevalence and risk factors for individuals in working contact with animals. J Clin Virol. 2013;58(3):504-8. http://dx.doi.org/10.1016/j.jcv.2013.08.030
8. Vollmer T, Diekmann J, Johne R, Eberhardt M, Knabbe C, Dreier J. Novel approach for detection of hepatitis E virus infection in German blood donors. J Clin Microbiol. 2012;50(8):2708-13. http://dx.doi.org/10.1128/JCM.01119-12
9. Juhl D, Baylis SA, Blumel J, Gorg S, Hennig H. Seroprevalence and incidence of hepatitis E virus infection in German blood donors. Transfusion. 2014;54(1):49-56. http://dx.doi.org/10.1111/trf.12121
10. Baylis SA, Gartner T, Nick S, Ovemyr J, Blumel J. Occurrence of hepatitis E virus RNA in plasma donations from Sweden, Germany and the United States. Vox Sang. 2012;103(1):89-90. http://dx.doi.org/10.1111/j.1423-0410.2011.01583.x
11. Slot E, Hogema BM, Riezebos-Brilman A, Kok TM, Molier M, Zaaijer HL. Silent hepatitis E virus infection in Dutch blood donors, 2011 to 2012. Euro Surveill. 2013;18(31):pii=20550.
12. Takahashi M, Tanaka T, Takahashi H, Hoshino Y, Nagashima S, Jirintai, et al. Hepatitis E Virus (HEV) strains in serum samples can replicate efficiently in cultured cells despite the coexistence of HEV antibodies: characterization of HEV virions in blood circulation. J Clin Microbiol. 2010;48(4):1112-25. http://dx.doi.org/10.1128/JCM.02002-09
13. Abravanel F, Lhomme S, Chapuy-Regaud S, Mansuy JM, Muscari F, Sallusto F, et al. Hepatitis E virus reinfections in solid-organ-transplant recipients can evolve to chronic infections. J Infect Dis. 2014 Mar 11 [Epub ahead of print]. http://dx.doi.org/10.1093/infdis/jiu032
14. Krumbholz A, Neubert A, Joel S, Girschick H, Huppertz HI, Kaiser P, et al. Prevalence of hepatitis e virus antibodies in children in Germany. Pediatr Infect Dis J. 2014;33(3):258-62. http://dx.doi.org/10.1097/INF.0000000000000077
15. Lu L, Li C, Hagedorn CH. Phylogenetic analysis of global hepatitis E virus sequences: genetic diversity, subtypes and zoonosis. Rev Med Virol. 2006;16(1):5-36. http://dx.doi.org/10.1002/rmv.482

The Italian national surgical site infection surveillance programme and its positive impact, 2009 to 2011

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Programmes surveying surgical site infection (SSI) have been implemented throughout the world and are associated with a reduction in SSI rates. We report data on non-prosthetic surgery from the Italian SSI surveillance programme for the period 2009 to 2011. Participation in the programme was voluntary. We evaluated the occurrence of SSI, based on protocols from the European Centre for Disease Prevention and Control, within 30 days of surgery. Demographic data, risk factors, type of surgery and presence of SSI were recorded. The National Coordinating Centre analysed the pooled data. On 355 surgical wards 60,460 operations were recorded, with the number of surveyed intervention doubling over the study period. SSI was observed in 1,628 cases (2,6%) and 60% of SSI were diagnosed through 30-days post discharge surveillance. Operations performed in hospitals with at least two years of surveillance showed a 29% lower risk of SSI. Longer intervention duration, American Society of Anesthesiologists' (ASA) score of at least three, and pre-surgery hospital stay of at least two days were associated with increased risk of SSI, while videoscopic procedures had reduced SSI rates. Implementation of a national surveillance programme was helpful in reducing SSI rates and should be prioritised in all healthcare systems.

Introduction

Surgical site infections (SSI) represent one of the main complications in patients undergoing surgery, with major implications in terms of morbidity, including additional surgical procedures or transfer to an intensive care unit (ICU), mortality, longer duration of hospital stay, and financial burden [1]. A considerable proportion of SSI could be avoided through the implementation of adequate preventive strategies. Thus SSI incidence has been recommended by the European Council and proposed as an indicator of healthcare quality in the context of clinical governance and performance monitoring, and is therefore a target of many healthcare systems [2-4].

Over the past four decades, national and international SSI surveillance systems have been implemented, aimed at gathering data on SSI and building programmes to reduce their incidence [5-7]. Although data from different hospitals may vary significantly, due to factors such as hospital and patient characteristics, benchmarking SSI incidence between hospitals and over time may allow identification of areas for targeted intervention and may help to better allocate resources. [8] In addition to documenting a relevant part of the healthcare system, surveillance itself, even without any specific intervention, has been associated with a reduction in SSI incidence, another reason to recommend implementation of national surveillance systems [5,8,9].

The Italian Centre for Disease Control and Prevention (Centro per il Controllo e la Prevenzione delle Malattie; CCM) funded, in 2005, the implementation of a national surveillance system for SSI (Sistema Nazionale Sorveglianza Infezioni del Sito Chirurgico; SNICh), with the aim to facilitate comparisons within and between hospitals and to participate to the European surveillance programme, coordinated by the European Centre for Disease Prevention and Control (ECDC). The objective of this study was to describe the main characteristics of the SNICh programme, and in particular to report its impact on SSI rates for the period from 2009 to 2011.

Methods

Settings and background

The study was performed within the national surveillance system, coordinated by the Regional Health Agency of the Emilia-Romagna Region (Agenzia

Sanitaria e Sociale Regionale Emilia-Romagna; ASSR) and funded by CCM. ASSR acted as the National Coordinating Centre. Participation in the SNICh programme is voluntary. Any single hospital ward, hospital, or regional network may participate.

Data collection

The procedures undergoing surveillance are those reported in the National Protocol for SSI surveillance [10]. For this study, procedures involving implants of prosthetic material were not considered due to the very different length of post-intervention follow-up that is required (one year vs one month) and because data regarding the one-year follow-up were not yet available at the moment of the analysis. Furthermore, intervention categories that did not reach 100 operations in the considered time frame were excluded. Information on SSIs were recorded by clinicians and/or nurses during post-operatory contacts with patients. This analysis included surgical procedures surveyed between 2009 and 2011 from all participating surgical wards.

Data on surgical operations are recorded, by law, for every procedure, in the hospitals' operation registries. Thus information on surgical unit, date of operation, procedure ICD-9CM codes, wound contamination class, American Society of Anaesthesiology (ASA) score, duration of intervention, whether the procedure was urgent and whether it was performed using an endoscopic/laparoscopic approach, was retrieved by hospital staff from the hospital operation registry. Demographic characteristics of patients (sex and age) were recorded in the discharge form (Scheda di Dimissione Ospedaliera; SDO) of every patient staying in the hospital. Dates of admission and discharge and the hospital identification code were also retrieved from the SDO.

Information on post-discharge contact were retrieved from three different sources, depending on the type of contact: (i) if the patient was readmitted to the hospital within the follow-up time frame, data were available via SDO; (ii) whenever the patient accessed the hospital for post-discharge visits, data were available via the regional ambulatory activity database (ASA); (iii) in case the information regarding the intervention follow-up was obtained by phone or on returning the post-discharge letter, a special form was filled in. If more than one type of information was available, the latest date within 30 days from the intervention was considered as the 'date of last information' and therefore recorded in the database. Data regarding the number of surgical procedures performed in Italy were retrieved from the Ministry of Health database [11].

Data were fed back to all participating centres in the form of written reports in three different formats: a pdf file for the national report published on the SNICh site, an html dashboard for regional reports and another html report for single-hospital reports. The national report is published once a year. The regional and single-hospital analyses are sent via email to all participating centres and to regional contact points once a year or on demand.

Definitions

The main outcome variable was the occurrence of an SSI within 30 days of the operation. SSIs were further classified as superficial, deep incisional, or organ/space. The definitions used for recording SSIs and classifying them for severity were those given by ECDC in the 'hospital acquired infection surgical site infection' (HAISSI) protocol [12].

Wound Classification, ASA score, and duration of intervention were used to calculate the SSI risk index [13]. Definitions by ECDC were used for this group of variables. The cut-off values for the duration of operative procedures categories, needed for the calculation of SSI risk index, were taken from the protocol of the National Health Surveillance Network (NHSN) [14]. ICD-9CM procedures codes were grouped into operative procedure categories according to the NHSN.

A variable indicating how long a hospital had been performing SSI surveillance was calculated for every procedure in the database as the difference between the surgery date and the date when the hospital started performing surveillance. When a hospital interrupted the surveillance for a full quarter, a new starting date was used for later procedures. The variable was then recoded as a binary one, indicating whether the hospital had been surveying for more than two years at the time of one particular surgery.

Statistical analysis

Continuous variables, such as age and duration of operation were recoded as categorical variables. Duration was recoded as a binary variable indicating whether the procedure lasted longer than the NHSN 75th percentile for that particular category (as it is done when calculating the SSI risk index.) Age was also recoded as a binary variable, by dividing patients into those younger than 65 years and those 65 years and older.

Statistical significance for univariate odds ratios was assessed with Fisher's exact test. Multivariate analysis was performed using generalised mixed models, in order to account for the correlation of episodes within hospitals and operative procedures. The model presented is a multilevel model with random intercepts and the outcome variable following a binomial distribution with a logit link.

The hospital and the operative procedure category were treated as random effects. Wound classification, ASA score, duration of operation, technique used (classical vs laparoscopic/endoscopic) and urgency of operation were treated as fixed effects, as were potential confounders such as age and sex. Finally, the variable indicating whether the hospital in which the operation

Table 1

Main characteristics of the operations recorded in the SNICh programme, Italy, 2009–2011 (n=60,460)

	Operations n (%)	Infections n (rate per 100 procedures)
Duration of operation		
Under 75th percentile	48,438 (80)	1,108 (2.3)
Over 75th percentile	12,022 (20)	520 (4.3)
ASA score		
1	18,085 (30)	285 (1.6)
2	26,019 (43)	712 (2.7)
3	9,410 (16)	422 (4.5)
4	1,804 (3)	116 (6.4)
5	152 (0)	9 (5.9)
NA	4,990 (8)	84 (1.7)
Wound class[a]		
I	29,055 (49)	478 (1.6)
II	23,844 (40)	673 (2.8)
III	4,947 (8)	318 (6.4)
IV	1,488 (3)	152 (10.2)
Technique of operation[a]		
Classic	46,911 (79)	1,414 (3.0)
Videoscopic	12,125 (21)	211 (1.7)
Hospital stay before operationa		
<2 days	28,499 (47)	485 (1.7)
≥2 days	31,917 (53)	1,141 (3.6)
Sex		
Male	20,298 (34)	668 (3.3)
Female	40,162 (66)	960 (2.4)
Age[a]		
0–1	399 (1)	7 (1.8)
2–5	470 (1)	6 (1.3)
6–15	955 (2)	23 (2.4)
16–45	21,778 (36)	376 (1.7)
46–65	16,262 (27)	461 (2.8)
66–85	18,533 (31)	690 (3.7)
≥85	1,955 (3)	65 (3.3)
Urgent operation[a]		
No	45,044 (75)	1,174 (2.6)
Yes	15,006 (25)	452 (3.0)
Operative procedure category[b]		
Caesarean section	12,970 (21)	222 (1.7)
Cholecystectomy	9,653 (16)	162 (1.7)
Breast surgery	8,724 (14)	156 (1.8)
Colon surgery	6,130 (10)	508 (8.3)
Herniorrhaphy	4,172 (7)	50 (1.2)
Open reduction of fracture	2,365 (4)	14 (0.6)
Appendectomy	1,957 (3)	51 (2.6)
Prostatectomy	1,558 (3)	49 (3.1)
Rectal surgery	1,412 (2)	126 (8.9)
Laminectomy	1,407 (2)	5 (0.4)
Thoracic surgery	1,010 (2)	11 (1.1)

ASA: American Society of Anaesthesiology; SNICh: Sistema Nazionale Sorveglianza Infezioni del Sito Chirurgico.

[a] Data are missing in these categories. Percentages are calculated on the available data: wound class (n=59,334), operation technique (n=59,036), hospital stay before operation (n=60,416), age (n=60,352), urgent operation (n=60,050).

[b] Only operation categories with ≥1,000 procedures are reported.

was performed had been continuously submitting data to the SNICh system for more than two years (at the time of operation) was also treated as a fixed effect.

Different model specifications were evaluated. Continuous variables were tested without being recoded as categorical ones, different groupings were tried for categorical ordinal variables, components of the SSI risk index were replaced by the index itself and random slopes were added to random effects in the hypothesis that operations characteristics have different effects on the outcome depending on the operative procedure category. The significance of the random effects was assessed by comparing the log-likelihoods of models. Alternative models either gave worse results than the one presented here (according to Akaike's and Bayesian information criteria) or introduced complexity without providing a significant improvement.

The model presented for the main outcome variable was also applied to a second end point, in-hospital detected severe infections (either deep incisional or organ/space).

Data were analysed with the statistical software R [15]. The R package *lme4* [16] was used for the multilevel modelling and the R package *exactci* [17] was used for calculating confidence intervals.

Results

The SNICh system collected data on 83,127 operations from 2009 to 2011, and the final number of operations considered for the study was 60,460. For 54,240 of these (89.7%) there was no missing information.

The surveyed operations increased from 14,616 in 2009 to 28,739 in 2011 (+96%). The top 10 interventions surveyed in 2011 represented 3% of the interventions performed at the national level, varying between 2.3% for appendectomy and 5.9% for breast surgery. A total of 355 wards, from 12 of the 20 Italian regions, contributed an average of 170 records (median: 64; interquartile range (IQR): 23–147.) Two thirds of the patients were females, and the combined average age was 53 years. Female patients were on average significantly younger (51 vs 59 years; t-test: 46.35; p<0.001), but the difference was entirely due to Caesarean section operations (after removing Caesarean sections, both sexes averaged at 59 years of age.)

Pre-operatory hospital stay lasted for a median of two days (IQR: 1–3), while post-operatory stay lasted for a median of three days (IQR: 1–6). Thirty percent of the patients were operated in a hospital which had been continuously reporting data to SNICh for more than two years (at the time of operation.) Distributions of characteristics of the operations are reported in Table 1.

An SSI was reported for 1,628 operations (2.6%); 544 infections were either deep incisional or organ/space:

Table 2

Variables associated with surgical site infections: univariate and multivariate odds ratios, Italy, 2009–2011 (n=1,628)

	Univariate analysis			Multivariate analysis[a]		
	OR	95% CI	p value	OR	95% CI	p value
Duration of operation[b]						
Under 75th percentile	1	-	-	1	-	-
Over 75th percentile	1.93	1.74–2.15	<0.001	1.52	1.32–1.74	<0.001
ASA score						
<3	1	-	-	1	-	-
≥3	2.19	1.96–2.43	<0.001	1.42	1.22–1.65	<0.001
Wound class						
I	1	-	-	1	-	-
II	1.74	1.54–1.96	<0.001	1.36	1.08–1.72	<0.05
III	4.11	3.55–4.75	<0.001	1.71	1.29–2.26	<0.001
IV	6.81	5.61–8.21	<0.001	2.51	1.83–3.44	<0.001
Technique of operation						
Classic	1	-	-	1	-	-
Videoscopic	0.57	0.49–0.66	<0.001	0.49	0.40–0.61	<0.001
Hospital stay before operation						
<2 days	1	-	-	1	-	-
≥2 days	2.14	1.92–2.39	<0.001	1.22	1.05–1.41	<0.05
Sex						
Male	1	-	-	1	-	-
Female	0.72	0.65–0.80	<0.001	1.10	0.96–1.27	0.166
Age						
<65 years	1	-	-	1	-	-
≥65 years	1.70	1.54–1.87	<0.001	1.01	0.88–1.16	0.891
Urgent operation						
No	1	-	-	1	-	-
Yes	1.16	1.04–1.29	<0.01	1.29	1.11–1.51	<0.05
Years of continuous participation in the surveillance						
<2 years	1	-	-	1	-	-
≥2 years	0.60	0.53–0.68	<0.001	0.71	0.59–0.84	<0.001

ASA: American Society of Anaesthesiology; CI: confidence interval; OR: odds ratio.

[a] Multilevel logistic regression. Values reported for fixed effects. Hospitals and operation categories modelled as random effects (both effects significant according to log-likelihood test; p<0.001).

[b] Duration compared with the National Health Surveillance Network 75th percentile for the given operation category.

the number accounts for about one third of all the infections.

Uni- and multivariate analysis

Variables commonly associated with higher risk of SSI showed a significantly higher proportion of operations resulting in an infection. Table 2 reports odds ratios (with levels of significance and confidence intervals (CI)) obtained both with univariate and multivariate analysis: longer intervention duration, ASA score of at least three, and duration of pre-surgery hospital stay of at least two days, were found to be associated with an increased risk of SSI, whereas videoscopic procedures were associated with reduced SSI rates.

Operations performed in hospitals with at least two years of surveillance behind them showed a 29% lower risk of SSI, after accounting for all the other predictors, including the operation category and the facility. When the same model was applied to the severe infections detected in hospital, either before discharge or on readmission, (n=313; 0.5%), the values obtained for odds ratios and CIs were similar to the ones from the model on the complete dataset, thus including infections detected in both in- and outpatients. In particular the odds ratio for operations performed in hospitals with at least two years of surveillance was 0.58 (95% CI: 0.36–0.92).

Post-discharge surveillance

Ten days after the operation, when 90% of patients were already discharged, barely over a half of the recorded SSIs had been detected. Over 80% of SSIs were detected by the day 16, and over 90% by day 22. The median length of post-intervention follow-up was 26 days (IQR 9–30 days). This figure is very close to the desired complete follow-up of 30 days. The date of last information for surveyed procedures, corresponding to the end of the follow-up, was defined in 39% of cases through an ambulatory visit, in 22% cases during hospital stay (either before first discharge, or during a readmission), and in the remaining 39% patients by telephone call or by returning the post-discharge letter.

The proportion of SSI identified through telephone call or pre-stamped letter was 22%. The proportion of non-superficial SSI identified in the post-discharge surveillance (PDS) was 11%. Finally, the proportion of SSI identified through the PDS programme varied among different interventions, between 51 and 96% (see Table 3).

Operations resulting in an SSI lead to an increased post-operation hospital stay. The global median hospital stay for infected patients was five days (IQR: 2–12 days), and was higher for non-superficial SSIs (eight days; IQR: 1–18 days). The median hospital stay was three days (IQR: 1–6 days) in non-infected operated patients.

Table 3

Proportion of surgical site infections identified through post-discharge surveillance, Italy, 2009–2011 (n=1,628)

Type of intervention	SSI identified with PDS n (%)
Appendectomy	33/51 (65%)
Breast surgery	150/156 (96%)
Cholecystectomy	131/162 (86%)
Colon surgery	259/508 (51%)
Caesarean section	211/222 (95%)
Rectal surgery	69/126 (55%)

PDS: post-discharge surveillance; SSI: surgical site infection.

Discussion

The first analysis of the Italian SSI surveillance system had two main results: (i) SSIs occurred at a lower rate for operations performed in hospitals that participate regularly to the surveillance, and (ii) the total number of surgical procedures surveyed doubled over the study period. Further interesting information that emerged from this study was the high proportion of SSI, over 60%, identified through PDS. Finally, the study confirmed that most of the risk factors already known to be associated with an increased or reduced risk of SSI were valid also for the Italian population. In fact, longer intervention duration, an ASA score of at least three and pre-surgery hospital stay of at least two days were found to be associated with an increased risk of SSI. On the other hand, videoscopic procedures were associated with reduced SSI rates.

There are several limitations to this study. As every national surveillance system, SNICh has intrinsic limitations, in particular diagnostic criteria, number of enrolled patients, and intensity of surveillance. Although we used the same definition throughout the country, it is possible that the clinical diagnosis varied between hospitals and even between wards of the same facility. This is at least partly related to the fact that SSI diagnostic criteria are not uniform in the medical literature, and are complex and difficult to apply in a consistent way [4]. Despite this, the most common SSI definitions have similar capacity to predict outcomes influenced by SSI [4]. As no interventions to improve diagnostic capacity have been performed to date, we feel that it is unlikely that intra-centre diagnostic difference had a considerable impact on SSI trends. On the other hand, since no internal validation of the diagnostic criteria has been performed to date, it is possible that some of the differences in SSI rates could be due to inter-centre diagnostic disparities. We feel that, if a problem of misdiagnosis exists, it has probably been similar over the whole study period.

Furthermore, the relatively short duration of the study, three years, should have also restricted the possibility of intra-centre variation. Low representativeness of the surveyed surgical procedures in our national programme represents a second limitation of the study. Not all regional healthcare systems participated in the surveillance programme, and those that did, surveyed very different numbers of interventions.

As a third limitation, it cannot be excluded in the absence of validation studies that the intensity of surveillance changed over the study period, either decreasing or increasing. However, the reduction in SSI incidence we observed was almost the same as reported by the German surveillance programme KISS (Krankenhaus-Infektions-Surveillance-System), and by the Dutch PREZIES (PREventie van ZIEkenhuisinfecties door Surveillance), i.e. 29% and 31% respectively [18,19]. Furthermore, the observed reduction in SSI was confirmed when considering severe SSI only, i.e. non-superficial SSI diagnosed during hospital stay (OR: 0.58, CI: 0.36–0.92); they constitute a more stable sample for comparisons because the variations in performing PDS are eliminated [20,21].

Finally, interventions including a prosthetic implant were excluded. This choice was based upon the difference in follow-up that is needed to rule out an infection with prosthetic material, i.e. one year. Although the exclusion of these interventions may limit the

comparability with other systems, the proportion of such procedures varies significantly in the different systems, representing from less than a third to over half of the surveyed interventions [9,19,22]. Despite these differences the reduction observed in the different systems was similar. We therefore hypothesise that the impact on comparability due to exclusion of orthopaedic intervention is small.

The implementation of a national surveillance programme for SSI is a difficult task, particularly in times of crisis, with financial restraints, staff reductions, and decreased investments, including those in new information technology, all factors that impact on management and efficacy of a surveillance programme. In 2006, the CCM funded the implementation of a surveillance programme focussing on SSI and infections in ICU to collect national data and send information to ECDC [12]. As shown here, the Italian national programme had positive effects such as data collection for the European surveillance system, a national standard for SSI surveillance, regional groups on SSI, and a unique surveillance database for SSI.

The most striking achievement of the project, representing the core target of any surveillance program, was the rapid reduction in SSI incidence within three years; hospitals participating for more than two years had a 29% reduction in SSI rate. It has to be pointed out that the observed reduction was not due to lower baseline SSI rates in the centres surveying for more than two years. In fact, with the specification of the hospitals as random levels in the multilevel analysis, potential differences in baseline SSI rates have been taken into account. The decrease was probably due to not only the implementation of the surveillance programme but also other prevention interventions that are often associated with such programmes. Our observations confirm what has been previously reported in the literature: a significant reduction in hospital-acquired infections is expected within three years from the implementation of the surveillance programme [5,9,19,22]. Interestingly, the same decline was observed after implementation of such systems under different conditions and therefore it seems independent of changes in patient characteristics and technological innovation [9]. Data from France and the Netherlands show that further improvement beyond the third year of surveillance is possible, reaching SSI rate reductions of more than 50% after five to nine years [5,19].

The number of surgical procedures undergoing surveillance doubled in the three-year study period. Similar results have been observed in the European surveillance programme where the number of surgical procedures undergoing surveillance increased 2.8-fold between 2004 and 2009 [1]. Participation in the national surveillance system increased also in the United States, where the number of procedures surveyed increased from about 550,000 in the 12-year period between 1992 and 2003, with an average of some 45,000 intervention per year, to about 800,000 in the three-year period between 2006 and 2008, i.e. over 260,000 intervention each year, a more than five-fold increase [23,24].

We would welcome a further and steady increase in participation at national level: if the observed reduction were applied to all surgical procedures performed in the country, some 14,000 SSIs per year could be avoided. This could potentially lead to some 25,000 hospital days less per year, prevent individual suffering, and result in significant financial savings. A recent Italian meta-analysis shows that the average cost of one SSI is about EUR 13,000 [25]. Based upon these estimates, the possible savings after three years would range, for the whole country, between EUR 50 million and EUR 175 million. Furthermore, a decrease in SSI would reduce the number of litigations against hospitals, probably representing even larger economic savings.

In contrast to other surveillance systems, SNICh has a high proportion of infection detected during PDS. The internal structure of our surveillance system implies higher SSI rates in centres performing more accurate PDS, and limits the comparability with other systems, such as KISS or PREZIES, and of participating hospitals within SNICh. Programmes with limited or no PDS detect lower SSI rates. Participation to the SNICh programme is voluntary, and each centre may decide which interventions to survey. The centres that perform surveillance and PDS therefore do so willingly. These aspects could limit the generalisability of the results. Aiming at a wider uptake of the programme, there is a need to identify the most efficient surveillance strategy, which could lead to a revision of PDS duration, probably the most resource-intensive part of the SSI surveillance programme. Data from our study show that restricting PDS to three weeks, i.e. to the period when a patient is generally receiving ambulatory care after a surgical procedure, would identify around 90% of the events.

In conclusion, our data show that national surveillance programmes are beneficial for health, ethical and financial targets. We feel that a progressive expansion of these programmes should be pursued strongly both at a central and local level; mandatory participation could represent an important public health target.

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Conflict of interest

None declared.

Authors' contributions

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References

1. European Centre for Disease Prevention and Control (ECDC). Surveillance of surgical site infection in Europe 2008-2009. Stockholm: ECDC; 2012. ISBN 978-92-9193-334-1. doi 10.2900/21096. Available from: http://www.ecdc.europa.eu/en/publications/Publications/120215_SUR_SSI_2008-2009.pdf
2. Council of the European Union. Council recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare-¬associated infections (2009/C151/01). Official Journal of the European Union. 3 Jul 2009. Available from: http://ec.europa.eu/health/patient_safety/docs/council_2009_en.pdf
3. Decision No 2119/98/EC of the European Parliament and of the Council of 24 September 1998 setting up a network for the epidemiological surveillance and control of communicable diseases in the Community. Official Journal of the European Union. 3 Oct 1998. L 268. Available from: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31998D2119:EN:HTML
4. Gibbons C, Bruce J, Carpenter J, Wilson AP, Wilson J, Pearson A, et al. Identification of risk factors by systematic review and development of risk-adjusted models for surgical site infection. Health Technol Assess. 2011;15(30):1-156, iii-iv.
5. Rioux C, Grandbastien B, Astagneau P. Impact of a six-year control programme on surgical site infections in France: results of the INCISO surveillance. J Hosp Infect. 2007;66(3):217-23. http://dx.doi.org/10.1016/j.jhin.2007.04.005
6. European Centre for Disease Prevention and Control (ECDC). Surveillance of healthcare-associated infections in Europe, 2007. Stockholm: ECDC; 2012. ISBN 978-92-9193-327-3. doi 10.2900/18553. Available from: http://www.ecdc.europa.eu/en/publications/publications/120215_sur_hai_2007.pdf
7. Jarvis WR. Benchmarking for prevention: the Centers for Disease Control and Prevention's National Nosocomial Infections Surveillance (NNIS) system experience. Infection. 2003;31(Suppl 2):44-8.
8. Moro ML, Morsillo F, Tangenti M, Mongardi M, Pirazzini MC, Ragni P, et al. Rates of surgical-site infection: an international comparison. Infect Control Hosp Epidemiol. 2005;26(5):442-8. http://dx.doi.org/10.1086/502565
9. Gastmeier P, Schwab F, Sohr D, Behnke M, Geffers C. Reproducibility of the surveillance effect to decrease nosocomial infection rates. Infect Control Hosp Epidemiol. 2009;30(10):993-9. http://dx.doi.org/10.1086/605720
10. Centro nazionale per la prevenzione e il controllo delle malattie (CCM). [National Center for the Prevention and Control of Diseases]. Sistema nazionale sorveglianza delle infezioni del sito chirurgico (SNICh) - protocollo. [National surveillance system for surgical site infections (SNICh) – protocol]. Bologna: ASSR Emilia-Romagna; 2011. Italian. Available from: http://assr.regione.emilia-romagna.it/it/servizi/pubblicazioni/rapporti-documenti/protocollo-sistema-nazionale-di-sorveglianza-delle-infezioni-del-sito-chirurgico-snich-aggiornamento-dicembre-2011
11. Italian database on hospital activity. Rome: Ministry of Health. [Accessed 27 May 2014]. Available from: http://www.salute.gov.it/imgs/C_17_sissezione_2_listaFile_itemName_1_file.xls
12. European Centre for Disease Prevention and Control (ECDC). Surveillance of surgical site infections in European hospitals – HAISSI protocol. Version 1.02. Stockholm: ECDC; 2012. ISBN 978-92-9193-320-4. doi 10.2900/12819. Available from: http://www.ecdc.europa.eu/en/publications/publications/120215_ted_ssi_protocol.pdf
13. Culver DH, Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG, et al. Surgical wound infection rates by wound class, operative procedure, and patient risk index. National Nosocomial Infections Surveillance System. Am J Med. 1991;91(3B):152S-7S. http://dx.doi.org/10.1016/0002-9343(91)90361-Z
14. Edwards JR, Peterson KD, Mu Y, Banerjee S, Allen-Bridson K, Morrell G, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. Am J Infect Control. 2009;37(10):783-805. http://dx.doi.org/10.1016/j.ajic.2009.10.001
15. R Development Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2012. ISBN 3-900051-07-0. Available from: http://www.R-project.org/
16. Bates D, Maechler M, Bolker B. lme4: Linear mixed-effects models using S4. R package version 0.999375-42. Vienna: R Foundation for Statistical Computing; 2011. Available from: http://CRAN.R-project.org/package=lme4
17. Fay MP. Two-sided exact tests and matching confidence intervals for discrete data. R Journal 2010;2(1):53-8.
18. Gastmeier P, Geffers C, Brandt C, Zuschneid I, Sohr D, Schwab F, et al. Effectiveness of a nationwide nosocomial infection surveillance system for reducing nosocomial infections. J Hosp Infect. 2006;64(1):16-22. http://dx.doi.org/10.1016/j.jhin.2006.04.017
19. Geubbels EL, Nagelkerke NJ, Mintjes-de Groot AJ, Vandenbroucke-Grauls CM, Grobbee DE, de Boer AS. Reduced risk of surgical site infections through surveillance in a network. Int J Qual Health Care. 2006;18(2):127-33. http://dx.doi.org/10.1093/intqhc/mzi103
20. Ming DY, Chen LF, Miller BA, Anderson DJ. The impact of depth of infection and post-discharge surveillance on rate of surgical-site infections in a network of community hospitals. Infect Control Hosp Epidemiol. 2012;33(3):276-82. http://dx.doi.org/10.1086/664053
21. Brandt C, Sohr D, Behnke M, Daschner F, Rüden H, Gastmeier P. Reduction of SSI rates associated with active surveillance; Infect Control Hosp Epidemiol. 2006;27(12):1347-51. http://dx.doi.org/10.1086/509843
22. Astagneau P, L'Heriteau F, Daniel F, Parneix P, Venier AG, Malavaud S, et al. Reducing surgical site infection incidence through a network: results from the French ISO-RAISIN surveillance system. J Hosp Infect. 2009;72(2):127-34. http://dx.doi.org/10.1016/j.jhin.2009.03.005
23. NNIS System. National Nosocomial Infections Surveillance (NNIS) system report, data summary from January 1992 to June 2003, issued August 2003. Am J Infect Control. 2003;31(8):481-98. http://dx.doi.org/10.1016/j.ajic.2003.09.002
24. Edwards JR, Peterson KD, Mu Y, Banerjee S, Allen-Bridson K, Morrell G, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. Am J Infect Control. 2009;37(10):783-805. http://dx.doi.org/10.1016/j.ajic.2009.10.001
25. Graf K, Ott E, Vonberg RP, Kuehn C, Schilling T, Haverich A, et al. Surgical site infections—economic consequences for the health care system. Langenbecks Arch Surg. 2011;396(4):453–9. http://dx.doi.org/10.1007/s00423-011-0772-0

ePathGen - a new e-learning package in pathogen genomics

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The public health application of pathogen genomics is a rapidly expanding field as evident in the Eurosurveillance 'Special issue on molecular epidemiology of human pathogens' [1, 2]. Within Public Health England (PHE), staff training and the development of training resources have been identified as urgent requirements to facilitate the translation of this work from research to public health practice.

'ePathGen - Pathogen Genomics for Epidemiology' is an e-learning package that has been developed by a multi-disciplinary team from PHE working with collaborating academics as a beginners guide to using genomic sequencing by public health microbiologists and epidemiologists and is now publicly available at http://public-health-genomics.phe.org.uk

It is intended to support public health workers who need to develop a basic understanding of the evolving field of whole genome sequencing (WGS), pathogen genomics and its application to epidemiology and public health. e-PathGen allows users to proceed step by step through epidemiological investigations using, interpreting and combining genomic data in combination with more familiar information. It includes videos, a collection of introductory tutorials and illustrated case studies.

After completing the e-learning, users should be able to:

- explain the basic principles of genomic sequencing important to health protection and epidemiology practice;
- critically evaluate the benefits and limitations of genomics to health protection and epidemiology practice;
- apply the principles of genomics and key genomics resources to solving a problem in health protection and epidemiology practice;
- communicate effectively and work collaboratively with microbiology and bioinformatics experts in PHE and partner organisations to investigate and solve problems in health protection and epidemiology practice, and
- reflect on how genomics may be integrated with and applied to health protection and epidemiology in own working context.

We would welcome feedback to support future developments. For further information or contributions to the development of future case studies please contact janet.mcculloch@phe.gov.uk

References

1. Carriço JA, Sabat AJ, Friedrich AW, Ramirez M, on behalf of the ESCMID Study Group for Epidemiological Markers (ESGEM). Bioinformatics in bacterial molecular epidemiology and public health: databases, tools and the next-generation sequencing revolution. Euro Surveill. 2013;18(4):pii=20382..
2. Struelens MJ, Brisse S. From molecular to genomic epidemiology: transforming surveillance and control of infectious diseases. Euro Surveill. 2013;18(4):pii=20386.