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Four treatment failures of pharyngeal gonorrhoea with ceftriaxone (500 mg) or cefotaxime (500 mg), Sweden, 2013 and 2014

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We describe four cases in Sweden of verified treatment failures of pharyngeal gonorrhoea with ceftriaxone (500 mg; n=3) or cefotaxime (500 mg; n=1) monotherapy. All the ceftriaxone treatment failures were caused by the internationally spreading multidrug-resistant gonococcal NG-MAST genogroup 1407 clone. Increased awareness of treatment failures is crucial particularly when antimicrobial monotherapy is used. Frequent test of cure and appropriate verification/falsification of suspected treatment failures, as well as implementation of recommended dual antimicrobial therapy are imperative.

This report describes four failures to treat pharyngeal gonorrhoea with ceftriaxone (500 mg; n=3) or cefotaxime (500 mg; n=1) in Sweden in 2013 and 2014.

Neisseria gonorrhoeae has developed resistance to all antimicrobials previously used as first-line treatment for gonorrhoea [1-4]. Clinical resistance is now emerging to the extended-spectrum cephalosporins (ESCs), i.e. cefixime (oral) and the more potent ceftriaxone (injectable). Many treatment failures with cefixime have been verified in Japan, Europe, Canada and South Africa. No failure to treat urogenital gonorrhoea with ceftriaxone (250 mg–1 g), the last remaining option for first-line empiric antimicrobial monotherapy, has been detected as yet. However, some few failures to treat pharyngeal gonorrhoea with ceftriaxone have been verified in Japan (n=1), Australia (n=3), Sweden (n=1) and Slovenia (n=1) [4-10]. In recent years, extensively drug-resistant (XDR) gonococcal strains with high-level ceftriaxone resistance were also reported from Japan, France and Spain [2,9-11].

Case descriptions

From February to May 2013, three cases of suspected failure to treat pharyngeal gonorrhoea with ceftriaxone 500 mg intramuscularly were reported from two clinics for sexually transmitted infections (STIs) in Sweden (Table). All three patients reported having had unprotected oral and vaginal sex with heterosexual contacts in Stockholm. Case A was a woman in her 30s, with pharyngeal symptoms including pharyngitis. Cases B and C, both in their 50s, were asymptomatic. Pharyngeal and urogenital samples were taken and all patients had a positive gonococcal pharyngeal culture. Furthermore, the urogenital samples from the Cases B and C were positive in a nucleic acid amplification test (NAAT) (BD ProbeTec GC Qx Amplified DNA Assay, Becton Dickinson). All three patients were administered a single dose of 500 mg ceftriaxone intramuscularly (Day 1). When returning for follow-up after seven to 22 days, all patients were asymptomatic but had persistent positive gonococcal pharyngeal cultures. All urogenital samples were negative. Finally, all three patients were successfully treated with a single dose of 1 g ceftriaxone intramuscularly between Day 7 and 27, which was confirmed at follow-up visits with negative pharyngeal cultures between Day 22 and 48 (Table).

In May 2014, one case of suspected failure to treat pharyngeal gonorrhoea with cefotaxime 500 mg intramuscularly was reported from an STI clinic in Karlskrona, Sweden. This patient (Case D), a man in his 30s, attended the clinic because he had had unprotected oral and vaginal sex with a woman diagnosed with gonorrhoea. On Day 1, the patient was asymptomatic and sampled from the pharynx, urethra, and rectum. The pharyngeal sample was positive for gonococci in culture and he was treated with a single dose of 500 mg cefotaxime intramuscularly. At the follow-up visit

Table

Details of three verified ceftriaxone and one verified cefotaxime treatment failure of *Neisseria gonorrhoeae* pharyngeal infection, Sweden, 2013–2014*

	Case A[a]		Case B[a]		Case C[a]		Case D[a]	
Sex	Female		Male		Female		Male	
Age (years)	30ties		50ties		50ties		30ties	
Sexual orientation	Heterosexual							
Place of exposure	Stockholm, Sweden						Karlshamn, Sweden	
Healthcare clinic	STI clinics (n=2), Stockholm, Sweden						STI clinic, Karlskrona, Sweden	
Visit	Day 1	Day 7	Day 1	Day 13	Day 1	Day 22	Day 1	Day 7
Symptoms	Pharyngitis	None	None		None		None	
Positive diagnostics	GC culture (pharynx)		GC culture (pharynx), NAAT (urogenital)	GC culture (pharynx)	GC culture (pharynx), NAAT (urogenital)	GC culture (pharynx)	GC culture (pharynx)	
Negative diagnostics	GC culture (urogenital), NAAT (urogenital)		GC culture (urogenital)	GC culture (urogenital), NAAT (urogenital)	GC culture (urogenital)	GC culture (urogenital), NAAT (urogenital)	GC culture (urogenital/rectal), NAAT (urogenital/rectal)	
Characteristics of cultured isolates								
MIC ceftriaxone (mg/L)	0.125	0.125	0.064	0.125	0.064	0.064	0.25	0.125
MIC cefixime (mg/L)	0.25	0.25	0.125	0.25	0.25	0.125	NA	NA
MIC azithromycin (mg/L)	1	1	1	2	2	2	0.25	0.25
MIC cefotaxime (mg/L)	0.25	0.25	0.5	0.5	0.25	0.25	0.5	0.5
NG-MAST ST (genogroup)	ST4706[b] (1407)	ST4706[b] (1407)	ST3149[b] (1407)	ST3149[b] (1407)	ST3149[b] (1407)	ST3149[b] (1407)	ST4539 (NA)	ST4539 (NA)
Treatment	Ceftriaxone 500 mg IM	Ceftriaxone 1 g IM[c,d]	Ceftriaxone 500 mg IM	Ceftriaxone 1 g IM[c,d]	Ceftriaxone 500 mg IM	Ceftriaxone 1 g IM[c,d]	Cefotaxime 500 mg IM	Ceftriaxone 250 mg IM + Azithromycin 1g p.o.[c,d]

GC: *Neisseria gonorrhoeae*; MIC: minimum inhibitory concentration; NAAT: nucleic acid amplification test; NA: not assessed; NG-MAST: *N. gonorrhoeae* multi-antigen sequence typing; ST: sequence type; IM: intramuscularly; p.o.: per os

[a] All four patients repeatedly reassured that they had not had any unprotected sexual contacts between the ceftriaxone/cefotaxime treatment and test of cure. Cases B and C were sexual contacts.

[b] Belonged to the internationally spreading multidrug-resistant gonococcal NG-MAST genogroup 1407 clone, which has caused many treatment failures with extended-spectrum cephalosporins [4-6,9,13].

[c] Successful final treatment on Day 7 (Case A), Day 21 (Case B), Day 27 (Case C), and Day 14 (Case D).

[c] Negative test-of-cure culture on Day 22 and Day 32 (Case A), Day 35 (Case B), Day 41 and Day 48 (Case C), and Day 26 (Case D).

(Day 7), the patient was still asymptomatic, however, a pharyngeal sample remained positive in culture. The patient was treated with a single dose of 250 mg ceftriaxone intramuscularly plus a single oral dose of 1 g azithromycin (day 14). On Day 26, the patient returned for test of cure and the pharyngeal culture was negative for gonococci (Table).

Characterisation of *N. gonorrhoeae* isolates

The pre- and post-treatment gonococcal isolates were species-confirmed by sugar utilisation test, Phadebact Monoclonal GC Test (Pharmacia Diagnostics) and MaldiTOF MS (Bruker Daltonics). The paired isolates from each case were indistinguishable using *N. gonorrhoeae* multi-antigen sequence typing (NG-MAST [12]) and the isolates from Cases A, B and C belonged to the NG-MAST genogroup 1407 clone [4,13] (Table). Using Etest (AB bioMérieux), the isolates from Cases A, B and C (ceftriaxone treatment failures) showed elevated minimum inhibitory concentrations (MICs), i.e. 0.064–0.125 mg/L, which is equal to the European resistance breakpoint (>0.125 mg/L) [14]. In Case D (cefotaxime treatment failure), according to the European resistance breakpoints [14], the paired isolates were resistant to cefotaxime (MIC: 0.5 mg/L) and the pre-treatment isolate also to ceftriaxone (MIC: 0.25 mg/L) (Table).

Sequencing of ESC resistance determinants [1,3,4,6,9,10,15] showed that all the paired isolates belonging to Cases A, B and C contained the *penA* mosaic allele XXXIV, which has been correlated with NG-MAST genogroup 1407, decreased susceptibility or resistance to ESCs and ESC treatment failures [1,4-6,9,11]. The isolates from Case D contained the *penA* mosaic allele XIII [10]. In addition, all isolates contained *mtrR* and *penB* alterations that further increase the ESC MICs [1,3-6,9-11,15].

Discussion

This paper reports four cases of verified pharyngeal gonorrhoea treatment failure in Sweden using injectable ESCs, i.e. ceftriaxone (n=3) and cefotaxime (n=1). The failures were verified in accordance with international recommendations [2,4], i.e. clinical records were obtained, reinfection was excluded, pre- and post-treatment isolates were identical using highly discriminatory molecular epidemiological typing, and the isolates had elevated ESC MICs and well recognised ESC resistance determinants. Reinfection was considered to be excluded as much as possible for all cases. Accordingly, all patients were strongly advised to abstain from any sexual contacts before their follow-up visit and all four patients repeatedly assured that they had not had any unprotected sexual contacts between the ceftriaxone/cefotaxime treatment and test of cure. Furthermore, Case D was infected by a casual sexual contact.

In the current emergent situation of fear that gonorrhoea may become untreatable [1-3,10], recommendations of using dual antimicrobial therapy (mainly ceftriaxone plus azithromycin) have been introduced in the United States [16] and Europe [17]. No appropriate well-designed international study has yet assessed the implementation of dual antimicrobial therapy. However, as observed by the authors in many international projects the implementation of these guidelines appears suboptimal in several European countries and monotherapy with ceftriaxone remains frequently used.

No failure to treat urogenital gonorrhoea with ceftriaxone (250 mg–1 g) monotherapy has been verified to date. However, the observed initial accumulation of failures treating pharyngeal gonorrhoea was not unexpected, because these infections are substantially harder to eradicate with most antimicrobials than urogenital gonorrhoea [1-4,6,18]. As shown in the present study, ceftriaxone 500 mg monotherapy can be sufficient to eradicate urogenital gonorrhoea but not the concomitant pharyngeal gonorrhoea in the same patient. The pharyngeal gonorrhoea of the patients was instead successfully treated with 1 g ceftriaxone monotherapy or 250 mg ceftriaxone plus 1 g azithromycin. Unfortunately, 1 g ceftriaxone monotherapy may only provide a short-term solution [1,2,4,19,20] judging from the failure to treat the pharyngeal gonorrhoea caused by the first gonococcal XDR strain with 1 g ceftriaxone [10], ceftriaxone MICs of all the identified gonococcal XDR strains [9-11], emergence of ceftriaxone resistance and its anticipated trend, and pharmacodynamic/pharmacokinetic simulations showing that the benefits of increasing the ceftriaxone dose from 500 mg to 1 g are limited when taking into account the high ceftriaxone MICs detected recent years [19]. Consequently, dual antimicrobial therapy, e.g. 500 mg ceftriaxone intramuscularly plus 2 g azithromycin orally, as recommended by the European gonorrhoea guideline [17], should ideally be implemented. It remains unknown if ceftriaxone and azithromycin act synergistically in vivo. However, most importantly, there are no indications, in vitro or in vivo, that they act antagonistically. According to a review from 2010, 99% of urogenital and 98% of pharyngeal gonorrhoea cases may be treatable with 2 g azithromycin monotherapy [21]. Consequently, nearly all gonorrhoea cases (ceftriaxone-resistant or not) are treatable with even 2 g azithromycin monotherapy. Nevertheless, azithromycin monotherapy is not recommended due to the spread of gonococcal strains with high-level resistance to azithromycin and the anticipated rapid selection of azithromycin resistance [1,17,20].

All ceftriaxone treatment failures in the present study (Cases A, B and C) were caused by the internationally spreading multidrug-resistant gonococcal NG-MAST genogroup 1407 clone, which has caused many ESC treatment failures internationally [4-6,9,15]. However, the cefotaxime treatment failure was caused by the unrelated NG-MAST ST4539, which shows that clinical resistance to injectable ESCs is emerging also in other gonococcal clones.

In conclusion, increased awareness of treatment failures particularly with antimicrobial monotherapy, improved implementation of recommended dual antimicrobial therapy (e.g. 500 mg ceftriaxone plus 2 g azithromycin [17]), frequent test of cure (ideally for all cases, and at least for all cases of pharyngeal gonorrhoea), and appropriate verification/falsification of suspected treatment failures (including subsequent tracing of sexual contacts of the index case with the treatment failure) are essential internationally. An enhanced focus on pharyngeal gonorrhoea is also crucial, with increased sampling and prevention, e.g. promotion of condom use also when practising oral sex. Ultimately, novel options for effective treatment of gonorrhoea are imperative.

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Conflict of interest

None declared.

Authors' contributions

MU, AKO, PL, TR, and HF designed and initiated this surveillance of treatment failures. DG, AKO, HJ, OE and MU performed and analysed all the laboratory work. PL, TR, HJ and OE collected clinical information. DG wrote the first draft of the paper and all co-authors were involved in finalising the paper.

*Erratum

The table was corrected and replaced on 12 August 2014.

References

1. Unemo M, Shafer WM. Antimicrobial resistance in Neisseria gonorrhoeae in the 21st century: past, evolution and future. Clin Microbiol Rev. 2014;27(3):587-613. http://dx.doi.org/10.1128/CMR.00010-14
2. Tapsall JW, Ndowa F, Lewis DA, Unemo M. Meeting the public health challenge of multidrug- and extensively drug-resistant Neisseria gonorrhoeae. Expert Rev Anti Infect Ther. 2009;7(7):821-34. http://dx.doi.org/10.1586/eri.09.63
3. Lewis DA. The gonococcus fights back: is this time a knock out? Sex Transm Infect. 2010;86(6):415-21. http://dx.doi.org/10.1136/sti.2010.042648
4. Unemo M, Nicholas RA. Emergence of multidrug-resistant, extensively drug-resistant and untreatable gonorrhea. Future Microbiol. 2012;7(12):1401-22. http://dx.doi.org/10.2217/fmb.12.117
5. Allen VG, Mitterni L, Seah C, Rebbapragada A, Martin IE, Lee C, et al. Neisseria gonorrhoeae treatment failure and susceptibility to cefixime in Toronto, Canada. JAMA. 2013;309(2):163-70. http://dx.doi.org/10.1001/jama.2012.176575
6. Lewis DA, Sriruttan C, Müller EE, Golparian D, Gumede L, Fick D, et al. Phenotypic and genetic characterization of the first two cases of extended-spectrum cephalosporin resistant Neisseria gonorrhoeae infection in South Africa and association with cefixime treatment failure. J Antimicrobial Chemother. 2013;68(6):1267-70. http://dx.doi.org/10.1093/jac/dkt034
7. Read PJ, Limnios EA, McNulty A, Whiley D, Lahra LM. One confirmed and one suspected case of pharyngeal gonorrhoea treatment failure following 500 mg ceftriaxone in Sydney, Australia. Sex Health. 2013;10(5):460-2. http://dx.doi.org/10.1071/SH13077
8. Chen YM, Stevens K, Tideman R, Zaia A, Tomita T, Fairley CK, et al. Failure of ceftriaxone 500 mg to eradicate pharyngeal gonorrhoea, Australia. J Antimicrob Chemother. 2013;68(6):1445-7. http://dx.doi.org/10.1093/jac/dkt017
9. Unemo M, Golparian D, Nicholas R, Ohnishi M, Gallay A, Sednaoui P. High-level cefixime- and ceftriaxone-resistant Neisseria gonorrhoeae in France: novel penA mosaic allele in a successful international clone causes treatment failure. Antimicrob Agents Chemother. 2012;56(3):1273-80. http://dx.doi.org/10.1128/AAC.05760-11
10. Ohnishi M, Golparian D, Shimuta K, Saika T, Hoshina S, Iwasaku K, et al. Is Neisseria gonorrhoeae initiating a future era of untreatable gonorrhea?: detailed characterization of the first strain with high-level resistance to ceftriaxone. Antimicrob Agents Chemother. 2011;55(7):3538-45. http://dx.doi.org/10.1128/AAC.00325-11
11. Cámara J, Serra J, Ayats J, Bastida T, Carnicer-Pont D, Andreu A, et al. Molecular characterization of two high-level ceftriaxone-resistant Neisseria gonorrhoeae isolates detected in Catalonia, Spain. J Antimicrob Chemother. 2012;67(8):1858-60. http://dx.doi.org/10.1093/jac/dks162
12. Martin IM, Ison CA, Aanensen DM, Fenton KA, Spratt BG. Rapid sequence-based identification of gonococcal transmission clusters in a large metropolitan area. J Infect Dis. 2004;189(8):1497-505. http://dx.doi.org/10.1086/383047
13. Chisholm SA, Unemo M, Quaye N, Johansson E, Cole MJ, Ison CA, et al. Molecular epidemiological typing within the European Gonococcal Antimicrobial Resistance Surveillance Programme reveals predominance of a multidrug-resistant clone. Euro Surveill. 2013;18(3):pii=20358.
14. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Version 4.0. Basel: European Society of Clinical Microbiology and Infectious Diseases; 1 Jan 2014. Available from: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Breakpoint_table_v_4.0.pdf
15. Zhao S, Duncan M, Tomberg J, Davies C, Unemo M, Nicholas R. Genetics of chromosomally mediated intermediate resistance to ceftriaxone and cefixime in Neisseria gonorrhoeae. Antimicrob Agents Chemother. 2009;53(9):3744-51. http://dx.doi.org/10.1128/AAC.00304-09
16. Centers for Disease Control and Prevention (CDC). Update to CDC's Sexually Transmitted Diseases Treatment Guidelines, 2010: Oral cephalosporins no longer a recommended treatment for gonococcal infections. MMWR Morb Mortal Wkly Rep. 2012;61(31):590-4.
17. Bignell C, Unemo M, European STI Guidelines Editorial Board. 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. Int J STD AIDS. 2013;24(2):85-92. http://dx.doi.org/10.1177/0956462412472837
18. Moran JS. Treating uncomplicated Neisseria gonorrhoeae infections: is the anatomic site of infection important? Sex Transm Dis. 1995;22(1):39-47. http://dx.doi.org/10.1097/00007435-199501000-00007
19. Chisholm SA, Mouton JW, Lewis DA, Nichols T, Ison CA, Livermore DM. Cephalosporin MIC creep among gonococci: time for a pharmacodynamics rethink? J Antimicrob Chemother. 2010;65(10):2141-8. http://dx.doi.org/10.1093/jac/dkq289
20. Ison CA, Deal C, Unemo M. Current and future treatment options for gonorrhoea. Sex Transm Infect. 2013;89(Suppl 4):iv52–6. http://dx.doi.org/10.1136/sextrans-2012-050913
21. Bignell C, Garley J. Azithromycin in the treatment of infection with Neisseria gonorrhoeae. Sex Transm Infect. 2010;86(6):422-6. http://dx.doi.org/10.1136/sti.2010.044586

Non-fatal case of Crimean-Congo haemorrhagic fever imported into the United Kingdom (ex Bulgaria), June 2014

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Crimean-Congo haemorrhagic fever (CCHF) was diagnosed in a United Kingdom traveller who returned from Bulgaria in June 2014. The patient developed a moderately severe disease including fever, headaches and petechial rash. CCHF was diagnosed following identification of CCHF virus (CCHFV) RNA in a serum sample taken five days after symptom onset. Sequence analysis of the CCHFV genome showed that the virus clusters within the Europe 1 clade, which includes viruses from eastern Europe.

Clinical description

A British man in his early 70s presented to a hospital in the United Kingdom (UK) in June 2014 following a recent trip to Bulgaria. He had a history of paroxysmal atrial fibrillation for which he was taking warfarin, but was otherwise fit and well. He travelled with his spouse on 26 May 2014 to a rural area of Burgas Province near the Black Sea. On 18 June, he was bitten by a tick while outdoors. He removed the tick that evening without difficulty. Approximately five days previously, he had removed a tick from a cat and crushed it between his fingers.

He became abruptly unwell on 22 June, with fever, sweats, cough, sore throat, myalgia, headache, diarrhoea and two episodes of collapse. He was admitted overnight to a private hospital on 25 June and returned to the UK the following day, where he was admitted to his local university teaching hospital.

On arrival, the patient was febrile with a petechial rash on his legs and bilateral crepitations on chest auscultation. There was no overt bleeding or bruising. He was thrombocytopenic, with a platelet count of 26 × 10^9/L (norm: 150–400 × 10^9 /L), neutrophils of 1.1 × 10^9/L (norm: 2.0–7.5 × 10^9/L) and lymphocytes of 0.4 × 10^9/L (norm: 1.5–4.0 × 10^9/L). His renal function was normal and the level of C-reactive protein was mildly elevated, at 22 mg/L (norm: 0–7.5 mg/L) as was that of alanine aminotransferase (ALT), at 64 units (U)/L (norm: 10–40 U/L). He was isolated in a side room and treated with antibiotics including doxycycline to cover the possibility of tick-borne rickettsial infection. Over the following 48 hours, his platelet count fell to a low of 15 × 10^9/L and neutrophils to 0.7 × 10^9/L.

Following discussion with the UK's Imported Fever Service, serum, urine and blood samples were sent to the Rare and Imported Pathogens Laboratory at Public Health England (PHE), Porton Down, to screen for tick-borne infections including rickettsia, tick-borne encephalitis and CCHF, in addition to other potential arboviral zoonoses.

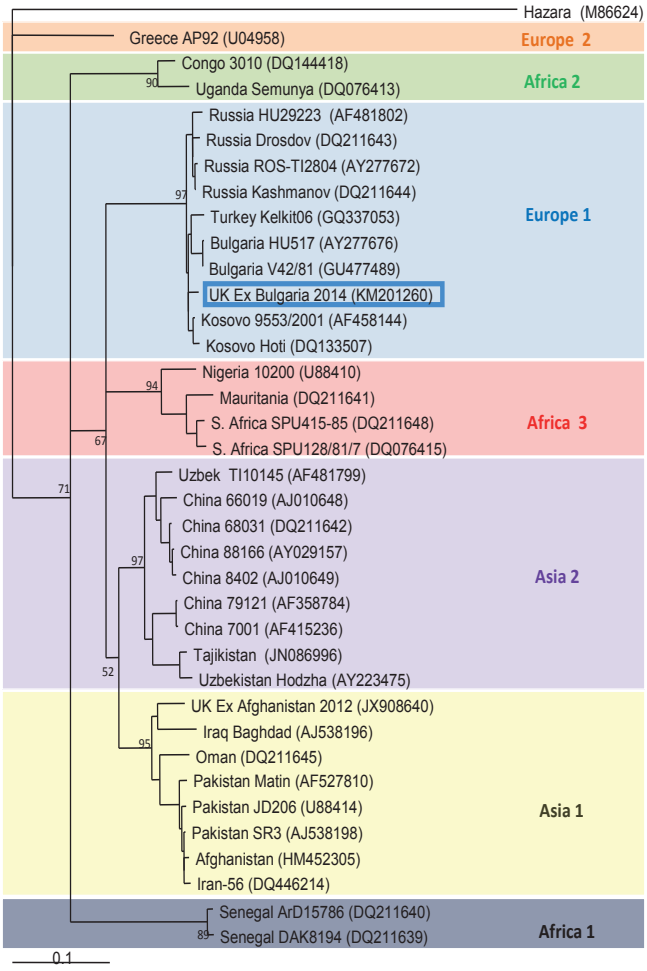
Laboratory findings

Initial diagnosis of CCHFV infection was made using a published real-time reverse transcription (RT)-PCR assay designed to detect the highly conserved panhandle loop formation of the CCHFV S segment [1]. A serum sample taken five days post onset of symptoms produced a positive result, with an estimated viral load of 1.5 × 10^5 S segment copies/mL in serum; urine and blood samples taken 10 days after symptom onset tested negative.

The serum sample taken five days post onset of symptoms was negative for CCHFV-specific antibodies tested for by enzyme-linked immunosorbent assay (ELISA) (in-house [2] and commercial Vector-Best assays) and immunofluorescence (Euroimmun); all assays demonstrated the production of reactive IgM and IgG antibodies in the samples taken 10 days post onset of symptoms.

Figure

Maximum likelihood phylogenetic tree of complete Crimean-Congo haemorrhagic fever virus S segments



The tree was constructed to determine the similarity and origin of the strain isolated from a United Kingdom traveller who returned from Bulgaria in late June 2014. It is rooted with the closely related Hazara virus. The genomic S segment of the virus from the UK traveller (GenBank accession number: KM201260) clusters with the Europe 1 group, showing close similarity to other strains from eastern Europe. All strains are listed with associated GenBank accession numbers for the S segment of the genome.

CCHFV was isolated in vitro from the PCR-positive serum sample within the Containment Level 4 laboratory at PHE Porton, using the human SW13 cell line. Sequence data for the complete S segment of the CCHFV genome were obtained using a sequencing strategy based on previously described protocols [3]. The sequence was submitted to GenBank on 15 July (GenBank accession number: KM201260). Phylogenetic analysis of sequence data using Clustal W placed this virus within the Europe 1 clade [4], along with strains of CCHFV isolated from nearby regions of eastern Europe (Figure).

Control measures

CCHF can be transmitted nosocomially, especially in cases presenting with extensive haemorrhagic manifestations or those requiring surgical intervention [5-9]. Therefore, following the laboratory diagnosis on 2 July 2014, the use of full personal protective equipment was mandated and contact tracing was commenced. As the patient was clinically improving and had no overt bleeding, care was continued at the local hospital rather than the national High Security Infectious Disease Unit. The patient made a steady improvement and was discharged on 9 July with normal blood indices. No onward transmission to contacts has been identified.

Discussion and conclusions

This report represents the second confirmed case of CCHF imported into the UK, the first being a case with a fatal outcome reported in 2012 [10]. In comparison with the case identified in 2012, who presented at hospital with overt haemorrhagic manifestations, the patient reported here suffered from a milder form of disease, without extensive haemorrhaging. The estimated viral load was 2–3 logs lower than that of the fatal case in 2012, when comparing samples taken five days post onset of symptoms; lower viral loads in the first week of illness are associated with patient survival [11]. Sequence analysis of the CCHFV S segment amplified from the patient's serum showed homology with other stains of CCHFV obtained from the same region of Europe.

The differences in clinical presentation and outcome between the two confirmed cases highlight the difficulties in rapidly identifying CCHF patients in the hospital setting. Early diagnosis is critical in reducing the potential for nosocomial transmission; however, the variation in disease severity and clinical symptoms increase the potential for a missed diagnosis. The Imported Fever Service, run by PHE in partnership with National Health Service (NHS) specialist tropical disease units in Liverpool and London, provides 24-hour on-call clinical advice and diagnostic capabilities for travel-related febrile illnesses, including viral haemorrhagic fevers [12]. The prompt identification of the pathogen, in both CCHF cases imported into the UK allowed infection control and public health actions to be taken in order to identify and minimise the potential for onward transmission.

To the best of our knowledge, this is the fourth laboratory-confirmed importation of CCHF into a non-endemic European country, following the fatal case imported into the UK from Afghanistan in 2012 [10], the medical evacuation of a United States soldier from Afghanistan into Germany in 2009 that resulted in a fatal outcome [13] and a non-fatal case imported into France from Senegal in 2004 [14]. In addition to these confirmed cases, a suspected case of CCHF was imported into the UK from Zimbabwe in 1997 [15] and an unpublished

case was imported into Germany from Bulgaria in 2001 [16].

CCHF is considered endemic in several parts of the Balkans, with over 1,500 human cases registered in Bulgaria up to 2009 [17,18]. Seroprevalence studies have shown human exposure to CCHFV in numerous districts across the country, with the highest rates in the Burgas region, where the UK traveller in this report was based [19]. As the route of infection is suspected to be via the bite of an infected tick, this case highlights the importance of tick awareness and bite prevention measures when travelling to regions endemic for pathogenic arboviral zoonoses including CCHF.

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Conflict of interest

None declared.

Authors' contributions

SL, BA, CP, MN, SG and RH wrote the paper; SL, BA, SD, JP, SS and JB performed laboratory diagnostics and viral characterisation; AS, EA and TB provided clinical and infection control advice; CP, MN and SG provided clinical care. All authors reviewed the manuscript before submission.

References

1. Atkinson B, Chamberlain J, Logue CH, Cook N, Bruce C, Dowall SD, et al. Development of a real-time RT-PCR assay for the detection of Crimean-Congo hemorrhagic fever virus. Vector Borne Zoonotic Dis. 2012;12(9):786-93. http://dx.doi.org/10.1089/vbz.2011.0770
2. Dowall SD, Richards KS, Graham VA, Chamberlain J, Hewson R. Development of an indirect ELISA method for the parallel measurement of IgG and IgM antibodies against Crimean-Congo haemorrhagic fever (CCHF) virus using recombinant nucleoprotein as antigen. J Virol Methods. 2012;179(2):335-41. http://dx.doi.org/10.1016/j.jviromet.2011.11.020
3. Atkinson B, Chamberlain J, Jameson LJ, Logue CH, Lewis J, Belobrova EA, et al. Identification and analysis of Crimean-Congo hemorrhagic fever virus from human sera in Tajikistan. Int J Infect Dis. 2013;17(11):e1031–7. http://dx.doi.org/10.1016/j.ijid.2013.04.008
4. Hewson R, Chamberlain J, Mioulet V, Lloyd G, Jamil B, Hasan R, et al. Crimean-Congo haemorrhagic fever virus: sequence analysis of the small RNA segments from a collection of viruses world wide. Virus Res. 2004;102(2):185-9. http://dx.doi.org/10.1016/j.virusres.2003.12.035
5. Hasan Z, Mahmood F, Jamil B, Atkinson B, Mohammed M, Samreen A, et al. Crimean-Congo hemorrhagic fever nosocomial infection in an immunosuppressed patient, Pakistan: case report and virological investigation. J Med Virol. 2013;85(3):501-4. http://dx.doi.org/10.1002/jmv.23473
6. Ergönül O. Crimean-Congo haemorrhagic fever. Lancet Infect Dis. 2006;6(4):203-14. http://dx.doi.org/10.1016/S1473-3099(06)70435-2
7. Mardani M, Keshtkar-Jahromi M, Ataie B, Adibi P. Crimean-Congo hemorrhagic fever virus as a nosocomial pathogen in Iran. Am J Trop Med. Hyg. 2009;81(4):675-8. http://dx.doi.org/10.4269/ajtmh.2009.09-0051
8. Tishkova FH, Belobrova EA, Valikhodzhaeva M, Atkinson B, Hewson R, Mullojonova M. Crimean-Congo hemorrhagic fever in Tajikistan. Vector Borne Zoonotic Dis. 2012;12(9):722-6. http://dx.doi.org/10.1089/vbz.2011.0769
9. Aradaib IE, Erickson BR, Mustafa ME, Khristova ML, Saeed NS, Elageb RM, et al. Nosocomial outbreak of Crimean-Congo hemorrhagic fever, Sudan. Emerging Infect Dis. 2012;16(5):837-9. http://dx.doi.org/10.3201/eid1605.091815
10. Atkinson B, Latham J, Chamberlain J, Logue C, O'Donoghue L, Osborne J, et al. Sequencing and phylogenetic characterisation of a fatal Crimean - Congo haemorrhagic fever case imported into the United Kingdom, October 2012. Euro Surveill. 2012;17(48):pii=20327.
11. Duh D, Saksida A, Petrovec M, Ahmeti S, Dedushaj I, Panning M, et al. Viral load as predictor of Crimean-Congo hemorrhagic fever outcome. Emerging Infect. Dis. 2007;13(11):1769-72. http://dx.doi.org/10.3201/eid1311.070222
12. Public Health England (PHE). Imported Fever Service. London: PHE. [Accessed 11 Jul 2014]. Available from: http://www.hpa.org.uk/ProductsServices/MicrobiologyPathology/LaboratoriesAndReferenceFacilities/RareAndImportedPathogensDepartment/ImportedFeverService/
13. Olschläger S, Gabriel M, Schmidt-Chanasit J, Meyer M, Osborn E, Conger NG, et al. Complete sequence and phylogenetic characterisation of Crimean-Congo hemorrhagic fever virus from Afghanistan. J Clin Virol. 2011;50(1):90-2. http://dx.doi.org/10.1016/j.jcv.2010.09.018
14. Jauréguiberry S, Tattevin P, Tarantola A, Legay F, Tall A, Nabeth P, et al. Imported Crimean-Congo hemorrhagic fever. J Clin Microbiol. 2005;43(9):4905-7. http://dx.doi.org/10.1128/JCM.43.9.4905-4907.2005
15. Stuart J. Suspected case of Crimean/Congo haemorrhagic fever in British traveller returning from Zimbabwe. Euro Surveill. 1998;2(8):pii=1256.
16. European Network for Diagnostics of "Imported" Viral Diseases (ENVID). Import of VHF and SARS to Europe. ENVID. [Accessed 12 Jul 2014]. Available from: http://www.enivd.de/over.htm
17. Vescio FM, Busani L, Mughini-Gras L, Khoury C, Avellis L, Taseva E, et al. Environmental correlates of Crimean-Congo haemorrhagic fever incidence in Bulgaria. BMC Public Health. 2012;12:1116. http://dx.doi.org/10.1186/1471-2458-12-1116
18. Papa A, Christova I, Papadimitriou E, Antoniadis A. Crimean-Congo hemorrhagic fever in Bulgaria. Emerg Infect Dis. 2004;10(8):1465-7. http://dx.doi.org/10.3201/eid1008.040162
19. Christova I, Gladnishka T, Taseva E, Kalvatchev N, Tsergouli K, Papa A. Seroprevalence of Crimean-Congo hemorrhagic fever virus, Bulgaria. Emerg Infect Dis. 2013;19(1):177-9. http://dx.doi.org/10.3201/eid1901.120299

Q fever epidemic in Hungary, April to July 2013

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We investigated a Q fever outbreak with human patients showing high fever, respiratory tract symptoms, headache and retrosternal pain in southern Hungary in the spring and summer of 2013. Seventy human cases were confirmed by analysing their serum and blood samples with micro-immunofluorescence test and real-time PCR. The source of infection was a merino sheep flock of 450 ewes, in which 44.6% (25/56) seropositivity was detected by enzyme-linked immunosorbent assay. *Coxiella burnetii* DNA was detected by real-time PCR in the milk of four of 20 individuals and in two thirds (41/65) of the manure samples. The multispacer sequence typing examination of *C. burnetii* DNA revealed sequence type 18 in one human sample and two manure samples from the sheep flock. The multilocus variable-number tandem repeat analysis pattern of the sheep and human strains were also almost identical, 4/5-9-3-3-0-5 (Ms23-Ms24-Ms27-Ms28-Ms33-Ms34). It is hypothesised that dried manure and maternal fluid contaminated with *C. burnetii* was dispersed by the wind from the sheep farm towards the local inhabitants. The manure was eliminated in June and the farm was disinfected in July. The outbreak ended at the end of July 2013.

Introduction

Coxiella burnetii is the causative agent of Q fever, a worldwide zoonotic disease [1,2]. Domestic ruminants are the most important recognised reservoirs of *C. burnetii*; they are often asymptomatic carriers, but the agent may also cause abortion in these animals [1,3]. Ticks may also act as reservoirs of *C. burnetii* in nature [1,4]. Domestic ruminants are considered the most important source of human Q fever infection. Outbreaks in human populations have been linked to slaughterhouses or dispersion of *C. burnetii* by wind from farms where infected ruminants were kept [1,5]. Q fever is typically an acute febrile illness with non-specific clinical signs such as atypical pneumonia and hepatitis in roughly 40% of cases, while 60% remain asymptomatic after infection [6]. A small percentage (ca 5%) of infected people may develop chronic infection with life-threatening valvular endocarditis [7,8].

Q fever is a notifiable disease in Hungary. Antibodies against *C. burnetii* were first detected in the sera of abattoir workers in 1950 [9], and infections were first diagnosed in 1956 in dairy and sheep farms [10]. The last major outbreaks were registered in the period of 1976–80. According to a recent survey (2010–11), seroprevalence among cattle and sheep in Hungary were 38.0% and 6.0%, respectively, by enzyme-linked immunosorbent assay (ELISA), which is in agreement with the European averages [3,11]. The number of yearly reported acute human infections in Hungary ranged between 36 and 68 between 2008 and 2012.

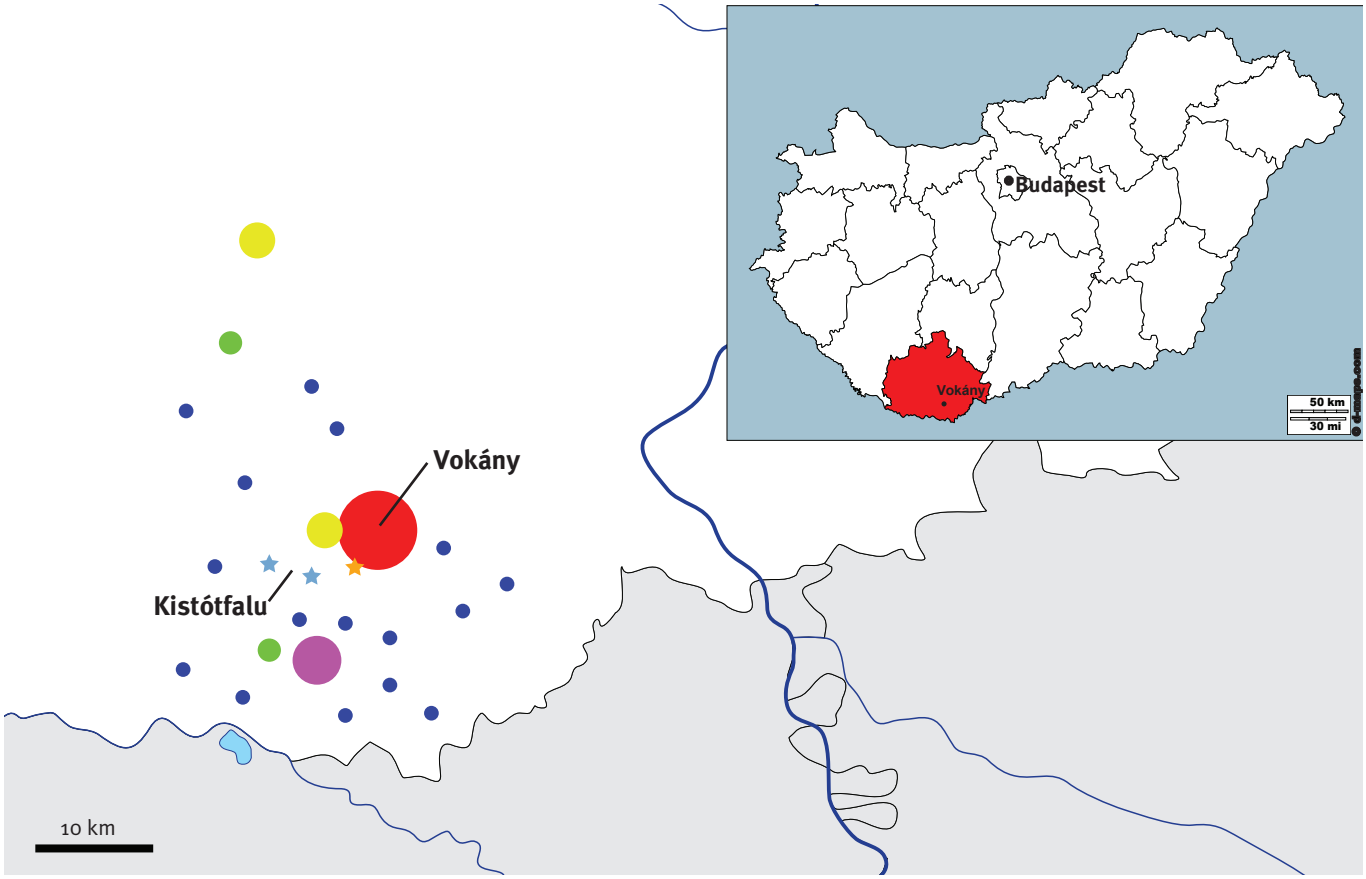
The aim of this study was the epidemiological, diagnostic and genetic investigation of the Q fever outbreak that occurred in Hungary during the spring and summer of 2013.

Methods

During the epidemic investigation a suspected human case was defined by high fever and radiological evidence of pneumonia occurring after 17 April 2013, and by geographic proximity to the outbreak area after 4 April. The human serum samples were tested with micro-immunofluorescence test (MIF) (Focus Diagnostics, United States). Based on MIF results of the first serum samples, the suspected human cases were evaluated as seronegative or possibly infected (showing seropositivity, i. e. any phase of specific IgM/IgG antibodies). Cases were considered confirmed if there was seroconversion and/or an elevated level (greater than 1:252 dilution) of IgG-II/IgG-I antibodies when paired sera were available. DNA was extracted from EDTA anticoagulated human blood and serum samples (collected in the one to three weeks after

Figure 1

Geographic expansion of the Q fever epidemic in Hungary, 2013



The epidemic occurred in Baranya county in southern Hungary (inset). Dots show the home towns of the 70 laboratory-confirmed human cases (red: 29 cases, pink: 11 cases, yellow: 6 cases, green: 2-3 cases, blue: 1 case) and stars represent the tested animal farms (orange: non-dairy merino sheep flock (450 ewes) near Vokány, light blue: cow herd (40 animals) and mixed flock of sheep and goats (20 animals)). The blank maps were downloaded from http://d-maps.com/carte.php?num_car=3576&lang=en and http://d-maps.com/carte.php?num_car=23250&lang=en.

onset of clinical symptoms) using the MagNA Pure LC total nucleic acid isolation kit (Roche Diagnostics, Switzerland).

Animal serum samples were tested with complement fixation test (CFT) (Virion/Serion GmbH, Germany) and ELISA (IDEXX Laboratories Inc., Switzerland). Questing ticks were collected using the dragging/flagging method. DNA was extracted from milk, manure and individual tick samples with the ReliaPrep gDNA Tissue Miniprep System (Promega Inc., United States).

All extracted DNA samples were screened with a real-time PCR assay targeting the *IS1111* element of *C. burnetii* [12]. Strong positive samples (with Ct values below 30) were further genotyped with multispacer sequence typing (MST) based on 10 loci and multilocus variable-number tandem repeat analysis (MLVA) based on six loci [13-15].

Results

Description of the epidemic area

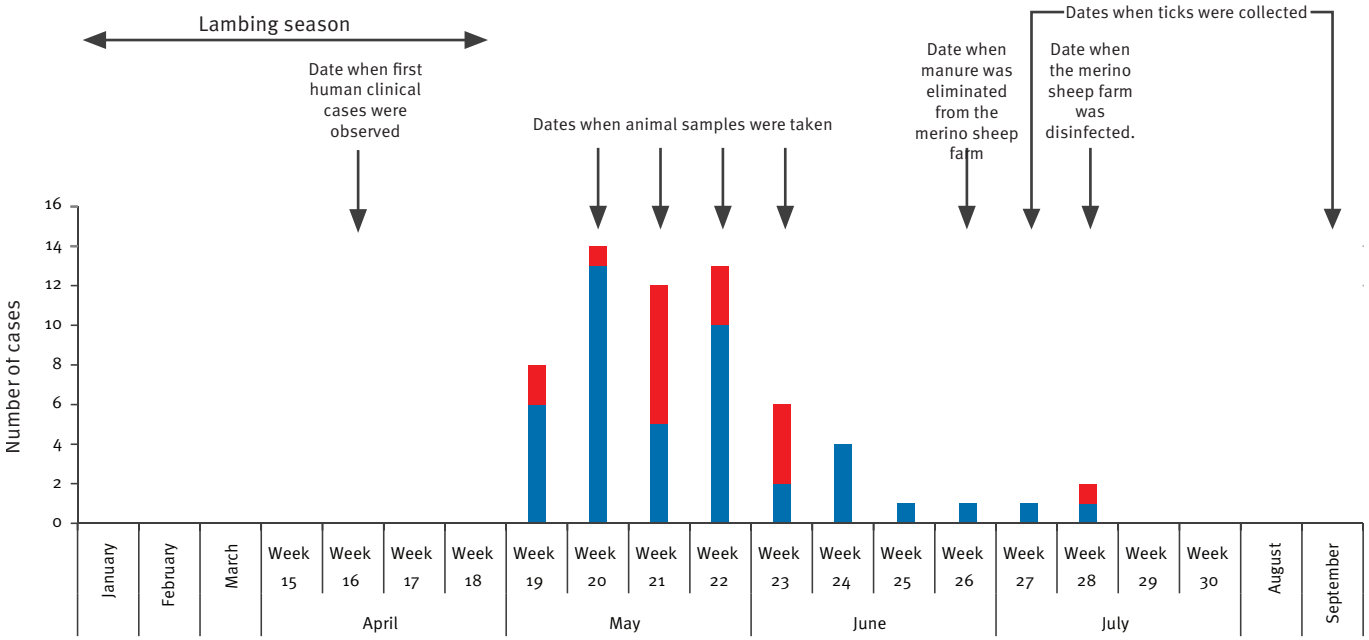
The centre of the outbreak region was a hilly area of approximately 10 km² encompassing primarily the small rural towns of Vokány (851 population) and Kistótfalu (321 population) of Baranya county in southern Hungary (45.90 °N, 18.33 °E) (Figure 1). Although the area has a continental climate, an unusually cold and snowy March was followed by a warm, dry and occasionally windy April in 2013. A non-dairy merino sheep flock (450 ewes) near Vokány, a small cattle herd (40 animals), a small mixed flock of sheep and goats (20 animals) and some individually kept animals were the only livestock in the region. The lambing season occurred from January to April in the area in 2013 (Figure 2).

Investigation of human cases

During systematic screening for respiratory pathogens, six patients of the initial cluster of eight febrile cases (since 17 April) showed *C. burnetii*-specific phase II IgM

Figure 2

Timeline of the epidemiological and diagnostic investigations during the Q fever outbreak in Hungary, 2013



Columns: number of laboratory-confirmed male (blue) and female (red) cases according to the date when first serum samples were taken.

positivity from serum samples received on 8 May, while other respiratory agents could be ruled out. After that laboratory finding, all suspected cases were tested for *C. burnetii* antibodies and an epidemiological investigation was initiated by the local authorities of Baranya County. The serological sampling was done primarily by general practitioners and extended to hospitalised patients living in the outbreak area. A centralised laboratory investigation was performed on all samples from suspected cases.

Starting on 17 April 2013 until 31 July, 176 possible human cases with high fever, respiratory tract symptoms, headache and retrosternal pain were reported. Of those, 103 were male and 73 were female. The age of the cases ranged from 14 to 84 years. Most of them were local residents of Vokány and Kistótfalu, although some had only transient connections with the region. Twenty-six patients needed hospital admission but no fatalities were recorded.

Based on MIF results of the first serum samples taken from the 176 suspected cases, 100 patients were evaluated as seronegative and 76 as possibly infected. Based on serological results, the infection was confirmed in 70 (60%) of 117 cases from whom paired sera were available. There was a predominance of men (45 male vs 25 female) in confirmed cases. Fifteen of the 26 hospitalised suspected cases were confirmed. *C. burnetii* real-time PCR was positive in three of the 26 anticoagulated blood samples and in one third (17/51, Ct: 29.4–36.1) of the tested serum samples collected in the one to three weeks after onset of clinical symptoms. The rate of PCR positivity decreased over time, as the samples taken in the first week of illness yielded the highest rate of PCR positivity (48%), with only 23% in the second and 0% in the third week. In the 20 PCR-positive human cases, seroconversion was detected in 19. Other important respiratory agents (*Mycoplasma pneumoniae, Chlamydophila pneumoniae, Chlamydophila psittaci, Legionella* spp.) were ruled out by laboratory examination (data not shown).

A three-week course of doxycycline therapy (200 mg daily) was administered to all laboratory-confirmed cases and also to the majority (no exact data are available) of the suspected cases living in the outbreak area. Serological follow-up was advised for all patients diagnosed with acute Q fever to control their IgG-I level because persisting high titres (≥800) may indicate chronic infection. As of July 2014, third serum samples have been sent from 21 of the 70 confirmed cases, and high titres of IgG2/IgG1 (≥512) were detected in all of them.

Animal and environmental investigations

Fifty-six serum and 20 milk samples were collected from the Vokány merino sheep flock and from all animals on other farms. Manure samples were also collected from the breeding stable of each farm within the outbreak region.

The CFT and ELISA examinations of the serum samples collected in the merino sheep flock revealed 23.2% (13/56) and 44.6% (25/56) seropositivity, respectively, while *C. burnetii* was detected in four of 20 (Ct: 30.1–33.5) of individual's milk and two thirds (41/65, Ct: 28.9–36.82) of manure samples collected from the merino sheep flock. Of the four sheep with PCR-positive milk, two were also seropositive by ELISA. The ELISA showed 11 of 40 and two of 20 seropositive animals in the cow herd and the mixed sheep and goat flock, respectively, and only one of the milk samples from a cow contained *C. burnetii* DNA (Ct: 33.7). The manure samples collected from these small farms as well as all samples (serum, milk, manure) collected from the individually kept animals in the epidemic region were negative for *C. burnetii* infection.

Seven questing ticks (five *Ixodes ricinus* and two *Haemaphysalis concinna*) were collected from the vegetation at the merino sheep farm pasture in July and September 2013. Another 115 archived ticks collected from two dogs (four *Dermacentor marginatus*) and 23 goats (91 *I. ricinus* and 20 *H. concinna*) residing with the merino sheep flock in 2011 and 2012 were also included in this study. *C. burnetii* DNA was detected in five archived *I. ricinus* (three larvae, one nymph, one female, Ct: 35.0–36.58) collected from goats kept in the merino sheep flock in 2011.

Genetic characterisation of *C. burnetii* strains

The MST examination of *C. burnetii* DNA detected in one human sample and two manure samples from the merino sheep flock revealed sequence type (ST)18. The MLVA pattern of the sheep and human strains were also almost identical, 4/5-9-3-3-0-5 (Ms23-Ms24-Ms27-Ms28-Ms33-Ms34). Genotyping of samples from the ticks collected in 2011 and from the cow milk failed because of their low *C. burnetii* DNA content.

Discussion

Seventy human cases were confirmed during the Q fever outbreak in Hungary in 2013. The laboratory diagnosis of the first patients based on serology and real-time PCR identified the aetiologic agent within a few days and enabled targeted screening and adequate therapy of further infected individuals. Combining these two methods was also an effective diagnostic strategy in the first two weeks after the onset of clinical symptoms. The merino sheep flock in Vokány village was identified as the source of the outbreak. Interestingly, the farmer had not observed an elevated abortion rate during the lambing season from January to April. The 44.6% seropositivity rate at this farm was far higher than the 6.0% recorded in other Hungarian sheep flocks and represents strong evidence of a localised outbreak [11].

The causative agent of the outbreak described here was an ST18 *C. burnetii* strain, which argues against a direct connection with the 2007–09 outbreak in the Netherlands which was caused primarily by ST33 [16,17]. ST18 has previously been detected in France, Germany, Italy, Romania and Slovakia [13]. A recent human serum sample from Belgium was also likely to be (or be closely related to) ST18 [17]. Our subtyping data confirmed that the source of the human Q fever infections was the merino sheep farm. The one VNTR difference between the ovine and human isolates at Ms23 is likely to be due to the rapid mutation capacity of this locus [15]. We hypothesise that dried manure and birth fluids contaminated with *C. burnetii* were dispersed by the wind from the sheep farm towards the towns and their inhabitants. This hypothesis is supported by the genotyped human sample. This patient had not had any direct contact with the merino sheep flock in Vokány. He was an inhabitant of a neighbouring town but was working on a hillside close to Vokány at the time of his supposed exposure. Based on the available epidemic information, laboratory data and the large number of human cases it is highly unlikely that this epidemic was caused either by tick-bites or raw milk consumptions. The origin of the ST18 strain at the merino sheep farm remains unknown. *C. burnetii* isolates originating from other parts of Hungary have been either ST20 (cattle) or ST28 and ST37 (sheep) genotypes [18].

Public health countermeasures included elimination of manure in June 2013, followed by disinfection of the merino farm (using VIROCID, Cid Lines Inc, Belgium and Disinflex, Hexachem Kft, Hungary) in July. In this region, no further acute human Q fever cases have been confirmed since July 2013. Manure and milk samples collected in May 2014 from the merino sheep flock in Vokány and other farms within a 30 km diameter, tested negative by real-time PCR. As a precaution, the merino farm in Vokány was disinfected in June 2014 as well.

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Conflict of interest

None declared.

Authors' contributions

MG, KS, and ÁD performed the PCR screening of livestock and tick samples, genotyped the positive samples, analysed the data and wrote the manuscript. EB, TM and AB performed the serological and PCR analysis of human samples and edited the manuscript. ZS and PB collected the livestock samples in the field. BD performed the serological examination of the livestock samples. SH collected and identified the ticks. HMH, TP and PK helped in genotyping and in the writing of the manuscript.

References

1. Porter SR, Czaplicki G, Mainil J, Guatteo R, Saegerman C. Q Fever: Current state of knowledge and perspectives of research of a neglected zoonosis. Int J Microbiol. 2011;248418.
2. Maurin M, Raoult D. Q fever. Clin Microbiol Rev. 1999;12(4):518-53.
3. Guatteo R, Seegers H, Taurel AF, Joly A, Beaudeau F. Prevalence of Coxiella burnetii infection in domestic ruminants: a critical review. Vet Microbiol. 2011;149(1-2):1-16. http://dx.doi.org/10.1016/j.vetmic.2010.10.007
4. Spitalska E, Kocianova E. Detection of Coxiella burnetii in ticks collected in Slovakia and Hungary. Eur J Epidemiol. 2003;18(3):263-6. http://dx.doi.org/10.1023/A:1023330222657
5. Arricau-Bouvery N, Rodolakis A. Is Q fever an emerging or re-emerging zoonosis? Vet Res. 2005;36(3):327-49. http://dx.doi.org/10.1051/vetres:2005010
6. Raoult D, Marrie T, Mege J. Natural history and pathophysiology of Q fever. Lancet Infect Dis. 2005;5(4):219-26.
7. Tilburg JJ, Melchers WJ, Pettersson AM, Rossen JW, Hermans MH, van Hannen EJ, et al. Interlaboratory evaluation of different extraction and real-time PCR methods for detection of Coxiella burnetii DNA in serum. J Clin Microbiol. 2010;48(11):3923-7. http://dx.doi.org/10.1128/JCM.01006-10
8. Landais C, Fenollar F, Thuny F, Raoult D. From acute Q fever to endocarditis: serological follow-up strategy. Clin Infect Dis. 2007;44(10):1337-40. http://dx.doi.org/10.1086/515401
9. Farkas E, Gerő S, Takátsy G. [The occurrence of Q-fever in Hungary]. Orv Hetil. 1950;91:717-8. Hungarian.
10. Romváry J. [Incidence of Q-fever in a cattle herd.] Magy Állatorv Lapja. 1957;12:25-7. Hungarian.
11. Gyuranecz M, Dénes B, Hornok S, Kovács P, Horváth G, Jurkovich V, et al. Prevalence of Coxiella burnetii in Hungary: screening of dairy cows, sheep, commercial milk samples, and ticks. Vector Borne Zoonotic Dis. 2012;12(8):650-3.http://dx.doi.org/10.1089/vbz.2011.0953
12. Loftis AD, Reeves WK, Szumlas DE, Abbassy MM, Helmy IM, Moriarity JR, et al. Rickettsial agents in Egyptian ticks collected from domestic animals. Exp Appl Acarol. 2006;40(1):67-81. http://dx.doi.org/10.1007/s10493-006-9025-2
13. Glazunova O, Roux V, Freylikman O, Sekeyova Z, Fournous G, Tyczka J, et al. Coxiella burnetii genotyping. Emerg Infect Dis. 2005;11(8):1211-7.
14. Klaassen CH, Nabuurs-Franssen MH, Tilburg JJ, Hamans MA, Horrevorts AM. Multigenotype Q fever outbreak, the Netherlands. Emerg Infect Dis. 2009;15(4):613-4.
15. Tilburg JJ, Rossen JW, van Hannen EJ, Melchers WJ, Hermans MH, van de Bovenkamp J, et al. Genotypic diversity of Coxiella burnetii in the 2007-2010 Q fever outbreak episodes in The Netherlands. J Clin Microbiol. 2012;50(3):1076-8. http://dx.doi.org/10.1128/JCM.05497-11
16. Tilburg JJ, Roest HJ, Buffet S, Nabuurs-Franssen MH, Horrevorts AM, Raoult D, et al. Epidemic genotype of Coxiella burnetii among goats, sheep, and humans in the Netherlands. Emerg Infect Dis. 2012;18(5):887-9. http://dx.doi.org/10.3201/eid1805.111907
17. Huijsmans CJ, Schellekens JJ, Wever PC, Toman R, Savelkoul PH, Janse I, et al. Single-nucleotide-polymorphism genotyping of Coxiella burnetii during a Q fever outbreak in The Netherlands. Appl Environ Microbiol. 2011;77(6):2051-7. http://dx.doi.org/10.1128/AEM.02293-10
18. Sulyok KM, Kreizinger Z, Hornstra HM, Pearson T, Szigeti A, Dán Á, et al. Genotyping of Coxiella burnetii from domestic ruminants and human in Hungary: indication of various genotypes. BMC Vet Res. 2014;10:107. http://dx.doi.org/10.1186/1746-6148-10-107

No evidence of transmission from an acute case of hepatitis A in a foodhandler: follow-up of almost 1,000 potentially exposed individuals, London, United Kingdom, April 2012

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Identification of acute hepatitis A virus (HAV) infection in a foodhandler in a London hotel led to a large incident response. We identified three potentially exposed groups: hotel staff who had regularly consumed food prepared by the case and shared toilet facilities with the case, patients who shared the same hospital ward as the case and hotel guests who consumed food prepared by the case. We arranged post-exposure HAV vaccination for all 83 potentially exposed hotel staff and all 17 patients. We emailed 887 guests advising them to seek medical care if symptomatic, but did not advise vaccination as it was too late to be effective for most guests. Through the International Health Regulations national focal points and the European Union Early warning and response system (EWRS), we communicated the details of the incident to public health agencies and potential risk of HAV transmission to international guests. Potentially exposed hotel staff and guests were asked to complete an online or telephone-administered questionnaire 50 days following possible exposure, to identify any secondary cases. Survey response was low, with 155 responses from guests and 33 from hotel staff. We identified no secondary cases of HAV infection through follow-up.

Introduction

On 10 April 2012, the local Health Protection Unit was alerted to a hospitalised patient with hepatitis A virus (HAV) IgM antibodies consistent with a recent HAV infection, who was a foodhandler at a busy London hotel in the United Kingdom (UK). The patient had returned from travel abroad four days before onset of symptoms (information obtained through a trawling questionnaire).

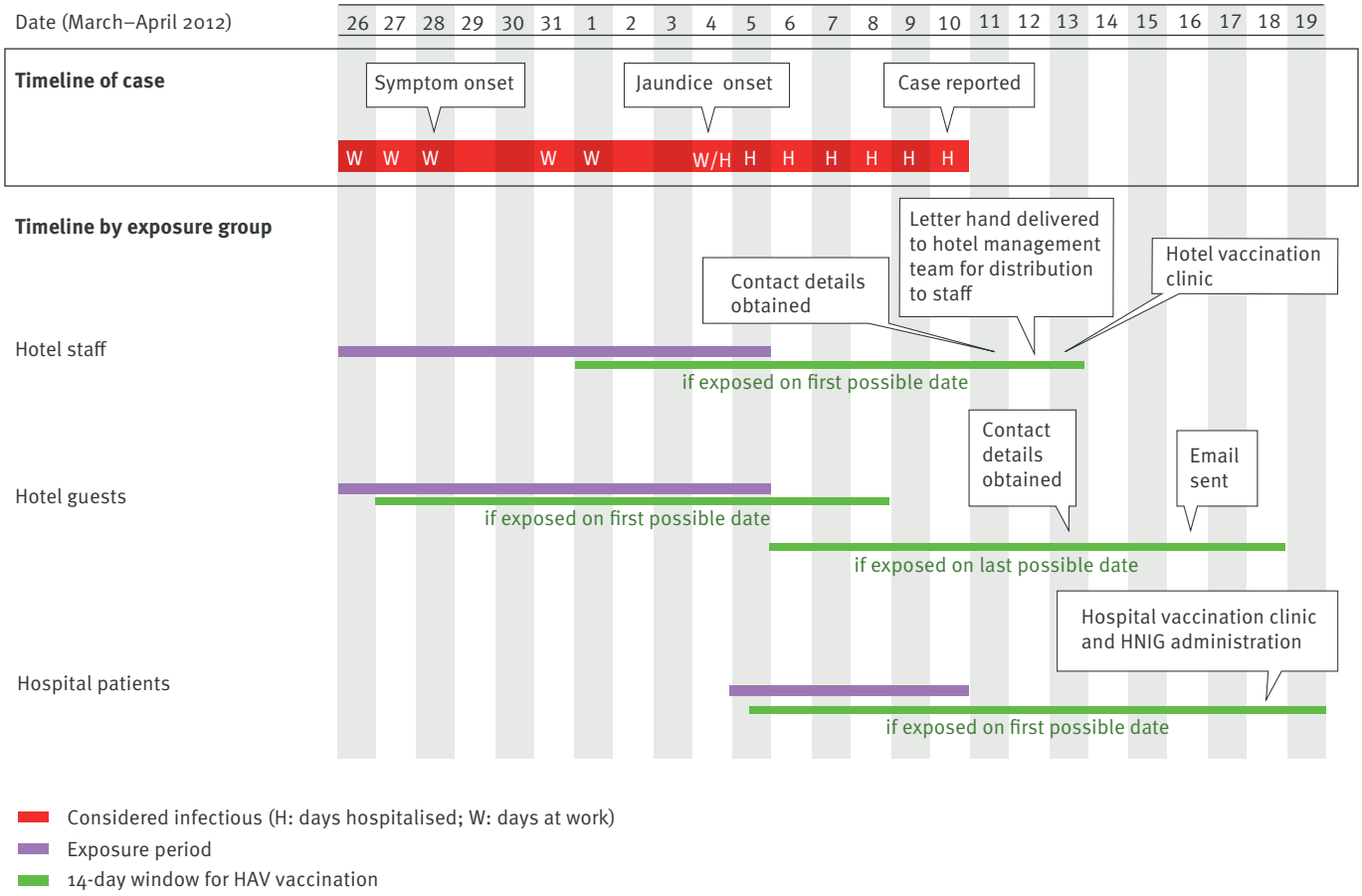
The patient was admitted to hospital with a seven-day history of fever, mild diarrhoea, vomiting and epigastric pain and developed jaundice on 4 April, which indicated a clinical suspicion of HAV infection. The patient was discharged home six days later once the clinical symptoms had resolved.

According to guidance from the Health Protection Agency (HPA) – now Public Health England since April 2013 – the case definition for a confirmed case of hepatitis A is a person who meets the clinical case definition (an acute illness with a discrete onset of symptoms AND jaundice or elevated serum aminotransferase levels) and is laboratory confirmed (IgM antibodies to HAV (anti-HAV) positive) [1]. The case was notified to the local Health Protection Unit when the infection was confirmed, although notification based on clinical suspicion would have increased the time for public health action and reduced the number of contacts for follow-up.

The infectious period is taken from two weeks before the onset of symptoms to one week after onset [1]. As the maximum incubation period is 50 days, a secondary case may not be symptomatic until 8 weeks after symptom onset of the first case [2]. In this incident, the case had worked for six days when they would have been infectious, preparing and handling uncooked food such as cold meats and bread rolls for the breakfast buffet and salads at the hotel's snack bar. Infectious foodhandlers with HAV, which is transmitted faeco–orally, are a recognised source of food-borne outbreaks [1,3]. The risk of transmission is increased if infectious foodhandlers prepare uncooked food or food that is handled after cooking [1-3]. In non-endemic countries such as the UK, where most of the population are susceptible

Figure

Timeline describing steps taken to identify individuals at risk following possible exposure to an acute case of hepatitis A, London, United Kingdom, April 2012



HAV: hepatitis A virus; HNIG: human normal immunoglobulin.

to HAV infection [4], outbreaks resulting from an infectious foodhandler have resulted in large numbers of secondary cases of HAV infection [5-7].

Secondary cases can be averted by timely administration of post-exposure HAV vaccination, up to two weeks after exposure, and human normal immunoglobulin (HNIG) can be given to those most vulnerable to infection (those aged over 50 years or with comorbidities) up to 28 days post exposure [1,8-10]. Given the infectiousness of HAV, and the opportunity to prevent secondary cases post exposure, the public health response to identification of an HAV-infected foodhandler can result in large-scale interventions [11,12].

Following the identification of the case in London in April 2012, we convened an incident response team, aiming to promptly identify individuals exposed to a potential infection risk in order to offer post-exposure vaccination and to inform hotel guests who were potentially at risk. We conducted a follow-up study aiming to identify any secondary cases of HAV infection among those exposed and hence to estimate the transmission risk in this incident. This would also add to the evidence base on the transmissibility of hepatitis A from infected foodhandlers.

Risk assessment and identification of exposed contacts

Our first step was to conduct a risk assessment according to guidance of the Health Protection Agency (HPA) – now Public Health England since April 2013 – which required consideration of the following: the symptom onset date for the case; duties carried out by the case; whether the case had undertaken a food hygiene course; the hotel's food preparation area and handwashing facilities; and the level of exposure of contacts and whether the possible exposure was single or continuous [1].

Symptom onset of the case was 28 March 2012, with appearance of jaundice on 4 April (Figure). The case was considered to be infectious from 14 March to 10 April. This corresponds to 14 days before the onset of

symptoms and 7 days after symptom onset. The case worked for six days while infectious, between 26 March and 4 April, and was symptomatic with diarrhoea and fever (temperature unknown) for three of those days (31 March, 1 and 4 April) (Figure). The case was hospitalised on 4 April, staying on an open ward from 5 April to 10 April, contrary to hospital infection control guidelines [1].

An inspection of the hotel kitchen and hygiene practices was conducted by an Environmental Health Officer and practices were assessed to be good, with adequate hand-washing facilities, appropriate staff food hygiene training and use of non-powdered latex gloves. The case was judged to have followed good hygiene practices, including appropriate hand-washing and wearing gloves when handling food, and had undertaken a food hygiene course.

Given their food preparation role, the number of contacts who had eaten food prepared by the foodhandler and the ongoing daily possible exposure of hotel staff, we considered that there were three groups of people at risk of infection: hotel staff, hotel guests and hospital patients (Figure). The foodhandler's close family members were vaccinated with HAV vaccine by a general practitioner (GP) on the day the case was notified.

The staff in the hospital ward in which the case stayed were deemed to be low risk as the case used toilet facilities independently, washing their hands after use, and there was no sharing of toilet facilities by the case and staff. Staff were assessed as using appropriate personal protective equipment, thus maintaining hospital infection control procedures where required by the hospital infection control team.

According to the HPA guidance, the time period for public health action is defined by the type of exposure. For continuous exposures, the definition of time since exposure is the number of days since onset of first symptoms, even if exposure actually started before this time during the pre-symptomatic infectious period. For single exposures, time since exposure should be calculated as either the number of days since onset of first symptoms in the index case or the number of days since exposure to the index case, whichever is the most recent. In the incident described here, the time since onset of first symptoms in the case was used, rather than the time since onset of jaundice, as the evidence for the post-exposure efficacy of HAV vaccine is based on its use within 14 days of first symptom onset in the index case [1].

Hotel staff were considered to have been exposed to an infection risk if they worked between 26 March and 5 April 2012, i.e. the period in which the case was infectious and at work, plus an additional day to include possible consumption of leftover food. These individuals were considered to have been potentially continuously exposed to the case, sharing bathroom facilities and eating breakfast and lunch prepared by the case. Although the case was at work on 28 March, their symptoms did not start until after their shift had ended: therefore, following the HPA guidance, their possible exposure was considered to have 'started' on 31 March, the first day the case was symptomatic and at work, until 5 April when they could have eaten leftover food prepared by the case on 4 April (Figure). Therefore, the 14-day window for issuing post-exposure vaccination started on 31 March.

Guests staying at the hotel between 25 March and 5 April were considered to have potentially had a 'single-point' exposure, as they could have eaten food prepared by the case during the case's infectious period. All guests had breakfast included in their tariff so those that arrived on 25 March may well have eaten breakfast and/or eaten from the snack bar on 26 March.

Hospital patients staying on the open ward with the case from 5 to 10 April were considered potentially to have had continuous exposure (Figure). While the HPA guidelines define the infectious period as lasting one week after symptom onset, thus implying the last date for infectivity was 4 April, we assessed that given the case was symptomatic with diarrhoea and sharing common bathroom facilities and the vulnerability of the other patients, all patients sharing the ward from 5 April to 10 April were at risk. They were given a letter informing them of their possible exposure, recommending them to be vaccinated and to visit their GP if they developed symptoms suggestive of HAV infection within the next 50 days. As it was considered that GPs would inform the public health team if any patients developed symptoms, the hospital patients were not included in our follow-up.

We considered that hotel guests had a lower risk of infection than hotel staff and hospital patients, as they did not share toilet facilities and had no direct contact with the case and the case's food hygiene was judged to be exemplary.

Public health action

We obtained a list of potentially exposed hotel staff, name, date of birth, address details and contact numbers on 11 April. Given the requirement for post-exposure vaccination to be issued within 14 days of the onset of symptoms in an index case, vaccination had to be arranged within two days to confer protection (Figure). With cooperation of hotel management and the local Primary Care Trust, we organised a vaccination clinic at the hotel on 13 April. All potentially exposed staff were contacted by letter, translated as required as many staff did not use English as a first language, which was hand delivered to the hotel management team on 12 April for distribution to both day and night hotel staff the same day. The letter explained the nature of the potential exposure and the recommendation of HAV vaccine and information on hepatitis A.

On 13 April, we obtained the contact details for guests who had made direct reservations and for booking agencies (who had arranged block bookings with the hotel). Contact details for guests who made direct bookings were limited to email addresses and we did not have postal addresses or country of residence. From email addresses, it was presumed that many guests were from outside of the UK. By this time, the 14-day post-exposure limit for vaccination had been exceeded for most guests (Figure). But it was not clear where the guests lived nor was it known how many other people had occupied each room, and it was logistically unfeasible to offer vaccination for all guests. We prepared a standard letter for all guests, providing information on the possible exposure and information on HAV that listed symptoms and advised them to seek medical attention if they developed symptoms suggestive of HAV infection [1]. We asked them to inform the local Health Protection Unit if they developed symptoms or were diagnosed with HAV infection by a health professional. We sent the letter by email to guests for whom we had email addresses and requested booking agencies to send the letter to their guests on our behalf.

We contacted other national public health agencies on 16 April to inform them of the potential risk of HAV transmission through the International Health Regulations (IHR) [13] National Focal Points and European Union Early warning and response system (EWRS) [14]. A dedicated email address was set up for use during the incident so that all responses were managed by the dedicated incident response team. We received email correspondence from 15 countries requesting further information, to which we replied to individually. Further to the emails received, we also had telephone conversations with two international public health departments. The reason for informing the public health authorities through the IHR National Focal Points and EWRS was to identify any secondary cases related to this incident following countries' own risk assessments, in the knowledge that they would contact the local Health Protection Unit with details of cases identified as having stayed at the hotel during the investigative period through their own reporting mechanisms.

Hospital staff organised vaccination on 19 April for potentially exposed patients still in hospital. All patients who needed HNIG were invited to attend a clinic at the hospital on the 19th to receive this (Figure). Where potentially exposed patients had been discharged from hospital, we telephoned them and their GPs to inform them of the possible exposure. Vaccination clinic times were arranged at the time of the call with the GP's practice and we advised patients to obtain vaccination at the practice at the arranged time.

Follow-up survey

At the end of May 2012, after the maximum incubation period for HAV (50 days after symptom onset in the case) had elapsed, we again contacted hotel staff and guests, requesting them to complete a brief survey, in order to identify any secondary cases of hepatitis A.
We set the following definitions for a secondary case of hepatitis A in this incident.

- Confirmed case: an individual who either worked in the same hotel as the infected foodhandler between 26 March and 5 April 2012 or stayed in the hotel between 25 March and 5 April or shared the hospital ward with the infected foodhandler between 5 April and 10 April and who reported having a blood test positive for HAV IgM, with the sample taken between 14 days after the first day of their exposure and 8 weeks after their first day of exposure.
- Probable case: an individual who either worked in the same hotel as the infected foodhandler between 26 March and 5 April 2012 or stayed in the hotel between 25 March and 5 April or shared the hospital ward with the infected foodhandler between 5 April and 10 April and who reported a clinical diagnosis of hepatitis A or jaundice, where the diagnosis was made between 14 days after the first day of their exposure and 8 weeks after their first day of exposure, and a blood test was not performed.
- For hotel guests, we created an online questionnaire using Select Survey [15]. In addition to questions on possible exposure (dates of stay, food eaten) and outcome (symptoms, clinical diagnosis, test results), we asked if they had previously received HAV vaccine, whether they took any action following our notification of their possible exposure and what their country of residence was, so we could check if there were any notifications from the country's public health authorities. Respondents were also asked to provide exposure and outcome information for guests sharing their room or for whom they booked rooms. We emailed a cover letter and hyperlink to the survey. For guests with missing email addresses we requested booking agencies to forward the email.

For hotel staff, we provided the hotel with paper questionnaires for self-completion by staff. A list of 74 staff with contact details was provided to us and non-responders were contacted by telephone. In addition to questions on outcome (symptoms, clinical diagnosis, test results), we asked if they had previously received HAV vaccine and what their country of birth was, as a proxy measure for likelihood of previous HAV infection.

Online survey responses were exported into Excel, as were the staff survey responses. Data cleaning and analysis was conducted in STATA v.12.

Results

Population exposed

We assessed that 83 hotel staff, 17 hospital patients and at least 887 hotel guests had possibly been exposed to HAV.

Public health action

All 83 potentially exposed hotel staff were vaccinated on 13 April 2012, within the 14-day time limit for the earliest possible exposure date, and seven also received HNIG. All 17 potentially exposed hospital patients were vaccinated within the 14-day time limit, and six also received HNIG. We sent emails about the incident to 642 individual guest email accounts and 11 block booking companies for onward distribution to around 245 guests (and received confirmation from the booking agencies that they had done so). The hotel guests resided in at least 31 countries.

Survey response

We sent the online survey directly to 642 guests and indirectly to 46 guests through their booking agencies. We were unable to send the survey to the rest (n=199) as their booking agencies were unwilling to participate. We received 137 responses, of which 125 were valid, including 27 who provided information for a total of 30 other guests who shared their rooms or bookings. The survey response was therefore considered to be 155/642 (24%). Three non-responders provided information on their exposure and outcome by email, so we had information on HAV status from 158 of the 887 guests potentially exposed. Of these 158 guests, 18 did not eat any food from the hotel during their stay and five did not stay overnight in the hotel during the exposure period. Therefore, 135 of the respondents were considered to have been exposed to food prepared by the case.

Staff surveys were self-completed by 19 staff. We contacted 55 non-responders for whom we received contact details and completed a further 14 telephone-administered questionnaires for non-responders (some of whom were no longer employed at the hotel); thus in total, 33 questionnaires were received.

Transmission of HAV to those exposed

No secondary cases of HAV were identified among those who were potentially exposed in this incident and responded to our follow-up survey. Given that potentially exposed hotel staff were immunised in time, the lack of transmission to these staff members was not very surprising.

Susceptibility to infection

Of the 135 hotel guests who responded to the survey and were considered to have been exposed, 65 (48%) may not have been susceptible to HAV infection as they either reported prior HAV vaccination or commented that they had previously been infected. Of the remaining 70, 32 reported that they were not vaccinated, and 38 did not know or did not answer this question.

Among the 33 hotel staff who responded, seven reported having previous HAV vaccination; nine were born in countries considered to be of high endemicity and 13 in intermediate-endemicity countries (using the World Health Organization categorisation of global HAV prevalence [16]). Therefore, at least 29 of the 83 potentially exposed staff may not have been susceptible to HAV infection.

Hotel guest response to the email alert about the incident

Of the 135 potentially exposed respondents, 35 (26%) visited a doctor following receipt of the letter. Five of the 35 were vaccinated in response to the alert, two additionally received HNIG and 21 were tested for HAV infection. Five did not see a doctor but checked their vaccination records. Of the 135 exposed respondents, 59 (44%) reported that they did not take any action on receipt of the letter; 36/135 (27%) potentially exposed respondents did not answer the question regarding their response to the alert.

Discussion

This large incident response required the commitment of considerable HPA resources, raised reputational concerns for the hotel and may have distressed the individuals contacted. Given the observed absence of secondary cases, it could be argued that such a response was not justified. We believe, however, that it was. Uncooked food prepared by an infected foodhandler with HAV is an established source of food-borne outbreaks [1,3,17]. The risk of transmission depends on foodhandler hygiene practices and the type of food they prepare [1,3,17]. It is difficult to accurately assess the hygiene standards of a foodhandler after exposure: in the incident reported here, the risk assessment was precautionary. Outbreaks where public health teams did not initiate post-exposure vaccination on the basis of satisfactory hygiene assessments have resulted in a failure to prevent secondary cases [5,7,18]. Public health professionals may overestimate the risk of transmission by foodhandlers since we assume that outbreaks due to infected foodhandlers are more likely to be published than the (probably frequent) incidents involving infected foodhandlers in which there are no secondary cases.

In this incident, the foodhandler demonstrated exemplary food hygiene and the food may have not been contaminated. However, given the potential risk, however small, we still needed to arrange post-exposure vaccinations. Additionally, the number of susceptible individuals who were potentially exposed in this incident may have been relatively low, as 68 of 158 guests and 29 of 33 hotel staff who responded were likely not to have been susceptible following prior vaccination or exposure.

The HPA guidance stated that HAV vaccination is required within a 14-day period from exposure, but due to delays in notification from the hospital and in obtaining information about guests from the hotel management team and the logistics of sending information through booking agencies, the 14-day window for vaccination (if exposed on the first possible date) would have been exceeded for most hotel guests. Although the hotel and most booking agencies were cooperative, there were delays and practical difficulties, with incomplete contact details and a room-booking system that did not capture the number of guests per room, so it is possible we have still underestimated the number potentially exposed.

Even if there had been no delays, would it have been justified to contact 887 guests and advise vaccination based on the risk assessment, given that we adjudged the risk to the guests as lower than that to the hotel staff? Would it have been still appropriate to take the action we did, i.e. advising guests to seek healthcare advice corresponding to their country of residence? Although the 14-day limit for vaccination had been exceeded for many guests when we informed them about the incident, we still advised them about their possible exposure. We believe it is important to be open with individuals about health hazards to which they may have been exposed. Furthermore, we considered that the letter might prompt earlier seeking of healthcare, diagnosis and management if individuals became symptomatic, thus potentially reducing the risk of tertiary cases.

Limitations of study

The main limitation was the low response rate to our survey and lack of follow-up of hospital patients in seeking to identify secondary cases of HAV infection. This, as with the logistic challenge of contacting guests, reflects the challenges of health protection responses and field epidemiology.

We did not manage to send the survey to all the individuals initially informed of their possible exposure, as some booking agencies declined to be involved and some hotel staff had left employment and changed their contact details. For hotel guests to whom we did manage to email the survey, the fact that it could only be sent 50 days after symptom onset (the maximum incubation period) may have affected their response. The low response rate may also reflect a lack of interest in the outcome and lack of collective concern as the hotel guests were not a connected group and may have no future contact with the hotel. Hotel staff had already been vaccinated so they may have not felt the need to respond to the survey. However, although the survey response rate was low, we also made use of other methods of identifying cases – by asking individuals in the first email communication to inform us if they became ill and by alerting other countries of the incident through the IHR National Focal Points and EWRS, through which we expected to be informed if they received a notification of a case of HAV infection linked to this incident. Despite this, we identified no secondary cases and therefore we found no evidence of transmission of HAV in this incident.

Conflict of interest

None declared.

Authors' contributions

Victoria Hall – joint first author planned, conducted and analysed the follow-up study; wrote and edited the manuscript. Asha Abrahams – joint first author; incident response; wrote first draft. Deborah Turbitt – incident response; advice on manuscript. Simon Cathcart – advice on follow-up study; Helen Maguire – supervision and advice on concept of study. Sooria Balasegaram – supervision of follow-up study; incident response. All authors revised the manuscript, approved the final version and agreed to be accountable for the work.

References

1. Thomas L, Hepatitis A Guidelines Group. Guidance for the prevention and control of hepatitis A infection. London: Health Protection Agency; 2009. Available from: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1259152095231
2. Klevens M, Lavanchy D, Spradling P. Hepatitis, Viral. In: Heymann DL, editor. Control of communicable diseases manual. 19th ed. Washington, DC: American Public Health Association; 2008. p. 278-300.
3. Advisory Committee on Immunization Practices (ACIP), Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55(RR-7):1-23.
4. Kurkela S, Pebody R, Kafatos G, Andrews N, Barbara C, Bruzzone B, et al. Comparative hepatitis A seroepidemiology in 10 European countries. Epidemiol Infect. 2012;140(12):2172-81.
5. Centers for Disease Control and Prevention (CDC). Foodborne hepatitis A--Missouri, Wisconsin, and Alaska, 1990-1992. MMWR Morb Mortal Wkly Rep. 1993;42(27):526-34.
6. Schmid D, Fretz R, Buchner G, König C, Perner H, Sollak R, et al. Foodborne outbreak of hepatitis A, November 2007-January 2008, Austria. Eur J Clin Microbiol Infect Dis. 2009;28(4):385-91.
7. Centers for Disease Control and Prevention (CDC). Foodborne transmission of hepatitis A--Massachusetts, 2001. MMWR Morbid Mortal Wkly Rep. 2003;52(24):565-7.
8. Health Protection Agency (HPA). Hepatitis A. Immunoglobulin handbook. London: HPA. [Accessed 22 Jul 2014]. Available from: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947366684
9. Winokur PL, Stapleton JT. Immunoglobulin prophylaxis for hepatitis A. Clin Infect Dis. 1992;14(2):580-6.
10. Sagliocca L, Amoroso P, Stroffolini T, Adamo B, Tosti ME, Lettieri G, et al. Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: a randomised trial. Lancet. 1999;353(9159):1136-9.
11. Department of Health (DH). The Health and Social Care Act 2008: Code of Practice on the prevention and control of infections and related guidance. London: DH; 2010. [Accessed 22 Jul 2014]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216227/dh_123923.pdf
12. Tricco AC, Pham B, Duval B, De Serres G, Gilca V, Vrbova L, et al. A review of interventions triggered by hepatitis A infected food-handlers in Canada. BMC Health Serv Res. 2006;6:157.
13. World Health Organization (WHO). International Health Regulations (2005). 2nd ed. Geneva: World Health Organization; 2008. [Accessed 29 Jul 2014]. Available from: http://whqlibdoc.who.int/publications/2008/9789241580410_eng.pdf?ua=1

14. European Commission Directorate-General for Health and Consumers (DG Sanco) Health Threat Unit. Early warning and response system. [Accessed 29 Jul 2014]. Available from: https://ewrs.ecdc.europa.eu/
15. classapps. SelectSurvey.net. classapps. [Accessed 29 Jul 2014]. Available from: http://selectsurvey.net/
16. World Health Organization (WHO). Hepatitis A. Surveillance and control. Geneva: WHO. [Accessed 29 Jul 2014]. Available from: http://www.who.int/csr/disease/hepatitis/whocdscsredc2007/en/index4.html
17. Fiore AE. Hepatitis A transmitted by food. Clin Infect Dis. 2004;38(5):705-15.
18. Massoudi MS, Bell BP, Paredes V, Insko J, Evans K, Shapiro CN. An outbreak of hepatitis A associated with an infected foodhandler. Public Health Rep. 1999;114(2):157-64.