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Afebrile meningoencephalitis with transient central facial paralysis due to Toscana virus infection, south-eastern France, 2014

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We report a case of meningoencephalitis caused by Toscana virus (TOSV) with central facial paralysis lasting over two days acquired in south-eastern France. The patient was not febrile either before or during the course of the disease. The diagnosis was established by both real-time RT-PCR and virus isolation with complete genome sequencing. This case emphasises the need to consider TOSV in non-febrile neurological syndromes in people living in or having travelled to the Mediterranean area.

In this report, we present a case of Toscana virus (TOSV) meningoencephalitis with a central facial paralysis and without fever, acquired in the close vicinity of Marseille, in southern France. This report should be a reminder for healthcare professionals to consider TOSV diagnosis even in afebrile patients with neurological symptoms.

Case report

On 11 July 2014, a French woman in her forties living in a small city at around 20 km from Marseille had a sudden onset of frontal and temporal lobe throbbing headaches upon awakening, without fever. Symptoms were severe and a few hours later she visited the emergency department of a local hospital with headache, nausea and photophonophobia. On admission, she was still non-febrile and the symptoms were persisting despite oral intake of paracetamol in hospital (1,000 mg). The patient's medical history consisted of asthma during childhood, and no history of recent travel abroad.

Neurological examination revealed (i) a slight stiff neck, (ii) a discrete left central facial paralysis, and (iii) the absence of abnormalities of cranial nerves except discrete left central facial paresis, sensorimotor loss, cerebellar or pyramidal syndromes. She received 20 mg intramuscular nefopam hydrochloride which alleviated the pain.

A lumbar puncture was performed and the analysis showed that the cerebrospinal fluid (CSF) was clear; it contained 475 cells/mm^3 (norm: < 10 cells/mm^3) (90% lymphocytes), and showed hypoglycorrhachia at 2.4 mmol/L (norm: > 3mmol/L)) and hyperproteinorachia at 1.78 g/L (norm: 0.4 g/L).

A diagnosis of meningoencephalitis was determined. The patient was treated with acyclovir, ceftriaxone and amoxicillin, and was transferred to the neurology department of the same hospital.

Further laboratory diagnostic and radiological tests

To search for the cause of the meningoencephalitis, a series of laboratory tests were performed. Liver function tests and ionogram were normal. Blood levels of glucose, urea nitrogen, albumin, creatinine, lactates, troponin T, C-reactive protein, and procalcitonin were normal. However, creatinine phosphokinase (CPK) level was moderately increased at 368 U/L (norm: < 170 U/L). There was a slight increase of fibrinogen rate at 4.76 g/L (norm: 2–4 g/L). Prothrombin time was 92% (norm: 70–100%). Blood cell count was 9,100 leukocytes/µL (norm: 4,000–10,000 leukocytes/µL) (81.5% neutrophils and 13.0% lymphocytes), haemoglobin 13.4 g/dL, and the platelet count 251,000/µL.

Blood cultures collected on day 1 remained sterile. PCR for *Listeria monocytogenes* was negative. CSF Gram staining and culture remained negative; real-time PCR for *Neisseria meningitidis*, *Streptococcus pneumoniae*, herpes simplex virus, varicella-zoster virus, and real-time RT-PCR for West Nile virus and enteroviruses were negative. In contrast, real-time RT-PCR for TOSV was positive (Ct 28) whereas there was no IgG or IgM specific for TOSV in the serum collected at the acute stage. No convalescent serum could be obtained.

As isolation of virus from clinical samples is the gold standard for diagnosis, although seldom performed,

the CSF was inoculated onto Vero cells. Five days later, a clear cytopathic effect was observed and virus isolation was confirmed by the complete genetic characterisation using next-generation sequencing (NGS) based on Ion Torrent technology. The full-length sequence was deposited into the GenBank database. Genetic and phylogenetic analyses using the complete sequence of this strain demonstrate that our patient was infected by a TOSV strain that belongs to the lineage B.

A brain magnetic resonance imaging (MRI) scan indicated a contrast enhancement on brainstem, probably of vascular origin. A second MRI was planned to distinguish between telangectasia and developmental venous abnormality. Computed tomography (CT) scans and the electroencephalogram (EEG) were normal.

On day 2, headache intensity had reduced and the facial paralysis was no longer present upon clinical examination. Antiviral and antibiotic treatments were stopped when PCR for TOSV proved to be positive. On day 3, the result of the neurological examination was normal; the patient complained of general fatigue and residual headaches reactive to paracetamol; she was discharged from hospital with pain relief medication.

Background

TOSV is an arthropod-borne virus that belongs to the genus *Phlebovirus* within the family *Bunyaviridae*. TOSV is transmitted from phlebotomine sandflies belonging to the subgenus *Larroussius*, such as *Phlebotomus perniciosus* and *Phlebotomus perfiliewi*, although other species might be involved in the circulation and maintenance of TOSV in nature [1]. The geographical area where the presence of TOSV is assessed directly (virus isolation or RT-PCR detection and sequence data) is much larger at present than 10 years ago. Roughly all countries bordering the Mediterranean Sea (southern Europe, northern Africa, and Middle East) are concerned. Since TOSV is an arbovirus (arthropod-borne) human cases of TOSV infection only occur during the period of activity of its sandfly vector, hence April to November, with peaks during the hottest period from July to September. Although TOSV can sometimes be responsible for mild febrile illness, it is commonly causing neurovirulent infections such as meningitis or meningoencephalitis. TOSV is one of the main viral causes of aseptic meningitis during the hot season in south-eastern France when enteroviruses and herpesviruses are most prominent [2,3].

Discussion and conclusion

In addition to the case described here, a bibliographic search in PubMed database from 1971 until now retrieved only two cases of facial paralysis in the context of TOSV infection: (i) a 30-year-old male patient admitted with headache and fever who developed an abrupt right facial paralysis [4], (ii) and a 68-year-old man returning from a 10-day stay in central Italy who developed a left central facial paralysis and a cerebellar syndrome [5]. The clinical manifestations observed in these two cases were co-incident with fever. The absence of fever from the onset of the disease until the favourable outcome is quite atypical and is noteworthy.

In contrast with the common belief that virus isolation is of poor sensitivity for diagnostic purpose [6], this case is the third successive case of a TOSV neuroinvasive infection for which virus isolation has been successful despite moderate or low virus load in the specimen [5, data not shown]. Accordingly, TOSV isolation should be attempted, whenever possible, as it is the gold standard technique for diagnosis, and it allows further genetic and phylogenetic documentation.

There are three genotypes of TOSV, more or less depending upon the geographical origin: lineage A strains were reported in Italy, France, Tunisia and Turkey; lineage B strains originated from Portugal, Spain, France and Morocco [7]; the lineage C was described recently in Croatia and Greece although the virus has not been isolated so far. In all the countries around the Mediterranean Sea TOSV is endemic and should not be considered anymore as an emerging pathogen but rather as a neglected pathogen. As previously reported, also south-eastern France is endemic for TOSV [8,9]. The average duration of the disease is seven days (3 to 10 days) [2]. Our patient was no exception to this rule. She acquired TOSV infection in July, i.e. during the period when the vector is more active. Encephalitis is frequently encountered in neuroinvasive infections due to TOSV [10]. Of interest is the hypoglycorachia that is unusual with viruses although sometimes reported with TOSV [10].

In conclusion, this case is of interest for the following reasons: (i) it is the first description of a TOSV meningoencephalitis without concomitant febrile syndrome, (ii) it is one of the few cases associated with facial paralysis, (iii) it emphasises the need to consider TOSV as possible cause of typical and especially atypical neurological syndromes in patients living in or returning from TOSV endemic areas, and consider it even in the absence of febrile syndrome.

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Conflict of interest

None declared.

Authors' contributions

Marion Cécile MARLINGE: collected laboratory data and wrote the draft.
Lydie CRESPY: clinical aspects.
Christine ZANDOTTI: laboratory data monitoring.
Géraldine PIORKOWSKI: sequencing and genetic analysis.
Elsa KAPHAN: clinical aspects.
Rémi N. CHARREL: wrote the manuscript.
Laetitia NINOVE: wrote the manuscript and organised the data.

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Preparedness for admission of patients with suspected Ebola virus disease in European hospitals: a survey, August-September 2014

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In response to the Ebola virus disease (EVD) outbreak in West Africa, the World Health Organization has advised all nations to prepare for the detection, investigation and management of confirmed and suspected EVD cases in order to prevent further spread through international travel. To gain insights into the state of preparedness of European hospitals, an electronic survey was circulated in August–September 2014 to 984 medical professionals representing 736 hospitals in 40 countries. The survey addressed the willingness and capacity to admit patients with suspected EVD as well as specific preparedness activities in response to the current Ebola crisis. Evaluable responses were received from representatives of 254 (32%) hospitals in 38 countries, mostly tertiary care centres, of which 46% indicated that they would admit patients with suspected EVD. Patient transfer agreements were in place for the majority of hospitals that would not admit patients. Compared with non-admitting hospitals, admitting hospitals were more frequently engaged in various preparedness activities and more often contained basic infrastructural characteristics such as admission rooms and laboratories considered important for infection control, but some gaps and concerns were also identified. The results of this survey help to provide direction towards further preparedness activities and prioritisation thereof.

Introduction

The unprecedented and devastating epidemic of Ebola virus disease (EVD) in West Africa, with over 15,000 reported cases and nearly 5,500 deaths as of 21 November 2014 [1], has ignited increasing global concerns about the potential introduction and further spread of the disease by international travel and repatriation [2–4]. For this reason, the World Health Organization (WHO) has advised all nations, including those not directly neighbouring currently-affected countries, to prepare for the detection, investigation and management of confirmed and suspected EVD cases [4]. In view of the non-specific nature of initial symptoms, suspected patients essentially include all travellers with unexplained febrile illness recently arrived from areas with ongoing EVD transmission, particularly when accompanied by gastrointestinal symptoms. The current assessment is that travel-associated cases will remain rare across Europe, but that the occurrence of EVD in returning healthcare workers is a realistic scenario [5,6]. The recent experiences with both types of EVD cases in the United States and Europe, with local transmission to healthcare workers, illustrate the importance of being prepared [7,8].

To gain insights into the preparedness of European hospitals and identify potential gaps in preparedness at hospital level, we conducted a survey of hospitals in 40 European and western Asian countries, focusing on the willingness and capacity to admit patients with suspected EVD and on specific preparedness activities of hospitals in response to the current Ebola crisis. It should be emphasised that the survey did not address preparedness for EVD at national levels but was solely intended to explore the preparedness at the hospital level.

This survey is an initiative of the PREPARE project. PREPARE (Platform for European Preparedness Against (Re-)emerging Epidemics) is an European Union

Table 1

Admission, guidelines and preparedness for patients with suspected Ebola virus disease in European hospitals, results from survey of representatives from 236 hospitals in 38 European and western Asian countries, August–September 2014

	Total (%)	Would admit patient with suspected EVD (%)	Would not admit patient with suspected EVD (%)	Do not know (%)	p-value
Hospital type	236	111 (47.0)	99 (42.0)	26 (11.0)	-
Primary	5 (2.1)	2 (1.8)	2 (2.0)	1 (3.8)	-
Secondary	46 (19.5)	13 (11.7)	23 (23.2)	10 (38.5)	-
Tertiary	185 (78.4)	96 (86.5)	74 (74.7)	15 (57.7)	-
National guidelines					
Yes	181 (76.7)	90 (81.1)	75 (75.8)	16 (61.5)	0.047
No	30 (12.7)	14 (12.6)	13 (13.1)	3 (11.5)	-
Do not know	25 (10.6)	7 (6.3)	11 (11.1)	7 (26.9)	-
Topics covered					
Triage criteria	165 (91.2)	83 (92.2)	70 (93.3)	12 (75.0)	0.78
EBOV diagnostics	160 (88.4)	84 (93.3)	64 (85.3)	12 (75.0)	0.09
Other diagnostics	143 (79.0)	79 (87.7)	54 (72.0)	10 (62.5)	0.01
Infection control	174 (96.1)	89 (98.9)	72 (96.0)	13 (81.2)	0.23
Clinical management	137 (75.7)	76 (84.4)	52 (69.3)	9 (56.2)	0.02
Hospital guidelines					
Yes	153 (64.8)	93 (83.8)	52 (52.5)	8 (30.8)	‹0.01
No	60 (25.4)	13 (11.7)	36 (36.4)	11 (42.3)	-
Do not know	23 (9.7)	5 (4.5)	11 (11.1)	7 (26.9)	-
Topics covered					
Triage criteria	146 (95.4)	90 (96.8)	49 (94.2)	7 (87.5)	0.46
EBOV diagnostics	123 (80.4)	82 (88.2)	38 (73.1)	3 (37.5)	0.02
Other diagnostics	133 (86.9)	90 (96.8)	38 (73.1)	5 (62.5)	‹0.01
Infection control	151 (98.7)	93 (100)	51 (98.1)	7 (87.5)	0.18
Clinical management	118 (77.1)	79 (84.9)	34 (65.4)	5 (62.5)	‹0.01
Preparedness efforts					
Revision protocols	168 (71.2)	95 (85.6)	64 (64.6)	9 (34.6)	‹0.01
Training HCW	131 (55.5)	81 (73.0)	46 (46.5)	4 (15.4)	‹0.01
Hospital OMT	121 (51.3)	79 (71.2)	41 (41.4)	1 (3.8)	‹0.01
National OMT	89 (37.7)	57 (51.4)	31 (31.3)	1 (3.8)	‹0.01
Exercise	67 (28.4)	51 (45.9)	16 (16.2)	0 (0)	‹0.01

EVD: Ebola virus disease; EBOV: Ebola virus; HCW: healthcare worker; OMT: outbreak management team.

Primary care: general practice and basic district hospital services; secondary care: district hospitals with basic specialty functions; tertiary care: specialised care, usually on referral from primary or secondary care, with facilities for special investigations and treatment.

(EU)-funded project that aims to establish preparedness for harmonised clinical research studies on epidemic infectious diseases, hence providing real-time evidence for clinical management of patients and to inform public health responses (www.prepare-europe.eu). PREPARE is a partnership of established and developing European clinical research networks, covering primary care (GRACE and TRACE) and hospital care (CAPNETZ, COMBACTE, ESICM and PENTA) in more than 40 European countries, including all EU Member States. The survey was performed in above-mentioned hospital care networks.

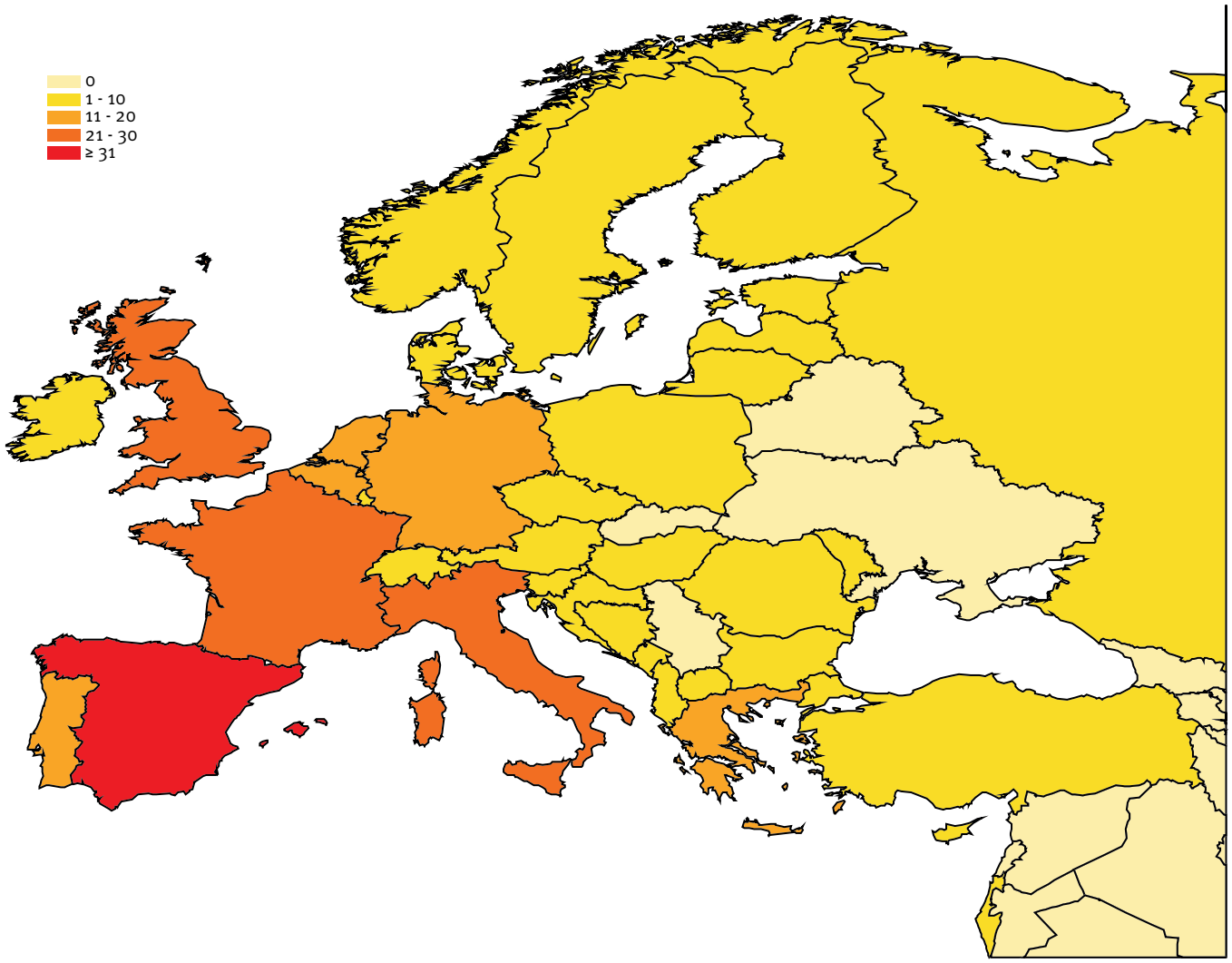
Methods

Survey

A questionnaire was developed in English, addressing: characteristics of the hospital such as the geographic location, type (primary, secondary or tertiary care) and size of the hospital; the availability and content of national and hospital guidelines or protocols for the management of patients with suspected or confirmed haemorrhagic fever; the performance of preparedness activities in response to the Ebola crisis (e.g. revision of protocols, exercises to test the protocols, formation of a hospital outbreak management team, training of healthcare workers, or immediate plans to do so); and arrangements for Ebola virus (EBOV) diagnostics.

Figure 1

Geographic distribution and numbers of responding hospitals, survey on willingness and capacity to admit patients with suspected Ebola virus disease, August–September 2014 (n=236)



In addition, the questionnaire asked whether hospitals would, in principle, admit patients with suspected EVD, and if not, whether local or national agreements were in place for transfer to another hospital. For hospitals that would admit patients with suspected EVD, additional questions were asked about the characteristics of admission rooms (e.g. presence of an anteroom, negative pressure, high-efficiency particulate air (HEPA) filtration). An open question was added to capture specific suggestions or needs in relation to EVD preparedness that could be addressed by the PREPARE project. Respondents could indicate whether or not permission was granted to use the anonymised results in reports or publications. The complete questionnaire is available upon request from the authors.

After pilot testing in three hospitals, an online link to the electronic questionnaire was circulated by email to 984 medical professionals representing 736 hospitals in 38 European and 2 western Asian countries (Turkey and Israel). All hospitals were affiliated with the PREPARE project through membership of one or more of the following clinical research networks: CAPNETZ (www.capnetz.de), COMBACTE (www.combacte.com), ESICM (www.esicm.org), and PENTA (www.penta-id.org).

The survey was started on 27 August 2014 and closed on 19 September 2014. Reminders to complete the survey were sent weekly during this three-week survey period.

Analysis

Descriptive statistics were used to analyse the survey data at the hospital level. In case of discrepant responses from multiple representatives of the same hospital, affirmative or negative answers took precedence over 'do not know' replies. Comparisons were made between hospitals that would admit patients with suspected EVD and those that would not or did not know. In addition, comparisons were made between hospitals in the four regions of Europe

(eastern, northern, southern, western) and western Asia, as defined by the United Nations Statistics Division's Geoscheme [9]. Differences between groups were analysed using chi-squared statistics. A p-value of less than 0.05 was considered significant. Analyses were performed using Microsoft Excel version 14.4.3 (Microsoft Corporation).

Results

Survey characteristics

Responses were received from 266 out of 984 (27%) medical professionals of whom 12 did not provide permission to use the data for reporting. The remaining 254 respondents represented 236 of 736 hospitals (32%) in 38 European and western Asian countries. The majority of respondents were intensivists (122, 48%), followed by internists/infectious disease specialists (49, 19%) and clinical microbiologists (42, 17%). Among the remaining respondents were infection control specialist (19, 8%) and paediatricians (9, 4%). Hospitals represented in the survey were mostly tertiary care centres (78%) and were widely distributed across Europe and western Asia (Table 1, Figure 1).

Admission of patients with suspected EVD and characteristics of admission rooms

Of 236 hospitals, 111 (47%) stated that they would admit suspected EVD patients, 99 (42%) indicated that they would not admit such patients, and 26 (11%) did not know whether such patients would be admitted (Table 1). In the 99 hospitals indicating they would not admit patients, local or national agreements for transfer of patients were in place in the majority (local 25 (25%), national 67 (68%)). Admission rooms of most of the 111 admitting hospitals, the majority of which were tertiary care centres (87%), had an anteroom (87%), availability of negative pressure (69%), and/or the presence of dedicated ventilation systems (59%) (Figure 2A). Less than half used HEPA filtration of exhausted air (42%). In five hospitals (5%), none of these assets were available.

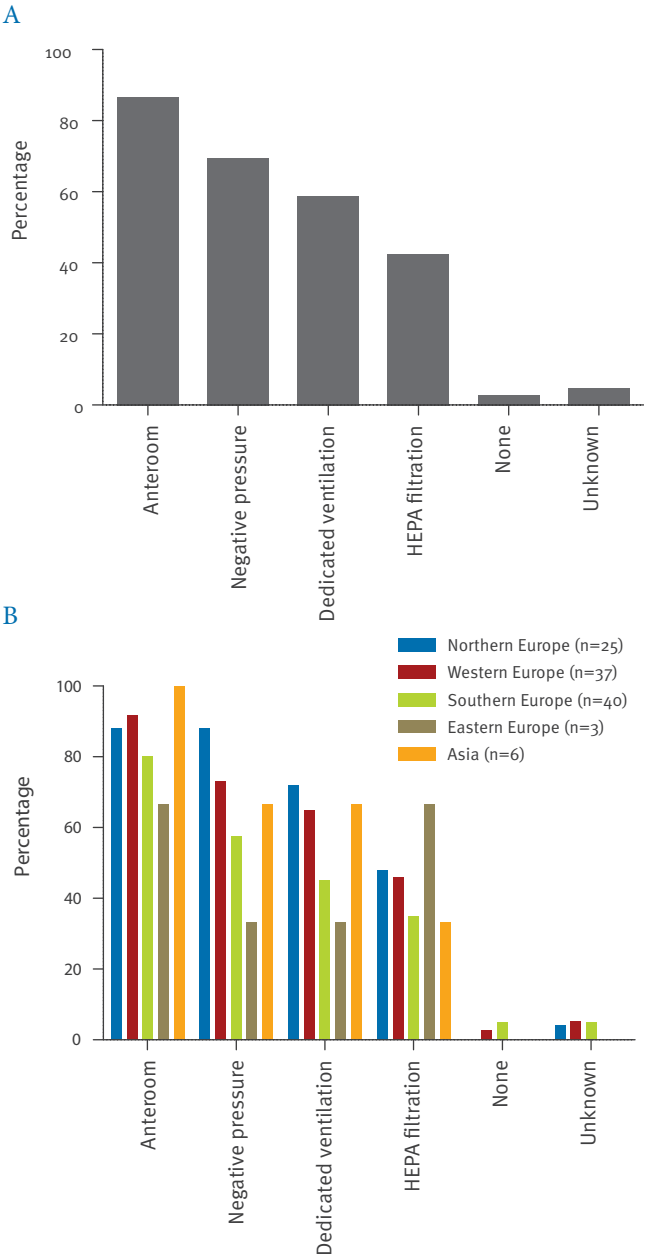
National and hospital guidelines for management of EVD patients

Respondents from 181 hospitals (77%) were aware of the existence of national guidelines for management of patients with haemorrhagic fever (including EVD) while 30 hospitals (13%) indicated these were not available. The remaining respondents did not know (Table 1). Available guidelines were based on those from WHO (63%), the European Centre for Disease Prevention and Control (ECDC) (43%) and/or the US Centers for Disease Control and Prevention (CDC) (34%), and covered triage criteria and infection control practices in more than 90% of guidelines, while diagnostics and clinical management were covered less frequently (Table 1).

Local hospital guidelines were available in 153 of 236 hospitals (65%), not available in 60 hospitals (25%) and the remaining respondents did not know (Table 1).

Figure 2

Characteristics of admission facilities in hospitals admitting Ebola virus disease-suspected patients, survey on willingness and capacity to admit patients with suspected Ebola virus disease, August–September 2014 (n=111)



HEPA: high-efficiency particulate air.
Percentages are represented overall (A) and per region (B).

Guidelines were based on national guidelines in 81% and on international guidelines in the remaining cases (19%). Similar to national guidelines, triage criteria and infection control practices were covered in more than 95% of local guidelines with less frequent coverage of other topics.

The availability of national, and even more so of hospital guidelines was highest in hospitals that would

Table 2

Laboratory infrastructure and diagnostics for patients with suspected Ebola virus disease in European hospitals, results from survey of representatives from 236 hospitals in 38 European and western Asian hospitals, August–September 2014

	Total (n=236) (%)	Would admit patient with suspected EVD (n=111) (%)	Would not admit patient with suspected EVD (n=99) (%)	Do not know (n=26) (%)
Microbiology laboratory present	231 (97.9)	109 (98.2)	97 (98.0)	25 (96.2)
BSL2				
Yes	132 (57.1)	76 (69.7)	49 (50.5)	7 (28.0)
No	26 (11.3)	9 (8.3)	16 (16.5)	1 (4.0)
Do not know	73 (31.6)	24 (22.0)	32 (33.0)	17 (68.0)
BSL3				
Yes	56 (24.2)	39 (35.8)	14 (14.4)	3 (12.0)
No	93 (40.3)	43 (39.4)	46 (47.4)	4 (16.0)
Do not know	82 (35.5)	27 (24.8)	37 (38.1)	18 (72.0)
Ebola virus diagnostics				
On site	17 (7.2)	14 (12.6)	1 (1.0)	2 (7.7)
National reference laboratory	140 (59.3)	64 (57.7)	65 (65.7)	11 (42.3)
International reference laboratory	30 (12.7)	22 (19.8)	8 (8.1)	0 (0)
Not performed	4 (1.7)	3 (2.7)	1 (1.0)	0 (0)
Do not know	45 (19.1)	8 (7.2)	24 (24.2)	13 (50.0)

EVD: Ebola virus disease; BSL: biosafety level.

admit patients with suspected EVD compared with those that would not admit patients or did not know (Table 1).

Laboratory infrastructure and Ebola virus diagnostics

Microbiology laboratories were present in nearly all hospitals (98%) (Table 2). In these laboratories, biosafety level (BSL) 2 and 3 facilities were available in 57% and 24%, respectively and not available in 11% and 40%, respectively. In the remaining cases respondents were not aware of the biosafety levels of the laboratory (32% and 36%, respectively). Availability of BSL 2 and 3 facilities was higher in hospitals that would admit patients (70% and 36%, respectively) compared with those that did not (51% and 14%, respectively).

EBOV diagnostics were performed on site in 17 hospitals, which included 14 hospitals that would admit patients, 1 that would not admit patients and 2 that did not know. For the majority of remaining hospitals, agreements and procedures were in place for performance of Ebola diagnostics in national (59%) or international (13%) reference laboratories.

Preparedness activities

Preparedness activities in response to the EVD outbreak included revision of hospital protocols or guidelines in 168 hospitals (71%), education and training of healthcare workers (HCWs) in 131 (56%), formation of an outbreak management team (OMT) in 121 (51%) and participation in regional or national preparedness committees in 89 (38%) (Table 1). In 67 hospitals (28%), exercises to test procedures and protocols were completed or planned in the immediate future. All preparedness activities were performed more frequently in hospitals that would admit patients (Table 1, Figure 3).

Regional differences in Europe

Northern and western Europe had the highest proportions of hospitals that would admit patients with suspected EVD (57% and 56% respectively) and this proportion was lowest in eastern European states (12%) (Table 3). Differences were noted between regions with respect to availability of national and local guidelines, laboratory infrastructure and preparedness activities, with highest frequencies mostly observed in western European countries, followed by southern, northern and eastern European states (Table 3, Figure 2B).

Inventory of needs and suggestions

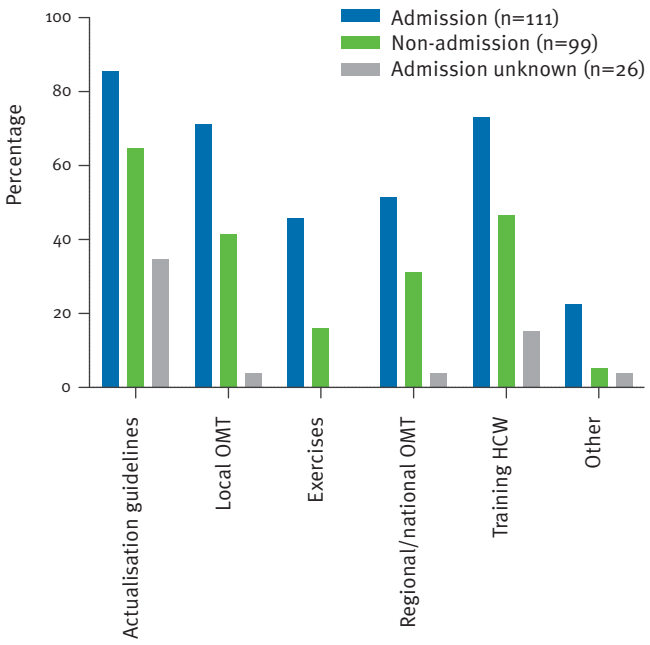
Suggestions were received from 60 of 266 respondents, of whom 42 (70%) emphasised the need for education, information and harmonised guidelines for infection control, diagnostic procedures and clinical management. Most remaining suggestions pertained to the need for support and clinical research in affected West African countries.

Discussion

Our exploratory survey was initiated less than three weeks after WHO's Public Health Emergency of International Concern (PHEIC) declaration on 8 August 2014 [4], to provide initial insights into the state of EVD preparedness in European hospitals at that time. It should be emphasised that this survey explored the

Figure 3

Preparedness activities for patients with suspected Ebola virus disease in European hospitals, results from survey of representatives from 236 hospitals in 38 European and western Asian countries, August–September 2014



HCW: healthcare workers; OMT: outbreak management team.

Percentages are shown separately for admitting and non-admitting hospitals and for those not aware whether Ebola virus disease-suspected patients would be admitted.

preparedness to admit patients with suspected EVD at the level of hospitals and no inferences can be made from the results of this survey with regards to preparedness at national levels.

At the time of the survey (August–September 2014), the vast majority of admitting hospitals were engaged in various preparedness activities such as revision of protocols, training of HCWs and implementation of a local OMT. Recent healthcare-associated cases in the US and Spain have demonstrated the importance of training of HCWs in personal protective equipment regimens [7,8], and the finding that 27% of hospitals indicated they had not performed or planned training of HCWs shows room for improvement. At the time of the survey, 46% of admitting hospitals had planned or carried out exercises to test protocols. Given the complexity of issues surrounding admission of patients with suspected EVD, such exercises are essential. Preparedness activities were significantly less frequent in hospitals that would not admit patients or were not sure whether they would. Although unlikely, suspected EVD patients may present at any healthcare setting, and so awareness of initial management of suspected cases is important for all settings, including non-admitting centres. Almost all respondents indicated the availability of initial triage protocols, suggesting that undetected hospitalisations are unlikely. However, some training of HCWs for this scenario also in non-admitting hospitals seems prudent.

Technical characteristics of admission rooms varied across admitting hospitals, with differences observed between European regions. Admission rooms in a substantial proportion of hospitals lacked one or more characteristics considered to be important for control of highly infectious pathogens and 5% of hospitals appeared to have none of these characteristics. The required conditions for treatment of EVD patients is an issue of some debate: EBOV is not considered to be transmitted by aerosol, which is the underlying assumption in the design of high-containment patient rooms, but the intensive-care setting may include exceptional circumstances where infectious droplets or aerosols may be generated, e.g. during intubation and ventilation [10,11]. Therefore, while standard contact precautions would generally suffice for management of EVD patients, this may differ for such high-care settings. Our analysis did not provide this level of detail. Of note, the proportions of hospital admission rooms with characteristics such as the presence of an anteroom and availability of negative pressure were higher than observed in a previous survey of emergency departments in 14 European countries (87% and 69% vs 46% and 42%, respectively) but, not unexpectedly, lower than those observed in a survey of 48 isolation facilities for highly infectious diseases in 16 European countries (100% and 90% respectively) [12,13].

With regards to laboratory infrastructure, our survey data lacked the resolution to assess in detail whether and to what extent laboratories are compliant with recommendations from WHO, ECDC and/or CDC. However, it should be noted that 8% of admitting hospitals did not appear to have the absolute minimal level laboratory containment (BSL2) needed for handling specimens from EVD patients, which indicates less than optimal capacity for biocontainment during processing blood specimens for EBOV diagnostics and/or routine supportive diagnostics. During the course of illness, clinical specimens can contain very high viral loads for extended periods of time [14,15], and a careful assessment of the risks for processing such specimens in the local laboratories is crucial. Laboratories without BSL2 containment should therefore be encouraged to upgrade their facilities and refer samples to laboratories with BSL2 or preferably BSL3 facilities in the meantime.

Availability of national and local hospital guidelines for management of patients with (suspected) haemorrhagic fever was indicated by a majority of respondents with highest availabilities observed in admitting hospitals and in western European countries. Of note, discordant responses from the same country in relation to availability of national guidelines were observed on several occasions (data not shown), indicating that differences in awareness of guidelines exist within countries. This might illustrate the importance and

Table 3

Geographical comparisons of hospitals and willingness and capacity to admit patients with suspected Ebola virus disease, results from survey of representatives from 236 hospitals in 38 European and western Asian countries, August–September 2014

	Geographical region[a]				
	Northern Europe	Southern Europe	Eastern Europe	Western Europe	Western Asia
Number of hospitals (%)					
Received questionnaire	138	257	106	219	16
Responded	44 (31.8	93 (36.2)	26 (24.5)	66 (30.1)	7 (43.8)
Would admit suspected EVD patient	25 (56.8)	40 (43.0)	3 (11.5)	37 (56.1)	6 (85.7)
Would not admit suspected EVD patient	14 (31.8)	41 (44.1)	18 (69.2)	25 (37.9)	1 (14.30
Do not know	5 (11.4)	12 (12.9)	5 (19.2)	4 (6.1)	0 (0)
National guidelines					
Yes	34 (77.3)	71 (76.3)	12 (46.2)	57 (86.4)	7 (100)
No	3 (6.8)	15 (16.1)	6 (23.1)	6 (9.1)	0 (0)
Do not know	7 (15.9)	7 (7.5)	8 (30.8)	3 (4.5)	0 (0)
Hospital guidelines					
Yes	26 (59.1)	57 (61.3)	12 (46.2)	53 (80.3)	5 (71.4)
No	11 (25.0)	28 (30.1)	10 (38.5)	10 (15.2)	1 (14.3)
Do not know	7 (15.9)	8 (8.6)	4 (15.4)	3 (4.5)	1 (14.3)
Preparedness efforts					
Revision of protocols	26 (59.1)	65 (69.9)	14 (53.8)	56 (84.8)	6 (85.7)
Training HCWs	17 (38.6)	50 (53.8)	15 (57.7)	44 (66.7)	5 (71.4)
Hospital OMT	18 (40.1)	46 (49.5)	9 (34.6)	43 (65.2)	5 (71.4)
National OMT	10 (22.7)	33 (35.5)	6 (23.1)	37 (56.1)	3 (42.9)
Exercise	8 (18.2)	24 (25.8)	3 (11.5)	31 (47.0)	1 (14.3)
Admission rooms					
Anteroom	22 (88.0)	32 (80.0)	2 (66.7)	34 (91.9)	6 (100)
Negative pressure	22 (88.0)	23 (57.5)	1 (33.3)	27 (73.0)	4 (66.7)
Dedicated ventilation	18 (72.0)	18 (45.0)	1 (33.3)	24 (64.9)	4 (66.7)
HEPA filtration	12 (48.0)	14 (35.0)	2 (66.7)	17 (45.9)	2 (33.3)
None	0 (0)	2 (5.0)	0 (0)	1 (2.7)	0 (0.0)
Unknown	1 (4.0)	2 (5.0)	0 (0)	2 (5.4)	0 (0.0)
Laboratories					
Microbiology laboratory	44 (100)	92 (98.9)	24 (92.3)	65 (98.5)	7 (100)
BSL2					
Yes	18 (40.9)	51 (55.4)	11 (45.8)	46 (70.8)	6 (85.7)
No	4 (9.1)	16 (17.4)	2 (8.3)	3 (4.6)	1 (14.3)
Unknown	22 (50.0)	25 (27.2)	11 (45.8)	16 (24.6)	0 (0)
BSL3					
Yes	10 (22.7)	19 (20.7)	2 (8.3)	24 (36.9)	1 (14.3)
No	11 (25.0)	44 (47.8)	11 (45.8)	21 (32.3)	6 (85.7)
Unknown	23 (52.3)	29 (31.5)	11 (45.8)	20 (30.8)	0 (0)

BSL: biosafety level; EVD: Ebola virus disease; HCW: healthcare worker; HEPA: high-efficiency particulate air; OMT: outbreak management team.

[a] European regions according to United Nations Geoscheme (United Nations Statistics Division, http://unstats.un.org/unsd/methods/m49/m49regin.htm) [7]. Included Asian countries are Israel and Turkey.

challenges of dissemination of guidelines, also at national levels. At the same time, the need and desire for guidance was illustrated by responses to our open request for suggestions, the vast majority of which emphasised a need for education, information and harmonised guidelines, especially for diagnostic issues and clinical management of patients.

Our survey has several limitations. First of all, although the geographical distribution of participating hospitals across Europe was excellent, the survey results may not be fully representative of European medical professionals and hospitals for several reasons. The survey was circulated only to hospitals actively participating in established clinical networks and these may not be representative of European hospitals overall. Furthermore, the response rate was fairly low: responses were received from 27% of colleagues representing 32% of hospitals, which means that the survey results may also not be fully representative of hospitals to which the survey was circulated. The majority of responses (78%) were from tertiary care hospitals, which might suggest overrepresentation of tertiary care settings. However, the extent of this possible overrepresentation could not be determined since no information was available about the settings (i.e. primary, secondary or tertiary care) of hospitals that did not participate in the survey. Nevertheless, as tertiary care centres generally have a central and leading role in preparedness efforts for emerging health crises, our survey results do serve as important indicators of the state of preparedness in Europe. Secondly, several of the questions in our survey remained unanswered ('do not know') a substantial proportion of respondents, likely due in large part to differences in medical background of respondents (ranging from intensive care specialists to clinical microbiologists) and the variety of topics addressed. However, close collaboration between these specialists is clearly needed to provide optimal and safe care for EVD patients. Thirdly, as the number of participating hospitals differed substantially between regions, with relatively low numbers from eastern Europe and western Asia, geographical differences in the results of this survey should be interpreted with caution. Finally, this survey represents a snapshot of the state of affairs six months after the EVD outbreak in West Africa became apparent to the world and three weeks after it had been declared a PHEIC. Since then, preparedness activities of hospitals, including training and exercises, will undoubtedly have intensified globally given the continuing and expanding crisis in West Africa and emergence of travel-associated cases elsewhere. It will be interesting to assess whether this is indeed the case in a future follow-up survey.

In summary, this survey has provided important initial insights into the preparedness and capacity to admit patients suspected for EVD in European hospitals. These results, including identified gaps or concerns, help to provide direction towards further preparedness activities and prioritisation thereof.

Platform for European Preparedness against (re-) emerging epidemics (PREPARE), and affiliated clinical networks Community-Acquired Competence Network (CAPNETZ www.capnetz.de), European Society of Intensive Care Medicine (ESICM www.esicm.org), COMbatting BACTerial resistance in Europe (COMBACTE www.combacte.com) and Pediatric European Network for the Treatment of AIDS (PENTA http://www.penta-id.org).

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Conflict of interest

None declared.

Authors' contribution

Designed the study: MDdJ, PH, MK, HG. Executed the survey: MB, J-DC, CQ, TW, FL, JS. Prepared and analysed data: MDdJ, CR, FL, JS. Interpreted the results: MDdJ, CR, PH, MK, HG. Wrote the first draft: MDdJ. All authors reviewed, provided comments and approved the final manuscript.

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Human and entomological surveillance of Toscana virus in the Emilia-Romagna region, Italy, 2010 to 2012

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Toscana virus (TOSV), transmitted by phlebotomine sandflies, is recognised as one of the most important causes of viral meningitis in summer in Mediterranean countries. A surveillance plan based on both human and entomological surveys was started in 2010 in the Emilia-Romagna region, Italy. Clinical samples from patients with neurological manifestations were collected during 2010 to 2012. The surveillance protocol was improved during these years, allowing the detection of 65 human infections. Most of these infections were recorded in hilly areas, where sandflies reach the highest density. Entomological sampling around the homes of the patients resulted in a low number of captured sandflies, while later sampling in a hilly area with high number of human cases (n=21) resulted in a larger number of captured sandflies. Using this approach, 25,653 sandflies were sampled, of which there were 21,157 females, which were sorted into 287 pools. TOSV RNA was detected by real-time PCR in 33 of the pools. The results highlighted the role of *Phlebotomus perfiliewi* as the main vector of TOSV and a potential link between vector density and virus circulation. This integrated system shows that an interdisciplinary approach improves the sensitiveness and effectiveness of health surveillance.

Introduction

Toscana virus (TOSV) (family *Bunyaviridae*, genus *Phlebovirus*), first isolated from phlebotomine sandflies sampled in the eponymous Italian region in 1971 [1,2], was associated with human disease more than 15 years later [3,4]. TOSV is considered not only the causative agent of a self-limiting syndrome, such as sandfly fever (caused by TOSV in Sicily and Naples) [5], characterised by influenza-like symptoms, but also of neurological diseases ranging from aseptic meningitis to meningoencephalitis [4,6].

TOSV is transmitted by some sandflies species, particularly *Phlebotomus perfiliewi* Parrot, 1911, and *Ph. perniciosus* Newstead, 1930 [1,6]. In experimental studies, vertical transmission in vectors was reported at rates over 40% in the first generation after infection [7,8], and has been suggested as a possible mechanism of environmental persistence of the virus [6,9,10]. The reservoir role of vertebrates is conceivable, but has been poorly investigated. TOSV circulates during the summer in several Mediterranean countries and was reported as one of the most important causative agents of viral meningitis since the 90s in central Italy [11,12] and since 2000 in France and Spain [9]. Nevertheless, TOSV ecology is still largely unknown: affected sandfly species are not defined and it is unclear whether a vertebrate reservoir exists [2,6,9].

Since the 80s, TOSV circulation has been increasingly reported in the Mediterranean basin, in Portugal, France, Spain, Greece, Bosnia-Herzegovina, Kosovo under UN Security Council Resolution 1244, Malta, Cyprus, Turkey [6,10,13], and since 2012 in Croatia, Morocco and Tunisia [14-16]. In Italy, the virus has been recognised as an agent of meningitis and has been detected in several regions: Tuscany, Piedmont, Marche, Umbria, Lazio, Campania and Sardinia [13]. Since 1999, autochthonous human cases of TOSV meningitis have been reported in the Emilia-Romagna region, indicating circulation of the virus [17,18]. In 2010, a surveillance plan to monitor the circulation of TOSV in the Emilia-Romagna region, based on the diagnosis and reporting of human cases and monitoring of vectors, was adopted and gradually improved over the years. Characteristics and data obtained from this surveillance during 2010 to 2012 are described here.

Methods

Surveillance of human cases

Human cases of TOSV infection were identified through the regional West Nile virus (WNV) surveillance system that collects samples from suspected cases (blood, serum, cerebrospinal fluid), i.e. hospitalised patients who presented with high fever (>38.5 °C) and neuroinvasive manifestations (e.g. encephalitis, meningitis, flaccid paralysis) or polyradiculoneuritis [19,20]; patients with febrile illness only were not included in this analysis. According to the regional WNV surveillance guidelines [21], the notification of every suspected case of WNV infection to the public health department is mandatory during the surveillance period, i.e. from June to November.

The diagnostic procedure for identification of TOSV infection has been improved over the years: in 2010, clinical samples collected in July to October for WNV surveillance were retrospectively tested for TOSV [17]; in 2011 and 2012, all WNV surveillance samples were simultaneously tested also for TOSV. Microbiological diagnosis for WNV and TOSV infection was performed by the Regional Reference Centre for Microbiological Emergencies (CRREM) of the Unit of Clinical Microbiology at the St Orsola-Malpighi University Hospital in Bologna, Italy.

On the basis of laboratory findings, TOSV infections were classified as acute (positive PCR with or without IgM detection) or recent (IgM detection alone).

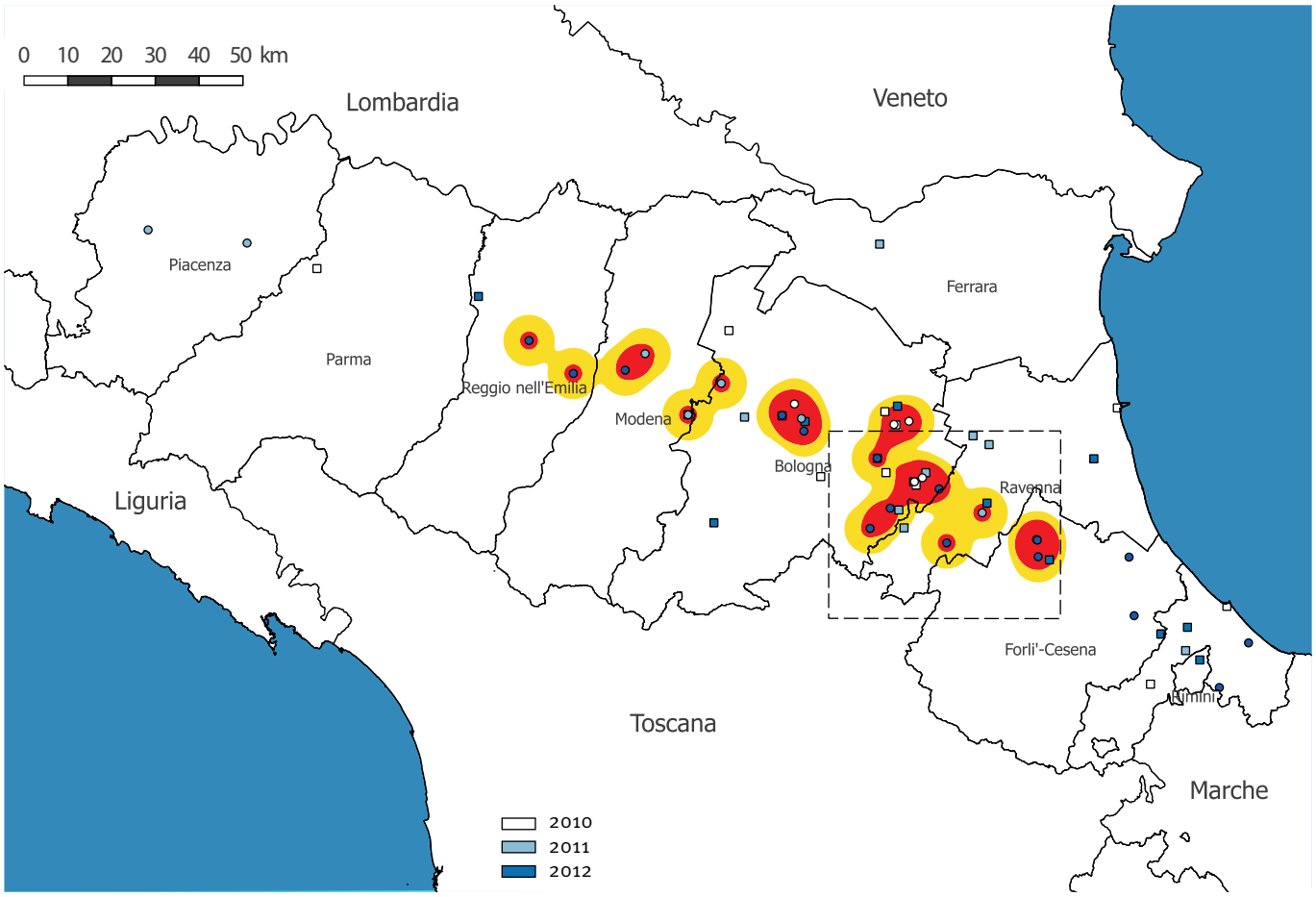
In order to get information about potential places of exposure, home location (urban/rural and hilly/plain), leisure-time habits and perception of the presence of the vector, each TOSV-positive patient was investigated using a standardised WNV surveillance form, administered via telephone by local public health units.

Surveillance of sandflies

Entomological surveillance was conducted using carbon dioxide-baited traps operating overnight in

Figure 1

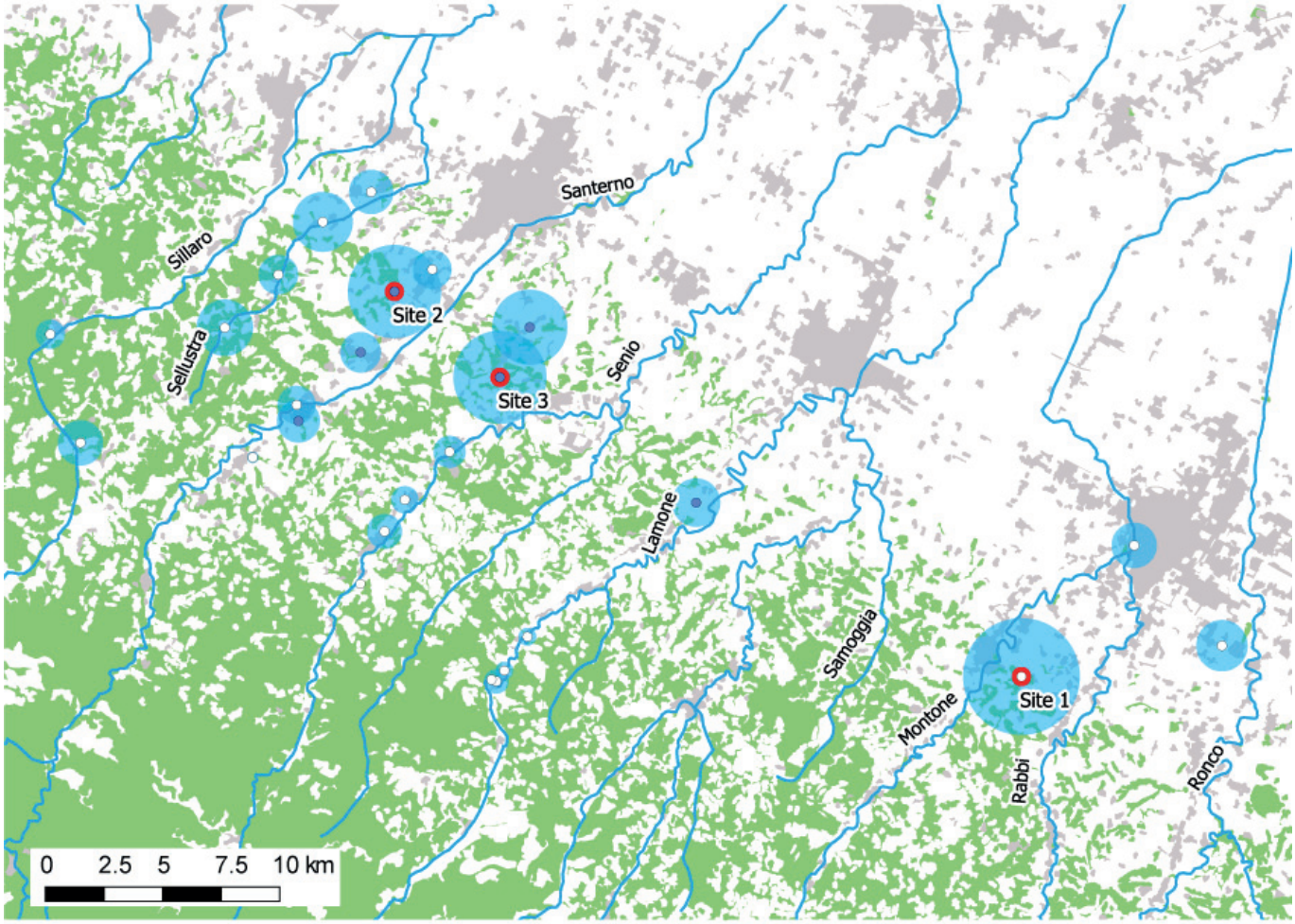
Location of human cases of Toscana virus infection by year, in patients resident in the Emilia-Romagna region, Italy (n=61)



The cases classified as autochthonous (n=29), i.e. they reported to have not travelled or spent nights away from home in the 15 days before symptom onset, used for the percentage volume kernel density estimation (red and yellow areas) are represented by a circle. The large square with the dashed line represents the area of entomological surveillance in 2012, which is shown in Figure 2.

Figure 2

Sites sampled for Toscana virus in sandflies in 2012 in the Emilia-Romagna region, Italy



The size of the azure circles is proportional to the number of sandflies collected in a site. Toscana virus-positive pooled female sandflies (red circles), the presence of *Phlebotomus perniciosus*-positive specimens (blue circles), urban areas (grey), and forest and semi-natural areas (green) are displayed.

The geographical location of the area is shown in Figure 1.

georeferenced sites in the summer, when adult sandfly vectors are present.

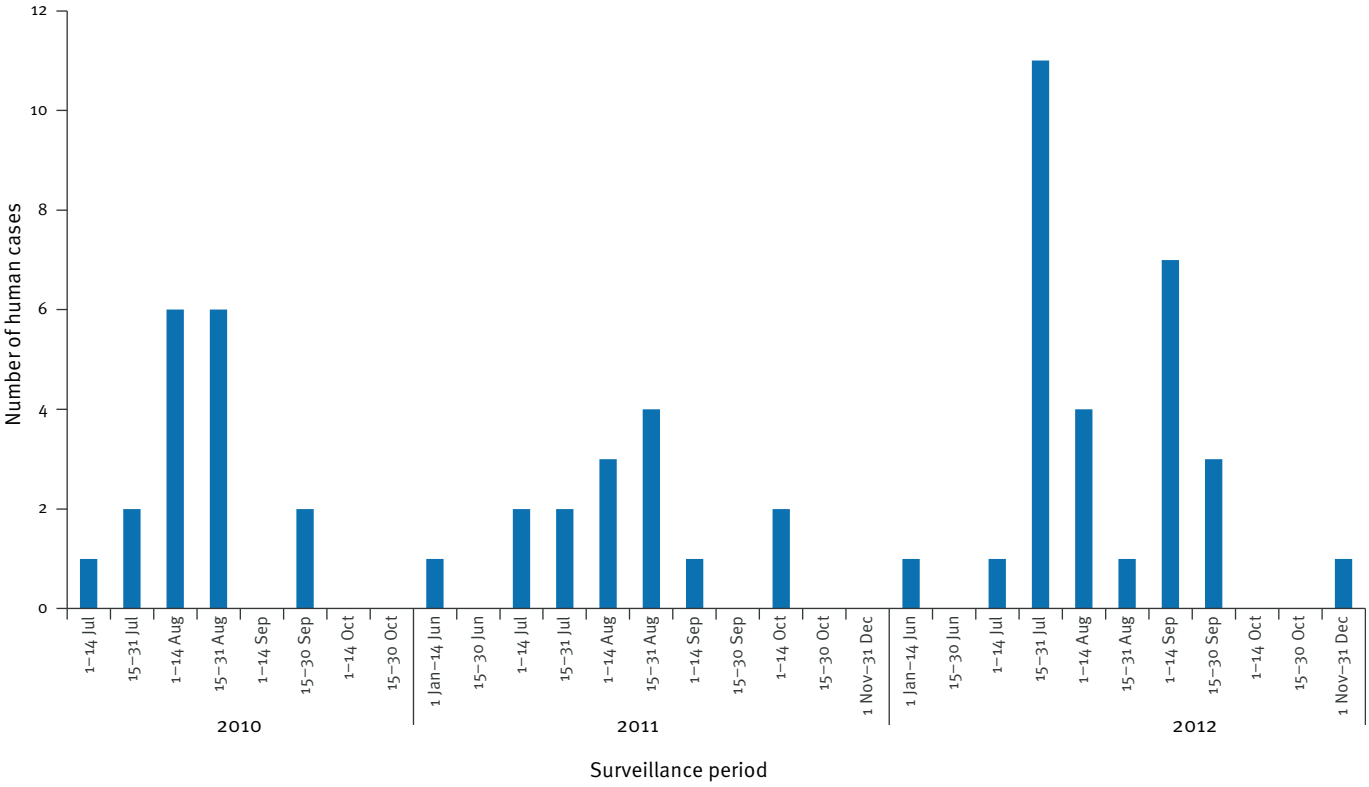
In 2010 and 2011, insects were collected for one night from a 200 m radius around each home (the supposed place of infection) of autochthonous human cases. In 2012, a different strategy was adopted. An area with a high incidence of reported cases was inferred by geographic information system (GIS) analysis: sandflies were collected in this area of about 870 km2 located in the hilly part of the region (Figure 1). A total of 25 sample sites were selected along the altitude gradient of different river valleys (from west to east: Sillaro, Sellustra, Santerno, Senio, Lamone, Montone and Ronco river valleys) (Figure 2); these sites were sampled twice during June to September. This area has a population density of about 258 inhabitants/km2 [22] and is characterised by cultivated fields intersected with hedges, badlands and woodlands, in which oaks, hornbeams and maples dominate. In this area, the warm temperate climate, characteristic of the region, according to Köppen-Geiger climate classification [23], is mitigated by the proximity of the Adriatic Sea.

If the number of sampled sandflies from a particular location was under 20, all specimens were identified at species level and not submitted to biomolecular analysis.

For samples with more than 20 specimens, the sandflies were divided into groups, up to a maximum of 100 per group, and then the males and females were separated according to the presence of male genitalia. All the males were morphologically identified; pooled females were ground in a 1.5 mL vial with 500 µL of phosphate-buffered saline using a pellet pestle, and then submitted for biomolecular analysis.

Figure 3

Distribution of human cases of Toscana virus infection resident in the Emilia-Romagna region, Italy, by date of symptom onset, 2010–12 (n=61)



Morphological identification was performed according to identification keys [24,25]. Specimens were observed under an optical microscope after chlorolactophenol clarification to detect morphological characteristics, particularly the shape of the aedeagus, (part of male genitalia) for males, and features of spermathecae and pharynx for females.

Virological analysis

Laboratory confirmation of human cases of TOSV infection involves molecular and serological testing. We tested for the presence of TOSV RNA in cerebrospinal fluid specimens using a real-time reverse transcription polymerase chain reaction (RT-PCR) for TOSV, targeting the TOSV N gene [26] while anti-TOSV IgG and IgM were detected in serum or plasma samples using an indirect immunofluorescence assay (Euroimmun, Lübeck, Germany). TOSV infections that were classified as acute or recent, as described above, were considered confirmed cases.

Sandfly RNA was extracted using TrizolLS Reagent (Invitrogen, Carlsbad, CA, United States); cDNA synthesis was achieved using random hexamers (Roche Diagnostics, Mannheim, Germany) and SuperScriptH II reverse transcriptase (Invitrogen, Carlsbad, CA) and then tested by a real time RT-PCR specific for TOSV detection [26].

Statistical and GIS analysis

Autochthonous human cases of TOSV infection from 2010 to 2012 were geocoded from the Public Health database. The pattern of spatial data was characterised by conducting nearest neighbour analysis on the locations of the human cases of TOSV infection. Analyses were performed using surveillance information on 60 TOSV-positive patients identified; such data were not available for one case.

Kernel density estimation was applied to the location of the autochthonous human cases, in order to assess TOSV cluster presence in the Emilia-Romagna region. This geospatial technique, based on a kernel function (a quadratic function in this analysis), was used to create a surface to indicate the intensity of a particular event; the mean distance between the autochthonous cases (8 km) was chosen as bandwidth. The cluster area of TOSV presence was estimated by the percentage volume contour of the TOSV kernel density estimation, which represents the boundary of the area containing 95% and 50% of the volume of the obtained kernel density estimation. Nearest neighbour analysis and kernel density estimation were performed using ESRI ArcGIS 9.3 and the Spatial Analyst extension.

To test whether the risk of TOSV infection is related to a patient's sex, a general linear model was applied and logistic regression used on the dataset of tested patients using the software Intercooled Stata 7.0

(probability of infection was the dependent variable and sex was the independent variable).

Maximum likelihood estimation of infected specimens for 1,000 female sandflies collected, for every dataset and sampled sites, was obtained using the United States Centers for Disease Control and Prevention pool infection rate Excel add-in version 4.0 [27].

Results

Human cases

During 2010 to 2012, samples obtained from 380 patients were screened within the framework of the regional surveillance system (120 in 2010, 140 in 2011 and 120 in 2012). Of these, 152 were female (62 in 2010, 45 in 2011, and 45 in 2012) and 228 were males (58 in 2010, 95 in 2011, and 75 in 2012).

TOSV infection was confirmed in 65 patients; of these, 61 (17 in 2010, 15 in 2011, and 29 in 2012) probably were infected inside the Emilia-Romagna region; the additional four laboratory-confirmed cases were excluded from our analysis because the patients were not resident in the Emilia-Romagna region and therefore were probably exposed to the infection elsewhere (two patients were from Tuscany, one from Marche and one from San Marino). In 2010 and 2011, the peak of cases was recorded in August, while in 2012 the maximum number of cases was detected at the end of July, with a possible second peak at the beginning of September (Figure 3).

Among the infected patients, a consistently high proportion of men was observed each year (44/61 in the whole period; 11/17 cases in 2010, 11/ 15 in 2011, 22/29 in 2012). In the whole period, the probability of tested patients being infected by the virus was 0.24 (95% CI: 0.18–0.30) for male patients and 0.13 (95% CI: 0.8–0.18) for female patients. Thus, tested patients infected with TOSV were about twice as likely to be male (odds ratio: 1.90 (95% CI: 1.04–3.47); $p<0.05$).

The median age of the TOSV-infected patients analysed was 41 years (range: 16–83); 29/61 were aged 25–44 years. The most frequent manifestation in the patients was meningitis (n=40). Of the 61 confirmed cases, 43 were classified as acute infections, according to positive PCR or both positive PCR and IgM detection (Table 1). Additional information on the surveillance form (available for 60 cases) indicated that 29 patients reported to have not travelled or spent nights away from home in the 15 days before symptom onset. So it is hypothesised that they acquired the infection nearby their home: these cases were classified as autochthonous cases. The place of residence of these cases was used in the kernel density estimation, which indicated that the areas at higher risk of TOSV circulation were located in the hilly part of the region (Figure 1).

Furthermore, 16 of the these 60 cases declared a perception of a high density of biting insects in the area

Table 1

Demographic and clinical characteristics of human cases of Toscana virus infection resident in the Emilia-Romagna region, Italy, 2010–12 (n=61)

Characteristic	Year			
	2010	2011	2012	2010–12
	Number	Number	Number	Number
Age group (years)				
0–14	0	0	0	0
15–24	2	2	2	6
25–44	8	9	13	30
45–64	4	4	6	14
≥65	3	0	8	11
Sex				
Male	11	11	22	44
Female	6	4	7	17
Clinical features				
Encephalitis	4	3	6	13
Meningitis	13	11	16	40
Meningoencephalitis	0	1	7	8
Type of infection				
Acute infection[a]	5	11	27	43
Recent infection[b]	12	4	2	18
Total	**17**	**15**	**29**	**61**

[a] Positive PCR [26] with or without IgM detection.

[b] Only positive IgM detection.

Table 2

Sandflies sampled in 2012 by river valley of collection, Emilia-Romagna region, Italy

River valley	Number of sites	Altitude range (metres above sea level)	Number of collected sandflies	Number female	Number male (P.pf/P.pn)
Sillaro	2	191–341	252	157	95 (95/0)
Sellustra	4	133–226	1,071	842	229 (229/0)
Santerno	6	78–175	5,305	3,655	1,650 (1,645/5)
Senio	6[a]	130–207	6,733	5,139	1,594 (1,589/5)
Lamone	5[b]	83–232	316	285	31 (30/1)
Montone	2	27–183	11,565	10,746	819 (819/0)
Ronco	1	32	411	333	78 (78/0)
Total	26	27–341	25,653	21,157	4,496 (4,485/11)

P.pf: *Phlebotomus perfiliewi*; P.pn: *Phelbotomus perniciosus*.

[a] Three sites with no sandflies captured.
[b] One site with no sandflies captured.

around their home and 40 used personal or home protection measures against biting insects.

Entomological findings

In 2010 and 2011, sandflies were collected in 15 sites in areas around the homes of human cases (nine in 2010 and six in 2011). This approach resulted in a small number of sandflies being captured; in seven of the sites, no sandflies were collected. In 2010, a total of 54 sandflies were collected from four sites; in 2011, a total of 200 specimens were captured in four sites (of these, 197 were collected in one site).

All sandflies identified in 2010 belonged to *Ph. perfiliewi* species; in 2011, 110 specimens were identified: two were *Ph. perniciosus* (in one site), while the other sandflies were identified as Ph. perfiliewi.

Due to the low number of sampled specimens, only two pools underwent biomolecular analysis, which gave negative results.

The change of strategy in 2012 greatly increased the number of sampled sandflies, leading to the detection of TOSV-infected vectors. A total of 26 selected sites, ranging in altitude from 27 m to 341 m above sea level were sampled twice in the season, about a month apart. From 26 July to 28 September, a total of 25,653 sandflies (21,157 female and 4,496 male) were captured in 22 of these sites (Table 2). The females were sorted into 287 pools, of which 33 tested positive for TOSV (Table 3).

The 33 TOSV-positive pools were from three sites, with the altitude of the positive sites ranging from 128 m to 207 m above sea level. At one of the sites (Site 2), TOSV-positive pools were detected on two different sampling days. The maximum likelihood estimation of each pool varied from 1.5 to 3.8 (Table 3).

Of the male sandflies analyses, *Ph. perfiliewi* was the preponderant species in the sampled areas (only 11 *Ph. perniciosus* males in a total of 4,496 male sandflies).

Table 3

Analysis of samples from sites in which Toscana virus was detected in sandflies, Emilia-Romagna region, Italy, 2012

Site	River	Altitude (metres above sea level)	Date in 2012	Number of sandflies collected	Number male (P.pf/P.pn)	Number female	Number of pools of females positive/total	MLE (lower limit–uppper limit)
1	Montone	183	2 Aug	9,295	727 (727/0)	8,568	19/93	2.5 (1.5–3.8)
			7 Sep	2,367	97 (97/0)	2,270	0/24	NA
2	Santerno	128	26 Jul	2,285	494 (494/0)	1,791	6/23	3.8 (1.6–7.9)
			30 Aug	2,400	1,075 (1073/2)	1,325	2/24	1.5 (0.3–4.9)
3	Senio	207	17 Aug	4,660	933 (930/3)	3,727	6/48	1.7 (0.7–3.5)
			28 Sep	10	1 (1/0)	9	0/2	NA
Total	–	–	–	**21,017**	**3,327 (3,322/5)**	**17,690**	**33/214**	**NA**

MLE: maximum likelihood estimation; NA: not applicable; P.pf: *Phlebotomus perfiliewi*; P.pn: *Phelbotomus perniciosus*.

All the *Ph. perniciosus* specimens were found in three neighbouring valleys (Santerno, Senio and Lamone) (Table 2, Figure 2).

Discussion

The fact that there were no patients under 14 years of age is in line with previous observations [28]. There may be two reasons for the lack of cases of TOSV infection in children: TOSV infection may occur at a lower rate in children or it may be more frequently asymptomatic or paucisymptomatic in children than in adults. A high proportion of adult cases and a larger presence of males among confirmed cases has already been reported in serological investigations in Italy [29] and could be linked to behaviour, with high levels of outdoor activities having been described as a risk factor of TOSV infection [9]. This observation may explain the greater likelihood of infection in males, as highlighted by our surveillance.

The location of most of the human cases (46/61) in hilly areas of the region is an expected result as these areas are the typical habitat for sandflies and support a very high density of vectors, as confirmed by the abundance of sandflies collected (Tables 2 and 3). Two species of sandflies were collected during the survey, *Ph. perfiliewi* (4,647/4,660; 99.7%) and *Ph. perniciosus* (13/4,660 0.3%). Both species are considered efficient vectors of TOSV [6], but due to its abundance, *Ph. perfiliewi* seems to be the main vector of TOSV in the Emilia-Romagna region. As the two species have a different distribution in the Mediterranean basin, *Ph. perniciosus* in western part and *Ph. perfiliewi* in eastern part, with an overlap between the two in the central Mediterranean area, [10], confirmation of the vectorial competence of both species enlarges the area of potential TOSV presence. There is, however, a need for precise data on the distribution of sandflies in Europe, data that are often not available [10].

A major role of vertical transmission in the persistence of TOSV in the environment has been hypothesised, but vertical transmission seems ineffective in ensuring such persistence of the virus over generations, at least in experimental studies [7,8]. Possible involvement of vertebrates in the TOSV life cycle could be hypothesised as antibodies against the virus have been detected in horses and sheep in Italy [13] and in horses, goats, pigs, cats, dogs, sheep and cows in Spain; in one of the goat samples, the virus was detected by real-time PCR [30]. However, it should be borne in mind that the presence of anti-TOSV antibodies in these animals does not imply that they play a role in the natural cycle of the virus. In a survey conducted in Italy between 1983 and 1985, one TOSV strain was isolated from a bat captured in 1984, which had tested negative in a serological test [2]. The possible involvement of other vertebrates, such as rodents, in the life cycle of various phleboviruses transmitted by sandflies has been suggested previously [5]. Further studies are needed to identify possible TOSV reservoirs but, considering that sandflies do not fly for long distances [31] and that TOSV was found in sandflies collected in rural areas, our study indicates that a putative reservoir, if present, could be looked for in such rural environments.

The initial approach of collecting sandflies in areas nearby the homes of the human cases gave poor results, probably due to the time elapsed (estimated to be about two weeks) between the onset of the human infection and the sampling of sandflies. This may have resulted in a reduction in the number of sandflies, as these insects show sharp peaks of abundance during the season and have a short lifespan, of about two or three weeks [10,25,31]. The 2012 sampling methodology, which focused on a hilly area with observed TOSV circulation in previous years, irrespective of whether human cases had been detected nearby, resulted in the capture of a greater number of sandflies. Interestingly, in all sampled sites in which TOSV was identified, the virus was detected, or a greater maximum likelihood estimation observed, in early samples, showing the highest circulation of the virus to be between the end of July and the beginning of August (Table 3). This is in agreement with human epidemiological data obtained in 2012, which showed a similar early peak in human cases at the end of July (Figure 3). This may be linked to the exceptional drought conditions recorded in 2012, a year with one of the driest Augusts recorded in the time series of regional meteorological services [32], which date back to 1950s. In 2012, the occurrence of human cases seemed to be different from that of previous years: in 2010–11, the peak of human cases was recorded in August (Figure 3), reflecting the classic dynamic described in the literature [4,13].

The different trends of human cases during the study period may be due to different population dynamics of the vector. This hypothesis seems to be confirmed by the detection of TOSV in the more abundant samples obtained during the 2012 survey, in which more than 18,000 specimens were collected, more than 70% of the sandflies collected throughout the study period. Moreover, it is thought that sandflies could be both the main reservoir and also have an amplifying role in the life cycle of TOSV [6,10]. Previous field evidence has linked the peak in human cases with periods of highest density of the vector [4]. Taken together, these results seem to suggest a strong correlation between the presence of the virus and sandfly density. If confirmed, this correlation could be a very useful tool for assessing the risk of TOSV infection. The importance of these findings is emphasised by different field studies that indicate an increasing in density and a northern spread of sandflies in Europe [33], with a consequent increasing burden of sandfly transmitted diseases [10,33].

The integrated surveillance system we have described was able to identify areas in which TOSV circulation was more intense and the risk of human infection was the highest. Improvements in the surveillance strategy over the years have resulted in the availability of epidemiological data about the TOSV life cycle, which may

be useful to obtain models to forecast TOSV circulation in the region. If the hypothesis of correlation between vector abundance and virus circulation is confirmed, this correlation could be used to develop effective and efficient actions intended to prevent virus transmission, such as vector monitoring, vector control policies and informative campaigns, to stimulate the adoption of personal protection measures in risk areas.

Conflict of interest

None declared.

Authors' contributions

MC: entomology field and laboratory work, data analysis, drafted the article. PA: organisation of surveillance, organisation of surveillance. RC: organisation of surveillance, data analysis. RB: entomology field work, drafted the article. AA: entomology field work, GIS analysis. PB: entomology laboratory work, data analysis. FC: laboratory work on human samples. MD: organisation of surveillance. PG: laboratory work on human samples. SN: organisation of surveillance. GM: laboratory work on entomological samples. MP: laboratory work on entomological samples. AM: data analysis, drafted the article. VS: laboratory work on human samples, drafted the article. AP: laboratory work on human samples, data analysis, drafted the article. MPL: laboratory work on human samples. GR: laboratory work on human samples. GS: organisation of surveillance. SC: organisation of surveillance. SV: laboratory work on human samples. CV: laboratory work on human samples, data analysis, drafted the article. EB: organisation of surveillance.

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Improving surveillance of sexually transmitted infections using mandatory electronic clinical reporting: the genitourinary medicine clinic activity dataset, England, 2009 to 2013

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A new electronic surveillance system for sexually transmitted infections (STIs) was introduced in England in 2009. The genitourinary medicine clinic activity dataset (GUMCAD) is a mandatory, disaggregated, pseudo-anonymised data return submitted by all STI clinics across England. The dataset includes information on all STI diagnoses made and services provided alongside demographic characteristics for every patient attendance at a clinic. The new system enables the timely analysis and publication of routine STI data, detailed analyses of risk groups and longitudinal analyses of clinic attendees. The system offers flexibility so new codes can be introduced to help monitor outbreaks or unusual STI activity. From January 2009 to December 2013 inclusive, over twenty-five million records from a total of 6,668,648 patients of STI clinics have been submitted. This article describes the successful implementation of this new surveillance system and the types of epidemiological outputs and analyses that GUMCAD enables. The challenges faced are discussed and forthcoming developments in STI surveillance in England are described.

Introduction

Sexually transmitted infections (STIs) are a major public health concern in England. The Department of Health (DH) has committed to improving the sexual health and wellbeing of the whole population and 'to continue to work to reduce the rate of STIs using evidence-based preventative interventions and treatment initiatives' [1,2]. Monitoring STIs and the impact of any public health initiatives requires high-quality and timely surveillance data to determine which specific population groups are at particular risk of STIs and how STI trends respond to interventions. Prior to 2009, STI surveillance in England depended on the collection of aggregated data on a paper-based form (known as the KC60 statistical return) from all genitourinary medicine (or STI) clinics in England.

Although the KC60 return provided reasonably robust data on STI trends, it was severely limited because: (i) it was not timely; (ii) it collected no information on patient area of residence, so that local area governments were unable to determine the extent and nature of sexual health problems in their residents; (iii) it collected only limited information on patient characteristics which are critical for identifying population groups at high risk ('core groups'); and (iv) as the KC60 return was aggregated it was not possible to link individual patient records for longitudinal studies or risk factor analyses.

The genitourinary medicine clinic activity dataset (GUMCAD) was developed to address these concerns and replace the KC60 return. This dataset is an electronic, pseudo-anonymised (i.e. contains the patient's gender, age and clinic/hospital number, but does not contain patient-identifiable information such as name, date of birth, or postcode of residence) patient-level data return that contains information on all STI diagnoses made and services provided in STI clinics in England along with patient demographic information. We describe this new surveillance system, the approach taken to implement it, and discuss how barriers and difficulties were overcome. We also present some of the insightful epidemiological analyses which are now being used to guide STI prevention activities in England and speculate on GUMCAD's future role in second and third generation surveillance.

Methods

Development, approval and implementation of the genitourinary medicine clinic activity dataset

Good planning, stakeholder engagement and adequate resources are crucial for the successful delivery of any major programme of work and were key to the successful implementation of this major new national surveillance system for STIs. The planning and approval

Table 1

Data items collected in the genitourinary medicine clinic activity dataset (GUMCAD), England

Variable	Definition/values
Clinic (service) ID code	An identifier for a clinic or facility
Local patient identifier number	This is a number used to identify a patient uniquely within a healthcare provider
Sexual health and HIV activity property code (SHHAPT)	STI related codes used to identify diagnoses and/or services received at the sexual health service. For full list see https://www.gov.uk/genitourinary-medicine-clinic-activity-dataset-gumcadv2
Gender	A self-defined classification of the current sex of the patient
0	Not known: the sex of the patient has not been recorded
1	Male
2	Female
9	Not specified: means indeterminate, i.e. unable to be classified as either male or female
Age at attendance date in years	This is usually derived as the number of completed years between the birth date of the patient and the attendance date.
999	Not known: date of birth not known and age cannot be estimated
Sexual orientation	The current sexual orientation of the patient as ascertained as part of the sexual history taken during the clinical consultation
1	Heterosexual
2	Gay/lesbian
3	Bisexual
9	Not known
Patient's ethnic category	The ethnicity of the patient, as specified by the patient.
	White
A	British
B	Irish
C	Any other white background
	Mixed
D	White and black Caribbean
E	White and black African
F	White and Asian
G	Any other mixed background
	Asian or Asian British
H	Indian
J	Pakistani
K	Bangladeshi
L	Any other Asian background
	Black or black British
M	Caribbean
N	African
P	Any other black background
	Other ethnic groups
R	Chinese
S	Any other ethnic group
Z	Not stated
Patient's country of birth	This is the country where the patient was born, as specified by the patient. The alphabetic code to be used is the 3-character alphabetic code available on the International Organization for Standardization website: http://www.iso.org/iso/home.htm
Primary care trust (PCT) of residence code[a]	This is the organisation code of the PCT derived from the patient's address. PCTs were administrative bodies of the National Health Service. PCTs were abolished on 31March 2013
Lower layer super output area (LSOA) of residence code	LSOA for where the patient is resident. LSOA is a geographical area with a mean population of 1,620 and is derived from the patient's address.
Attendance type	–
1	First attendance face to face
2	Follow-up attendance face to face
3	First telephone or telemedicine consultation
4	Follow up telephone or telemedicine consultation
Date of attendance	yyyy-mm-dd

HIV: human immunodeficiency virus; ID: identity; STI: sexually transmitted infections.

[a] No longer required as of 1 April 2013.

processes for GUMCAD, funded by the DH, started in 2005 and involved the participation and agreement of a wide range of stakeholders led by the Health Protection Agency (HPA) (now part of Public Health England – PHE). Two key groups were established at the start: a steering group to advise on dataset items, coordinate approval processes, and monitor rollout; and an implementation group (overseen by the steering group) to coordinate software upgrades in clinics, resolve any technical issues that arose, and oversee the initial collections from all 205 STI clinics in England. The steering group included representation from PHE, DH, the British Association for Sexual Health and human immunodeficiency virus (HIV) (BASHH), which represents sexual health clinicians, and other key public health bodies, service commissioners (i.e. those who plan and pay for sexual health services and who therefore require high quality data to assess the sexual health needs of their local population) and academics. The implementation group comprised primarily PHE national and regionally-based information managers and clinic software providers. As GUMCAD is an electronic return, all patient management software providers (i.e. private software companies who are contracted to provide clinics' patient management systems) were involved at an early stage to identify technical and practical concerns, contribute to their

Table 2

Percentage of the genitourinary medicine clinic activity dataset individual attendance records with 'known' information for selected variables, England, 2008–2013

Year	N[a]	Gender %	Age %	Sexual orientation %	LSOA[b] of residence %	Country of birth
2008	1,931,056	99.95	99.97	54.22	66.93	76.86
2009	2,208,698	99.92	99.98	67.49	90.15	89.20
2010	2,223,814	99.92	99.96	75.08	95.59	91.51
2011	2,364,257	99.98	99.97	86.18	97.04	93.60
2012	2,422,181	99.98	99.96	90.87	97.84	93.44
2013	2,539,572	99.98	99.95	93.95	98.07	93.11

LSOA: lower super output area.

[a] Number of genitourinary medicine clinic activity dataset individual attendance records.

[b] LSOA is a geographical area with a mean population of 1,620 and is derived from the patient's address.

resolution, and implement the necessary changes to clinics' patient management software systems.

In England, all new surveillance systems and mandatory data collections from healthcare providers in the National Health Service (NHS) undergo rigorous scrutiny and evaluation by the NHS Standardisation Committee for Care Information (SCCI; before April 2014, this was known as the Information Standards Board (ISB)) before approval is granted. This body ensures that the proposed data collection is necessary, feasible, cost-effective, standardised and in line with other data collections, avoids duplication and is not an excessive administrative burden on service providers.

As part of this process, the recording, collection, extraction and analysis of GUMCAD was piloted in ten STI clinics between March and September 2007. These ten clinics were distributed throughout England and used the three patient management software providers with the majority (>90%) of the market share. After the pilot, clinic staff were invited to provide structured feedback on the practicalities, time burden and technical challenges of recording and reporting the required data, and to comment on their experiences. Questionnaires were returned by seven of the ten pilot sites, five of which had already been collecting all the proposed GUMCAD data items. The two remaining clinics collected all but one of the data items, but indicated that collecting the additional item (country of birth and sexual orientation, respectively) would pose a minimal impact (<20 seconds per patient registration) on the time taken to record patients' details. Overall, the feedback received was positive and resulted in minor revisions to the proposed collection. It also demonstrated that, in addition to providing more detailed and timely surveillance data, the recording and reporting of an electronic data return used considerably less staff time (50–67%) and resource to extract and submit data than the existing paper-based system. This evidence enabled PHE to better advocate the value of GUMCAD to busy healthcare professionals thus facilitating more timely implementation.

GUMCAD was finally approved as the new national mandatory data standard for STI surveillance by the NHS ISB in February 2008. Service and software providers were given formal notice to implement the necessary changes to clinic software to enable extraction of GUMCAD data in March 2008, after which national roll-out commenced. PHE staff regularly contacted clinics and providers to facilitate and support implementation of clinic software updates and to expedite extraction and reporting of the new dataset. GUMCAD and KC60 data were collected from January 2008 to March 2009 to enable comparison and validation of the new system and data, before cessation of the KC60 return in April 2009.

Dataset specification

The GUMCAD dataset consists of twelve variables all of which are mandatory and must be submitted by the clinic. To ensure inter-operability between different service providers and end-users regardless of the software or platforms used, all variables and codes specified in GUMCAD were developed in accordance with national standards defined by the NHS data model and dictionary [3]. The following patient demographic data are collected: gender (a self-defined classification of the current sex of the patient), age, sexual orientation, ethnicity, country of birth and area of residence (Table 1); with the exception of ethnicity and area of residence, these variables are all included in the enhanced set of variables for European Union-wide STI surveillance [4]. Residence information is collected at lower super output area (LSOA) level, a geographical area with a mean population of 1,620, which is derived at the clinic from the patient's address [5]. Information on diagnoses and the services provided are coded using a combination of 68 available sexual health and HIV activity property type (SHHAPT) codes. Each record contains a local patient identifier number enabling

patient records (within a given clinic) to be linked, enabling longitudinal analyses.

Ensuring submission compliance and data quality
It is an accepted truth that the generation of high-quality surveillance information relies on high-quality data. For GUMCAD, this was achieved by developing a rigorous system of data validation checks, data cleaning and quality assurance systems. Each clinic is required to generate and submit to PHE a quarterly data extract of all patient attendances and associated diagnoses within six weeks of the end of each calendar quarter. The dataset must be submitted to PHE in a standardised pre-defined format through a secure web-based interface. Data submissions undergo basic automated checks for errors in data format, coding and duplication and are accepted into the database only if they are more than 90% free of errors. Records with errors are automatically returned to the clinics for correction and resubmission. Data submissions undergo a further cleaning process before epidemiological analysis and publication which includes the generation of unique episodes of care. For example, an individual patient is permitted only one record of gonorrhoea in a six week period; repeat codes for gonorrhoea within this period are removed to prevent over-counting of diagnoses [6].

As was the case with KC60, no financial incentives are given to report surveillance data; however, each annual STI data publication includes a list of reporting sites with the proportion submitting all four quarters of data [7]. Additionally, after substantial health system reform in 2013 [8], local government is required to contribute to national surveillance for public health and must ensure that all contracts with sexual health service providers include provision to collect and supply mandatory data including GUMCAD [9]; high quality, timely local STI data are vital for service planning. Finally, each STI clinic is sent a comprehensive automated feedback report which, in addition to providing demographic breakdowns, STI trends, rates of STI reinfection and HIV test uptake and coverage of their patients, provides comprehensive information on the quality, completion and timeliness of information submitted, and how this compares with national standards.

Patient confidentiality

All staff within PHE have a legal duty to keep patient information confidential. Information on STIs is considered particularly sensitive and the rights of the patient for confidentiality must be maintained at all times while balancing against the need to collect information for public health action. Although no patient-identifiable information such as name, date of birth or postcode were specified in GUMCAD, the inclusion of pseudo-anonymised data (i.e. the patient's clinic ID number) meant the data were considered highly sensitive. Guidelines for publishing and sharing the data were developed to ensure that the risk of deductive disclosure of individuals due to small cell sizes would be negligible [10].

Results

Progress with implementation, data quality and timeliness to date

Data submissions

Between 2008 and 2013, the number of STI clinics commissioned in England varied between 204 and 209 clinics. By November 2008, only a fifth (41/208) of clinics had had the GUMCAD software installed. This had increased to 56% (115/206) by April 2009 and to 100% (206/206) by December 2009. Because the software enabled retrospective submissions, all clinics in England were able to provide GUMCAD data from the beginning of 2009 and, furthermore, 84% (171/204) of clinics provided data from the beginning of 2008. Since 2009, only one or two clinics each year have been unable to submit GUMCAD data; reporting compliance was however 100% in 2012 (208/208) and 2013 (208/208). Between 2009 and 2013, over twenty-five million clinical records from 6,668,648 patients with 13,689,578 attendances at English STI clinics were submitted to PHE.

Reporting timeliness

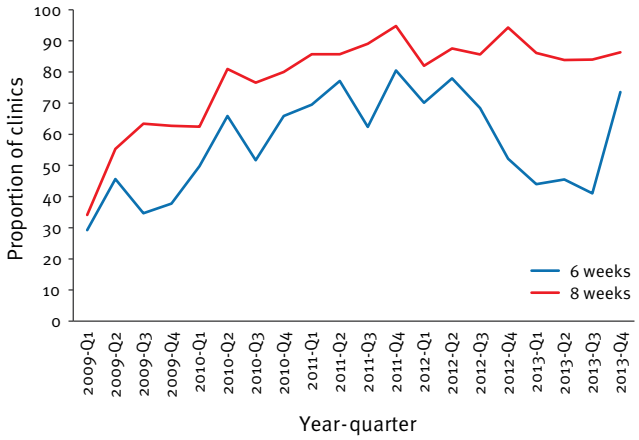
Compliance with the required data submission deadline was relatively poor in 2009, but has improved considerably: as of 31 December 2013, 85% (177/208) of clinics reported within eight weeks of the end of the calendar quarter (Figure 1).

Variable completeness

Some of the required data variables were not consistently collected by all GUM clinics before GUMCAD

Figure 1

Proportion of sexually transmitted infection clinics[a] submitting data to the genitourinary medicine clinic activity dataset (GUMCAD) within 6 and 8 weeks of the end of each calendar quarter, England, 2009–2013[b]

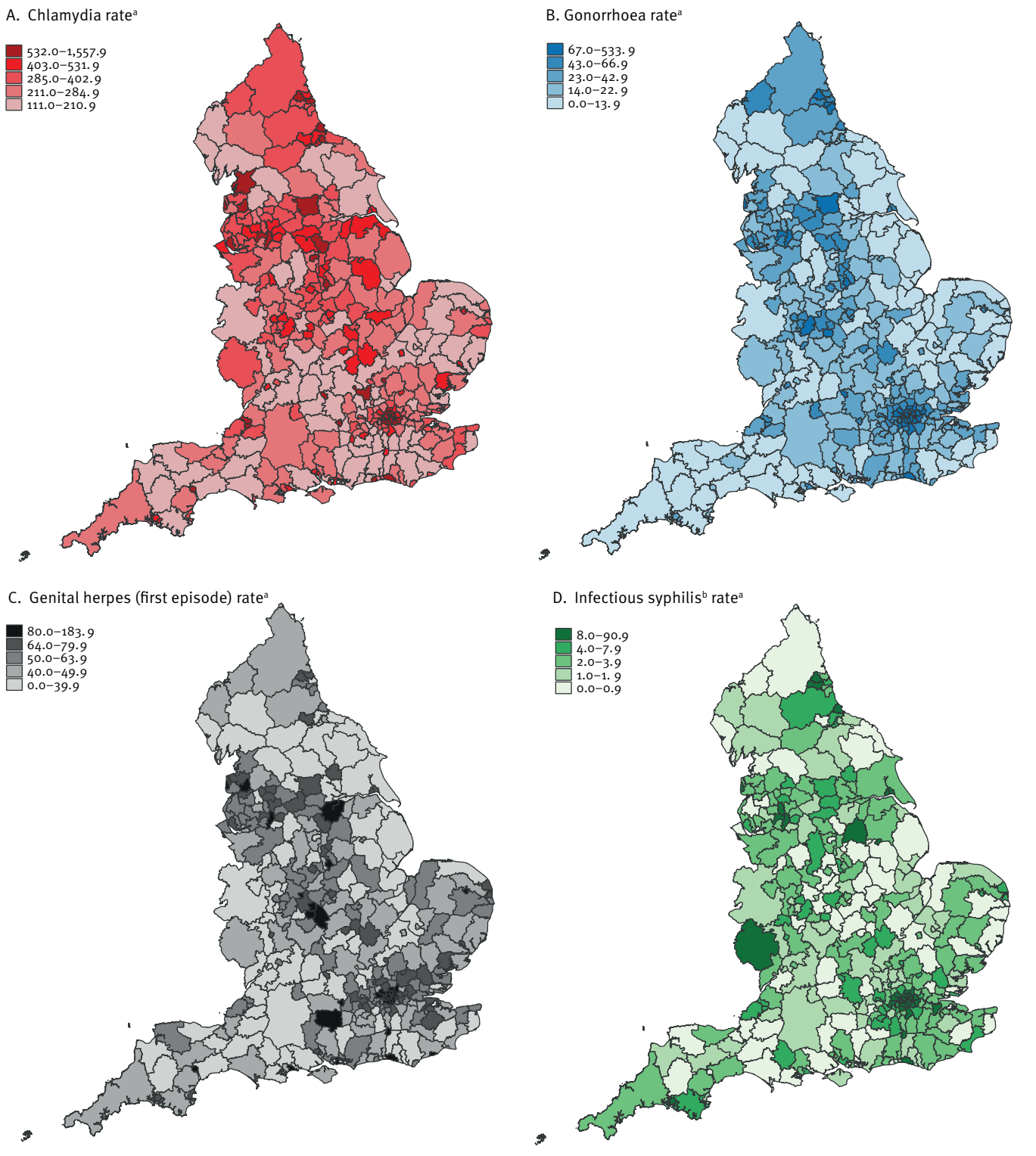


[a] Also known as genitourinary medicine (GUM) clinics.

[b] For both years 2009 and 2010 the number of clinics submitting data to the GUMCAD was 206. In 2011, 209 STI clinics provided data, while for the respective years 2012 and 2013 the number of clinics was 208.

Figure 2

Diagnosis rates[a] of selected sexually transmitted infections by lower-tier local authority of patient residence, England, 2013



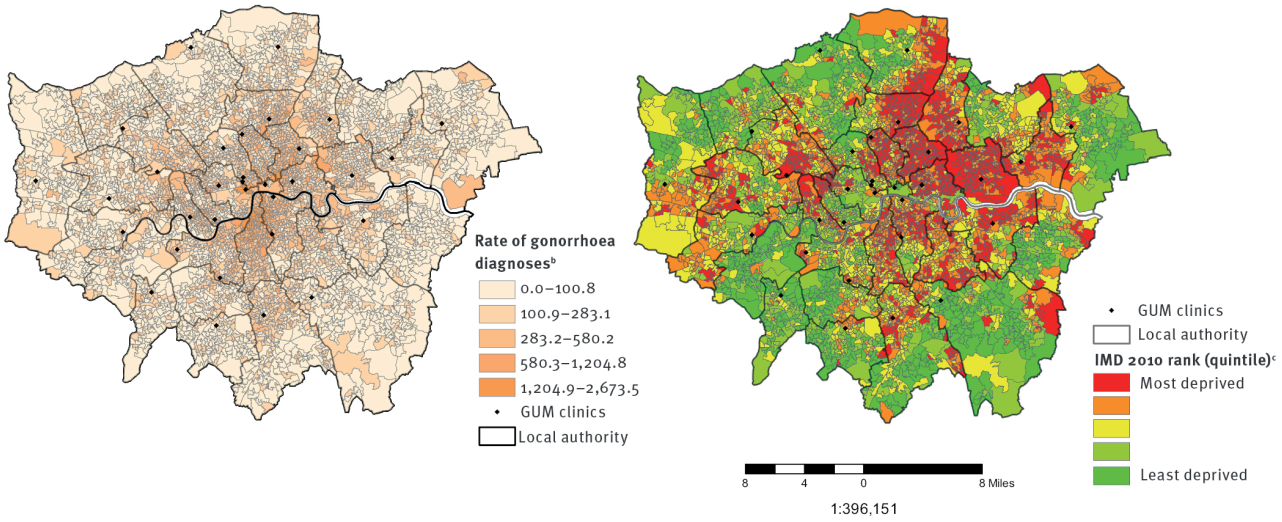
[a] Per 100.000 population.

[b] Primary, secondary and early latent syphilis.

Data source: routine sexually transmitted infection clinic, also known as 'genitourinary medicine' (GUM) clinic, returns to the GUM clinic activity dataset (GUMCAD).

Figure 3

Location of sexually transmitted infection clinics[a] and (i) rate of gonorrhoea diagnoses[b] by lower super output area (LSOA) in 2013, and (ii) index of multiple deprivation in 2010[c] by LSOA and lower-tier local authority, London



IMD: index of multiple deprivation; GUM: genitourinary medicine.

[a] Also known as GUM clinics.

[b] The rate of gonorrhoea diagnoses is per 100,000 population.

[c] IMD 2010 ranks are categorised into quintiles.

Data sources: Routine sexually transmitted infection clinic, also known as GUM clinic, returns to the GUM clinic activity dataset (GUMCAD) and the English indices of Deprivation 2010 (Department of Communities and Local Government). Contains National Statistics and Ordnance Survey data. Crown copyright and database right 2014. Reproduced with permission of Public Health England.

implementation. Hence some variables in the earlier data submissions contained an unacceptably high percentage of records reported as 'not known', i.e. sexual orientation, ethnicity, country of birth and lower super output area, but this has improved considerably over the years (Table 2).

Epidemiological outputs and analyses

National and local reports

The aim of any infectious disease surveillance system is to provide 'information for action'. One of the key objectives of GUMCAD was to enable the production of timely outputs and analyses to inform national and local STI service planning, needs assessments and the development of tailored prevention initiatives. Responding to evolving priorities and needs has been an ongoing process, which has been resource-intensive and, at times, technically challenging.

PHE publishes national-level STI tables (the official STI statistics) annually on the PHE website [7] and has also developed sexual and reproductive health profiles, a publicly available interactive tool using the Fingertips webtool, that present sexual health data at different geographical levels [11]. More detailed data are available through a restricted-access web-portal which allows local public health professionals involved in service planning and commissioning to view and download their local quarterly STI data aggregated by risk group, time and place from two weeks after the submission deadline. Since 2011, PHE has also produced confidential detailed epidemiological reports for each of the 208 STI clinics and 326 local government authorities using their local data. They include numbers and population based-rates of new STI diagnoses by risk group, LSOA of residence and over time, as well as repeat infection rates and HIV testing uptake and coverage as markers of intervention effectiveness. These epidemiological reports facilitate robust assessment of local service needs and priorities for targeted prevention. They have been programmed in statistical software (Stata v13.0, StataCorp LP, College Station, Texas, US) to enable rapid production and dissemination.

Understanding geographical inequalities using spatial mapping

By collecting information on patient area of residence and socio-demographic characteristics, GUMCAD allows detailed geographical mapping of the burden of STIs and testing and treatment services, which can help local government assess and plan improvements

to service provision (Figures 2–3). Such geographical comparisons can be made using the sexual and reproductive health profiles described above [11]. More in-depth exploratory analyses of the inequalities associated with STIs are also possible by combining GUMCAD data with other data sources such as the index of multiple deprivation (IMD, which is a measure of area level deprivation in England) [12,13] (Figure 4) and a Bayesian spatial modelling approach has been used to identify local sexual network effects associated with gonorrhoea in London [14].

Improving knowledge on risk groups and emerging infections

GUMCAD provides comprehensive data on patient age, gender, sexual orientation, ethnic group and country of birth which facilitates assessments of the burden of sexual ill-health in high risk, often vulnerable populations. These data have shown that men who have sex with men (MSM), young people and certain black ethnic minorities experience particularly high rates of STIs in England [15,16]. The collection of data on single year of age rather than age-group has helped provide evidence that the decline in diagnoses of genital warts seen in women aged 15 to 19 years between 2009 and 2013 may partly be as a result of a protective effect of human papillomavirus (HPV)-16/18 vaccination against genital warts [17,18]. Furthermore, GUMCAD data have been used to develop exceedance algorithms and a spatio-temporal model to detect outbreaks of STIs in local areas [19].

Crucially, the flexibility of the coding system enables new codes to be introduced in response to need and to help monitor outbreaks or unusual STI activity. For example, codes for sex workers and prisoners were introduced in 2011 allowing routine national surveillance of STIs in these particularly vulnerable populations for the first time [20]. During the London Olympics in 2012, temporary codes were introduced to STI clinics in London and Weymouth to record Olympics-related attendances and thereby assess the impact of the games on sexual health services [21]. PHE has recently received approval for codes for *Shigella* spp. infection, which has become endemic among MSM in England [22], as well as a suite of dummy codes for release upon recognition of emerging public health concerns.

Longitudinal analyses

An important advantage of electronic patient-level data is that data in this form facilitate record linkage and longitudinal analyses, such as Cox proportional hazards modelling to determine risk factors for STI/HIV co-infections and repeat infections. This can be used to develop targeted clinic-based interventions by determining the characteristics of those at particularly high risk of STIs or HIV and how this changes over time. Thus far, GUMCAD has been used to estimate risk factors associated with HIV incidence, STI acquisition among those who are HIV-positive, and repeat infection with gonorrhoea [6,23,24].

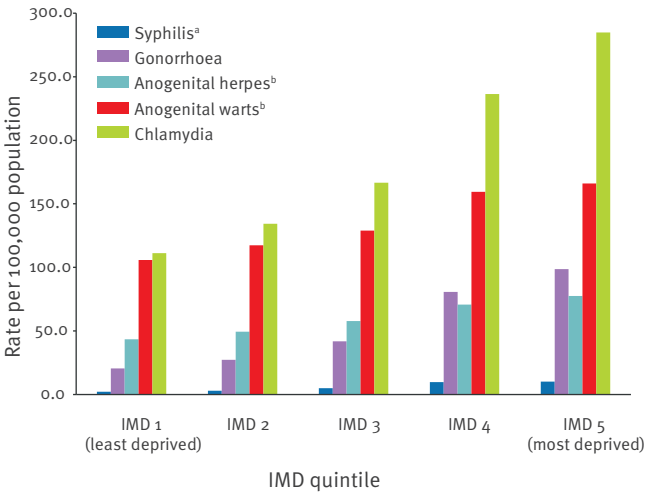
Discussion

The introduction of GUMCAD has ensured that England now has a timely, comprehensive and sophisticated STI surveillance system which compares favourably with STI surveillance systems in other western industrialised countries [25,26]. It is particularly noteworthy because of the large population it covers and the level of detail collected, a major accomplishment given that there were ca 450,000 diagnoses of STIs in 2013 in England [16]. Its introduction was facilitated by having an established network of open-access (i.e. anyone can attend without a referral), publically-funded STI clinics in England. These services dominate STI and HIV healthcare in England and are linked to an influential clinical professional body (BASHH) with a strong public health focus.

There are, of course, limitations to GUMCAD. Longitudinal patient data are only available within a particular clinic or service – attendances by the same patient at different clinics cannot be monitored. While one of the strengths of GUMCAD is that it is a mandatory surveillance system, all proposed changes need to be piloted then go through a formal approval process by SCCI. The volume of records held in GUMCAD also leads to technical challenges for data storage, manipulation and analysis. Recruiting and retaining staff with the required technical and scientific expertise is vital for maximising GUMCAD's potential.

Figure 4

Diagnosis rate of selected sexually transmitted infections by quintiles of the index of multiple deprivation (IMD), England, 2013



[a] Primary, secondary and early latent.

[b] First episode.

Source: genitourinary medicine clinic activity dataset (GUMCAD) returns 2013 (Public Health England, extract date: 29.5.2014), and 2010 IMD by lower super output area (LSOA) (Department of Communities and Local Government), mid-2012 population estimates by LSOA (Office for National Statistics, ONS). Crown copyright. Reproduced with permission of Public Health England.

The implementation of a new surveillance system is often complex and challenging and GUMCAD was no exception. A key lesson is that planning for a new surveillance system should start many years before the anticipated start date. A long lead-in time is required to ensure engagement and awareness is widespread among stakeholders and data providers, and that there is adequate time for software development, piloting, feedback and resolution of technical and other issues. The GUMCAD steering and implementation groups spent many months ensuring that the relevant professional bodies and clinicians were fully engaged with and supportive of the proposal. Regular newsletters providing updates on progress were sent to STI clinics and other interested parties, and these remain a useful tool for disseminating important updates and providing feedback. Furthermore, clinic-specific data quality and epidemiology reports enabled clinics to easily identify and resolve persistent data quality issues, and were particularly well received by consultant clinicians. These reports have been one of the key levers in ensuring GUMCAD's success.

However, improvements in data quality also led to issues with data continuity that had not been anticipated. Unlike the aggregate KC60 return, GUMCAD enabled errors in data coding to be identified and corrected. This raised concerns about the interpretation of long-term time trends, as following removal of duplicate records the number of STI diagnoses and services reported reduced on average by ca 3%. To enable fair time-trend analyses over the transition between these two surveillance systems, numbers of diagnoses reported through KC60-based surveillance in years before 2009 had to be statistically back-adjusted using an algorithm based on the percentage difference in diagnoses reported through GUMCAD and KC60 during parallel running in 2008 and 2009. This had not been anticipated and resulted in a significant delay in the annual publication of official STI statistics in 2009.

While the vast majority of sexually transmitted infections in England are diagnosed either at a GUM clinic or are referred to a GUM clinic from general practice, there are a growing number of other services that offer STI testing, diagnosis and treatment [27,28]. These include specific young people's clinics or other sexual health and reproductive services which primarily provide contraception services and STI testing [28]. Since 2012, GUMCAD has been rolled out to these services and data collection is underway (the new system with the inclusion of these additional data is known as GUMCADv2). These data are currently, as of August 2014, being checked and validated, and will be published for the first time in 2015.

GUMCAD is a huge advance on its predecessor paper-based system but all surveillance systems should evolve and adapt to changing technical, political, epidemiological and microbiological developments. GUMCADv2 has already broadened system coverage. Planning for the next version of GUMCAD (GUMCADv3), which aims to capture information on sexual risk behaviours, drug and alcohol use, and partner notification outcomes, is already underway and includes a pilot in nine STI clinics across England [29]. In the future, GUMCADv3 will be linked to other healthcare datasets to enable greater understanding of care pathways (the 'patient journey') and identification of missed intervention opportunities, and with microbiological datasets (including whole genomic sequencing data on STIs) to investigate the behavioural and contextual factors which are associated with poor sexual health outcomes, and the sexual network effects associated with rapid STI and resistance spread. Indeed, GUMCAD has already been linked with molecular typing data from the Gonococcal Resistance to Antimicrobials Surveillance Programme in England and Wales, an annual patient survey at sentinel STI clinics monitoring trends in gonococcal resistance, to demonstrate rapid clonal spread of strains with reduced sensitivity to cephalosporins in dense sexual networks [30]. GUMCADv3 will also facilitate linkage with one-off quantitative or qualitative clinic-based surveys. In England, information on reproductive health and contraceptive services is also collected from sexual health service providers. A move towards harmonisation of this dataset with GUMCAD would be welcomed by commissioners and service providers, and is now a priority of PHE.

There is considerable inequality in the distribution of STIs across the population. Prevention efforts, such as improved health promotion, better sexual health education, greater STI screening coverage and easier access to sexual health services, are vital for controlling infection transmission. Underpinning all these efforts is the need to have good quality and timely surveillance data showing the groups most at risk of infection to better target prevention activities and to monitor their effectiveness. The successful introduction of GUMCAD has been an important step towards better STI control in England.

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Conflicts of interest

None declared.

Authors' contributions

All authors contributed to the drafting, writing, and reviewing the manuscript.

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Overcoming healthcare workers' vaccine refusal – competition between egoism and altruism

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Vaccination reduces the risk of becoming infected with and transmitting pathogens. The role of healthcare workers (HCWs) in controlling and limiting nosocomial infections has been stressed repeatedly. This has also been recognised at a political level, leading the European Council of Ministers in 2009 to encourage coverage of 75% seasonal influenza vaccine in HCWs. Although there are policies, recommendations and well-tolerated vaccines, still many HCWs refuse to get vaccinated. This article uses literature from psychology and behavioural economics to understand vaccination decisions and the specific situation of HCWs. HCWs are expected to be highly motivated to protect others. However, their individual vaccination decisions follow the same principles (of weighting individual risks) as everyone else's vaccination decisions. This will lead to decisional conflict in a typical social dilemma situation, in which individual interests are at odds with collective interests. Failure to get vaccinated may be the result. If we understand the motivations and mechanisms of HCWs' vaccine refusal, interventions and campaigns may be designed more effectively. Strategies to increase HCWs' vaccine uptake should be directed towards correcting skewed risk perceptions and activating pro-social motivation in HCWs.

Vaccination reduces the risk of a person becoming infected with pathogens as well as transmitting them to another person. The benefit of vaccination in healthcare settings has been shown in numerous studies [1,2], especially those regarding vaccination against influenza [3]. As a result, vaccination is an important measure to control and reduce outbreaks or transmission of infectious diseases such as influenza in hospital settings [4]. In most countries, there are policies, recommendations and well-tolerated vaccines available [5]. According to the 2009 Council of the European Union recommendation, uptake of 75% of seasonal influenza vaccination is desirable [6]. However, vaccination rates among healthcare workers (HCWs), particularly against influenza, are too low [4]. In Europe, uptake rates for seasonal influenza vaccine are below 32% [2]. The corresponding rates in the United States have risen from 40% to 50% and then to 60–70% due to intense promotion efforts and, in part, mandatory vaccination in some healthcare units [3]. Why do many HCWs refuse to get vaccinated? In this perspective article, I provide a psychological view of vaccination decisions and the specific situation of HCWs, and discuss strategies to increase vaccine uptake among HCWs.

Skewed risk perceptions as reasons against vaccination

In 2009, a study summarised the most important reasons why some HCWs do not get vaccinated against influenza [7]. Across a large number of studies, HCWs most frequent reason against vaccination was a fear of side effects [2]. Studies have repeatedly shown that today's vaccines are well-tolerated [8]. Severe side effects are extremely rare and the frequency of their occurrence is usually overestimated [8]. However, perceptions of risk are subjective judgments and do not necessarily mirror objective numbers [9,10]. Still, they may very well impact behaviour. When the *perceived* risk of vaccination is high, vaccination is less likely; when the *perceived* risk of infection is high, vaccination is more likely [11,12].

The perceived risk of becoming infected indeed affects HCWs' vaccination decisions: low perceived risk of infection is among the top five reasons against vaccination [2,7]. Most evidence, however, indicates that the incidence of nosocomially acquired influenza among HCW is significantly higher when vaccination rates are low [1,2]. Moreover, some HCWs exhibited a lack of concern, potentially because they believed that the risk of transmitting influenza virus to their patients was low [3]. Again, most studies show that this perception differs from reality, as influenza transmission in healthcare settings, as well as patient morbidity, is significantly higher when vaccination rates are low (for an overview, see [1] and [2], but also [13]). Overall, skewed risk perceptions are among the most important reasons why HCWs do not get vaccinated. As discussed,

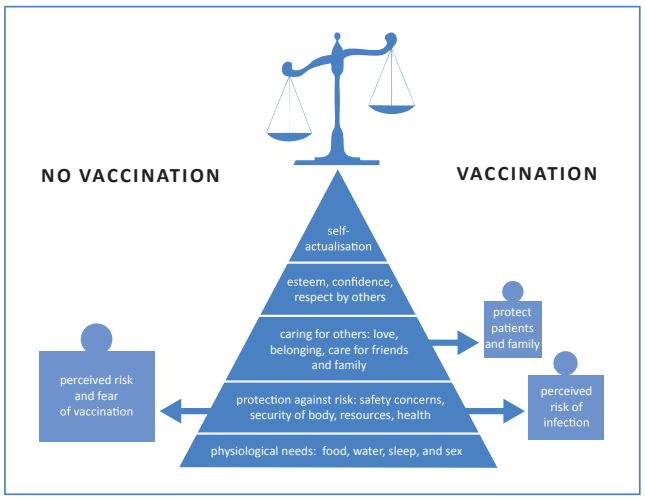
frequently the perceived risks deviate from objective, or at least empirically substantiated, levels of risk.

Protecting oneself against risks and threats is a fundamental motivator behind human behaviour. This follows directly after the instincts to fulfil physical needs for food, water, sleep and sex, as illustrated in Maslow's pyramid of needs [14] (Figure). In the eighteenth century, for example, infectious diseases used to represent a great risk against which individuals sought protection, e.g. by means of vaccination [15,16]. People saw first-hand others affected by and dying from severe diseases. With increased vaccine uptake, two diseases, poliomyelitis and smallpox, are in the process of being or have been completely eradicated, and, with that, the vivid pictures of affected neighbours have disappeared. Simultaneously, however, reports of vaccine adverse events have increased in number. This is due primarily to the growing number of vaccinations taking place [17]. However, more or less organised anti-vaccination communications that announce alleged side effects also play a key role [18-21]. The most prominent example may be the false claim that vaccination against measles, mumps and rubella may cause autism [21,22]. This damaged people's confidence in vaccination over the years and is still in people's minds today, even though there is no scientific evidence for the claim and the paper had to be retracted [8,22]. Similarly, increased incidence of narcolepsy seen in some European countries after administration of the influenza A(H1N1)pdm09 vaccine [23] may falsely create the idea that seasonal influenza vaccines may also lead to the same consequences. However, narcolepsy following the A(H1N1)pdm09 vaccination has been observed in a limited area and has not been observed following any other vaccination [23].

Thus, given the low incidence of vaccine-preventable diseases and alleged and real adverse events, modern vaccines can represent a risk that individuals want to protect themselves from because they fear side effects. Such fear is a very powerful force in reducing vaccination intentions. In a study during the 2009 influenza pandemic, fear of side effects was shown to significantly reduce vaccination intentions, even when fear of infection was also high [24]. If fear of side effects had been lower, vaccination rates may have been substantially higher. In another study, pregnant women's perceived risk of vaccine-related adverse events was much higher than their perceived risk of influenza infections [25]. Given these risk perceptions and assuming that future mothers want to protect themselves and their unborn children from risks, the logical decision would seem to be for them to omit vaccination. Thus vaccination decisions appear to be the result of weighing risks of infection and risks of side effects (Figure). Perceptions of risk do not necessarily need to be rooted in reality; they depend on stories a person hears, their education and experiences, and reports in the media. If fear of side effects increases, vaccination becomes even more unlikely.

Figure

How basic human forces compete and may pull healthcare workers' vaccination intentions in different directions



When making vaccination decisions, human motivational forces of protecting against risk and caring for others may sometimes compete and pull in different directions. This is mainly due to skewed risk perceptions and fear of vaccination. The major goal of educational interventions and campaigns should be to have both forces pull in the same direction by correcting false risk perceptions and stressing the importance of caring for others.

The relative size of the weights illustrates the relative importance of the predictors [7,11,24]. The pyramid represents Maslow's pyramid of needs [14].

Protecting others as a reason for vaccination

In addition to protection against risks, a second powerful force motivates human behaviour: care for family and friends – doing good for others (Figure)) [14]. Vaccination provides a person with the chance to do good for others because it reduces transmission of pathogens [26]. The more people become immunised in a population, the more difficult it becomes for a disease to spread. People who are too young or ill to get vaccinated will be protected through herd immunity [26]. With a sufficient number of people immunised, some diseases can be eliminated – as is currently the goal of the World Health Organization European Region measles and rubella initiative [27].

For HCWs, caring for others is their job. Patients will expect that HCWs' motivation to protect them will be at a maximum. But does the motivation to protect others impact vaccination behaviour? The answer: it depends. Scientists in the United States assessed whether individuals are generally motivated to protect others by being vaccinated themselves [28]. They found that individuals indeed decide to get vaccinated if others can benefit from their vaccination. However, this was only the case if their personal risk of vaccination was low. If their personal risk was high, they refused to get vaccinated to help others. In a German study, individuals intended to get vaccinated when they were informed that their vaccination had a social benefit,

but only if the costs – such as time or money – were low [29]. These two studies point to the same conclusion. Vaccination for the benefit of others? Yes, if the costs and personal risks are low.

In order to explore HCWs' pro-social motivation, we can compare two interestingly different vaccinations: against hepatitis B and against influenza. For example, in the United States Centers for Disease Control and Prevention recommendations for HCWs [30], hepatitis B is described as the greatest infectious hazard for HCWs. The description includes the incidence of chronic liver disease due to hepatitis B as well as numbers of deceased HCWs in the previous year. Reasons for recommending influenza vaccination, in contrast, include the disruption of healthcare, transmission to patients, and morbidity and mortality in nursing homes. Thus, while the reasons for hepatitis B vaccination are directly related to protecting HCWs' health, the reasons for getting vaccinated against influenza are more or less exclusively related to the environment of the HCW and aim at saving resources and protecting others (e.g. patients). This difference in reasons for the recommendations may lead to different vaccination rates. Indeed, a recent German study with medical students showed that vaccination rates were much higher for hepatitis B than for influenza (87% vs 35% [31]), even though both vaccinations are not mandatory for HCWs in Germany. Similarly, data from 2003 showed that an estimated 75% of HCWs in the United States had been vaccinated against hepatitis B, while only 40% were vaccinated against influenza [30]. Thus, when their own health is at stake, as communicated in the hepatitis B recommendation, HCWs appear more inclined to get vaccinated than when the major reasoning of the recommendation is to protect patients. Hollmeyer et al. arrived at a similar conclusion: 'If HCW get immunized against influenza, they do so primarily for their own benefit and not for the benefit to their patients' [7, p. 3935].

Competing human forces: protecting the self versus caring for others

It is HCWs' professional duty to ensure maximum patient safety, care and professional effectiveness during infectious disease outbreaks [3]. Moreover, some of them must take care of immunocompromised patients, for whom infection with influenza would lead to severe illness. This view may lead to the assumption that HCWs who do not get vaccinated are neglecting their professional obligations and doing a poorer job than their vaccinated colleagues. However, there is an alternative interpretation: competing motivational forces.

The human motivational forces, protection against risk and caring for others, may sometimes compete with each other and pull in different directions (Figure). An individual's desire to help others may be in conflict with the costs and risks that they must face and that reduce the person's benefit as a result of the action. Consider, as an example, the process of eradicating polio. High vaccine uptake is necessary to reach the collective benefit of eradication. Fortunately, in most countries today, the probability of contracting polio is nearly zero. The subjective risk of suffering from adverse events after vaccination against polio, however, may be larger than zero [8].

This structure of the decision problem renders the vaccination decision a social dilemma [29,32]. In a social dilemma, individual interests are in conflict with collective interests: as long as a large number of individuals in the population are vaccinated, the individually rational strategy is to 'free-ride', i.e. omit vaccination and thus avoid the costs associated with vaccination while enjoying the benefits of herd immunity. This choice is in opposition to the collective benefit, because herd immunity cannot be reached when too much free-riding takes place [26].

Once a disease is nearly eradicated or eliminated, the perceived risk of infection is very likely to be lower than the perceived risk of vaccine-related adverse events [17]. Further, the situation is also structurally equivalent in each case in which the risk of infection is perceived to be low and risk of vaccination is perceived to be high (as described above, HCWs perceive their risk of contracting influenza as low and they fear side effects). The collective benefit of HCWs' influenza vaccination may therefore be higher than the HCWs' individual benefit.

As outlined above, the decision to get vaccinated against influenza is difficult for HCWs, as weighing individual risks – based on skewed risk perceptions – may suggest that the vaccination should be avoided. The following section discusses strategies to overcome HCW's vaccine refusal by considering the competing motivations and the incentive structure of the decision situation.

Potential strategies to increase vaccine uptake in healthcare workers

Mandatory vaccination

In the United States, seasonal influenza vaccination rates have risen due to extensive efforts to promote vaccination by combining free-of-charge vaccination with educational campaigns [2] as well as mandatory vaccination in some healthcare facilities [3]. In Europe, mandatory vaccination is discussed critically, with a preference for voluntary policies [3]. Still, it may be possible to increase HCW's vaccination by making the alternative to vaccination unattractive – e.g. requiring non-vaccinated HCWs to wear a mask while working, which is uncomfortable and stigmatises unvaccinated HCWs. There is evidence that such an intervention can significantly increase vaccination rates [33]. From a game theory point of view [32], wearing masks can be viewed as a punishment for failing to contribute to the public good. In economic public goods games, a public

good (which benefits everyone) can only be reached or maintained when most individuals contribute some portion of their resources [34]. Punishing those who do not contribute increases their subsequent contributions in public goods games [34]. Thus, the requirement to wear masks when unvaccinated may be a concrete way to 'punish' those who refuse vaccination and simultaneously increase patient protection from the illness.

Where voluntary policies are preferred, however, it is important to identify effective voluntary advocacy approaches to increase HCW's vaccine uptake.

Advocacy

A framework for vaccine advocacy was formulated as 'Vaccination Adoption = Access + Acceptance' [35, p. 1]. In the remainder of this paper, this framework serves as guidance for summarising promising strategies to increase HCWs' vaccine uptake.

Access

Generally, access to healthcare should not be a problem for HCWs when compared with global access issues of insufficient vaccine supply and inadequate healthcare systems. Rather, in this context, access means facilitated access, e.g. lowering or eliminating costs or using mobile units to save HCWs' time. These measures are not new and usually of low effectiveness [3], especially when applied as isolated strategies [2]. However, low-cost vaccination (both regarding time and money) should be combined with focused communication and education strategies [2], as detailed below.

Acceptance: education and interventions

HCWs' acceptance of vaccination may be reached through education about risks and correcting myths as well as interventions highlighting the importance of vaccination.

In order to correct skewed risk perceptions, curricula early in the course of the educational process should inform HCWs about their risk of becoming infected and infecting their patients and families as well as the fact that vaccination may reduce this risk. Importantly, fear of side effects must also be corrected. Systematic ways of debunking vaccination myths should be used to reduce fear [36,37], as misperceptions are also common in future HCWs, i.e. medical students [12]. This may help to move the vaccination decision out of the social dilemma structure: as long as the perceived risk of infection is larger than the perceived risk of vaccine-related adverse events, the benefit to the individual from being vaccinated is larger than that from not being vaccinated, which should encourage vaccination behaviour [29].

Education could also be used to anchor and strengthen HCWs' pro-social values in the course of their education. Research has shown that social value orientation influences behaviour in economic games that are structurally similar to the vaccination decision [38]. Pro-social orientations increased cooperation, indicating that strong pro-social motivation may increase vaccination rates.

Pro-social motivation can also be activated by interventions. Communication strategies should be used that activate positive, other-regarding preferences ('protection of others') (for an overview, see [34]). If such preferences are activated, they are likely to affect behaviour accordingly [38,39]. In the context of vaccination, it has been shown that these effects occur only if the costs of vaccination are low [29,40]. Thus, the activation of social motives will be likely ineffective as an isolated strategy; rather, it must be combined with easy access, as discussed above.

In addition, incentivising HCWs contingent on the vaccine uptake reached in their healthcare unit represents an additional possible strategy that is based on the social dilemma structure. Economic experiments have shown that hypothetical vaccination rates increased in an experimental game when individuals were paid according to the group rather than individual outcome [28]. The practical feasibility of this intervention, however, remains to be tested.

Conclusion

According to the analyses discussed above, strategies to increase HCWs' vaccination uptake should have two goals: (i) correct skewed risk perceptions; and (ii) activate pro-social motivations in HCWs while simultaneously reducing the costs of getting vaccinated. Strategies may be more effective if they take driving human forces into consideration, i.e. protection against risk and caring for others. Without appropriate education and the correction of skewed risk perceptions, these forces may pull in different directions, as illustrated in the Figure. Education and interventions should thus aim to make the two forces pull in the same direction, in order to increase vaccination uptake.

Conflict of interest

None declared.

Authors' contributions

The author is solely responsible for the full text.

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