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First two autochthonous dengue virus infections in metropolitan France, September 2010

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In September 2010, two cases of autochthonous dengue fever were diagnosed in metropolitan France for the first time. The cases occurring in Nice, south-east France, where *Aedes albopictus* is established, are evidence of dengue virus circulation in this area. This local transmission of dengue calls for further enhanced surveillance, active case finding and vector control measures to reduce the spread of the virus and the risk of an epidemic.

Dengue fever is the most important mosquito-borne viral disease in the world and is endemic in Africa, Asia, Caribbean and Latin America. According to the World Health Organization, there are annually more than 50 million cases and 22,000 deaths [1]. Dengue fever is caused by viruses of the Flaviviridae family and transmitted by mosquito vectors of the Aedes genus, mainly *Ae. aegypti* and *Ae. albopictus* [2].

In Europe, the last dengue epidemic was reported from 1927 to 1928 in Greece with high mortality and *Ae. aegypti* was implicated as the vector [3]. Since the 1970s, mainly through global trade of car tyres, *Ae. albopictus* has become increasingly established in European Union Member States, including France, Greece, Italy, the Netherlands (though only in greenhouses), Slovenia and Spain [4]. This mosquito species is also established in neighbouring countries such as Albania, Bosnia and Herzegovina, Croatia, Monaco, Montenegro, San Marino, Switzerland and Vatican City [2,5]. Imported cases of dengue fever in travellers returning from countries where dengue is endemic or where dengue epidemics are taking place have been frequently reported in European countries in recent years [6-10].

In metropolitan France, sporadic *Ae. albopictus* mosquitoes were first detected in Normandy in 1999 [11], but the mosquito is known to have been established since 2004 in south-east France [12]. Since 2006, and the widespread epidemic of chikungunya in Réunion which had posed an increased risk of importation of cases, enhanced surveillance is implemented each year from May to November in the departments where *Ae. albopictus* is established, as part of the national plan against the spread of chikungunya and dengue viruses in metropolitan France [13]. Enhanced surveillance, compared with routine surveillance, allows the reporting and confirmation of suspected cases to be accelerated. The laboratory network surveillance system, the most sensitive routine system in France, detected around 350–400 imported dengue cases per year between 2006 and 2009 in metropolitan France [14,15]. During the same four-year period, enhanced surveillance reported a total of 33 imported dengue cases (including 11 cases in 2009). Between 1 May and 17 September 2010 (i.e. the first 4.5 months of surveillance), 120 imported cases of dengue have been reported by the enhanced surveillance system [16], which represents an 11-fold increase when compared with the entire 2009 season. This increase in imported cases is mostly related to the ongoing epidemics in the French West Indies, Martinique and Guadeloupe, since the beginning of 2010. Here we report on the two first cases of autochthonous dengue virus infection ever diagnosed in metropolitan France and the public health measures subsequently implemented.

Case 1

The first case was detected through the routine enhanced surveillance system. The patient was a man

in his 60s, resident in Nice, Alpes-Maritimes department, who developed fever, myalgia and asthenia on 23 August 2010. He was hospitalised on 27 August 2010, but his clinical condition remained stable. A temporary thrombocytopenia with a minimal platelet count of 48,000/µl (norm: 150,000–400,000) on day five of the illness resolved without complications and he recovered within a few days after disease onset.

Laboratory findings

A panel of sera obtained during the acute and recovery phases on days five, seven, 11 and 25 of the illness was investigated by serological tests (in-house MAC-ELISA and direct IgG ELISA) and real-time RT-PCR. Moreover, a serum sample collected during a previous medical examination in May 2010 was tested retrospectively. Presence of IgM and IgG against dengue virus antigens was documented in all samples except for the serum sampled in May 2010. Antibody titration revealed sharp increases in IgM titres from 1:800 to 1:12,800 and in IgG titres from 1:32,000 to >1:128,000 over the 25 days follow-up. Anti-dengue virus IgA (Assure Dengue IgA rapid test, MP Biomedicals) were also detected on days five and seven. The dengue NS1 antigenic test (Dengue NS1 strip, Biorad) was positive on days five and seven but negative on day 11, demonstrating the active replication of a dengue virus during the symptomatic period. RT-PCR for dengue virus was positive on day five and negative thereafter. Molecular typing identified a dengue virus serotype 1.

It is of interest to note that high levels of specific anti-dengue IgG were detected during the acute phase of disease. Our hypothesis is that these IgG might result from activation of memory B cells (original antigenic sin) related to an ancient primary infection with a heterologous serotype of dengue virus. Seroneutralisation tests will be informative on the immunological status of the patient regarding a possible previous infection with a dengue virus of another serotype. Virus isolation and sequencing are also ongoing. No serum cross-reactions were observed with tick-borne encephalitis and West Nile viruses and no markers of chikungunya virus infection were found (absence of IgM and IgG antibodies, negative RT-PCR). The patient had been vaccinated against yellow fever 28 years ago.

Friends from the French West Indies had stayed with him since April 2010. He had no recent history of international travel or blood transfusion. Consequently, the patient was considered a confirmed autochthonous case of dengue virus infection.

Control measures

This classification prompted an immediate reaction of public health authorities to reduce the risk of further spread of the virus. Various measures were undertaken by health authorities as laid out in the national plan against the spread of dengue in France (level 2 of the plan) [13]: (i) 200 metres perifocal vector control activities centred on the case's residence, including spraying for adult mosquitoes and destruction of breeding sites; (ii) active case finding in the neighbourhood of the case's residence and in other areas visited by the case; (iii) providing information about dengue virus to health professionals, including incitation for screening suspected dengue cases and information to the public. The active case finding conducted by physicians and laboratories will be continued on a weekly basis up to 45 days after the onset of symptoms of the last autochthonous case.

The routine laboratory network surveillance system noticed that six recently imported confirmed dengue cases, including four with a RT-PCR positive for dengue, had been detected in Nice between 24 July and 23 August 2010. One of them had returned from Martinique and lives about 200 metres from the autochthonous case. This imported case was reported too late to implement vector control measures which routinely follow imported viraemic dengue cases in those departments where the vector is present, and could therefore be a potential source of infection of local *Ae. albopictus*. As of 24 September 2010, the active case finding has detected nine new suspected autochthonous cases of dengue fever in the neighbourhood of the index case. In four of them, no markers of dengue virus infection were found (absence of IgM and IgG antibodies, negative RT-PCR), results from epidemiological and laboratory investigations for further four patients are still pending. One case was confirmed to be infected by dengue virus; the latter patient is the second autochthonous dengue fever case ever diagnosed in metropolitan France.

Case 2

This second case is an 18 year-old man who had no recent history of international travel. He lives approximately 70 metres from the first autochthonous case. He developed fever, myalgia, headache and asthenia on 11 September 2010. He was hospitalised briefly because of fever of unknown origin and thrombocytopenia with a mild clinical disease. The thrombocytopenia (platelet count 53,000/µL on day seven of the illness) was temporary and moderate, and he has recovered fully.

Laboratory investigations

Laboratory tests conducted on an early serum sample on day three of illness indicate negative serology for IgG and IgM antibodies but strongly positive RT-PCR for dengue virus. Molecular typing identified a dengue virus serotype 1. The strain appears to be quite similar to those which currently circulate in Martinique; more detailed analyses are ongoing.

Discussion

The identification of two autochthonous cases of dengue fever which are clustered in space and time is strongly suggestive that a local transmission of dengue virus is ongoing. Therefore level 3 of the national plan against the spread of dengue virus has been activated [13]. It entails additional measures to those taken

at level 2: (i) active case finding of autochthonous cases in hospital emergency wards, at present in Nice and surrounding towns, (ii) implementation of vector control measures in hospitals, together with protection of potential viraemic patients against mosquito bites using electric light traps, electric diffusers for insecticides, and repellents, and vector control measures around the port and the international airport of Nice including enhanced entomological surveillance, and (iii) toxicovigilance related to the wide use of insecticides.

Based on the currently available information, these are the first confirmed cases of autochthonous transmission of dengue fever in metropolitan France and Europe, since the epidemic in Greece in the late 1920s and apart from one nosocomial case of dengue infection reported from Germany in 2004 [17]. The event is not entirely unexpected, as reflected in a specific preparedness plan and taking into account the increase in imported cases from the French West Indies and other endemo-epidemic areas. It is known that France, as well as other countries in Europe, has competent vectors for transmitting this flavivirus. The chikungunya outbreak in Italy that occurred in 2007, with over 300 cases reported, has shown that non-endemic arboviruses can be efficiently transmitted in continental Europe [18].

Whether the transmission of dengue virus in France followed a bite from an infectious mosquito imported to the area via airplanes or boats, or one already present in the area after biting a viraemic person residing or visiting Nice, remains to be determined. However, with the second confirmed case, the latter scenario is the most likely one. Therefore, taking into consideration the longest possible incubation period for dengue fever, 15 days, it can be considered that the conditions for successful transmission of dengue virus to humans existed in Nice during August 2010. To date, only two autochthonous cases of dengue fever have been detected in Nice, but the identification of new dengue cases in the near future cannot be excluded. The enhanced surveillance and strict vector control measures are expected to limit the risk for further spread as much as possible.

At this stage, the risk for further spread to humans in Europe, as well as the possibility of the establishment of dengue virus transmission in Nice or in neighbouring areas in France, may appear limited but needs to be closely monitored. Recent evidence demonstrates that compared with *Ae. aegypti*, which has been implicated in the majority of large dengue outbreaks worldwide, *Ae. albopictus* is a less efficient vector of this virus [2]. Nevertheless, it was involved in outbreaks in Japan from 1942 to 1945 [19], the Seychelles in 1977 [20], Hawaii from 2001 to 2002 [21] and Réunion island in 2004 [22]. Vertical transmission of dengue virus from mosquitoes to their offspring does not seem very efficient, and therefore overwintering of the virus in continental European *Ae. albopictus* populations is unlikely [2] but cannot be excluded [23,24]. The public health consequences of the presence of *Ae. albopictus*, in this context, appear to be more important for the transmission of chikungunya for example, for which experimentally better competence has been demonstrated, although the competence of local *Ae. albopictus* for dengue virus is far from being negligible [25]. It should also be noted, that the currently affected area of France as well as other countries in Europe is faced with a high number of imported dengue cases every year. However, despite this and established mosquito populations being potentially able to transmit arboviral diseases, local transmission of the dengue virus with *Ae. albopictus* as the vector in mainland Europe has never been observed before this reported emergence in the south-east of metropolitan France. The high vector density in Nice and the increase in the number of imported cases in this area in 2010, mainly due to intense epidemics in the French West Indies, are two major factors to explain this emergence and highlight the need to maintain an appropriate active surveillance.

In terms of blood safety, reported dengue infection following blood transfusion in dengue endemic areas is rare [26-28] but is also difficult to detect as a large proportion of the population would already have antibodies against the virus. However, as dengue infection is mild or asymptomatic in 40–80% of infected persons, depending on the area and the epidemiological context [29-31], it does pose a risk to blood safety. The two identified cases in Nice are suggestive that other infected persons may have lived in the city during the same period of exposure, without showing any symptoms. Asymptomatic carriers of dengue virus could pose a potential risk to blood safety if they donate blood while being viraemic. It is possible however, that the duration of viraemia in mild or asymptomatic cases is shorter and the virus titre is lower than in symptomatic persons, but this hypothesis is far from proven. Moreover, the limited extend of current virus dissemination, as shown by the actual clustering of confirmed autochthonous cases, does not indicate that such asymptomatic infections could have been spread around the whole city of Nice. At present, it is difficult to quantify this risk, and only a retrospective survey of blood supplies from Nice between July and September 2010 would allow to estimate it better. In France, authorities in charge of blood routinely exclude all febrile donors from donation. No additional exclusion measures have been implemented after the two neighbouring cases as the risk for dengue transmission has been considered very low.

Further investigations to identify the likely source of exposure of the two cases, as well as extensive comparison of the dengue virus genotypes between the locally identified viruses and the strains currently circulating in the French West Indies, will hopefully allow a better understanding of this event. The reactive surveillance in addition to the routine enhanced surveillance

is likely to identify new symptomatic cases in the area, determining also the potential geographic extension of the risk. Finally, better understanding is needed on how the vector abundance, activity and competence of *Ae. albopictus* for dengue transmission influence the risk for further transmission in the region [25,32].

Conclusion

The current clustering of cases of locally transmitted dengue fever in Nice is a significant public health event, but is not unexpected and more cases can be predicted. Such transmission was anticipated by the development of a national plan. Although this plan should be adjusted in the light of this experience, this event shows the advantage of such preparedness in order to implement rapid and proportionate measures of surveillance and control. Previous events, including a mosquito-borne arbovirus outbreak in Italy, the occurrence of vector-borne diseases around airports and other ports of entry and a previous risk assessment on dengue virus introduction in European Union countries [4] indicate that autochthonous transmission in continental Europe is possible, as confirmed by the present event. However, according to the available epidemiological information, the risk for establishment of dengue transmission in south-eastern France or further spread in Europe currently appears limited. Further data available in the near future will allow us to re-assess this likelihood.

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The Hajj: communicable and non-communicable health hazards and current guidance for pilgrims

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The Hajj has become the epicenter of mass migration of millions of Muslims of enormous ethnic diversity. No other mass gathering can compare, either in scale or in regularity. Communicable disease outbreaks of various infectious diseases have been reported repeatedly, during and following the Hajj. The Hajj 2010 starts in the first week of November 2010 and this report is a timely reminder that many infectious diseases can be avoided or averted by adopting appropriate prophylactic measures.

Introduction

Hajj is the annual pilgrimage to Mecca in the Kingdom of Saudi Arabia (KSA). Every year the KSA hosts more than four million people from around 160 countries worldwide for both the Umra and Hajj season. From the European Union close to 45,000 pilgrims arrive to KSA each year. Hajj is thus one of the largest mass gatherings today (Table 1, Figure).

Extended stays at Hajj sites, physical exhaustion, extreme heat, and crowded accommodation encourage disease transmission, especially of airborne agents. Hajj-related transmission of infectious diseases and Hajj–related environmental and public health hazards are well described (Table 2) [1].

In 2009, Hajj was attended by over 2.5 million Muslims, of whom at least 1.6 million were foreign visitors. The vast majority (88% of all pilgrims) arrived by air (Figure 1) and although the Hajj ritual only takes one week many will gather for the month-long Hajj season.

TABLE 1

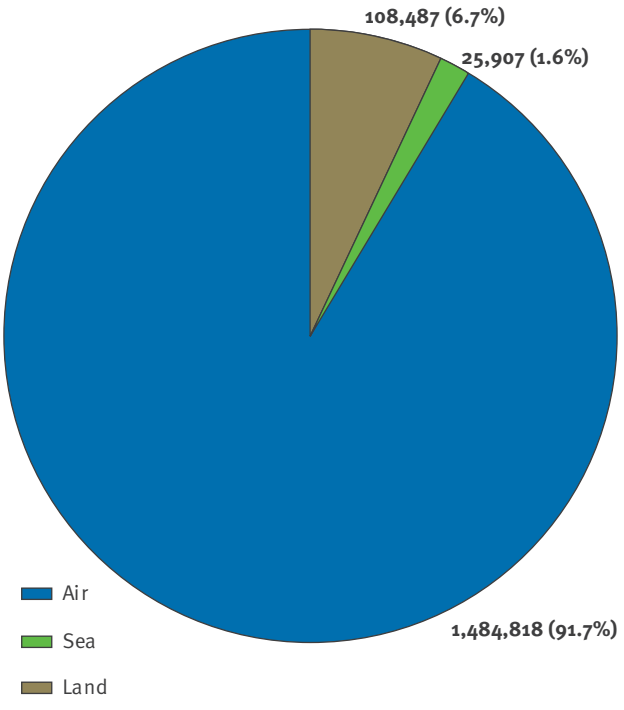
The number of pilgrims travelling to the Hajj, Saudi Arabia, 2006-2009 (1427-1430H)

Year	Total number of international pilgrims
2006 (1427H)	1,653,912
2007 (1428H)	1,708,314
2008 (1429H)	1,729,669
2009 (1430H)	1,619,212

This event requires the planning and co-ordination of all government sectors of the KSA the whole year in advance. One of the major contributors to the planning and strategising for the well-being of the guests is the Ministry of Health (MoH), whose Infection Control and Preventive Medicine Policies are established every year, based on knowledge of current global outbreaks, epidemiology of infectious diseases, and established effective preventive medicine strategies. Most recently, the KSA administered the 2009 Hajj amid a declared global H1N1 pandemic. The Saudi response in preparing for and ensuring public health security for this mass gathering during such an unprecedented event has alerted international stakeholders to the complex implications and opportunities afforded by mass gatherings in advancing global health [2,3,4].

FIGURE

Arrival of pilgrims according to ports of entry into Saudi Arabia in 2009 (n=1,619,212)



Preventive measures during Hajj in Saudi Arabia

The KSA provides free healthcare to all pilgrims during the Hajj and also implements stringent infection control measures. In 2009, the KSA MoH prepared 24 hospitals with a total bed capacity of 4,964, of which 547 were critical care beds. Moreover 136 healthcare centers in the vicinity of the Hajj were equipped with the latest emergency management medical systems and staffed with 17,609 specialised personnel to provide state of the art healthcare to all pilgrims free of charge.

Along the pilgrimage route, the primary medical centers of the MoH, the Saudi National Guard, the Internal Security Forces and the Ministry of Defense and Aviation provide 24-hour free medical care.

Assisting in the Hajj planning and coordination are 24 supervisory committees reporting to the Minister of Health. The preventive medicine committee is one of the committees which oversee all key public health and preventative matters during the Hajj. The committee supervises a large number of public health officers who control the ports of entry for all pilgrims (land, sea and airports) and ensure compliance with Saudi MoH requirements for performing Hajj. In addition 39 public health teams are distributed around where the Hajj takes place. These include 18 stationary teams located in healthcare facilities and 21 mobile teams which rotate through the different pilgrim camps.

At the Hajj terminal based at King Abdulaziz International Airport in Jeddah, the key port of entry for the majority of pilgrims, an independent, newly renovated Hajj terminal now accommodates 80,000 pilgrims at any one time. At each of its 18 hubs receiving pilgrim flights there are two clinical examination rooms and a large holding area to assess arriving pilgrims and check their immunisation status and administer any recommended prophylactic medicines. Any pilgrim with a suspected communicable disease requiring isolation will be escorted back through the airport grounds by ambulance to a nearby dedicated 200 bed hospital.

The public health teams (stationary and mobile) as well as the ports of entry teams report directly to the command center on nine communicable diseases using an electronic surveillance form based on an updated disease case definition submitted via mobile phones. These diseases include influenza, influenza-like illness, meningococcal disease, food poisoning, viral hemorrhagic fevers, yellow fever, cholera, polio, and plague.

Communicable disease at the Hajj

Meningococcal disease

During the Hajj, carrier rates for meningococcal disease (MCD) rise to a level as high as 80% [5] due to intense overcrowding, high humidity and dense air pollution. When rates of carriage rise to this level, the risk for meningococcal outbreaks becomes a real concern. The largest meningococcal outbreak among pilgrims occurred in 1987 with meningococcal serogroup A affecting pilgrims in Mecca and internationally [6]. Further to implementing vaccination with the bivalent A and C meningococcal vaccine as a requirement for attending the Hajj, no further outbreaks due to serogroup A occurred. In the years 2000 and 2001, two large outbreaks of meningococcal serogroup W135 occurred among pilgrims and their families in Saudi Arabia and internationally [7]. A change of the Hajj pilgrimage requirements from bivalent to quadrivalent (A,C,Y, W135) meningococcal polysaccharide vaccine eliminated future meningococcal outbreaks [8]. Concerns still persist about hyporesponsiveness to the serogroup C component of the polysaccharide quadrivalent meningococcal vaccine despite repeat dosing [9]. Lack of herd immunity and persistence of meningococcal carriage among vaccinated pilgrims with the polysaccharide vaccine prompted the Saudi MoH to replace the local recommendations for meningococcal vaccination from polysaccharide to conjugated meningococcal vaccine [10]. Excessive cost of available conjugated meningococcal vaccines prohibited the MoH from mandating this recommendation to all international pilgrims.

Respiratory tract infections

Acute respiratory tract infections are very common during the Hajj, particularly so when the pilgrimage falls in the winter season. The close contact among pilgrims during periods of intense congestion, their shared

Table 2

Communicable and non-communicable diseases hazards at the Hajj

Communicable hazards	Non-communicable hazards
Meningococcal meningitis	Trauma e.g. stampede and motor vehicle accident
Respiratory tract infections (upper and lower) including tuberculosis, viral infections and community-acquired pneumonia	Slaughter related injuries
Polio virus	Heat stroke and heat exhaustion
Blood-borne diseases	Sunburn
Food poisoning	Dehydration
Zoonotic diseases	Fire related injuries

sleeping accommodations (mainly in tents) and the dense air pollution all combine to increase the risk of airborne respiratory disease transmission. A viral etiology of upper respiratory tract infection (URTI) is most commonly implicated at the Hajj but bacterial superinfection often follows. More than 200 viruses can cause URTI but at the Hajj the main culprits are respiratory syncytial virus (RSV), parainfluenza, influenza and adenovirus [11].

The intense congestion, living in close proximity with vast crowds and the increasing percentage of elderly pilgrims, are all factors magnifying tuberculosis (TB) risk. Additionally many Muslims travel from countries of high TB endemicity. The exact risk of TB transmission among pilgrims is difficult to quantify. A study among 357 Singaporean pilgrims revealed that 10% showed a substantial rise in immune response to the QuantiFERON TB assay antigens post-Hajj when compared to a pre-Hajj test [12].

Pertussis is another respiratory tract infection of concern during Hajj. One study found a high incidence of pertussis in Hajj pilgrims with an overall incidence of pertussis (1.4%) during this one month long pilgrimage [13] Hajj pilgrims would therefore benefit from pertussis vaccination prior to their departure.

In an attempt to reduce the risk of respiratory tract infections during the Hajj, the Saudi MoH encourages pilgrims to wear surgical face mask when in crowded places. In addition the MoH recommends that international pilgrims be vaccinated against seasonal influenza before arrival into the kingdom of Saudi Arabia with World Health Organization approved strains specific to the northern or southern hemispheres, particularly those with pre-existing conditions (e.g. the elderly, people with chronic chest or cardiac, hepatic or renal disease). In KSA seasonal influenza vaccine is recommended for internal pilgrims particularly those with pre-existing conditions and all healthcare workers working in the Hajj premises.

Blood-borne diseases

Muslim men observe completion of a successful Hajj by shaving their heads. Head shaving is an important means of transmission of blood-borne disease, including hepatitis B, C and HIV. Illegal unlicensed barbers continue to operate at the Hajj, shaving hair at the roadside with non-sterile blades, which are re-used on multiple scalps. The Saudi MoH encourages all pilgrims to receive the full series of hepatitis B vaccination prior to travel to Hajj [1] As well all pilgrims should avoid unlicensed barbers and seek approved licensed barber facilities at the Hajj premises to shave their heads [1].

Diarrhoea and food poisoning

Traveller's diarrhoea is common during the Hajj, although few studies have documented its incidence and etiology. The last study was done in 2002 showing that diarrhoea was the third most common cause for hospitalisation during Hajj. Cholera, an acute bacterial enteric disease caused by Vibrio cholerae accounted for several outbreaks after the Hajj [14,15]. The last reported by the MoH was in 1989 affecting 102 pilgrims. Significant improvement in water supply and sewage treatment has eliminated such outbreaks. Concerns still persist about importing cholera with pilgrims from affected countries which will cause widespread outbreaks in Mecca. The MoH has strict guidelines on food importation by pilgrims. Food carried by visitors and pilgrims is banned and not allowed into the country. Only properly canned foods and in very small amounts, enough for one person for the duration of the visit are allowed.

Poliomyelitis is an acute viral infection that is acquired by fecal-oral or oral transmission. International spread of polio through pilgrimage is a major concern for Saudi Arabia. Only four countries (Afghanistan, India, Nigeria and Pakistan) have never completely interrupted the transmission of wild polio virus. All pilgrims from these four countries, regardless of age and vaccination status, should receive one dose of oral polio vaccine (OPV). Proof of OPV vaccination at least six weeks prior departure is required to apply for an entry visa for Saudi Arabia. These travellers will also receive a dose of OPV at border points when arriving in Saudi Arabia. All visitors age under the age of 15 travelling to Saudi Arabia from countries reinfected with poliomyelitis should be vaccinated against poliomyelitis with OPV. Proof of OPV vaccination is required six weeks prior to the application for an entry visa. Irrespective of previous immunization history, all visitors under 15 years arriving in Saudi Arabia will also receive a dose of OPV at border points.

Non-communicable hazards at the Hajj

When Hajj falls during the summertime temperatures in the Hajj premises may reach from 37 to 45°C. Heat exhaustion and heat stroke could become a major cause of morbidity and mortality in pilgrims if appropriate precautions are not taken such as reducing their level of activity, drinking additional water, consume salty food and increase the amount of time they spend in air conditioned environment [16]. Other hazards include trauma/crush injuries and fire related injuries

Pre- and post-Hajj travel advice

Hajj presents a unique challenge that impacts the international public health as an increasing number of humans become more mobile. Clinicians everywhere must be aware of potential risks disease transmission and suggest appropriate strategies, which can be applied before departure and implemented in the field. Practitioners must also be aware of the risks presented by the returned pilgrim, and be alert to diagnose post-Hajj illness.

Increasingly, international collaboration (in planning vaccination campaigns, developing visa quotas, arranging rapid repatriation, managing health hazards

at the Hajj and providing care beyond the holy sites) has become essential. Planning and supporting Hajj has become a forum for collaboration crossing any political considerations. The Saudi MoH every year publishes the Hajj requirements for the upcoming Hajj season which is a good guide to all needed precautions to ensure safe Hajj for all pilgrims. This year Hajj recommendations were published in the Journal of Infection and Public Health [17] and will be published the WHO WER issue No.43, Volume 85, scheduled for release 22 October 2010.

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Outbreak of Legionnaires' disease in a nursing home, Slovenia, August 2010: preliminary report

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We report an outbreak of Legionnaires' disease in a nursing home in Slovenia in August 2010 affecting 15 of 234 residents. To date, Legionnaires' disease has been confirmed in four patients. Further serum analyses and genotyping of isolates are ongoing. The building's water distribution system with dead end sections has been identified as the probable source of infection.

The regional institute of public health Celje, Slovenia, was informed on 19 August 2010 that one resident from a nursing home in the region had been hospitalised with pneumonia caused by *Legionella pneumophila*, serogroup 1. On 20 August 2010, an epidemiological investigation was launched that revealed an outbreak of Legionnaires' disease with the onset of symptoms in the first case on 8 August. For the investigation of the outbreak, the case definition of the European Working Group for *Legionella* Infections were applied [1]. A case was classified as confirmed when they met the clinical and laboratory criteria for Legionnaires' disease [2].

In total, 15 of 234 residents of the nursing home showed clinical signs of the Legionnaires' disease between 8 August and 28 August 2010 (Table, Figure). The average age of cases was 55 years (ranging from 37 to 80 years) and 10 were male. None of them had left the institution during the incubation period. No further cases have been detected as of 29 September 2010.

In the following short report we would like to share our experience with others who have been involved in management of similar outbreaks.

Clinical findings and hospitalisation

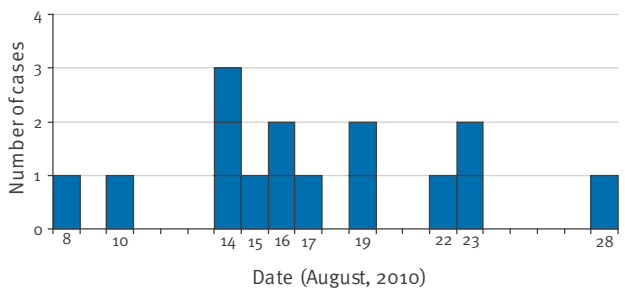
All patients in this outbreak had fever (≥39oC) and some experienced dyspnoea (n=5), coughing (n=5), muscle and joint pain (n=4), chills (n=2), malaise (n=2), abdominal pain (n=2) and vomiting (n=2). Three patients experienced confusion, restlessness and/or headache. Twelve patients were mentally or psychologically impaired and in addition, patients had other pre-existing illnesses including conditions following ischaemic cerebrovascular insult, diabetes, asthma, chronic obstructive lung disease, urogenital cancer, plasmocytoma, spastic tetraparesis, multiple sclerosis and arterial hypertension (Table). Nine patients were smokers and two were former alcohol addicts. One patient was receiving immunosuppressive therapy during the incubation period for *Legionella*.

The C reactive protein values from samples taken at the onset of each patient's symptoms ranged from 100 to 350 mg/L.

Six patients were hospitalised with a medium length of hospital stay of 7.5 days (ranging from 2 to 15 days). Chest radiographs, taken from these six patients at various times of their hospitalisation, showed an infiltrate. Three of them received antibiotic therapy with fluoroquinolone (moxifloxacin) which is appropriate for *Legionella* [3, 4]. One patient, who was admitted with heart failure eight days before the index case, was not subject to diagnostic tests for Legionnaires' disease at that time. After the index case was confirmed, we also tested his serum for *Legionella* with a positive result for IgG (1:512) (IgM ‹1:16), urine tested negative. The two patients, hospitalised before the index case was confirmed.

Figure

Epidemic curve for Legionnaires' disease cases by date of onset of symptoms, Slovenia, August 2010 (n=15)



The remaining nine patients were treated as outpatients. Before the index case with Legionnaires' disease was identified on 19 August 2010 they had received antibiotics that were not appropriate for legionellosis. After *L. pneumophila* was suspected as the cause of their disease, they were treated with fluoroquinolone antibiotics.

None of the 15 patients identified in the outbreak needed mechanical ventilation. All made a full recovery.

Laboratory investigations

The microbiological diagnostics were performed by the regional microbiology laboratory in Celje and the Institute of Microbiology and Immunology at the medical faculty in Ljubljana. Urine samples from the 11 patients were analysed using the BinaxNOW immunochromatography test. We have confirmed four cases positive for soluble antigen against *L. pneumophila* sg. 1 in the urine (Table). We could not collect urine samples from four incontinent patients.

Sputum for cultivation and identification of *Legionella sp.* was collected from six patients, who were able to produce enough material. Samples were analysed by real-time PCR using the reagent set *Legionella* species r-gene Primers/Probe (Argene) with the DICO Ampli r-gene DNA as internal control. For two patients, *Legionella sp.* DNA was confirmed in the sputum, and for one of these two, *L. pneumophila* sg. 1 was additionally confirmed through cultivation (Table). Genotyping of the isolates is currently in progress.

First blood samples were collected from 14 patients and analysed for specific IgM and IgG antibodies against *Legionella pneumophila* sg. 1-14 by indirect immunofluorescence (R-Biopharm) (Table). Serological investigation of paired sera is ongoing.

Environmental investigation and control measures

After the outbreak was identified on 20 August, a chemical disinfection of the cold and hot water system was done in the nursing home [5]. In addition, thermal disinfection was used for the hot water distribution system. Interventions also included maintaining appropriate water temperature of 55°C for hot water and below 20°C for cold water and disinfectant concentration, ensuring unobstructed flow in the hot and cold water distribution system by additional rinsing, identification and

Table

Laboratory results and existing conditions of Legionnaires' disease cases, Slovenia, August 2010 (n=15)

Patient	Onset of disease	Hospitalised	Urine sample	Sputum sample	Sputum sample	Serum 1. sample	Serum 1. sample	Existing conditions
				Culture	PCR	IgM	IgG	
1	8 August	No	Negative	Negative	Negative	1:128	1:256	Schizophrenia, head injury
2	10 August	Yes	Negative	-	-	<1:16	1:512	Schizophrenia
3	14 August	No	Negative	Negative	-	1:16	<1:128	Schizophrenia
4	14 August	Yes	Positive	-	-	-	-	Ischaemic cerebrovascular insult, arterial hypertension
5	14 August	No	-	-	-	1:64	<1:128	Epilepsy, cerebral atrophy
6	15 August	Yes	Positive	Positive (*L. pneumophila* sg. 1)	Positive	1:128	1:512	Schizophrenia
7	16 August	Yes	Positive	-	-	-	-	Schizophrenia
8	16 August	No	Negative	-	-	1:256	1:2048	Schizophrenia, diabetes
9	17 August	No	Negative	Negative	-	01:16	<1:128	Schizophrenia
10	19 August	No	Negative	-	-	01:16	<1:128	Asthma
11	19 August	No	-	-	-	01:16	<1:128	Chronic obstructive lung disease, urogential cancer
12	22 August	No	-	-	-	<1:16	<1:128	Oligophrenia
13	23 August	No	-	-	-	01:32	1:256	Dementia
14	23 August	Yes	Negative	Negative	Negative	01:16	<1:128	Schizophrenia, spastic tetraparesis, multiple sclerosis
15	28 August	Yes	Positive	Negative	Positive	<1:16	<1:128	Plasmocytoma

Negative means negative laboratory result.
Positive means positive laboratory result.
"-" means the sample was not taken (patients were not able to produce enough material).

removal of dead end sections, removal of sediment, cleaning of meshes, and inspection of problem areas where the water temperature and/or disinfectant concentration were found to be inadequate. In addition, we recommended that exposure of the residents to aerosols should be avoided (prohibition of showering and bathing). Considering the underlying conditions of the residents, we recommended brushing teeth with bottled water and drinking either bottled water or tea [6]. All these measures were performed until 17 September.

On 20 August 2010 we collected 23 environmental samples at the nursing home from different locations for cold and hot water before and after rinsing (sink faucets and shower heads in the shared bathrooms, sink faucets in the patient rooms, air condition devices, etc.). The presence of *Legionella* was confirmed according to the ISO standardised method using the Oxoid *Legionella* Latex Test, which can identify the following serotypes: *L. pneumophila* serotype 1, *L. pneumophila* serotype 2-14, and *Legionella sp.* [7], *L. pneumophila* serotype 1 and *L. pneumophila* serotype 2-14 and *Legionella sp.* was detected in concentrations ranging from ≤ 10 to 61,000 colony forming units (CFU)/1,000 ml.

Following the interventions described above, until 6 September, we collected additional 30 samples to monitor the effect of implemented measures. The results of environmental sample testing after the interventions ranged from ≤ 10 to 14,000 CFU/ 1,000 ml. According to these values, the disinfection in some places was inadequate and the interventions followed by sample testing had to be repeated [5]. We repeated 13 environmental samples. The results of repeated samples ranged from ≤ 10 to 80 CFU/1,000 ml and only *Legionella sp.* was isolated.

Genotyping of the environmental and human isolates is currently in progress.

Conclusions

We describe the first confirmed outbreak of Legionnaires' disease in residents of a nursing home in Slovenia. The underlying conditions of affected patients were relevant in this outbreak similarly to what has been described in the scientific literature [6,8]. The combination of several factors hindered earlier detection and control of this outbreak: the delayed x-ray examination of the first hospitalised patients, and the fact that the first four patients were treated in three different hospitals so that it was more difficult to establish a link between the cases. An earlier x-ray examination would have lead to the earlier detection of pneumonia and eventually Legionnaires' disease and environmental investigations could have started more timely. However, the rapid and positive interdisciplinary cooperation of epidemiologists and hygienists in the region after the detection of the index case has enabled us to control the outbreak shortly hereafter. The fact that no further cases have been detected as of 28 August 2010, indicates that the measures taken to control the outbreak have been successful so far.

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Decrease in number of genital *chlamydia* cases in Norrbotten, Sweden, October – November 2009: an indirect effect of pandemic influenza A(H1N1)?

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A sudden reduction in the number of reported genital chlamydia cases was observed in Norrbotten County, Sweden, during October to November 2009. After exploring other possibilities, such as a reduction in the number of chlamydia tests analysed or a new *Chlamydia trachomatis* variant that had been undetected in standard laboratory tests, it was found likely that the decrease was an indirect effect of the 2009 influenza A(H1N1) pandemic due to reduced social interactions among young adults.

Background

Genital chlamydia infection has been a mandatorily notifiable disease in Sweden since 1988 [1]. Contact tracing is also mandatory for every case [1]. Since October 2009, the number of reported cases of genital chlamydia has decreased dramatically in Norrbotten, the northernmost Swedish county, which has a sparse population of 250,000 inhabitants. When comparing the number of monthly reported cases of genital *Chlamydia trachomatis* infections during the period January 2008 to October 2009 with that from November 2009 to July 2010, a 37% reduction was seen. This represents a fall in the monthly incidence from 33 per 100,000 population to 21 per 100,000 population. We have therefore investigated the possible causes of this sudden decrease.

Number of genital chlamydia tests conducted

One possible explanation for the decrease in the number of reported genital chlamydia cases is that there had been a reduction in the number of people tested for *C. trachomatis*. All *C. trachomatis* samples in the county are analysed at the microbiology laboratory at Sunderby Hospital in Luleå, Sweden. When comparing the mean number of monthly *C. trachomatis* tests at the laboratory during the period January 2008 to October 2009 with that from November 2009 to July 2010, there had been only a 13% reduction (Figure 1), from 1,004 to 877 tests. The reason for this slight drop is not known. During August to September 2010, the number of tests increased again, and reached the level seen before October 2009. As the number of genital chlamydia cases fell by 37% during November 2009 to July 2010, however, it would seem that a reduction in testing was not the main explanation for the fall in the number of reported cases. As seen in Figure 1, by September 2010 the number of reported cases of genital chlamydia had reached the level seen before October 2009.

Testing for a new variant of *C. trachomatis*

The spread of a new variant of *C. trachomatis* in Sweden, which had been initially undetected due to a deletion in the cryptic plasmid, has been described previously [2,3]. In order to exclude the presence of a new, undetected variant, urine samples from 165 consecutive cases during March to April 2010 that were found to be *C. trachomatis* negative by real-time DNA amplification assay, using ProbeTec ET (Becton Dickinson), were analysed for the *C. trachomatis* ompA gene at the Section of Clinical Bacteriology, Department of Medical Sciences, Uppsala University, Sweden, using a modified method previously described [4] with other outer primers [5]. If a previously unknown variant had caused the decrease, at least five additional cases would have been found by this method. However, all samples were negative. We therefore consider it unlikely that there has been a new *C. trachomatis* variant circulating that has not been detected in standard laboratory tests.

Number of sexual partners among persons with genital chlamydia

In Norrbotten County, the number of sexual partners found per laboratory-confirmed case of genital chlamydia is used to monitor the quality of contact tracing. The number of sexual partners of confirmed cases, determined through contact tracing, was not seen to decrease from the period January 2008 to October 2009 to that from November 2009 to September 2010 (Figure 2). Although contact tracing might not reveal the true number of partners, it seems unlikely that a sudden decrease in the actual number of partners would have passed unnoticed with this method. Hence, we consider that a sudden decrease in the number of

Figure 1

Reported cases of genital chlamydia and samples analysed for *Chlamydia trachomatis* (two-week moving averages), Norrbotten County, Sweden, by month, January 2008 – September 2010

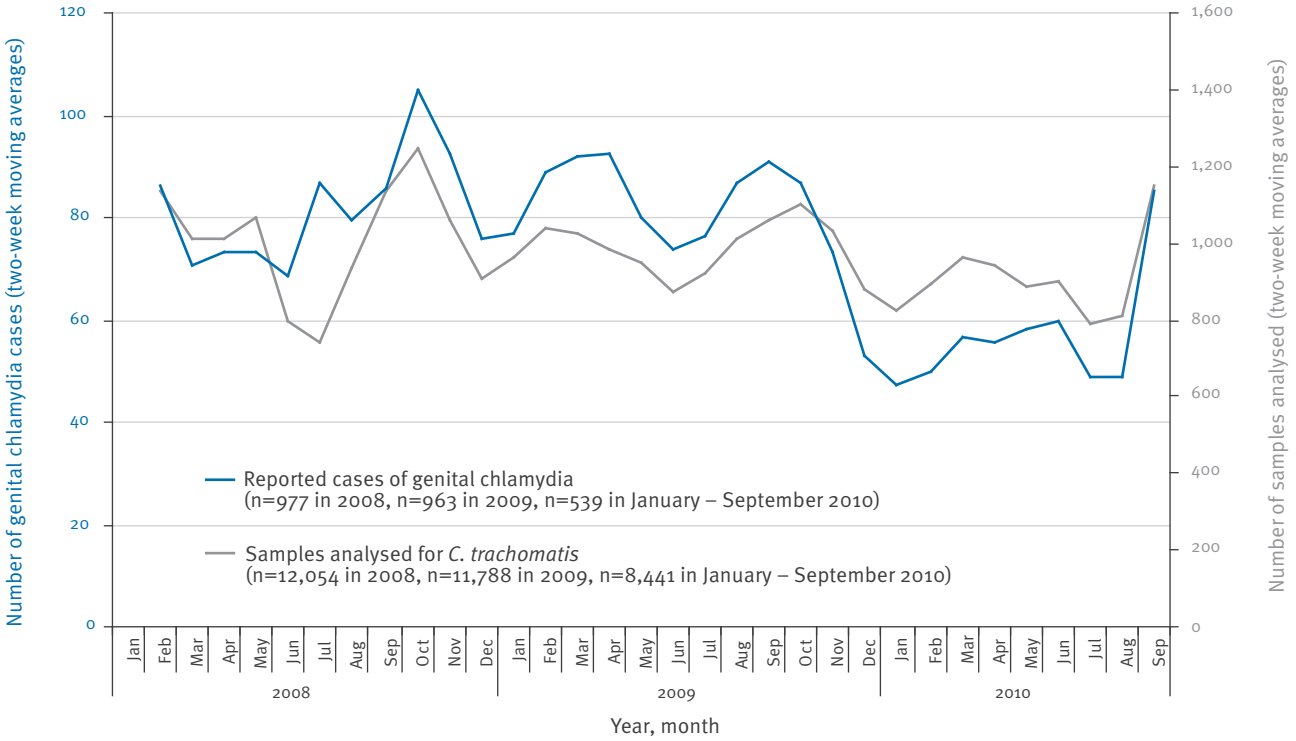
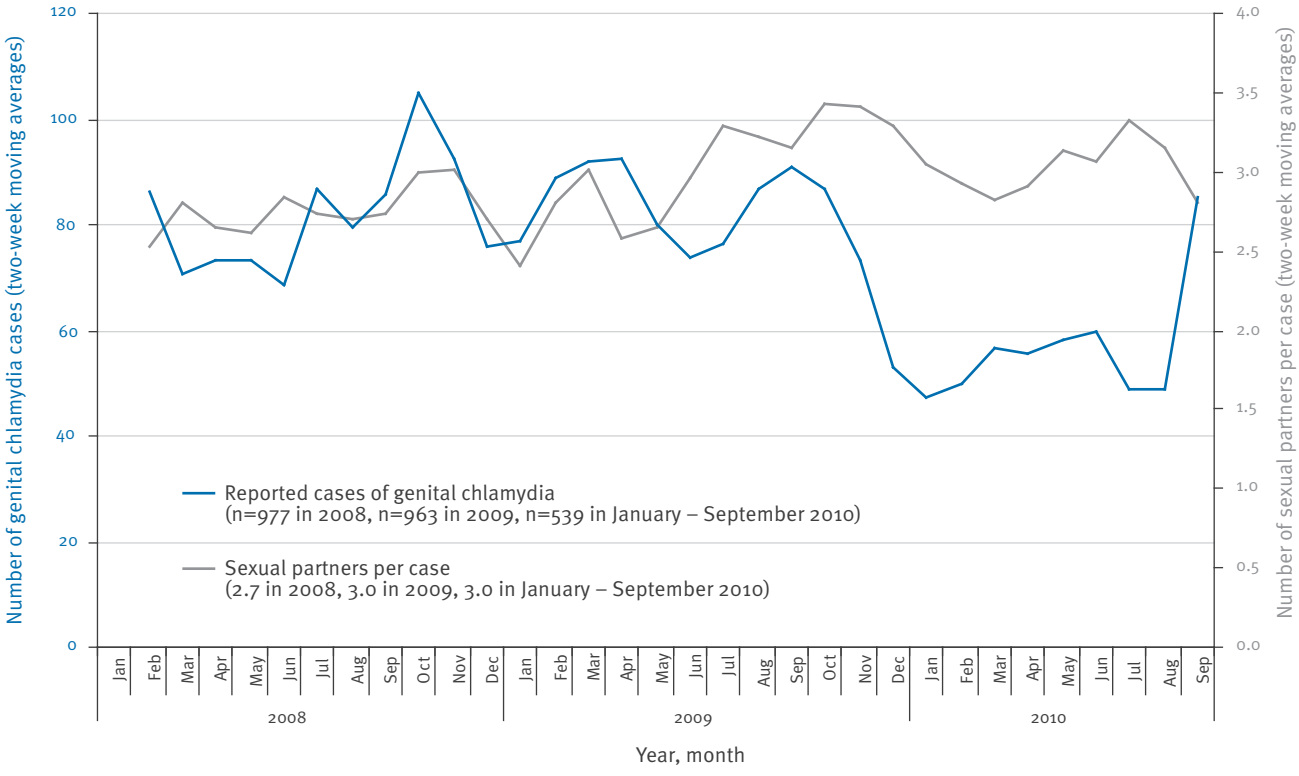


Figure 2

Reported cases of genital chlamydia and sexual partners per case determined by contact tracing (two-week moving averages), Norrbotten County, Sweden, by month, January 2008 – September 2010



sexual partners among persons with confirmed genital chlamydia is not a plausible explanation for the observed decrease in the number of reported cases of *C. trachomatis* infection.

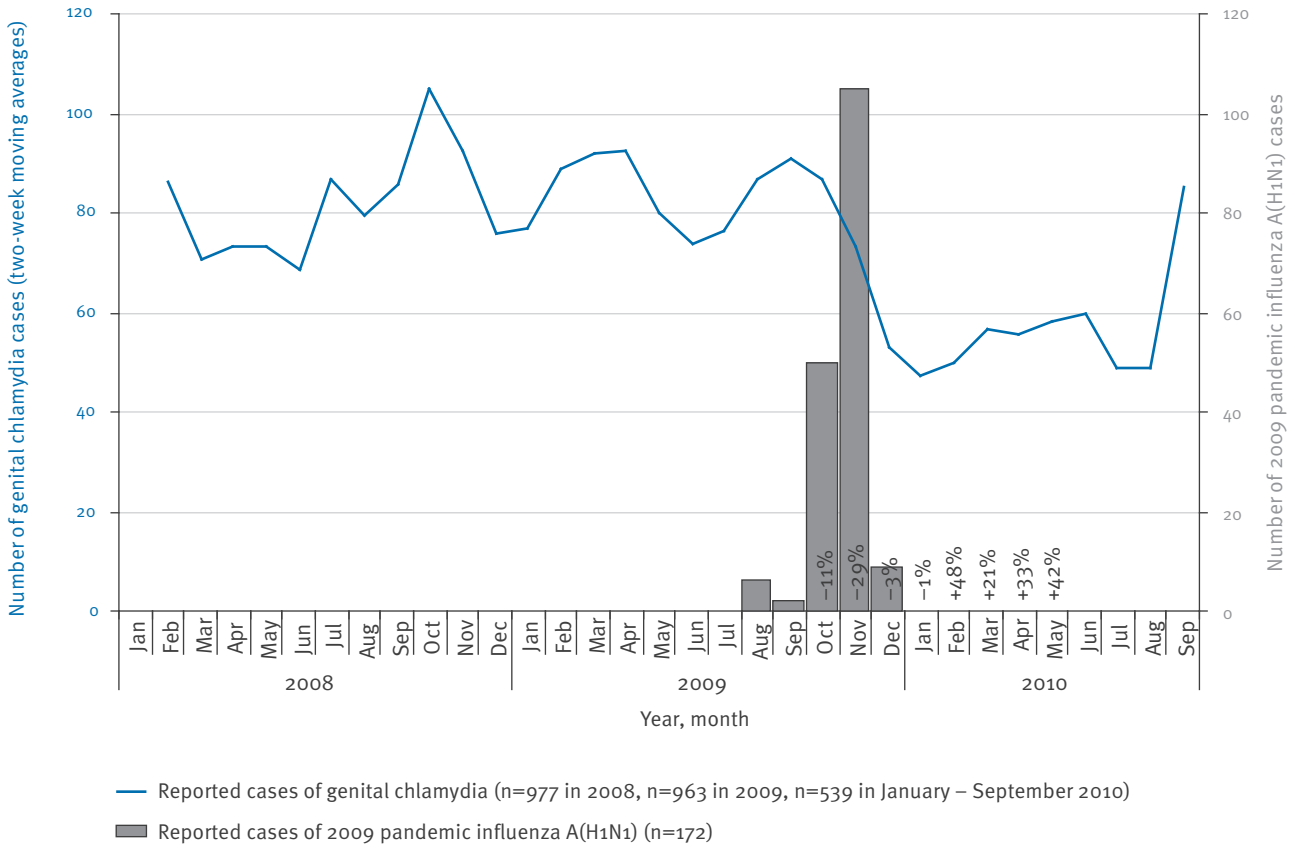
Effect of pandemic influenza on social interactions among young adults

Assuming that social interactions at nightclubs are related to sexual interactions, and thus may affect the spread of genital chlamydia, we also analysed whether the 2009 pandemic influenza A(H1N1) might have hampered nightclub visits among young adults. We chose to study the attendance of persons aged 18 to 25 years at the largest nightclub in the major city of the county as a representative of such social interactions. The nightclub usually opens in late September and closes at the end of May. During October to December 2009, the nightclub registered 15% fewer visitors compared with the same period the previous year. During the period January to May 2010, the number of visitors increased to a level exceeding that of the corresponding period in 2009 by 28%. There is a clear concurrence between the influenza A(H1N1) pandemic in the region, the reduction in the number of nightclub visitors, and the dramatic decrease in number of reported genital chlamydia cases (Figure 3). Considering the increase in the number of nightclub visitors during February to May 2010, the monthly number of reported genital chlamydia cases would be expected to increase accordingly. As seen in Figure 3, by September 2010 the number of reported genital chlamydia cases has climbed to the level seen before October 2009 and the pandemic influenza A(H1N1) in the region.

In summary, the sudden decline in reported genital chlamydia cases in Norrbotten County, Sweden, from October to November 2009 was unlikely to be explained by fewer persons being tested or by a new *C. trachomatis* variant that had escaped detection. No new prevention programmes for sexually transmitted infections were introduced in the county after 2008, and it seems unlikely that earlier interventions could explain the sudden decline. However, there is an obvious coincidence in time between the regional occurrence of the 2009 pandemic influenza A(H1N1), the reduction of social interactions among young adults, and the dramatic decrease in the number of reported genital chlamydia cases. Thus, it seems likely that this reduction in the number of reported genital chlamydia cases was an indirect effect of the influenza pandemic. This is supported by the fact that in September 2010 the number of reported genital chlamydia cases had

Figure 3

Reported cases of genital chlamydia (two-week moving averages), number of reported 2009 pandemic influenza A(H1N1) cases, and percentage difference in number of nightclub visitors, Norrbotten County, Sweden, by month, January 2008 – September 2010



Percentages in black show the monthly recorded increase or decrease in the number of nightclub visitors compared with the numbers seen in the same month the previous year.

climbed to the level seen before October 2009 when the influenza pandemic occurred in the region.

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Hepatitis C virus infection in HIV-infected men who have sex with men: sustained rising incidence in Antwerp, Belgium, 2001–2009

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During the last decade, outbreaks of acute hepatitis C virus (HCV) infection have been reported among human immunodeficiency virus (HIV)-infected men who have sex with men (MSM) in several European countries. To study this emerging infection in MSM in Antwerp, Belgium, we reviewed all cases of newly acquired HCV infection in HIV-positive MSM followed from 2001 to 2009 at the HIV/sexually transmitted infection (STI) reference clinic of the Institute of Tropical Medicine in Antwerp. Newly acquired HCV infection was considered as certain or probable according to local definitions. During the study period, 69 episodes of newly acquired HCV infection (40 certain and 29 probable) were diagnosed in 67 HIV-infected MSM. In only 10 episodes (14%) were the patients symptomatic. The annual incidence of HCV infection in our population of HIV-infected MSM rose steadily from 0.2% in 2001 to 1.51% in 2008, and then peaked to 2.9% in 2009. For 60 episodes (87%), another STI (mainly syphilis and lymphogranuloma venereum) had been diagnosed within the six months before the diagnosis of HCV infection. All but one patient with available genotyping (n=54) were found to be infected with the difficult-to-treat HCV genotypes 1 or 4. Our results therefore demonstrate the rising incidence of HCV infection in HIV-positive MSM in Antwerp, since 2001, which reached an alarming level in 2009. Targeted awareness campaigns and routine screening are urgently needed to limit further HCV spread and its expected long-term consequences.

Introduction

Since 2000, the prevalence and incidence of hepatitis C virus (HCV) infections have increased in human immunodeficiency virus (HIV)-infected men who have sex with men (MSM) in large cities in the Netherlands [1], United Kingdom [2], France [3], the United States [4] and Australia [5]. Although sexual transmission of HCV is known to be rather inefficient in discordant heterosexual couples, recent observations suggest that this is the most likely mode of HCV acquisition among HIV-infected MSM [1,6-8]. High prevalence of ulcerative sexually transmitted infections (STIs), mainly syphilis and lymphogranuloma venereum (LGV), has been reported in HIV/HCV co-infected MSM [9,10] suggesting that HCV infections among MSM epidemiologically follow the epidemics of syphilis (observed since the beginning of 2000 [11-13]), and of LGV (which emerged a few years later) [14-16]. Recently, rough sexual techniques such as fisting and use of recreational drugs, in particular gamma hydroxyl butyrate (GHB), have been identified as independent risk factors for HCV transmission in MSM, beside intravenous drug use (IDU) and HIV infection [1,7,17]. In addition, phylogenetic analyses have revealed a high degree of HCV clustering among HIV/HCV co-infected MSM in Amsterdam, the Netherlands [1,7] and the existence of a large, international network of HCV transmission in HIV-positive MSM has been demonstrated in several European countries [18].

Hepatitis C is therefore increasingly perceived as an emerging and expanding STI in HIV-infected MSM. It is well known that the clinical management of HIV/HCV co-infection is complex [6] and poses specific epidemiological challenges [7,8], hence the importance of surveying the incidence and prevalence of HCV infection in this specific group. The main purpose of this study was to quantify the rising number of new HCV infections in HIV-infected MSM in the HIV/STI reference clinic of the Institute of Tropical Medicine, Antwerp, Belgium, over the past decade. A second objective was to document the current management and clinical outcome of these co-infected patients.

Methods

A retrospective study was conducted at the reference HIV/STI clinic of the Institute of Tropical Medicine in Antwerp. By the end of 2009, 1,844 HIV-positive individuals had been actively followed up in our clinic (in 2001, there were 914). Some 70% of these were men; half of them had acquired their HIV infection through homo- or bisexual contacts. For this study, we reviewed the records of all HIV-infected MSM who had been

diagnosed with a newly acquired HCV infection from January 2001 to December 2009.

The standard HIV management during the study period was as follows: HIV-positive individuals were seen by a physician and screened for HIV-related co-infections (including viral hepatitis) at the first consultation in our clinic. They were seen thereafter every three to four months for routine clinical HIV care and for laboratory measurements, including regular determination of the CD4 cell count, the HIV RNA load, and level of liver alanine aminotransferase and aspartate aminotransferase. Additional consultations were possible at any time between routine visits for any health problem including suspicion of another STI. Patients with a negative HCV serological result at the initial HIV consultation were re-tested for HCV if there was a subsequent increase in the level of liver aminotransferases. Since 2005, (because of ongoing HCV outbreaks in neighbouring countries), HIV-infected MSM attending our clinic were also systematically tested for HCV after each STI episode or after sexual contact with an HCV-infected partner, even if the level of liver aminotransferases was normal. Also, those considered by the treating physician as being at high risk for HCV infection (for example, those with multiple sexual partners, GHB users and frequent visitors to known high-risk discotheques or saunas) were tested at least once a year for HCV.

Hepatitis C virus tests

The HCV test used for serological screening throughout the study period was Vitros ECI Immunodiagnostic System (Ortho Clinical Diagnostics) and the confirmatory serological test was INNO-Line Immuno Assay HCV Score (Innogenetics). When the confirmatory serological test was positive, molecular qualitative detection of HCV RNA was performed using COBAS Amplicor HCV test, version 2.0 (Roche Diagnostics), with a detection limit of 50 IU/mL. If genetic material (HCV RNA) was detected by qualitative testing, it was then quantified by reverse transcription polymerase chain reaction, using the COBAS Amplicor HCV Monitor Test, version 2.0 (Roche Diagnostics), with a detection limit of 600 IU/mL). Since November 2006, qualitative as well as quantitative molecular HCV RNA testing was performed using Abbott RealTime HCV assay. If molecular testing was positive, viral genotyping was performed by line probe assay: up to 2006, INNO-LiPA (Innogenetics) was used; since 2006, Versant HCV genotype 2.0 assay LiPA (Siemens) According to the manufacturer, genotyping was expected to be successful in 95% of samples with HCV RNA levels greater than 1,000 IU/mL.

Definitions of newly acquired HCV infection

We defined an episode of newly acquired HCV infection as certain if HCV-antibody seroconversion could be documented, that is, a screening serological test and a confirmatory serological test were positive, and the screening test had been negative in the previous 24 months. A newly acquired HCV infection was considered as probable if both the screening and confirmatory serological tests were positive and aminotransferase levels were elevated, with exclusion of other causes of hepatitis, in a person with a negative serological test documented longer ago than the previous 24 months. This limit of 24 months was chosen pragmatically in this study for diagnosing a recent HCV infection, since HCV testing was not done systematically in the early phase of the study. However, on the basis of these definitions, we excluded patients newly diagnosed simultaneously with HIV and HCV infections and patients who had never been tested previously for HCV before their HCV diagnosis. In such cases the duration of HCV infection is unknown and we would probably have included a substantial number of chronically infected patients who were not necessarily epidemiologically linked to the increase in HCV infection observed since 2001.

Determination of level of liver aminotransferases

The level of liver aminotransferases was determined on the day of HCV diagnosis. The serum level of the alanine aminotransferase (ALT) enzyme was graded according to the following scale:

- grade 0 – normal value of alanine aminotransferase;
- grade 1 – between the upper limit of normal (ULN) of alanine aminotransferase and 2.5 times the ULN;
- grade 2 – between 2.5 and five times the ULN;
- grade 3 – between five and 10 times the ULN;
- grade 4 – more than 10 times the ULN.

Testing and treatment of patients

Patients diagnosed with newly acquired HCV infections were retested six months later to determine whether they remained chronically infected (presence of HCV RNA persisting after six months). In such cases, liver biopsy was systematically offered according to the current standard of care in Belgium for HIV patients chronically infected with HCV. All patients with viral or histological criteria for therapy were offered standard combination treatment of pegylated interferon and ribavirin for one year.

Incidence calculations

To calculate the annual incidence of reported newly acquired HCV infection, the total number of episodes diagnosed each year (certain and probable infections) was divided by the mean of the number of HIV-infected MSM actively followed at the beginning and at the end of the relevant year.

Associated sexually transmitted infections

An STI was considered as associated with the newly acquired HCV infection when it had been diagnosed within six months before the diagnosis of HCV infection. STIs were diagnosed by culture or molecular demonstration of pathogens in relevant fluids or secretions, or by unequivocal serological results (seroconversion or single high antibody titre against *Treponema pallidum* and/or *Chlamydia trachomatis*) in a suggestive clinical context.

Results

A total of 69 episodes of newly acquired HCV infection (40 certain, 29 probable) were retrospectively diagnosed in 67 HIV-infected MSM from 2001 to 2009 (Table 1). Two patients had a second HCV infection after documented spontaneous clearance of the virus. Two of the 67 patients reported intravenous drug use. The origin of all but four patients was a European country (mostly Belgium, n=59). The mean age of the patients was 41 years (range: 21–58 years). The median duration of HIV infection before HCV diagnosis was 47 months (range: 1–211 months). At HCV diagnosis, the median CD4 cell count was 508/µL (range: 13–1,355); 56 patients were undergoing antiretroviral therapy and 51 of them had a level of HIV RNA below 400 copies/mL (with no significant differences between certain and probable episodes). Eight of the 67 patients had also chronic hepatitis B. Of note, an additional 11 HCV infections, although clinically very suspect, were not included because recent HCV acquisition could not be ascertained (as no anti-HCV screening had been available before the HCV diagnosis).

The annual incidence of reported newly acquired HCV infection (confirmed and probable) among the HIV-infected MSM is shown in Figure 1. The incidence rose from 0.2% (0.2 infections per 100 HIV-infected MSM) in 2001 to 2.9% in 2009 and doubled from 2008 to 2009. When considering confirmed infections only, the incidence rose from 0% in 2001 to 2.3% in 2009. For the patients with certain newly acquired HCV infection, the median interval between last negative HCV serological result and HCV diagnosis was nine months (range: 3–24); for the patients with probable newly acquired HCV infection, the median interval was 32 months (range: 25–61).

As shown in Table 2, HCV testing was performed between routine visits in 10 episodes because the patients presented with symptoms: acute jaundice (n=5), severe asthenia (n=3) and nausea and vomiting (n=2).

Diagnosis of HCV infection was made for 55 asymptomatic episodes because of an increase in the serum level of alanine aminotransferase at a routine visit and in the four remaining episodes without any suggestive clinical or laboratory abnormality through systematic screening because of high-risk behaviour or STI occurrence. At HCV diagnosis, in only a minority of episodes (31; 45%) patients presented with moderate to severe elevation of the serum level of liver alanine aminotransferase (more than five times the ULN).

STIs were documented together with or within the previous six months of the HCV diagnosis in 60 (87%) of all episodes. The STIs diagnosed were syphilis (n=27), LGV (n=18), both syphilis and LGV (n=12), gonorrhoea (n=2) and genital herpes (n=1). Gonococcal infection was present in two additional patients: in one of these patients, it was present together with syphilis, and in the other, together with syphilis and LGV.

Four patients were lost to follow-up before the determination of HCV RNA levels. Seven episodes of HCV infection cleared probably spontaneously (HCV RNA could not be detected despite a positive HCV confirmatory test or disappearance of HCV RNA within six months after RNA had been detected). HCV RNA was still detected more than six months after HCV diagnosis in the remaining 58 episodes (defining a chronic course of infection). Table 3 shows the viral characteristics and outcome data of those 58 who developed chronic HCV infection (as of April 2010). All but one episode with successful genotyping (n=54) were due to genotype 1 or with genotype 4, which are notoriously difficult to treat [6]. In about 70% of chronic infections (n=40), the HCV RNA load was high (greater than 850,000 IU/mL). As of April 2010, 37 patients had undergone a liver biopsy, which revealed moderate to severe fibrosis

Table 1

Annual number of episodes of newly acquired HCV infections (certain and probable) among HIV-infected men who have sex with men[a], Antwerp, Belgium, 2001–2009 (n=69)

Year	Number of HIV-infected MSM[b]	Number of episodes of newly acquired HCV infections diagnosed in HIV-infected MSM		
		Certain	Probable	Total
2001	418	0	1	1
2002	450	0	2	2
2003	508	0	1	1
2004	539	0	3	3
2005	607	2	1	3
2006	686	2	7	9
2007	756	6	4	10
2008	858	9	4	13
2009	922	21	6	27

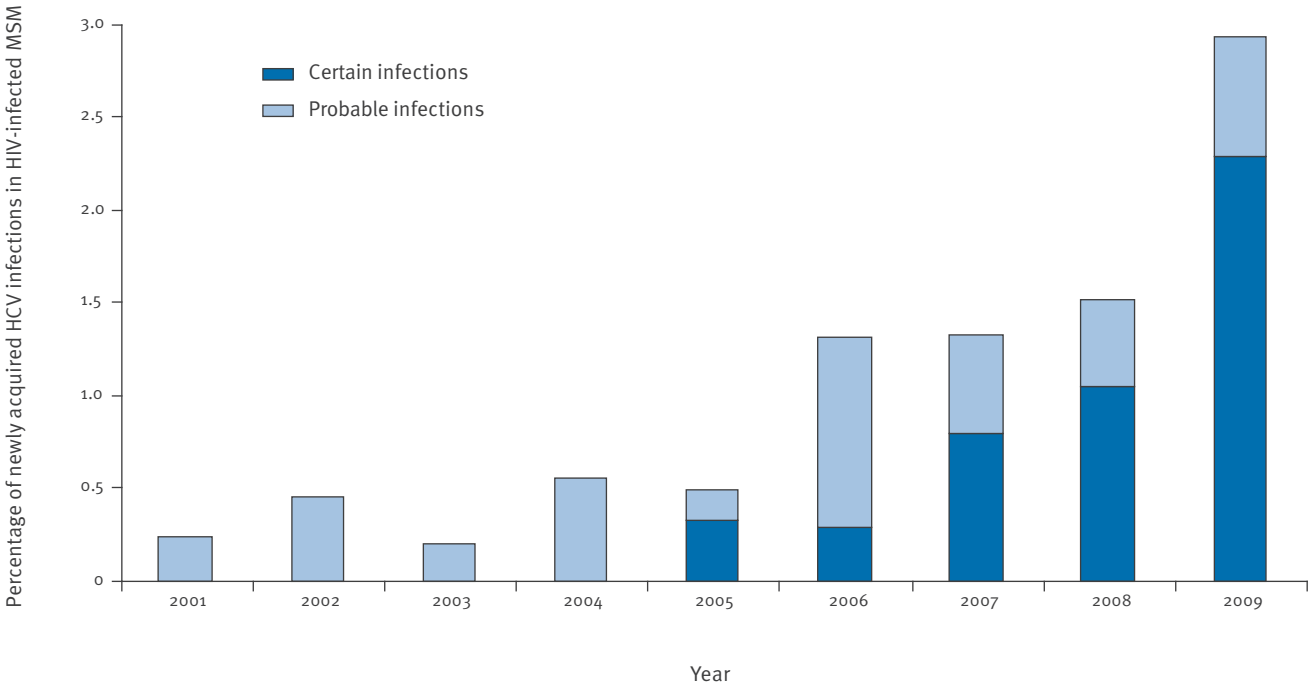
HCV: hepatitis C virus; HIV: human immunodeficiency virus; STI: sexually transmitted infection.

[a] Followed from 2001 to 2009 at the HIV/STI reference clinic of the Institute of Tropical Medicine, Antwerp, Belgium.

[b] Mean value of the numbers of HIV-infected MSM actively followed at the beginning and at the end of each relevant year.

Figure

Annual incidence of episodes of newly acquired HCV infection among HIV-infected men who have sex with men[a], Antwerp, Belgium, 2001–2009 (n=69)



[a] Followed from 2001 to 2009 at the HIV/STI reference clinic of the Institute of Tropical Medicine of Antwerp, Belgium.

Table 2

Clinical features and evolution of episodes of newly acquired HCV infection diagnosed in HIV-infected men who have sex with men[a], Antwerp, Belgium, 2001–2009 (n=69)

Feature or outcome	Newly acquired episodes of HCV infection diagnosed in HIV-infected MSM		
	Certain n=40 Number (percentage)	Probable n=29 Number (percentage)	Total n=69 Number (percentage)
Reason for HCV testing			
Clinical symptoms	5 (13)	5 (17)	10 (14)
Asymptomatic increased level of liver aminotransferases	32 (80)	23 (79)	55 (80)
Exposure to risk	3 (7)	1 (3)	4 (6)
Level of liver alanine aminotransferases at HCV diagnosis			
Grade 0 (normal values)	3 (7)	1 (4)	4 (6)
Grade 1 (between ULN and 2.5 times ULN)	11 (28)	11 (40)	22 (32)
Grade 2 (between 2.5 and 5 times ULN)	7 (18)	2 (17)	12 (17)
Grade 3 (between 5 and 10 times ULN)	9 (22)	7 (24)	16 (23)
Grade 4 (greater than 10 ULN)	10 (25)	5 (17)	15 (22)
Other STIs			
Concomitant or recent STI at HCV diagnosis	35 (87)	25 (86)	60 (87)
Evolution of episodes of HCV infection			
Probable spontaneous HCV clearance	4 (10)	3 (10)	7 (10)
Proven chronic HCV infection	34 (85)	24 (83)	58 (84)
Lost to follow-up	2 (5)	2 (7)	4 (6)

HCV: hepatitis C virus; HIV: human immunodeficiency virus; STI: sexually transmitted infection; ULN: upper limit of normal.

[a] Followed from 2001 to 2009 at the HIV/STI reference clinic of the Institute of Tropical Medicine, Antwerp, Belgium.

(stage F2 or F3 in the METAVIR histological score) in 22 of them, including 12 (56%) of 18 certain infections and 10 (53%) of 19 probable infections. Liver biopsy was performed with a median interval of seven months (range: 3–36 months) after diagnosis of HCV infection, and was refused by many patients.

As of April 2010, 27 of the patients who developed chronic HCV infection have initiated anti-HCV treatment; most (n=22) were undergoing antiretroviral therapy for HIV infection and had a CD_4 cell count of greater than 350/µL and an HIV RNA level of less than 400 copies/mL at treatment initiation. The median interval between liver biopsy and the start of HCV treatment was three months (range: 1–12). Sustained viral response to treatment (absence of HCV RNA from serum samples six months after completion of therapy) was observed in only five patients, while one patient stopped treatment because of side effects and eight did not respond (no response after three months' treatment (n=5), no response after six months (n=3)). The remaining 13 patients are still undergoing treatment or follow-up (six months post-treatment). Two patients died, one because of decompensated HCV-related cirrhosis five years after the diagnosis of acute hepatitis C (with no response to treatment) and the other because of non-Hodgkin lymphoma. No difference was observed between certain and probable infections in terms of baseline clinical and laboratory features, viral and histological characteristics, time between liver biopsy and HCV treatment, and outcome data.

Discussion

Over the last decade, we observed a sustained increase in the incidence of hepatitis C in our cohort of HIV-infected MSM. The same trend has also been reported in several HIV clinics of other European cities such as London, Amsterdam and Paris. However, the incidence we observed in 2009 (almost 3% of HIV-infected MSM) is high compared with that reported in other studies [8], suggesting that ongoing HCV transmission has reached a worrying level. In addition, the very high prevalence of other STIs in HIV-infected MSM newly infected with HCV supports the hypothesis that some STIs fuel the HCV epidemic in this population [1,6,17]. The short-term and expected long-term morbidity is of concern, given the very high proportion of patients infected with genotypes 1 and 4, the low rate of spontaneous HCV clearance, the important proportion of high HCV loads (resulting in lower response to treatment), patients' low acceptance rate of liver biopsy and HCV treatment, the sizeable subset of patients with moderate to severe liver fibrosis within a short period of time, as already observed [19] and the disappointing cure rates [20,21].

Our study has the usual limitations of a retrospective single-centre design, that is, it is highly dependent of the quality of data reporting when reporting

Table 3

Characteristics and clinical outcome of HIV-infected men who have sex with men who developed chronic HCV infection[a], Antwerp, Belgium, as of April 2009 (n=58)

Characteristic or clinical outcome	Chronic HCV infections in HIV-infected MSM		
	Certain n=34 Number (percentage)	Probable n=24 Number (percentage)	Total n=58 Number (percentage)
Genotyping			
Unsuccessful	3 (9)	1 (4)	4 (7)
Genotype 1	21 (62)	13 (54)	34 (59)
Genotype 2	1 (3)	0	1 (1.5)
Genotype 4	9 (26)	10 (41)	19 (33)
HCV RNA load			
<850,000 IU/L	11 (32)	7 (29)	18 (31)
≥850,000 IU/L	23 (68)	17 (71)	40 (69)
Liver biopsy			
Performed	18 (53)	19 (79)	37 (64)
Not performed	14 (47)	5 (21)	21 (36)
Clinical outcome			
Death	1 (3)	1 (4)	2 (4)
Not yet treated	17 (50)	12 (50)	29 (50)
Ongoing treatment or follow-up	10 (29)	3 (12)	13 (22)
Treatment stopped (no viral response; dropped out)	5 (15)	4 (17)	9 (16)
Sustained viral response	1 (3)	4 (16.5)	5 (9)

HCV: hepatitis C virus; HIV: human immunodeficiency virus; ULN: upper limit of normal.

[a] Followed from 2001 to 2009 at the HIV/STI reference clinic of the Institute of Tropical Medicine, Antwerp, Belgium.

has not been structured systematically and does not allow immediate generalisation to other settings. Also, periodic HCV screening was not systematically performed throughout the whole study period, nor was the whole MSM population of Antwerp included. It is therefore probable that some HCV infections have been missed and it is also possible that some more chronic HCV infections (without an epidemiological link to the increase of infections observed since 2001) have been included erroneously. However, we used a time-restrictive definition for probable newly acquired infections, and observed that the interval between last negative HCV test and HCV diagnosis did not exceed three years in most episodes of probable infection, This provides some reassurance that these HCV infections were rather recent and were likely to be linked to the increase seen since 2001 (although no definitive molecular proof exists). Also, episodes of certain and probable infection did not differ significantly in terms of clinical, viral, histological features and outcome, suggesting that both groups were similar and the vast majority of the HCV infections were likely to be truly recent. In fact, as mentioned, the actual incidence was probably underestimated during the first years of the study when HCV testing was performed only following clinical suspicion. Numbers reported after 2006 are more likely to reflect the actual incidence because of the much higher proportion of episodes in which there was documented seroconversion, diagnosed through enhanced clinical awareness and more systematic serological testing of patients at risk.

Establishing enhanced surveillance for HCV infection in MSM has been proven feasible [22], although the asymptomatic course of most acute HCV infections strongly complicates case detection. Most of our study participants had no symptoms and were diagnosed after routine consultation when the laboratory reported increased levels of liver aminotransferases in the samples. Also, these liver disturbances were in most episodes very moderate at the time of HCV diagnosis, and might have gone unrecognised in patients with multiple other possible causes of liver enzyme abnormality. This observation questions the accuracy of the 2007 United States Centers for Disease Control and Prevention (CDC) case definition of acute hepatitis C, which includes the presence of jaundice or alanine aminotransferase levels greater than 400 IU/L in addition to serological or molecular confirmation [23]. This case definition is very specific in diagnosing acute HCV infections but, if used as such for surveillance purposes, would miss a substantial number of true acute infections, with serious public health implications. Finally, the small subset of HCV patients with normal levels of liver aminotransferases who were diagnosed through enhanced surveillance underlines the limitation of a surveillance strictly based on laboratory findings. Research should focus on identifying the subset of HIV-infected MSM most in need of intensive follow-up, since costly and repeated molecular testing might become necessary to detect HCV re-infections in high-risk patients who would remain serologically positive even after spontaneous or post-treatment HCV clearance.

The fact that an HIV-positive patient presents with an STI is a sign of ongoing unsafe sexual practices [24]. For more than 25 years, MSM remain the group most affected by HIV and other STIs, and newly diagnosed HIV infections among MSM have been increasing in recent years [12]. Indicators commonly used for monitoring purposes, such as unprotected anal intercourse, condom use, number of sexual partners and HIV testing, all confirm the increase in sexual risk behaviour in MSM in several European countries [24]. Large transmission clusters of HIV infection have been demonstrated in MSM and serosorting – restricting unprotected sexual relations to partners claiming that they have the same (negative or positive) serostatus – which is sometimes used by HIV-negative MSM as a risk reduction strategy, may play a role in HIV transmission. A fraction of MSM who believe themselves to be HIV-negative could in fact be infected since continuous reliance on negative testing results does not adequately address the problem of the highly contagious serological window, for example [24]. Similarly, HIV-infected MSM practicing serosorting may contract HCV infection from each other: HIV infection is by itself a risk factor for HCV acquisition in MSM and HIV/HCV co-infected MSM were often unaware of their HCV serostatus [7]. In addition, the serological window for HCV is often much longer than for HIV. Nevertheless, even if sexual risk behaviour increases in MSM, the specific emergence of HCV infection in the HIV-positive population remains poorly understood. There is probably more involved than sexual transmission alone: blood–blood transmission through rough sexual intercourse or traumatic practices (with shared sex toys or external devices) is another possible route [17]. Gay-friendly Antwerp has some renowned high-risk settings for a particular group of MSM with a risk of further regional and international HCV spread [18]. We think therefore that the detection of hepatitis C in HIV-positive MSM should not only lead to the clinical consideration for HCV therapy, but also to enhanced counselling and specialised support from a psychologist and/or sexologist.

Public health action

Raising awareness and increasing risk perception are the recommended public health actions to limit the spread of viral hepatitis among MSM [7,8]. We reported the rising incidence of hepatitis C to the authorities in Belgium responsible for disease surveillance, in more detail than routine reporting. General practitioners were urged through widely read local medical journals to include hepatitis C testing for any MSM patient consulting for STI screening. The rising incidence was also picked up by the press. We also brought this growing problem to the attention of the Flemish organisation that is responsible for prevention of STIs (Sensoa). In collaboration with representatives of the gay scene, new prevention campaigns have been specifically

designed for HCV prevention in order to try to influence the target group, in particular in local risk settings and through specific Internet sites.

As reported previously, more research is needed to identify more clearly the circumstances of HCV transmission in HIV-positive MSM presenting with recurrent STIs [24]. Unprotected receptive anal intercourse, rough sexual techniques (receptive and insertive fisting) and nasal intake of recreational drugs have repeatedly been associated with increased risk of hepatitis C infection [7,17]. However, in our cohort a substantial number of infected patients do not report any of these practices (preliminary data of an ongoing case–control study). It remains unclear how far specific practices like those reported in certain hardcore clubs may also be incriminated in the spread of HCV, and to what extent the shared use of lubricants, sex toys (such as vibrators, clamps, chains and, dildos) or other more invasive devices (such as tubes for anal douching and urethral catheters) may also play a role in HCV transmission. As long as these questions are not fully answered it will be difficult to give evidence-based advice to some hard-to-reach subgroups of MSM (for example, fetishists and sadomasochists). We are now undertaking a case–control study looking at the incidence of HCV infection in our HIV-positive MSM population in relation to specific sexual practices. The reasons for the specific vulnerability of HIV-infected patients for HCV acquisition should also be clarified [7]. Further sociological and biomedical research should focus on the relative contributions of behavioural aspects (such as serosorting or traumatic practices) or of possible cellular or molecular mucosal modifications enhancing specifically STI and/or HCV acquisition in HIV-infected individuals [18].

Conclusion

Intensified and tailored surveillance is necessary to further document the rising incidence of HCV infection in MSM attending HIV/STI clinics in Europe. Identifying more accurately the risk factors for HCV acquisition and designing appropriate and highly contextualised prevention messages for risk groups are the two other major challenges healthcare providers are now facing. In the HIV-infected MSM population, HCV infection has become the most severe STI as its long-term impact may be devastating and its treatment options are far from optimal.

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Dengue virus infection in travellers returning from Benin to France, July – August, 2010

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To the editor: In a recent issue of Eurosurveillance, Gautret *et al.* report two cases of dengue fever in travellers returning from Benin [1]. The authors noted that serology tests indicated the presence of anti-dengue virus (DENV) IgM and IgG antibodies in serum samples obtained from the travellers from Benin, where limited data are available on dengue outbreaks.

In 2010, our laboratory confirmed a case of DENV-3 infection in a traveller returning from Benin [2]. Isolation of DENV-3 in both east and west Africa suggests that the serotype has emerged or re-emerged in various parts of Africa [3]. As indicated by Gautret *et al.*, further studies are needed to understand the extent of DENV-3 outbreak in Africa, and to reinforce disease surveillance.

Laboratory investigation of all suspected cases of DENV infection is conducted in Japan as a part of surveillance for imported cases of DENV infection. As of 19 September 2010, 163 imported cases of DENV infection have been reported, as required by the Japanese Infectious Diseases Control Law. All were confirmed by laboratory tests in the Japanese National Institute of Infectious Diseases or in local public health institutes. Due to the complexity of identifying DENV in the laboratory, virus isolation or a four-fold rise in acute and convalescent serum antibody titre is required for confirmatory diagnosis. In our laboratory, all suspected cases of DENV infection are tested for the virus using reverse transcription-polymerase chain reaction (RT-PCR), commercial anti-DENV IgM and IgG enzyme-linked immunosorbent assay (ELISA), virus isolation and nonstructural protein 1 (NS1) antigen ELISA. Our laboratory data and current data on evaluation of commercial kits for the detection of NS1 antigen by other investigators demonstrated that NS1 could be detected in patients with DENV infections up to 14 days after onset of symptoms [4]. It is probable that in combination with IgM and IgG assay results, as acknowledged by Gautret *et al.*, NS1 antigen ELISA may increase the confidence of the diagnosis of DENV infection in travellers [1].

As discussed by Gautret *et al.*, it is highly probable that the French travellers returning from Benin were infected with DENV-3. It is therefore important to examine if these patients develop high neutralizing antibody titres to DENV-3. Taken together, our findings and those of Gautret *et al.* suggest local DENV transmission in Benin. With the increase in the number of cases of DENV infection reported annually worldwide and the identification of local DENV infection in non-endemic areas, including France [5], more attention needs to be paid to identification of epidemics, disease management and enhanced surveillance of travellers returning from endemic areas.

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