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Autochthonous dengue fever in Croatia, August–September 2010

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After information about a dengue case in Germany acquired in Croatia, health professionals and the public in Croatia were alerted to assess the situation and to enhance mosquito control, resulting in the diagnosis of a second case of autochthonous dengue fever in the same area and the detection of 15 persons with evidence of recent dengue infection. Mosquito control measures were introduced. The circumstances of dengue virus introduction to Croatia remain unresolved.

Introduction

The epidemiology service of the Croatian National Institute of Public Health (CNIPH) has registered six imported cases of dengue virus (DENV) infection since 2007. All except one were Croatian citizens who had spent time in areas with local transmission of this disease (Southeast Asia, South America) and had a mild clinical presentation of dengue fever. The sixth case occurred in 2007 in a tourist visiting Croatia who developed haemorrhagic fever and had previously travelled in South-east Asia [1,2]. Although a seroepidemiology study conducted in 1980 in a limited area of north-eastern Croatia in healthy young inhabitants proved the presence of antibodies to DENV type 2 (3,9%) and type 1 (2,1%) [3], no cases of dengue fever were registered by the health services.

Aedes albopictus was for the first time recorded in Croatia in 2004 in the area surrounding Zagreb [4]. Within two years, *Ae. albopictus* was found on the entire territory of the Adriatic coast from northern Istria to Dubrovnik in the south. According to routine monitoring of mosquitoes and published articles, *Ae. albopictus* is now permanently established in the coastal but not yet in the continental areas of Croatia [5].

Soon after reports on the first autochthonous DENV infection diagnosed in France in September 2010 [6], the Epidemiology Service of the CNIPH was notified on 30 September by the Robert Koch Institute (RKI) in Germany of a German citizen, who fell ill with symptoms of dengue fever immediately after returning to Germany from a 15-day stay on the Pelješac peninsula in Croatia. Virological investigation revealed the presence of DENV-specific IgM, a rise in DENV-specific IgG and the presence of NENV NS1 antigen in the patient's blood [7]. As this was the first case of dengue fever probably acquired in Croatia, an epidemiological investigation was conducted and outbreak control measures implemented. We present here the first results of the epidemiological investigation.

Active case finding

According to information received by the RKI, the German citizen travelled from Germany via Austria and Slovenia along the Croatian coast in August 2010 and stayed on the Pelješac peninsula and the island of Korčula for 15 days. The disease onset was on the day after he returned to Germany. The information received from RKI on the first autochthonous case of dengue fever was sent to the World Health Organization (WHO) via the International Health Regulations (IHR) information network [8] by the national IHR focal point (the epidemiology service of the CNIPH) and disseminated to the Croatian and international public via the media in order to increase local and international awareness.

The epidemiological investigation started in Pelješac and Korčula, and will be gradually expanded to the entire Croatian littoral. The CNIPH released a circulatory letter informing all epidemiology services and hospital infectology clinics in the country to consider the possibility of dengue fever in clinically compatible cases including those with no history of travelling

abroad. The circulatory letter contained the entire range of clinical manifestations of dengue fever, and for the purposes of the epidemiological investigation, a question on diseases accompanied with fever occurring in the village where the German tourist had stayed. At the time of the first epidemiological investigation among local physicians in the beginning of October 2010, there were no such acute diseases in the area. In the following weeks, a number of clinically suspect cases were reported and serum samples were sent to the CNIPH, but tested negative for dengue virus (Anti-Dengue virus Elisa IgM/IgG, Euroimmun, Germany).

On 22 October 2010, a possible case of dengue fever was reported in a resident of the same village where the German patient had stayed. The Croatian patient, a woman in her fifties, who had not travelled outside her place of residence, developed symptoms compatible with dengue fever on 17 October, including temperature up to 39°C, skin rash, chill, headache and joint and muscle pain, and was admitted to the infectology ward at Dubrovnik hospital on day 6 after onset of disease.

Laboratory diagnosis

A serum sample was taken from the Croatian patient on admission to hospital and sent to the National Reference Laboratory for Arboviral Infections at the Virology department of the CNIPH in Zagreb. Virological analysis by ELISA (Anti-Dengue virus ELISA IgM/IgG Euroimmun, Germany) detected DENV-specific IgM (ratio 1.9). The sample was negative for DENV-specific IgG (10 relative units (RU)/ml), West Nile virus (WNV) IgM and IgG (Anti-West Nile virus ELISA IgM/IgG, Euroimmun, Germany), and chikungunya virus IgM and IgG. (Anti-Chikungunya virus ELISA, IgM/IgG, Euroimmun, Germany).The patient had not been vaccinated against yellow fever or tick-borne encephalitis (TBE). The village of residence as well as whole southern Croatia is not endemic for TBE [9]. Considering the current epidemiological situation in Croatia these laboratory results pointed to a diagnosis of dengue fever [10].

The patient's first serum was also sent to the regional reference laboratory in Ljubljana (Slovenia) where an RT-PCR was negative for dengue virus [11]. The second (paired) serum was taken on day 19 after onset of illness when the patient was already discharged and recovered, and the sample was analysed at CNIPH with the following results: DENV: IgM-positive (ratio 4.9) and IgG-positive (110 RU/ml); WNV: IgM-positive (ratio 1.2) and IgG-negative; and chikungunya virus: IgM- and IgG-negative. These results confirmed this case as the second autochthonous case of dengue fever in Croatia.

Analysis of serum samples collected in the area

We collected 14 blood samples from healthy inhabitants living near the case's place of residence. The samples were analysed by ELISA for the presence of DENV and WNV IgM/IgG antibodies. Nine of those were found positive for DENV infection (IgG) and seven had positive or borderline results for DENV-specific IgM (Table 1).

A further 112 sera collected from anonymous patients who had sought medical care from various reasons during October 2010 were available at the laboratory of the local health centre. These sera were tested at

Table 1

Distribution of antibodies to dengue virus in nine persons from a pool of 14 neighbours of the autochthonous case from Pelješac, Croatia, October 2010

Examinee number	DENV IgM (ratio) [a]	DENV IgG (RU/ml) [b]
1	+ (2.4)	+ (155)
2	+/- (1.04)	+ (126)
3	+ (2.2)	+ (98)
4	+ (1.2)	+ (140)
5	- (0.3)	+ (170)
6	- (0.5)	+ (155)
7	+ (2.3)	+ (138)
8	+ (2.4)	+ (94)
9	+ (2.6)	+ (170)

DENV: dengue virus.

[a] ‹0.8negative (-), 0.8-1.1 borderline (+/-), ≥1.1 positive (+). Results are expressed as ratio according to the manufacturer's specifications.

[b] ‹16 negative (-), 16-22 borderline (+/-), ≥22 positive (+). Results are expressed in RU/ml according to the manufacturer's specifications.

Table 2

Distribution of antibodies to dengue virus in six anonymous serum samples, Croatia, October 2010

Examinee number	1	2	3	4	5	6
DENV IgM (ratio)[a]	+/- (0.9)	+/- (0.8)	+/- (1.08)	+ (4.6)	+ (2.2)	-
DENV IgG (RU/ml)[b]	+ (72)	+ (46)	+ (40)	+ (46)	+/- (‹2)	+ (153)

DENV: dengue virus.

[a] ‹0.8 negative (-), 0.8-1.1 borderline (+/-), ≥ 1.1 positive (+). Results are expressed as ratio according to the manufacturer's specifications.

[b] ‹16 negative (-), 16-22 borderline (+/-), ≥ 22 positive (+). Results are expressed in RU/ml according to the manufacturer's specifications.

Table 3

Adult mosquitoes caught in Podobuče, Orebić and Korčula, Croatia, October 2010

Species	Number
Aedes albopictus	49
Ochlerotatus mariae	4
Ochlerotatus sp.	2
Culex pipiens	5
Culiseta annulata	1
Total	**61**

CNIPH for the presence of DENV and WNV antibodies. Ethics approval was not required and informed consent was not sought. The work was carried out under the Communicable Disease Protection and Control Act which provides statutory support for investigations conducted for the purpose of communicable disease control.

Of those 112 samples, six were positive for DENV-specific antibodies. In all six positive sera, DENV-specific IgG was found (one sample with a borderline value). DENV-specific IgM were found in five sera: clearly positive in two and borderline in three (Table 2). All 112 sera were negative for WNV IgM and IgG.

Entomological investigation

During the field investigation the presence of mosquitoes was noticed, despite mandatory disinsection implemented on the entire Croatian territory. Mosquitoes were caught in the place of probable transmission and also on the island of Korčula in October 2011 with the aim of identifying the mosquito species present and determining whether they were carrying DENV. Two days after the mosquito had been caught, adulticidal and larvicidal disinsection was conducted at the village where the German patient had stayed.

The 61 caught mosquitoes were identified by an entomologist (Table 3). The species *Ae. albopictus* dominated (49 of 61).

Virological investigation was conducted for 44 *Ae. albopictus* adults in eight pools containing between five and seven mosquitoes. All eight pools tested negative for DENV in the RT-PCR conducted at the WHO Regional Reference Laboratory for Arboviruses at the Institute for Microbiology and Immunology in Ljubljana, Slovenia [11].

Discussion

After France, Croatia is the second country in Europe in which autochthonous transmission of dengue infection has been shown, which had not been recorded in Europe since the epidemic in Greece in 1925 to 1928 [12-15]. According to data of the communicable disease epidemiology service of the CNIPH, registered imported cases of dengue are not frequent (six cases in three years). Although until recently dengue fever was not a notifiable disease in Croatia, it is unlikely that the epidemiology service network which collaborates with the laboratories that conduct the diagnosis would have missed the occurrence of a confirmed case of imported dengue fever.

The assumption that the German tourist acquired dengue fever in the region of the Pelješac peninsula was confirmed by the identification of a second case of dengue fever in a local citizen who had not travelled outside the area. Although the antigen was not confirmed by RT-PCR in the acute serum of the patient, taken six days after illness onset, the presence of specific IgM antibodies (IgG was negative) pointed to acute infection. This was confirmed in a sample taken on day 19 of the illness when IgM and IgG antibodies were found.

Nine of the 14 samples taken from the Croatian patient's neighbours, none of whom had travelled outside Croatia, were IgG-positive, and we assume that these were relatively recent infections because seven of them were also IgM-positive. Some of them reported having an influenza-like disease in August and early September. Moreover, DENV-specific antibodies were found in 5.4% of the anonymous serum samples collected in October 2010 by the laboratory that covers the area of Pelješac and Korčula. Five of the six DENV-positive sera in this panel showed borderline or positive values of IgM antibodies against DENV. Based on the available serological and epidemiological data we therefore assume that a cluster of acute DENV infection occurred in the area, most probably during August and September 2010.

Each cluster of infectious diseases is reported using the national communicable diseases early warning system. During summer 2010 there were no such reports from Pelješac. Only four of the DENV-positive villagers contacted health services for febrile illness in August and September and were not recognised as an outbreak. At that time of year, there is an increased circulation of enteroviruses which can manifest with similar symptoms, but we believe that the main reason why dengue fever was not suspected in these patients is the fact that this illness had not been registered in Croatia or Europe so far and is therefore not considered in persons who have no travel history to endemic areas. Although the health services had been alerted of the possibility of new diseases transmitted by *Ae. albopictus*, particularly following the chikungunya fever outbreak in Italy in 2007 [16], it was only after our circulatory letter in October that dengue virus infection in local inhabitants was suspected by general practitioners and subsequently confirmed in the second autochthonous Croatian case described in this paper. There may also have been other dengue virus infections with an inapparent or mild course. We believe that other tourists staying in the area may have returned to their home countries with dengue fever, but there have been no reports of exported cases other than the German case.

It is likely that the dengue virus was imported into this community during the summer months of 2010. Regarding the manner of importation, we can only speculate. It could have been through infected travellers arriving from endemic areas in whom the infection was not recognised. Bearing in mind that *Ae. albopictus* species have spread along the Adriatic coast, also in the region of Pelješac and Korčula mainly through transport by sea [5], importation of infected mosquitoes in the same manner cannot be excluded. Since the role of transovarial transmission in mosquitoes is questionable [17,18], it is not likely that importation

happened through infected eggs or larvae (e.g. in used car tires).

Croatia will continue to alert health practitioners to the presence of this disease. Larvicidal and adulticidal mosquito control measures already applied in the affected area will be continued and expanded to the entire country to prevent further establishment of dengue fever or other diseases transmitted by the same vector, such as chikungunya fever [19,20]. Selection of blood donors in the country is in line with all internationally accepted criteria, in that any febrile illness in a potential donor presents a contraindication including the period of convalescence. This covers dengue virus infections well, as cases are only infective during the febrile phase and there is no chronic infection stage. A short prodromal period can pose a risk, but the regular delayed use of blood donations allows to investigate all donors who fall ill in the first two days after donation and to discard their blood if necessary. However, the possibility of transient asymptomatic dengue viraemia needs to be taken into account in practice if the disease were to become established.

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Evolution of the haemagglutinin gene of the influenza A(H1N1)2009 virus isolated in Hong Kong, 2009–2011

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Phylogenetic analysis of the haemagglutinin (HA) gene shows that the influenza A(H1N1)2009 viruses collected in Hong Kong clustered in two main branches characterised by the E391E and E391K amino acids. The main branch E391K evolved in two sub-branches with N142D and S202T mutations that first appeared in March and July 2010, respectively, with the latter becoming the predominant strain. These genetic variants that emerged display similar antigenic characteristics. Concurrent with genetic surveillance, laboratories should continue monitoring the circulating viruses antigenically.

Introduction

Influenza A(H1N1)2009 virus is a reassortant of swine, avian and human influenza viruses which is antigenically different from seasonal influenza A(H1N1) viruses circulating previously [1]. In Hong Kong, the first case was detected in a visitor from Mexico on 1 May 2009. The infection spread locally in June 2009 and reached its peak in September 2009 (Figure 1).

Intense selection by the host immune system drives antigenic change which results in the continuous replacement of circulating strains with new variants to re-infect individuals and cause widespread illness. Although the influenza A(H1N1)2009 virus has been circulating worldwide since April 2009, and the haemagglutinin (HA) antigenic sites have been under increasing antibody-mediated selection pressure [2], recent isolates were still antigenically similar to the vaccine virus A/California/7/2009 [3-5]. It is important to characterise the HA in order to monitor any emerging variants while the virus continues to circulate in the community. Genetically, one of the characteristic differences between the epidemic viruses collected between March and September 2009 and the vaccine virus [6] was substitution at position 220 with almost all currently circulating viruses having S220T amino acid change (the amino acid positions of HA sequence are denoted using full HA coding region, i.e. amino acid position 18 corresponds to position 1 of the HA without the signal peptide) [7,8]. In addition to this mutation, the E391K substitution grew rapidly globally between July and December 2009 [9] and two other substitutions, N142D and S202T, have recently been described in 2010 [4,5].

Here we describe temporal sequence changes in the HA gene of the influenza A(H1N1)2009 virus isolated in Hong Kong from 2009 to 2011.

Sample collection and sequence analysis

For this analysis, we included 338 full HA sequences of influenza viruses isolated from respiratory samples obtained from 40 public and private hospitals and clinics in Hong Kong between June 2009 and January 2011. The proportion of sequences analysed was in accordance with the positive isolation rate in each institution. Only one isolate from each patient was included. With the exception of June 2009, when only two full HA sequences were included at least four isolates from patients with either mild or severe respiratory illness were selected randomly per month. The PCR amplification and DNA sequencing of the full length of HA gene were performed using six different in-house designed primers: H1v-m0044-F (5'-AGTATACGACTAGCAAAAGCAGGGG-3'), H1v-0323-R(5'-TAACACGTTCCATTGTCTGA-3'), H1v-0898-R(5'-TGGGTGTTTGACAAGTTGTA-3'), H1v-0805-F(5'-AGATATGCATTCGCAATGGA-3'), H1v-1348-F(5'-AGAACTTTGGACTACCACGA-3'), H1v-1752-R (5'-CCGTGTCAGTAGAAACAAGGGTGTTT-3'). H1v-m0044-F, H1v-0898-R, H1v-0805-F and H1v-1752-R were used as the PCR primers; in addition to these four primers, H1v-0323-R and H1v-1348-F were used as the sequencing primers.

Sequence data were compiled and edited using the Lasergene sequence analysis software package (DNASTAR Inc). Multiple alignment of nucleotide sequences and translation of amino acid sequence was carried out by using BioEdit (http://www.mbio.ncsu.edu/bioedit/bioedit.html). In order to show the major evolutionary pattern of HA gene, only sequences shared by more than one isolate were included for the construction of a phylogenetic tree using MEGA (http://www.megasoftware.net/). According to this strategy, 33 sequences representing 217 isolates (64.2%,

217/338) were selected for phylogenetic analysis. One sequence (A/HongKong/2213/2010) that has been used as reference in EuroFlu Weekly Electronic Bulletin [10] and the National Institute for Medical Research [11] was also included for reference.

Results

Over the study period, the amino acid at position 391 was either E or K. Phylogenetic analysis of the HA gene showed that the influenza A(H1N1)2009 viruses collected in Hong Kong clustered into two main branches characterised by this position (Figure 2).

With the emergence of E391K viruses in July 2009, the proportion of viruses with E391E fluctuated between 8% and 98% during the period from July 2009 to February 2010 and was gradually displaced by the evolving E391K viruses (Figure 3).

Within the main branch E391E, a sub-branch characterised by S145P reported previously [11] was also observed (Figure 2). The four strains A/Hong Kong/2213 (the reference strain used in EuroFlu Weekly Electronic Bulletin and the National Institute for Medical Research), A/Hong Kong/1886/2010, A/Hong Kong/2212/2010, A/Hong Kong/2200/2010 collected between April and July 2010 belonged to this sub-branch and all had V216A and I312V substitutions while A/Hong Kong/2200/2010 and A/Hong Kong/2212/2010 also had additional substitutions K180T and P288S (not shown in Figure 2).

In the main branch with the E391K substitution, two sub-branches characterised by N142D and S202T mutation were observed (Figure 2). The isolates in the sub-branch characterised by N142D first appeared in March 2010 and its proportion appeared to peak in May 2010 and declined thereafter. The isolates in the sub-branch with the mutations S202T first appeared in July 2010 and their proportion increased sharply displacing the isolates with N142D in September 2010. This sub-branch continued to predominate since then (Figure 3).

Discussion

In Hong Kong, with a sizable proportion of the population becoming infected during the first wave of pandemic in September in 2009 [12] and the implementation of a vaccination programme using a monovalent vaccine in December 2009 [13], the resulting immunological pressure may have driven virus evolution as shown by the displacement of E391E by E391K, a site important for membrane fusion [9], and the emergence of the two genetic sub-branches characterised by N142D and S202T amino acid substitutions involving the antigenic sites Sa and Sb respectively. These antigenic sites contain many amino acids involved in neutralising epitopes near the receptor binding pockets [2]. All the genetic variants that emerged, however, displayed similar antigenic characteristics when assessed by haemagglutination inhibition assay using A/California/07/2009 ferret antisera [3-5]. Although a single amino acid substitution involving one antigenic site may be sufficient to cause antigenic change, more

Figure 1

Monthly influenza virus isolation rates by type and subtype, Centre for Health Protection, Department of Health, Hong Kong, 2009–2011

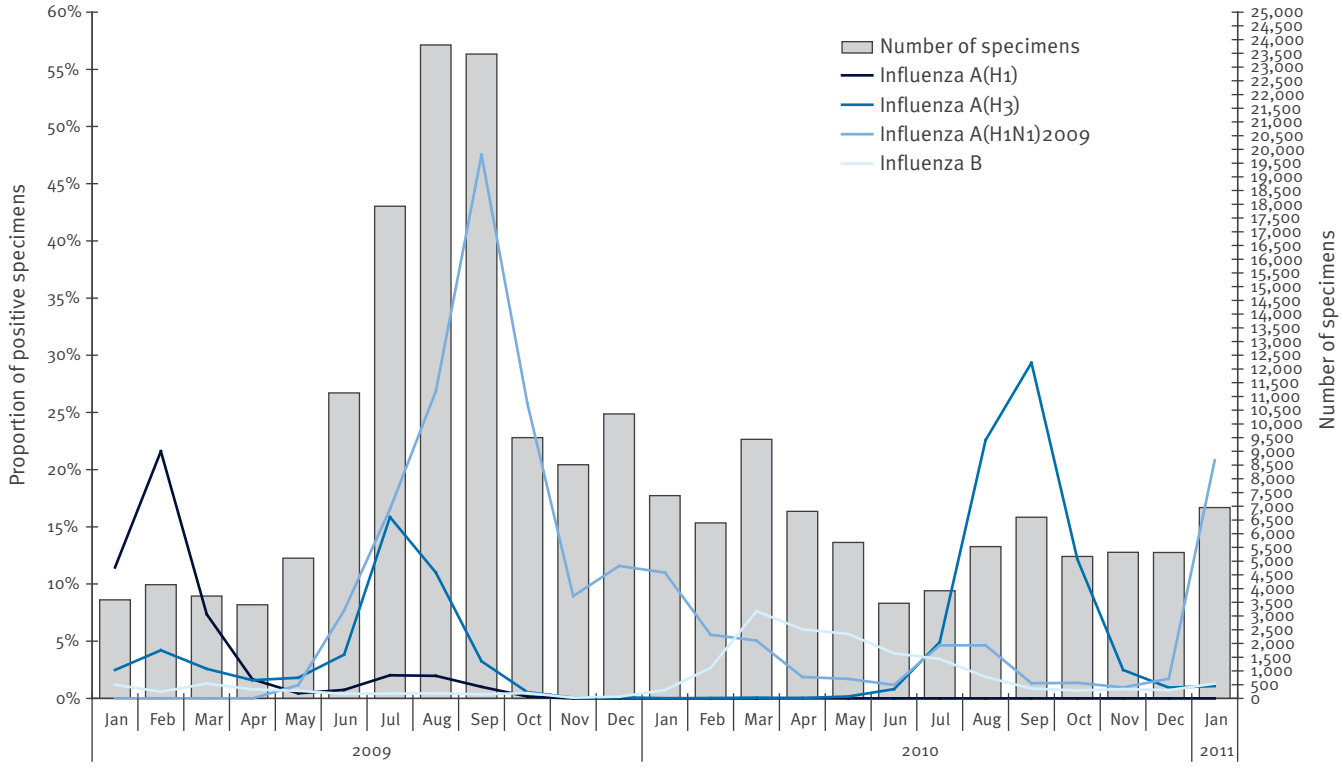
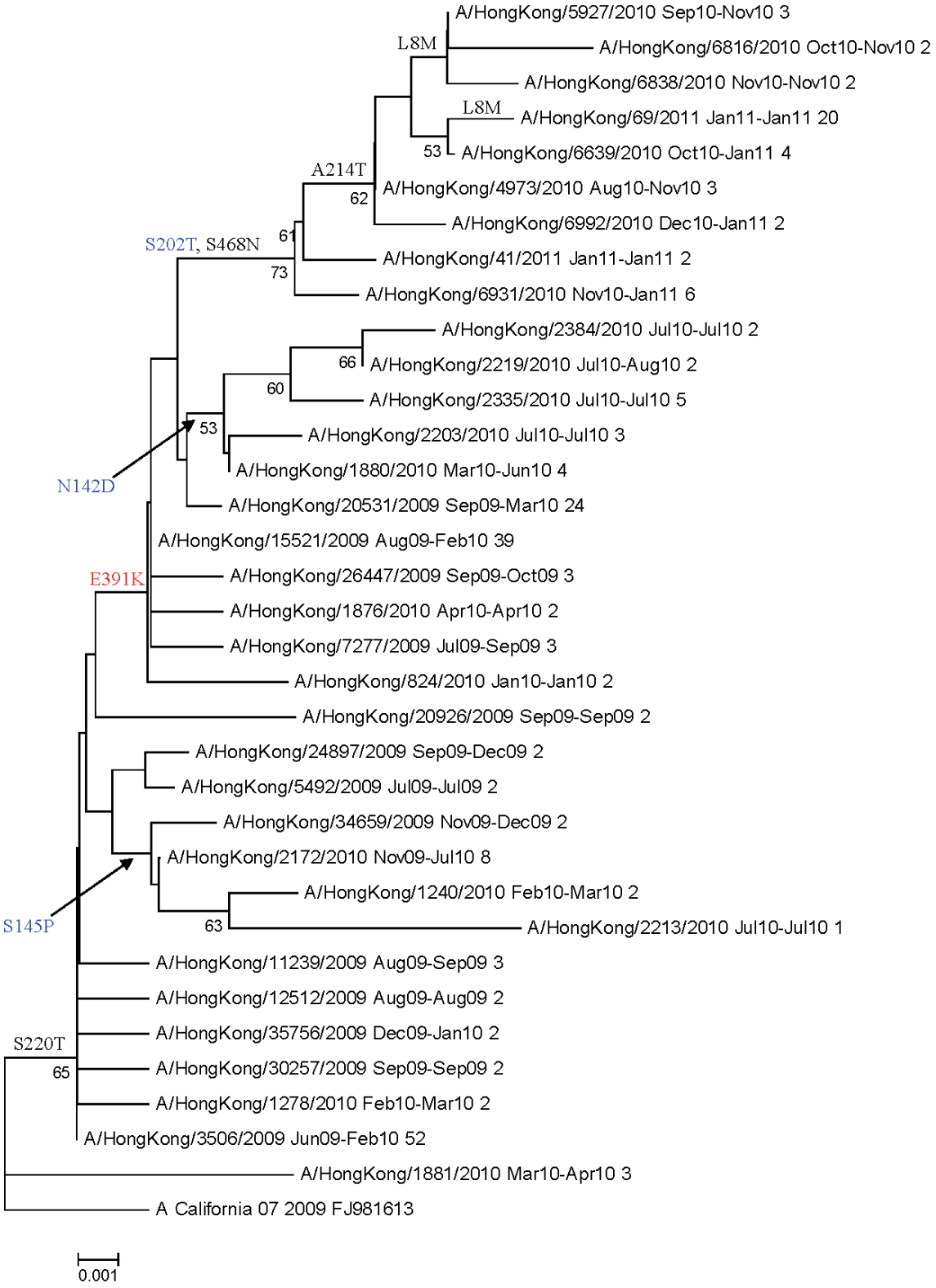


Figure 2

Phylogenetic tree of the full-length haemagglutinin sequences of influenza A(H1N1)2009 virus circulating in Hong Kong from 2009 to 2011



Only the sequences shared by more than one isolate were included for the construction of a phylogenetic tree. The phylogenetic analysis was performed by use of the MEGA programme and the neighbour-joining method. The percentages of bootstrap frequencies over 50% are indicated. The tree was rooted with the vaccine strain A/California/07/2009. Amino acid substitutions in sub-branches are described under the internal branches. Each leaf node contains three sections: designated name of isolate, the time period isolates with this sequence were detected, the number of isolates with this sequence.

The main branch substitution is shown in red colour and the sub-branch substitutions are shown in blue colour.

commonly antigenic drift variants of epidemiological importance have resulted from changes of at least four amino acids across two or more antigenic sites [14,15]. In fact, the prevalence of the influenza A(H1N1)2009 virus remained low in Hong Kong between March and December 2010 and was displaced during that period by the highly active influenza type A(H3N2) virus (Figure 1).

However, at the start of the traditional winter influenza season in Hong Kong in January 2011, the influenza A(H1N1)2009 virus belonging to the genetic sub-branch with E391K and S202T substitutions increased in number rapidly and became the predominant strain. While it is interesting to note the emergence of new genetic sub-branches and see how viruses circulating worldwide are selected and share the same HA mutations, mutations may often be an evolutionary 'dead end' and do not have much significance [16]. It is thus important that laboratory surveillance continues to include virus isolation and monitors the circulating viruses antigenically. Concurrent genetic surveillance would facilitate early detection of antigenic sites that are selected for the virus to escape immunological restraint.

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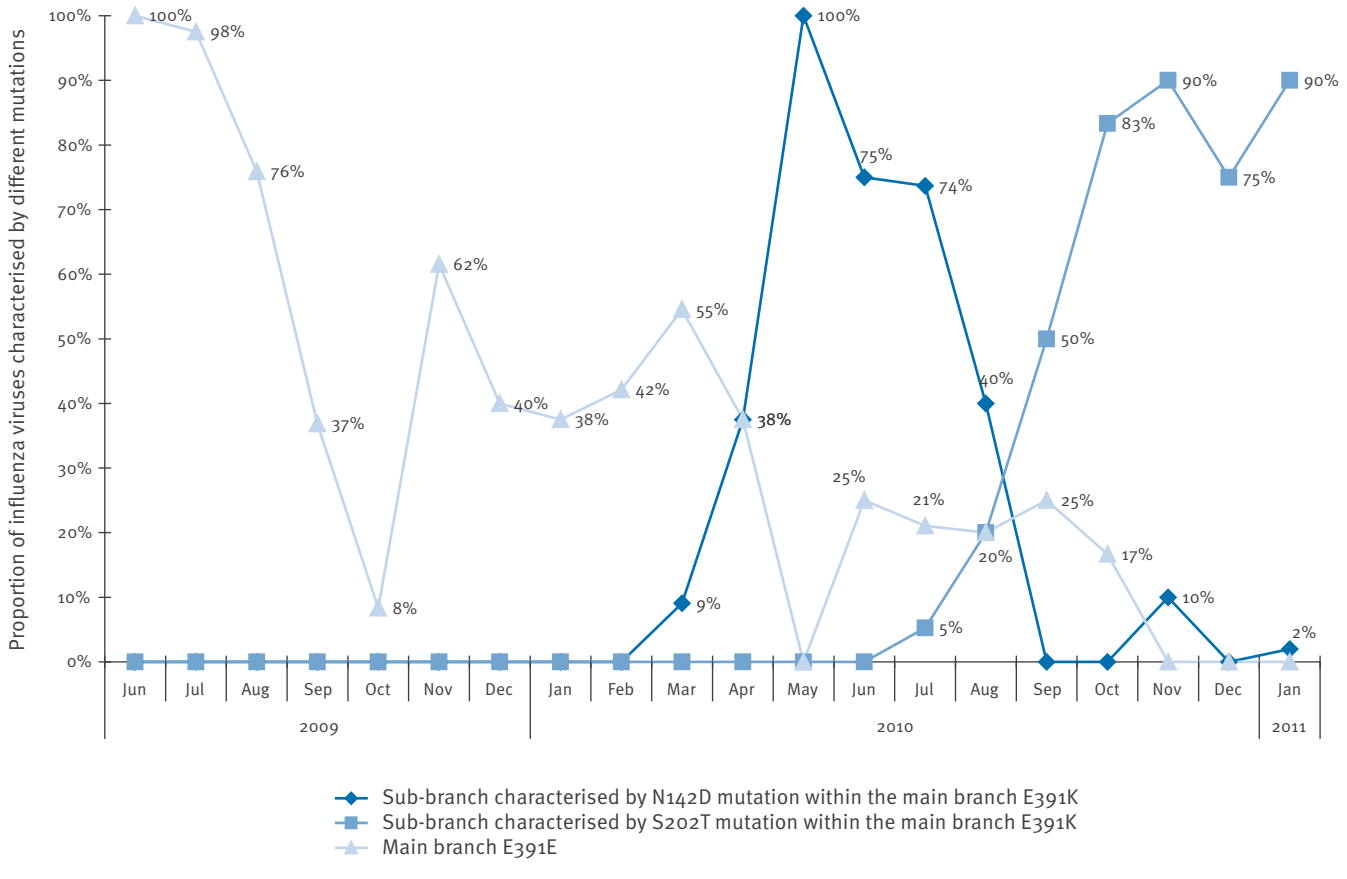
Figure 3

Monthly proportion of influenza A(H1N1)2009 viruses characterised by E391E or E391K with either N142D or S202T, Centre for Health Protection, Department of Health, Hong Kong, 2009–2011 (n=338)



Since some viruses did not have N142D or S202T, the sum of the proportion may not add up to 100%.

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Hepatitis A outbreak predominantly affecting men who have sex with men in Northern Ireland, October 2008 to July 2009

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We describe an outbreak of hepatitis A which evolved in Northern Ireland between October 2008 and July 2009, against a background of large concurrent hepatitis A outbreaks in various parts of Europe. Thirty-eight cases were defined as outbreak cases using a stratified case definition; 36 were males with a median age of 29 years and of the 28 males whose sexual orientation was known, 26 were men who have sex with men (MSM). Detailed descriptive epidemiology data collected through standardised questionnaires, together with sequencing of a 289 bp fragment of the VP1/2PA region of the virus, significantly aided the understanding of the spread of the outbreak when non-MSM cases occurred. The sequence of the outbreak strain, genotype IA, was indistinguishable from that involved in a large outbreak in the Czech Republic. Although seeded in a generally susceptible Northern Ireland population, the outbreak remained mostly contained in MSM, showing this sub-population to be the most vulnerable despite ongoing hepatitis A vaccination programmes in genito-urinary medicine clinics.

Introduction

Hepatitis A is an acute, usually self-limiting disease caused by infection with the hepatitis A virus (HAV) [1]. Transmission is usually by the faecal-oral route, including person-to-person spread, contaminated water or food products, but has also been associated with outbreaks in injecting drug users and men who have sex with men (MSM) [2-4]. The mean incubation period is 28 days (range 15-50 days). Asymptomatic and mild disease is common in children but the majority of adults who become infected are symptomatic, often with acute jaundice [5]. With increasing hygiene in developed countries, hepatitis A infection has become much less common leading to populations with a large majority of people who are not immune. One consequence of this is that proportionately more susceptible adults are infected when outbreaks do occur, and consequently more severe clinical symptoms are seen [6]. Peak infectivity occurs two weeks before onset of jaundice and falls rapidly thereafter. The diagnosis is made by serological detection of anti-HAV IgM which becomes detectable at the onset of symptoms and can persist for up to six months. HAV RNA is also a marker of acute infection and is present in the patient's serum prior to the appearance of anti-HAV IgM [7]. In regions with a low incidence of HAV infection, sequencing of HAV RNA can be used to link apparently sporadic cases and outbreaks [8].

Monovalent and combined hepatitis A vaccines have been available since 1995 and are all highly immunogenic. Nearly 100% of adults will develop protective levels of antibody within one month after a single dose of vaccine [9]. In the United Kingdom (UK), pre-exposure vaccination is recommended for selected risk groups, including MSM who have multiple partners, particularly during periods when outbreaks are occurring [5,10]. Hepatitis A vaccine alone or combined with human normal immunoglobulin can be effectively used in preventing infections in contacts of cases, if administered within 14 days of the onset of symptoms in the index case [5]. Since 2006, MSM attending the healthcare services specialised in sexually transmitted infections, the genito-urinary medicine (GUM) clinics, in Northern Ireland have been offered combined hepatitis A and B vaccination, in line with guidance from the British Association of Sexual Health and HIV-Clinical Effectiveness Group (UK BASHH) [10]. However, vaccination coverage among MSM is not known.

Hepatitis A is a notifiable disease in Northern Ireland (population 1,775,000). Patients presenting with clinical symptoms which are confirmed by the Regional Virology Laboratory are reported to the regional surveillance unit of the Public Health Agency. Since 2003, there have been between zero and seven sporadic cases

reported annually (Figure 1). After a decade of decrease of hepatitis A incidence in Europe an outbreak began in the autumn of 2007 in Latvian injecting drug users followed by spread into the general population and lasted until the end of 2008 [11]. In autumn 2008, the Czech and Slovak Republics reported large outbreaks initially in injecting drug users and Roma communities respectively, followed by community spread within the general population [12,13]. Subsequently outbreaks among MSM have been reported from Spain (Barcelona) [14] and Italy (Rome) [15].

In October 2008, two hepatitis A cases were reported in Northern Ireland, followed by another four in November after a median time interval of 30 days. All cases were in MSM, aged between 25 and 40 years. An outbreak control team was convened in December 2008 to coordinate outbreak investigations and to undertake control measures. An urgent letter was issued to alert healthcare providers. The aim of the epidemiological study was to describe the course of the outbreak and identify any possible common exposures for further investigation.

Methods

Epidemiological investigation

Initially, an outbreak case was defined as any resident of Northern Ireland who tested positive for anti-HAV IgM after 1 October 2008. In January 2009 cases began to occur in heterosexual males and females. At this time the outbreak control team asked for all positive samples to be sequenced in order to understand the progress of the outbreak which transcended the MSM population. Unfortunately, as sequencing of anti-HAV IgM-positive samples was not a routine activity at the time, a number of samples had insufficient volume for sequencing and others had been discarded. After sequencing information became available a stratified case definition was used to describe the outbreak. A possible outbreak case was classified as a resident of Northern Ireland who tested positive for anti-HAV IgM after 1 October 2008. A possible case was upgraded to a confirmed outbreak case if the case was found after sequencing to have the genotype IA outbreak strain (referred to hereafter as the outbreak strain). Any case found to be epidemiologically linked to a confirmed case was defined as a probable outbreak case. A case was considered to be epidemiologically linked if they had been sharing the same household or had been in intimate contact with a confirmed case in the two months before becoming ill. A case was defined as sporadic if any non-outbreak strain was identified in an anti-HAV IgM-positive resident of Northern Ireland during the study period.

A standardised questionnaire administered by environmental health officers, part A, was used to collect the patients' demographic and clinical characteristics (age, sex, sexual orientation, occupation, place of residence, nationality, symptoms, onset date, and hospitalisation status), as well as details of selected food exposures (consumption of shellfish, raw salad, take-away food or eating outside the home), travel abroad, and contact with a symptomatic hepatitis case in the two months before onset of illness. Part B of the standardised questionnaire was administered by GUM specialists and used to collect details of sexual orientation, number of sexual partners, condom use, visiting and/or having sex in gay venues, and other sexual behaviours, in the two months prior to onset of symptoms. Diagnoses of new and past co-infections were also collected. The questionnaires were collated at the Public Health Agency surveillance unit and data entered into an enhanced surveillance database and STATA (Stata Statistical Software: Release 10, StataCorp 2007) was used to produce descriptive statistics.

Virological analysis

Serological diagnosis was performed by the regional virology laboratory at Royal Victoria Hospital in Belfast using the Abbott Architect anti-HAV IgM assay. Where residual sample volume was available this was forwarded to the virus reference department (VRD) of the Health Protection Agency for HAV RNA detection and sequencing. The HAV RNA was extracted from serum and reverse-transcribed into cDNA by random hexamers. Amplification of the VP1/2PA junction was performed by nested PCR as described previously [16] using primers HAV6, HAV7 in this reference for primary amplification, and BR-9 and BR-5 for secondary amplification. The PCR products were sequenced, resulting in a 289 bp sequence, and genotype assignment was preformed by alignment and comparison with sequences of known genotype in MegAlign (DNASTAR) followed by confirmation using BLAST (http://www.ncbi.nlm.nih.gov/blast/).

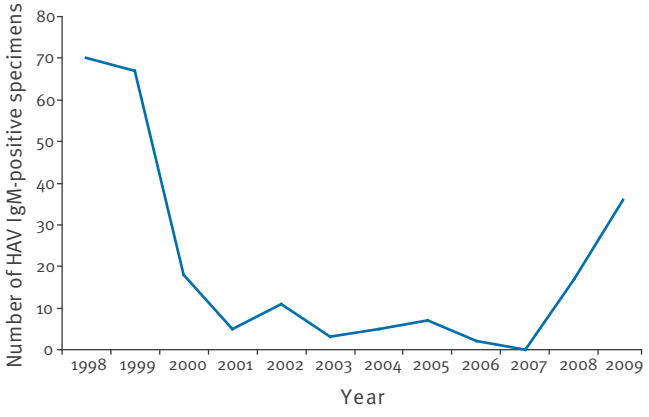
Results

Descriptive epidemiology

From 4 October 2008 to 1 July 2009, a total of 43 acute hepatitis A cases were reported; of those, 38 were classified as outbreak cases and five as sporadic cases.

Figure 1

Laboratory reports of hepatitis A, Northern Ireland, 1998–2009 (n=241)



HAV: hepatitis A virus; IgM: immunglobulin M.

Twenty-eight of the 43 cases occurred between week 50 2008 and week 15 2009 (Figure 2).

Outbreak cases (n=38)

Of the 38 outbreak cases, 24 met the case definition for a confirmed outbreak case, 10 cases were defined as possible and four were classified as probable. The basis for the classification of the three of the four probable cases was that they were MSM who had household contact with confirmed cases. The fourth probable outbreak case was a man whose female sexual partner was found to have the outbreak strain.

Thirty-six cases were male, with a median age of 29 years (range: 18–51 years). Information on sexual orientation was available for 28 males, 26 of whom were MSM. All ten possible cases were MSM. With the exception of the index case who was from another European country, all other cases were British or Irish citizens. Of the 33 cases for whom occupational details were available, eight were food-handlers and two were healthcare workers. The eight food-handlers worked in eight different retail premises none of which were recognised gay venues. Information on clinical symptoms was available for 31 patients, 30 of whom presented with jaundice. Other symptoms were nausea (n=21), loss of appetite (n=17), abdominal pain (n=16), fatigue (n=14), and fever (n=13). Twenty-five cases were admitted to hospital.

Food history was recorded for 18 cases. No common food product, take-away or other catering establishments was identified. None of the eight premises where the food-handling cases worked during their incubation period was named by any other case.

Seven of the 31 cases with known travel history reported travel abroad in the two months prior to illness. Two MSM cases travelled in the four weeks prior to onset of symptoms, one to Prague, Czech Republic, and one to Dublin, Republic of Ireland. The other five cases travelled within the UK, two of them in the two weeks before the onset of symptoms.

Twenty of the outbreak cases, all males, attended a GUM clinic where they completed a standardised questionnaire and were screened for coinfections. Eight cases, all MSM, were diagnosed with coinfections on that occasion: three with syphilis, one with human immunodeficiency virus (HIV), one with HIV and gonorrhoea, and three with non-specific urethritis.

Data on sexual behaviour in the two months prior to onset of illness was only available for 18 of the male cases who attended GUM services. Twelve reported having sex with another male in the two months before illness; the median number of partners was one (range 1–3). Of the 12 male cases who reported having anal sex with another man, only six declared consistent condom use ('always'). Of the remaining six males reporting no sexual contact in the two-month period, three had visited gay clubs during that time.

Information on history of hepatitis A vaccination was not available for the cases.

Sporadic cases (n=5)

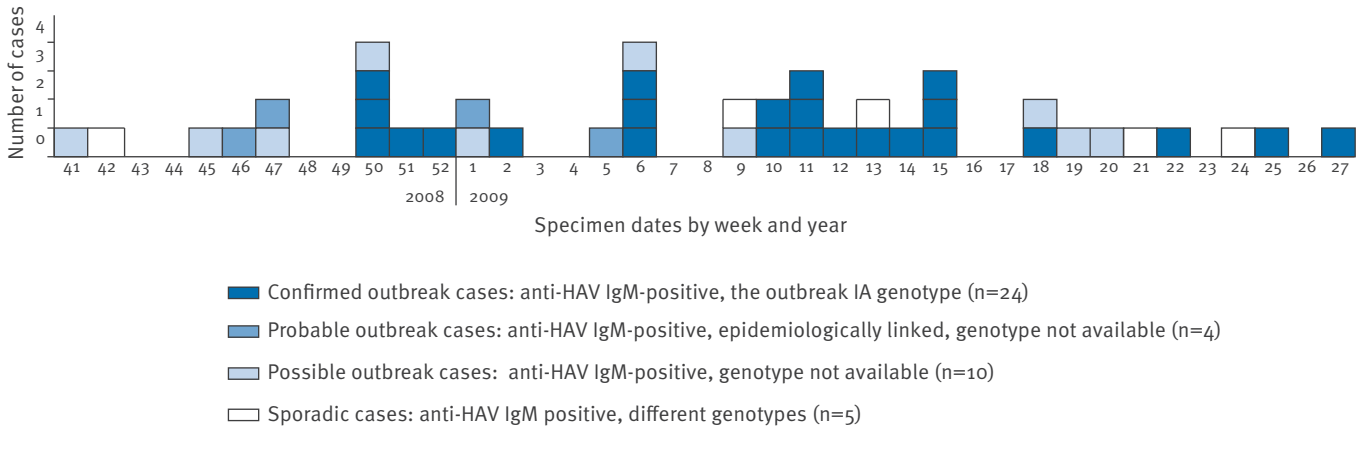
From 14 October 2008 to 8 June 2009, five sporadic cases were reported. Three cases were male, aged 20-49 years, and two female, aged 20-24 years. Two were MSM whose dates of onset were separated by an interval of six months, and who reported travel to Budapest, Hungary, and Barcelona, Spain, in the two months prior to onset of illness. The third male case declared only shellfish consumption as a risk factor. Two female cases reported travel to England and Africa during the incubation period.

Virology

Twenty-nine of the 43 anti-HAV IgM-positive specimens were available for HAV RNA detection and sequencing. Sequences of the 289 bp VP1/2PA fragment derived from 23 of these samples were indistinguishable from

Figure 2

Hepatitis A cases by specimen date and genotype, Northern Ireland, 4 October 2008-1 July 2009 (n=43)



HAV: hepatitis A virus; IgM: immunglobulin M.

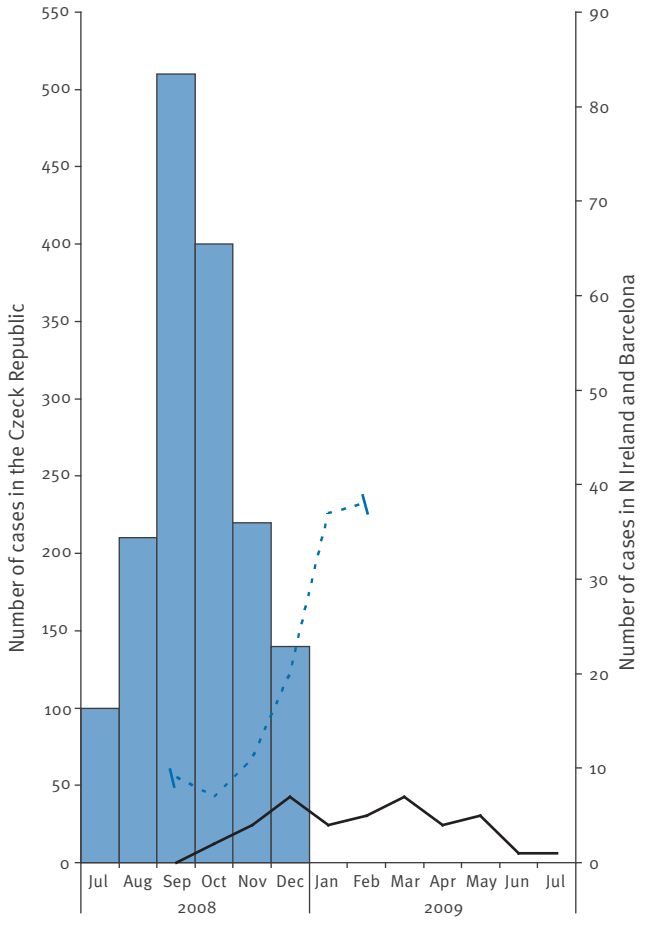
each other and of genotype IA; this was designated as the outbreak strain. A further sample had a 99.7% homology (one mutation in the 289 bp fragment) to the outbreak strain. Given the low incidence of HAV in Northern Ireland and the common risk of MSM we took this to be an indication that this strain was related to the outbreak. The outbreak strain was unlike any strain previously sequenced at the VRD. Comparison of the outbreak strain with other strains isolated from recent outbreaks in Europe found it to be indistinguishable over 289 bp from the strain involved in the outbreak in the Czech Republic in 2008 (kindly provided by H Vennema).

Viruses isolated from two non-outbreak MSM cases shared the same sequence; the two isolates belonged to genotype IA but had only 96.9% homology to the outbreak strain. This strain had been observed at the VRD in other sporadic cases but these had all occurred in mainland England. Comparison of this sequence with other European outbreak strains found it to be indistinguishable from the strain involved in the MSM community in Barcelona, in 2008 and 2009 (kindly provided by R Pinto).

The remaining three samples sequenced were genotype IB and were all distinguishable from each other. The homologies of these strains to the outbreak strain were 91.7%, 90.3% and 84.1%.

Figure 3

Hepatitis A outbreak in Northern Ireland (n=40), the source outbreak in the Czech Republic (n=1,580) and the concurrent outbreak in Barcelona (n=122), 2008-2009



Source of data for the cases in the Czech Republic and Barcelona: graphs published in [9,12].

Control measures

Each case was visited at home or interviewed by telephone by the environmental health officers, in order to identify any environmental risk factors and exposures and to trace close contacts. All cases were referred to GUM clinics and their family and sexual contacts were referred to the general practitioner or to the GUM clinic to receive hepatitis A vaccine and human normal immunoglobulin as appropriate. In cases known to be food handlers a risk assessment of the food premise was conducted and preventive information was provided. Outreach activities were undertaken in two of the most frequented gay venues in Belfast over a period of two months: hepatitis vaccines were offered according to personal history, and testing was offered for HIV, syphilis, hepatitis and chlamydia infection. Information on hepatitis A and safe sex were distributed in gay venues with the assistance of 'Rainbow' Sexual Health Project volunteers using fliers and posters. Information on the outbreak and details on hepatitis A clinical presentation and prevention were posted on their web-site (http://www.rainbow-project.org).

Discussion

This is the first outbreak of hepatitis A in Northern Ireland following a decade of low incidence. It occurred against a background of large concurrent European outbreaks all reported to have started in at-risk groups followed by spread into the general population (Figure 3) [2-4,10,12,13]. The index case became ill after having travelled to Prague in September 2008, when the Czech outbreak was reaching its peak incidence [12]. Comparison of the HAV RNA sequence derived from this outbreak with that of the Czech virus appears to confirm an association.

Contrary to the experience with other European outbreaks occurring in 2008-2009 in the Czech Republic, Latvia and Slovakia, the outbreak reported here remained largely confined to the MSM sub-population, despite the majority of the general population in Northern Ireland being susceptible to HAV infection [17]. The potential for spread to the community was highlighted by the fact that cases occurred in food handlers and healthcare workers. The eight food handlers in particular had the potential to disseminate the virus widely given that they worked at eight different premises. Prompt public health action through contact tracing and post exposure prophylaxis, publicity within the gay community and the provision of

outreach sessions at selected implicated venues have contributed to the apparent control of the outbreak. Collaboration between public health, environmental health, GUM specialists and the voluntary sector was essential.

Our study did not allow an in-depth ascertainment of transmission pathways, given that less than half of the outbreak cases returned the questionnaires on sexual risk behaviour. Similarly we were unable to document a specific venue associated with this outbreak. Notably, three MSM cases reported they had not had sex in the two month prior to illness but had visited gay venues. This raises the possibility that transmission may have occurred through environmental contamination, a finding also noted in other outbreaks [18]. Transmission via food does not seem likely as no common food source or catering venue (among food handler cases or subsequent cases) was identified.

UK national policy recognises that MSM are a vulnerable group for hepatitis A and recommends they are offered pre-exposure vaccination at times of ongoing outbreaks [5]. Our experience shows this is important even in a region of low incidence, given the potential for rapid seeding of outbreaks from elsewhere.

This is further emphasised by the finding of two sporadic MSM cases during this outbreak with a common sequence indistinguishable from that implicated in the large MSM outbreak in Barcelona. That neither of them seeded an outbreak suggests either that they did not have sex in Northern Ireland while infectious (probable explanation for the case in October 2008) or that the preventive control measures were already effective and the MSM community alerted (probable explanation for the case in May 2009).

Although sequencing of HAV RNA did not significantly aid the management of the outbreak, it enabled us to define the sporadic cases and demonstrate that the outbreak was not spreading to the general community. In this setting of low HAV incidence, HAV sequencing was a valuable tool in linking apparently unlinked cases to the outbreak. Sequencing results derived from the outbreak enabled us to link the outbreak in Northern Ireland to the larger outbreak in the Czech Republic and to show that two sporadic cases, only one of which had been to Spain, shared the same strain circulating in the MSM outbreak in Spain. Comparison of the sequences from these two large outbreaks was only possible thanks to the sharing of information from the laboratories that performed the sequencing because at the time, there was no specific database for HAV sequences in the public domain.

Conclusion

This outbreak highlights the importance of timely diagnosis and reporting of cases to allow for appropriate and targeted control measures. The high rate of other sexually transmitted infections (STI) among MSM cases confirms the worth of STI testing during such an outbreak. Awareness of the value and availability of hepatitis A vaccination among MSM in Northern Ireland must be increased. Sequencing the virus and collaborating with other countries involved in similar epidemics helped us understand how this outbreak spread; sequencing of all HAV cases has continued since this time. It has subsequently come to light that HAV sequences can be sent to the Food-borne Viruses in Europe (FBVE) network for comparison with their database [19]: this network is currently making its HAV sequence database publically available.

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Evaluation of syndromic surveillance in the Netherlands: its added value and recommendations for implementation

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In the last decade, syndromic surveillance has increasingly been used worldwide for detecting increases or outbreaks of infectious diseases that might be missed by surveillance based on laboratory diagnoses and notifications by clinicians alone. There is, however, an ongoing debate about the feasibility of syndromic surveillance and its potential added value. Here we present our perspective on syndromic surveillance, based on the results of a retrospective analysis of syndromic data from six Dutch healthcare registries, covering 1999–2009 or part of this period. These registries had been designed for other purposes, but were evaluated for their potential use in signalling infectious disease dynamics and outbreaks. Our results show that syndromic surveillance clearly has added value in revealing the blind spots of traditional surveillance, in particular by detecting unusual, local outbreaks independently of diagnoses of specific pathogens, and by monitoring disease burden and virulence shifts of common pathogens. Therefore we recommend the use of syndromic surveillance for these applications.

Background

In the last decade, syndromic surveillance has increasingly been implemented to detect and monitor infectious disease outbreaks, as early detection and control may well mitigate the impact of epidemics [1-3]. In the United Kingdom, for example, a telephone health helpline (NHS Direct) is used for syndromic surveillance [1]; in France, a syndromic surveillance system based on hospital emergency data has been deployed [4]; and in North America several syndromic surveillance systems exist using data such as telephone helpline calls [5] and hospital emergency department visits [2,6]. Traditional outbreak detection based on astute clinicians and laboratory diagnoses can have blind spots for emerging diseases, because patients reporting with common symptoms (e.g. pneumonia) associated with the disease may not alarm clinicians, and uncommon or new pathogens can remain undetected by laboratories (such as initially happened in the outbreak of severe acute respiratory syndrome (SARS) in 2003). Syndromic surveillance may reveal such blind spots of traditional surveillance by monitoring elevations of common symptoms or clinical diagnoses such as shortness of breath or pneumonia.

The increasing use of syndromic surveillance seems driven by two factors: (i) high-profile disease events (e.g. the 2001 anthrax attacks, 2003 SARS outbreak, the threat of a new influenza pandemic, excess mortality due to heat waves) stressing the need for improved early warning surveillance; and (ii) the increased availability of electronic healthcare data, making large-scale monitoring of non-specific health indicators increasingly feasible.

There is, however, an ongoing debate about the added value of syndromic surveillance. Some scepticism exists about the potential workload it may generate if used for real-time outbreak detection (i.e. if the system creates many false-positive signals) [7]. In the Netherlands, this debate has led to a research project to evaluate the potential value of syndromic surveillance for infectious disease surveillance and control, and to make recommendations for its implementation. The questions addressed were: (i) what syndromic data types track known dynamics of infectious diseases in the general population, and thus will also be likely to reflect emerging pathogen activity? (ii) can syndromic surveillance improve the monitoring of disease burden and/or detect shifts in the virulence of common pathogens? (iii) can syndromic surveillance detect local outbreaks that have a limited number of signals in time, independent of laboratory detection of the causative pathogens?

We addressed these questions by retrospectively analysing syndromic data from six Dutch healthcare registries, and also by *ad hoc* use of syndromic surveillance for upcoming infectious disease problems. To select

Table 1

Syndromic data registries included in the syndromic surveillance evaluation study, the Netherlands

Data type	Registry	Period evaluated	Population coverage (%)[a]	Syndrome information[b]	Data analysed	International coding system	Prospective implementation of surveillance
Absenteeism	National absenteeism registry by Statistics Netherlands (CBS)[8]	2002–03	80 (of the working population of 8 million)	Employees reported sick, no further medical information	Sick leave reports by employers	–	NA[c]
General practitioner consultations	Netherlands Information Network of General Practice (LINH, by NIVEL-the Netherlands Institute for Health Services Research) [9]	2001–04	1–2[d]	Symptoms and diagnoses indicating infectious disease	Symptoms and diagnoses recorded in general practice or telephone consultations, and home visits	International Classification of Primary Care (ICPC)	Real-time system currently being implemented
Pharmacy prescriptions	Foundation for Pharmaceutical Statistics (SFK) [10]	2001–03	85	Prescribed medications indicating infectious disease	Prescription medications dispensed in Dutch pharmacies	Anatomical Therapeutic Chemical Classification System (ATC)	Currently monthly data updates are feasible in *ad hoc* public health situations
Hospitalisations	Dutch National Medical Register (LMR) by Dutch Hospital Data (DHD) [11]	1999–2007	99	General symptoms and diagnoses and specific biological agent diagnoses	Discharge and secondary diagnoses and date of hospitalisation	International Classification of Diseases, Ninth,Revision Clinical Modification (ICD-9-CM)	No prospective implementation possible in the short term (annual data updates will continue)
Laboratory submissions (negative and positive results)	National Infectious Diseases Information System (ISIS-MML) [12]	2001–04	16	Submissions for specific microbiological diagnostic tests	Laboratory submission requests for diagnostic testing	–	NA[c]
Mortality	Cause of death and crude mortality registry by Statistics Netherlands (CBS)[13]	1999–2004 for cause-of-death data; 1999–2009 for crude mortality data	100	General symptoms and/or diagnoses and biological agent-specific diagnoses	Date of death, primary cause of death, complicating and other additional causes of death	International Classification of Diseases, 10th revision (ICD-10)	Currently weekly crude mortality surveillance (pilot phase)

NA: not applicable.

[a] Calculated as a percentage of the total population (16.3 million in 2006 [14]), unless otherwise indicated.

[b] Detailed syndrome definitions available from the authors on request.

[c] The laboratory submissions registry (ISIS-MML) and the national absenteeism registry ceased to exist during our study.

[d] The GP registry coverage will increase to 5% in the next few years as part of the Surveillance Network Netherlands (SUNN), which is predominantly focused on influenza surveillance [15].

Table 2

Tracking of infectious disease dynamics using three syndromes and six data types from healthcare registries, syndromic surveillance evaluation study, the Netherlands

Data types	Respiratory syndromes	Gastroenteritis syndromes	Neurological syndromes
Absenteeism	Winter peaks concurrent with peaks in influenza virus, RSV and other respiratory pathogens; 68% of variations explained by respiratory pathogens; 2 weeks ahead of RSV, 4–5 weeks ahead of influenza [19]	Not evaluated[a]	Not evaluated[a]
General practitioner consultations	Winter peaks concurrent with peaks in influenza, RSV and other respiratory pathogens: 86% of variations explained by respiratory pathogens, 1 week behind RSV, 1–2 weeks ahead of influenza [19]	Winter peaks and summer peaks concurrent with rotavirus and *Shigella/Salmonella/Campylobacter* peaks, respectively: 29% of variations explained by gastroenteral pathogens (51% for those aged 0–4 years, two weeks ahead of rotavirus) [20]; an increase in winter of 2002/03 possibly related to norovirus activity [21]	No clear reflection of known disease dynamics
Pharmacy prescriptions	Winter peaks concurrent with peaks in influenza, RSV and other respiratory pathogens: 80% of variations explained by respiratory pathogens; 1 week behind RSV, 0–2 weeks ahead of influenza [19]	Relatively low winter peaks and higher summer peaks concurrent with rotavirus and *Shigella/Salmonella/Campylobacter* peaks, respectively	Not evaluated[b]
Hospitalisations	Winter peaks concurrent with peaks in influenza, RSV and other respiratory pathogens; 84% of variations explained by respiratory pathogens; in concurrence with RSV, 1–2 weeks ahead of influenza [19]	Relatively high winter peaks and lower summer peaks concurrent with rotavirus and *Shigella/Salmonella/Campylobacter* peaks, respectively: 40% of variations explained by gastroenteral pathogens (85% for those aged 0–4 years one week ahead of rotavirus) [20]; an increase in winter of 2002/03 possibly related to norovirus activity [21]	The general neurological syndrome did not clearly reflect known disease dynamic. A viral neurological syndrome showed summer peaks concurrent with enterovirus peaks: 62% of its variations was explained by enterovirus notifications [22]
Laboratory submissions (negative and positive results)	Winter peaks concurrent with peaks in influenza, RSV and other respiratory pathogens: 61% of variations explained by respiratory pathogens; 2 weeks behind RSV, 0–1 week ahead of influenza [19]	Relatively low winter peaks and higher summer peaks concurrent with rotavirus and *Shigella/Salmonella/Campylobacter* peaks, respectively	No clear reflection of known disease dynamics
Mortality	Winter peaks concurrent with peaks in influenza, RSV and other respiratory pathogens; 78% of variations explained by respiratory pathogens; 3 weeks behind RSV, 0–1 week ahead of influenza [19]	No obvious reflection of known seasonal pathogen activity: an increase in winter 2002/03 possibly related to norovirus activity [21]	No clear reflection of known disease dynamics

RSV: respiratory syncytial virus.

The table summarises per data and syndrome type whether syndrome peaks concurred with pathogen peaks, what percentage of the syndrome variations is explained by variations in pathogen counts, and what the differences in timeliness were between the syndrome and pathogen data. The latter are assessed by the optimised lags of pathogen counts in time-series models that explain the syndrome variation [19].

[a] The absenteeism data lacked medical information, but its time series reflected respiratory pathogen activity; therefore the other syndromes were not evaluated for this registry.

[b] No data on pharmacy prescriptions specific for neurological conditions were available for analysis.

potential syndromic data sources, we asked Dutch healthcare registry owners to provide information on predefined criteria (coverage, timeliness of data entry and potential for transition to real-time data availability). Table 1 shows the registries included in the study, with data on work absenteeism, general practitioner (GP) consultations, pharmacy prescriptions, laboratory submissions, hospitalisations and mortality. Data were available for 1999–2009 or part of this period.

On the basis of available literature cited in PubMed on bioterrorism and natural infectious disease threats, we selected syndromes that were expected to reflect the clinical presentations of both high-threat (i.e. capable of causing major outbreaks of severe illness) and common pathogens [16,17]. This not only makes it possible to use common pathogen activity as a test case for these syndromes, but also implies that emergence of the high-threat pathogens concerned will be relatively difficult to recognise by clinicians. We selected respiratory syndromes (e.g. for high-threat pathogens such as *Bacillus anthracis* or a new pandemic influenza variant), gastroenteritis syndromes (e.g. caused by *Vibrio cholerae* infection) and neurological syndromes (e.g. caused by West Nile virus infection). The syndromes were defined for each registry, guided by a list of syndrome definitions defined by the United States Centers for Disease Control and Prevention [18] and experts in infectious diseases and medical microbiology at the Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment, RIVM). The syndromes were then evaluated per registry for their potential use in signalling infectious disease dynamics and outbreaks.

In this article, we present our perspective on the added value of syndromic surveillance for infectious disease surveillance and control, based on the results of our evaluation study and in light of the literature up to and including 2010.

Main findings of syndromic surveillance evaluation

Tracking infectious disease dynamics in the general population

The first question we addressed was to what extent trends in respiratory, gastroenteritis and neurological syndromes in the various registries reflect known pathogen activity, as measured by counts of detected pathogens (available from routine laboratory surveillance). This indicates whether these registries have the potential to reflect emerging pathogen activity (Table 2).

Of the three syndromes, respiratory syndromes were most closely associated with laboratory pathogen counts (Table 2), displaying higher levels in winter, which corresponded to higher counts of respiratory pathogens [19]. Up to 86% of the weekly syndrome variations (i.e. variance) in time were explained by weekly variations in respiratory pathogen counts, particularly of influenza viruses and respiratory syncytial virus (RSV), which is in line with other studies [23,24]. However, the respiratory syndromes in our study were zero to five weeks ahead of laboratory counts of influenza viruses, suggesting better timeliness of these syndromes. For RSV, the pathogen counts were concurrent with respiratory syndromes from hospitalisation registry data, which would be expected as most RSV tests are performed on hospitalised young children [25,26]. Most respiratory syndromes from other registry data lagged behind the RSV counts, which suggests that young children are affected relatively early in the annual RSV season.

The gastroenteritis syndromes showed winter peaks concurrent with increased rotavirus activity, and summer peaks concurrent with peaks in *Shigella, Campylobacter* and *Salmonella* activity (Table 2). Variation in the reporting of gastroenteritis syndromes explained by pathogen counts was lower (29–40%) than in the respiratory syndromes, although it increased up to 85% when limiting the analysis to young children, with the syndromes' counts one to two weeks ahead of the laboratory rotavirus counts [20].

The reported general neurological syndromes did not clearly reflect known patterns of pathogen activity (Table 2). However, a more specific viral neurological syndrome – unexplained viral meningitis syndrome – in the hospitalisation registry data did: 62% of the variation in the reporting of this syndrome was explained by known seasonal enterovirus activity, suggesting that elevated levels of unexplained viral meningitis indicate undiagnosed enterovirus infections [22].

The general practitioner consultations, pharmacy prescriptions, hospitalisations and mortality registry data thus showed good performance in timely tracking of respiratory and/or gastrointestinal disease, and the hospital registry data also showed moderate performance for neurological disease (Table 2). The advantage of using these four complementary registries together would be that they cover mild to very severe morbidity. The absenteeism registry data seemed most timely (ahead of laboratory surveillance data), but showed only moderate performance in tracking respiratory disease. This could be due to the fact that medical information is not available in this registry, and thus the data are a mix of all kinds of disease, although respiratory disease is clearly reflected in the time-series pattern. The laboratory submissions registry data showed, at most, a moderate performance for the three syndromes evaluated.

Monitoring disease burden and detecting virulence shifts

The second research question we addressed was whether syndromic surveillance improves the monitoring of disease burden and detects shifts in the virulence of common pathogens. We evaluated this by relating time series of syndromic surveillance data with

pathogen-specific surveillance data to quantify the disease burden due to common pathogens over time. We found a clear association over time of norovirus laboratory surveillance data with mild-to-severe morbidity and even deaths in elderly people, observed in recent years, coinciding with emergence of new norovirus variants [21]. The emergence of these variants had been suspected but could not be assessed by any other routine surveillance system. In addition, for influenza we detected previously unknown shifts in the annual numbers of hospitalisations and deaths related to the number of influenza-like illness (ILI) cases, coinciding with shifts in the antigenicity of circulating viruses [27]. Such analyses can also be used for investigating the severity of pandemic influenza A(H1N1)2009 infection compared with that of seasonal influenza [28].

Detecting local outbreaks

The third question we addressed was whether syndromic surveillance can detect unexpected disease outbreaks in a timely manner. For this purpose, analysis of aggregated nationwide data may not be very sensitive: the large volume of the data (e.g. tens of thousands of respiratory syndrome hospitalisations per year) makes it impossible to detect outbreaks when they are still small. Local detection of syndrome elevations using a space–time algorithm might signal emerging outbreaks much sooner [29]. To test this, we used known outbreaks of Legionnaires' disease as positive controls of realistic severe respiratory disease outbreaks due to uncommon or new pathogens that may not be detected by traditional surveillance in a timely manner. Simulating prospective surveillance, we were able to timely detect these known outbreaks in syndromic hospital data using space–time scan statistics [29]. The fact that the overall alarm rate was modest (a mean of five local clusters detected per year) suggests that syndromic surveillance of hospitalisation data for respiratory disease can indeed be a useful early-warning tool for local outbreak detection. Using the same approach, previously unknown disease clusters plausibly due to Q fever were detected [30], thus illustrating that on some occasions syndromic surveillance can identify outbreaks that otherwise would remain undetected. These analyses were motivated by the clinical detection of a large Q fever outbreak in 2007 and the subsequent years, which raised the question whether smaller outbreaks might have preceded the 2007 outbreak. Real-time detection and investigation of these previously unknown clusters could possibly have led to earlier awareness of increased Q fever activity.

Assessing the absence or limited size of unusual disease events

In public health practice, besides timely detection of unusual outbreaks, being able to assess and communicate the absence or limited size of unusual disease events can also be important. For example, Blendon *et al*. suggested that better communication to the public during the 2003 SARS outbreak might have prevented economic loss due to unnecessary precautions taken by the public (e.g. many people stayed away from crowded places, even in areas with a relatively low level of spread of the virus) [31]. Also during high-profile public events (e.g. the Olympics or G8 summits) [32,33], syndromic surveillance will mainly confirm the absence of major, unusual disease outbreaks, since such outbreaks are rare events.

We also examined the value of syndromic data in assessing the absence or limited size of unusual disease triggered by specific public health concerns. For West Nile virus (WNV) infection, enhanced surveillance was established in the Netherlands by laboratory testing of cerebrospinal fluid (CSF) from patients with unexplained viral meningitis/encephalitis [22]. None of the CSFs collected in 2002 to 2004 tested positive for WNV, but the probability that WNV was indeed absent in the country could only be assessed from the annual count of unexplained viral meningitis/encephalitis cases (as a denominator in relation to the number of CSF samples tested). For hepatitis E and Ljungan virus infections, we inspected time series of unexplained hepatitis and abortion/perinatal death, respectively, and found no signs of emerging activity of these viruses. Rumours about a continuing increase of impetigo in children were countered by inspection of a time series of GP consultations for the infection.

Other spin-offs of syndromic surveillance

In addition to the above described applications, other uses of syndromic surveillance were illustrated during the 2009 influenza A(H1N1) pandemic. We used respiratory syndromic data on hospitalisations and GP consultations to plan the diagnostic capacity that would be needed if a larger proportion of the persons with respiratory symptoms would be tested – as is the case in the early stages of a pandemic [34]. Also early in the pandemic, the reaction of the public to media reports on pandemic influenza was illustrated by sharp elevations in the number of oseltamivir prescriptions [35]. This information was used to urge physicians to exercise restraint in prescribing oseltamivir, in order to decrease the risk of oseltamivir shortage and viral resistance later in the pandemic.

Data requirements

The results of our project suggest specific data requirements for successful syndromic surveillance. Data quality is important for all applications of syndromic surveillance, but probably mostly for local outbreak detection. Here, relatively small artefacts – for example, duplicate details of the same patient in one registry – can result in false alarms, as we experienced when using hospital data for space–time cluster detection [29,30]. In a real-time setting (e.g. daily or weekly data updates), reporting delays can also lead to data artefacts and false alarms, if, for example, there is a delay in hospitals submitting their data [36]. In addition to having few data artefacts, data need to be representative, and for local outbreak detection, they also need to have a high coverage (preferably close

to 100%) to be able to timely detect local outbreaks in any region. By using data with relatively low coverage levels, sensitivity for local outbreaks obviously will be reduced [37,38]. Nordin *et al*. used simulated anthrax attack data, and integrated the simulated data into actual physicians' visit data to show that the sensitivity for detecting respiratory outbreaks resulting from bioterrorism was not very high [37]. However, the authors evaluated a maximum system coverage of only 36% of the population. In another study, Balter *et al*. reported that a syndromic surveillance system in New York City sometimes missed several gastroenteritis outbreaks due to data quality (e.g. miscoding of patients' chief complaints) and coverage problems (e.g. some hospitals did not participate in the system) [38].

For effective signal verification, sufficient information on individual patients' characteristics and concurrent laboratory trends has to be available to identify possible causes of generated signals. For example, we interpreted local respiratory syndrome clusters in relation to local influenza or RSV activity: if the age distribution of cases reflected the usual pattern for these viruses, we regarded further investigation unnecessary [29]. Also, the rise in oseltamivir prescriptions early in the 2009 influenza A(H1N1) pandemic could be ascribed to the 'worried well', because laboratory surveillance showed that influenza virus activity had not increased [35]. Without such verification options, the value of syndromic surveillance is limited [38].

Cost-effectiveness of real-time surveillance systems

An important question is whether syndromic surveillance is cost effective. Events such as a bioterrorist attack, a SARS epidemic or an influenza pandemic are rare and the question arises how much of the public health budget should be spent on a detection system for such rare events.

The costs of a surveillance system can be easily estimated. Studies that report the operating costs associated with real-time syndromic surveillance found annual operating costs ranging from US$ 130,000–150,000 to US$ 280,000 [39]. However, estimating its benefits is less obvious. Kaufmann *et al*. reported that the economic damage caused by a bioterrorist attack can amount to millions or even billions of dollars [40]. The SARS epidemic in 2003 and the influenza pandemic in 2009 showed that the economic damage caused by naturally occurring outbreaks can be similarly high [41,42]. If similar disease events emerge every few years, and syndromic surveillance leads to earlier detection and control of such outbreaks, then the benefits of syndromic surveillance are likely to outweigh its costs. The question here is whether earlier detection would indeed lead to control or at least reduced impact of a new disease, for instance, SARS or influenza A(H1N1)2009 infection. Simulation studies could help to further evaluate which specific types of major disease events syndromic surveillance could probably lead to interventions that limit the economic damage.

Possibly just as important as the benefits arising from earlier detection and control is the downscaling of unnecessary interventions during ongoing outbreaks. This requires quick assessment of the limited size and severity of outbreaks. For example, if the severity of a new pandemic can be quickly assessed – as the World Health Organization (WHO) requires [43] – by reliable syndromic hospital surveillance of severe respiratory infections, costly interventions such as quarantine and prophylactic treatment or vaccination could be downscaled or stopped earlier if the disease is only mild.

In the Netherlands, prospective surveillance has now started for crude mortality data, with weekly data collection and analysis since the 2009 influenza pandemic. The existing mortality registry allows prospective implementation at relatively low extra cost. Real-time data collection is currently also being implemented for the Dutch GP registry (Table 1). Including hospital data and other data types in future syndromic surveillance systems may also be feasible at limited cost, if the data collection can be integrated into already planned real-time, future data infrastructures such as the Dutch national health-information-exchange system [44].

Recommendations

On the basis of our evaluation, we recommend the use of syndromic surveillance to reveal blind spots of traditional surveillance, in particular by detecting unusual, local outbreaks independently of laboratory diagnoses of specific pathogens, and by monitoring disease burden and virulence shifts of common pathogens.

Our results are mostly based on retrospective analysis of syndromic data of high quality and coverage. If prospective collection of such syndromic data is not feasible, real-time early warning for local outbreaks should not be performed, since true outbreaks will probably be missed while at the same time numerous false alarms will be generated. For real-time early warning, sufficient laboratory and epidemiological information is needed, in order to be able to quickly verify possible causes of syndromic signals, and thus recognise relevant signals that might need a response. Retrospective analyses as performed in our evaluation can validate the relevant data and analyses before prospective implementation of a syndromic surveillance system.

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