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West Nile virus: the Italian national transplant network reaction to an alert in the north-eastern region, Italy 2011

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We report four cases of West Nile virus (WNV) transmission following a single multiorgan donation in north-eastern Italy. The transmissions were promptly detected by local transplant centres. The donor had been tested for WNV by nucleic acid amplification test (NAT) prior to transplantation and was negative. There were no detected errors in the nationally implemented WNV safety protocols.

Case reports

In August 2011, a multiorgan and tissue retrieval was carried out in north-eastern Italy from a donor who was a resident in the same area. The donor's organs (kidneys, lungs, heart and liver) were successfully transplanted to recipients in other Italian regions, including the north-eastern region. The donor's health status was confirmed prior to donation, by blood- and instrumental-tests and detection of markers for transmissible diseases (hepatitis B surface antigen, hepatitis C virus antibodies, human immunodeficiency virus 1/2 antibody, *Treponema pallidum* Particle Agglutination Assay), in addition to interviews with relatives. In line with transplant procedures, the donor cause of death was not related to any transmissible disease. Moreover, due to special procedures in place for prevention of West Nile virus (WNV) in this part of Italy, a donor blood sample had tested negative for WNV by nucleic acid amplification test (NAT).

Ten days after transplantation, two patients who had each received a respective kidney, developed fever and neurological symptoms, suggestive of West Nile neuroinvasive disease. The purpose of this rapid communication is to describe how, despite testing strategies in place for WNV, transmissions occurred and how the Italian National Transplant Network responded to the WNV transmissions associated with a multiorgan transplant, in the context of negative nucleic acid amplification test (NAT) results in the donor.

Background

Due to WNV circulation and documented infections in humans in north-eastern Italy [1], several preventive measures related to WNV transmission to humans have been implemented. Since 2008, the Italian National Transplant Network, in collaboration with the regional health authorities, started an epidemiological surveillance programme in order to detect WNV in organ donors in north-eastern Italy [1-3]. Moreover, in the same area, plans are in place in the medical and veterinary fields for active surveillance and monitoring of WNV infection in animals and humans [4-7]. In addition to this epidemiological monitoring, the Italian National Transplant Network decided to perform NAT within 72 hours of donation on all donors living in areas where WNV had been demonstrated to be endemic [1,7,8]. These measures are carried out from 15 July to 15 November 2011 in order to prevent WNV transmission from organ and/or tissue donations to recipient patients.

Laboratory investigations and control measures

On the basis of time schedules foreseen by rules and protocols issued for prevention of WNV (within 72 hours from donation) [1], virological testing was carried out on the blood sample collected before donor death by the virology laboratory of Padua University, using a NAT technique (cobas TaqScreen West Nile Virus Test – Roche). No signs of fever or malaise had been documented in the week prior to donation. The result of the test on the donor was negative. About ten days after transplant, two transplant centres reported to the Italian National Transplant Centre suspected neurological symptoms in patients who had received a kidney

transplant from this donor. Between four and five days after transplantation, both kidney recipients had developed fever and ongoing encephalitis, symptoms compatible with WNV neuroinvasive disease [9,10]. The WNV NAT test performed with the same technique as with the donor, on both patients resulted positive (blood and urine samples). Following a protocol that had been successfully used in similar situations [11,12], high titre West Nile intravenous immunoglobulin was only administrated to one of the two kidney recipient, since the other one had already produced anti-WNV antibodies. After the reports of suspect symptoms in the two kidney recipients, virological tests on donor materials were repeated again using the NAT technique (cobas TaqScreen West Nile Virus Test – Roche) by the virology laboratory at the National Institute for Infectious Disease "L. Spallanzani" in Rome. The negative initial test result was confirmed, whereas serological tests showed the presence of anti-WNV antibodies (immunofluorescence assay – Euroimmun Italia) (Table). After this, NAT and serological tests were performed on the further three organ recipients who had received heart, lung and liver from the same donor. The NAT results for the heart and liver recipients were negative. The NAT result of the lung recipient was positive.

Thirty seven days after transplantation, one of the kidney recipients was more critically ill than the other kidney recipient; investigations on a possible link between the severity of the clinical condition and a genetic disease affecting the first patient are ongoing. Also at 37 days after transplantation, the NAT test- negative liver and heart recipients were in good health, while the lung recipient, who tested positive for WNV, presented neurological symptoms that can possibly be ascribed to immunosuppressive therapy toxicity.

As soon as it was suspected that WNV transmission from the donor could have occurred in the organ recipients, further use of all remaining tissues from the donor was stopped.

Conlusion

When the first report of symptoms indicating suspected transmission of WNV from donor to recipient was detected ten days after the transplantation, the Italian National Transplant Network promptly followed all communication and clinical protocols. First, the other transplant centres where the three recipients of heart, lungs and liver had been operated were alerted. At the same time, the National Transplant Centre and the Interregional Centre of competence, in cooperation with a national expert on infectious diseases (in charge of giving a "Second Opinion" on particular donation case) agreed and coordinated the clinical measures to be put in place to prevent further transmission and to insure adequate managing and care of the organ recipients. In particular, we took all therapeutic measures currently available for WNV, using stocks of plasma collected from donors positive for antibodies to WNV as a result of infections recorded in 2008 and 2009 in the north-east of our country. As no errors in safety protocols pre-donation occurred, it is assumed that virus concentration in the donor was not sufficient to be detected by the NAT technique.

The rapidly available test results and traceability of materials allowed prevention of further use of all remaining tissues from the donor. Testing the donor sample, earlier than within the required 72 hours post-donation, would not have been useful because of the likely low-level viraemia in the donor. It is however necessary to follow recommendations given in 2010 by the Italian Higher Health Council [13], that advised to screen donors by testing for viral RNA by the NAT technique within 72 hours of donation. This measure should be enhanced by the search for antibodies which should be carried out in a limited number of references laboratories, so as to ensure high quality standards. Clearly, traceability of donor organs through a national transplant network is crucial to facilitate tracing back to the donor also to other recipients of the latter, and to allow the study of suspected transmissions. In our case, rapid detection of the viral transmission facilitated the prevention of further transmissions to other tissue recipients.

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Table

Molecular and serological test results for West Nile virus infection on samples from organ donor and recipients, Italy 2011 (n=6)

	NAT test result	Antibodies determination
Donor	Negative on blood	Positive (IgG and IgM) on blood
First kidney recipient	Positive on blood and spinal fluid	Positive (IgG and IgM) on blood and spinal fluid
Second kidney recipient	Positive on blood and spinal fluid	Positive (IgG and IgM) on blood and spinal fluid
Heart recipient	Negative on blood	Negative on blood
Liver recipient	Negative on blood	Positive (IgG and IgM) on blood
Lung recipient	Positive on blood	Positive (IgG and IgM) on blood

NAT: Nucleic acid amplification test.

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Detection of *Citrobacter koseri* carrying beta-lactamase KPC-2 in a hospitalised patient, Greece, July 2011

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This report describes the detection of *Citrobacter koseri* carrying *K. pneumoniae* carbapenemase (KPC-2) isolated in July 2011 from a Greek patient, who was also colonised by a *Klebsiella pneumoniae* strain co-producing KPC-2 and Verona integron-encoded metallo-beta-lactamase (VIM)-1.

Case description

On July 2011, a Greek male in his early 80s was admitted to the University Hospital of Larissa, Greece, due to an acute myocardial infarction. He had chronic hypertension due to diabetes and had been hospitalised in the same hospital two months earlier, due to suspicion of tuberculosis, which was later ruled out (sputum and bronchoalveolar lavage cultures were negative for *Mycobacterium tuberculosis*). His respiratory tract symptoms soon remitted and he was discharged.

On admission for the myocardial infarction in July, he was given an empirical prophylactic antibiotic regimen of amoxicillin and clindamycin. On the fourth day of hospitalisation, he became febrile (40 °C) and cultures taken from various samples (blood, vein catheter, urine, sputum and bronchoalveolar lavage) were examined. Gram staining of the bronchoalveolar lavage showed the presence of Gram-negative rods along with leucocyte infiltration, indicating a respiratory tract infection. The presence of the Gram-negative bacterium was confirmed by culture, while the rest of the clinical samples were negative.

Using the VITEK 2 system (bioMérieux, France), the isolate was found to be *Citrobacter koseri* with reduced susceptibility or resistance to beta-lactams, including carbapenems (cefotaxime, ceftazidime, cefepime, aztreonam and ertapenem), but susceptible to fluoroquinolones (ciprofloxacin) and aminoglycosides (amikacin and gentamicin) (Table). Identification of *C. koseri* was further confirmed by PCR (amplifying the 16S ribosomal (r) RNA) and sequencing [1]. Non-beta-lactam antibiotics, such as quinolones and aminoglycosides, were active against the isolate (Table). The antimicrobial chemotherapy was altered to ciprofloxacin and the fever abated within days. Screening of faecal samples for carbapenem-resistant *Enterobacteriaceae* performed with McConkey agar supplemented with 1mg/L imipenem showed that the patient's gastrointestinal tract was colonised by an imipenem-resistant *Klebsiella pneumoniae* (Table).

Ten days later and while still on treatment with ciprofloxacin, the patient had a second febrile episode and imipenem-non-susceptible *K. pneumoniae* isolates were recovered from three cultures (two from blood and one from a vein catheter). The antibiotic resistance profiles of these three isolates were similar to that of the *K. pneumoniae* isolate from the faecal sample (Table). The patient was then successfully treated with a combination of tigecycline and gentamicin.

Background

The emergence of *Enterobacteriaceae* producing class A beta-lactamases of *K. pneumoniae* carbapenemase (KPC) type is a major clinical and public health concern as these enzymes have the potential to compromise treatment with all beta-lactams, including carbapenems. They are typically transposon-encoded determinants and therefore have the ability to move between plasmids and across bacterial species.

C. koseri, an environmental, Gram-negative bacterium, is occasionally found as a coloniser of the human gastrointestinal tract.* Although the potential virulence of the species is considered low, it is sporadically implicated in serious nosocomial infections [2]. Furthermore, *C. koseri* has the ability to easily incorporate antibiotic-resistance determinants [3]. Although there are several reports of *C. koseri* isolates bearing extended-spectrum beta-lactamase (ESBL) genes, the detection of *C. koseri* isolates producing a carbapenemase is rare [4-6]. To our knowledge, there is only one report of a *C. koseri* isolate producing Verona integron-encoded

metallo-beta-lactamase VIM-(1) [7]. Here, we present the first report of a *C. koseri* clinical isolate producing KPC-2.

Laboratory investigations

All five bacterial strains isolated from the patient (one *C. koseri* and four *K. pneumoniae*) were studied further. The minimum inhibitory concentration of various antiobiotics were determined by Etest (bioMérieux, France) and the results were interpreted according to the criteria of the European Committee on Antimicrobial Susceptibility Testing [8]. The modified Hodge test was used for phenotypic detection of carbapenemase production of either KPC or VIM type: all five isolates were positive. Meropenem-boronate and meropenem-ethylenediaminetetraacetic acid (EDTA) combined disk tests, performed as described elsewhere [9], indicated the presence of a KPC in the *C. koseri* isolate and the co-production of KPC and metallo-beta-lactamase (MBL) in the *K. pneumoniae* isolates.

PCR assays were used to screen all five isolates for *bla* genes encoding KPC, VIM, SHV, TEM, OXA-1, CMY and CTX-M [10-12]. Sequencing of the entire amplified genes revealed the carriage of bla_{TEM-1} and bla_{KPC-2} by *C. koseri* and bla_{TEM-1}, bla_{KPC-2}, and bla_{VIM-1} by *K. pneumoniae*. No nucleotide differences were observed in the bla_{TEM-1} and bla_{KPC-2} genes (which are known to be highly conserved) in the *C. koseri* and *K. pneumoniae* isolates.

The genetic relatedness of the *K. pneumoniae* isolates was investigated by multilocus sequence typing based on seven housekeeping genes (*rpoB, gapA, mdh, pgi, phoE, infB* and *tonB*) [13]. All four isolates were found to belong to ST147.

It was not possible to determine whether *C. koseri* could be found in the patient's gastrointestinal tract. Detection of *C. koseri* in faecal samples relies on amplification of 16S rRNA by PCR; however, this would amplify almost all bacteria that colonise the gastrointestinal tract.

Control measures taken

As recommended by the Greek health authorities, patients are not screened for carbapenem-resistant bacteria on admission or during hospitalisation. Weekly carrier screening is performed only in wards where a carbapenemase-producing bacterium is isolated.

When *C. koseri* was isolated from the patient, faecal samples were taken from the other six patients who were being treated in the same unit. None were found to be colonised by a KPC-positive *Enterobacteriaceae*. The patient was isolated in a single-bed room, under strict infection control measures.

Discussion

Previous studies have presented evidence for horizontal dissemination of bla_{KPC} genes among enterobacterial species worldwide [14-17]. However, to our knowledge, this is the first report of *C. koseri* producing KPC-2.

Enterobacteriaceae producing KPC were introduced in Greece in 2007 [18]. Since then, the prevalence of these microorganisms has risen to epidemic proportions, especially in teaching hospitals in the main urban areas [19]. This can be attributed to the overcrowded patient population in these hospitals, serious shortage of specialised personnel and consequently inadequate infection control. In the hospital in Larissa, where the prevalence of KPC-positive *K. pneumoniae* is approximately 27%, similar to that in other teaching hospitals in Greece [20], isolates of various species, such as *Serratia marcencens*, *Escherichia coli* and *Enterobacter aerogenes* carrying bla_{KPC} genes have been occasionally isolated from infected or colonised patients.

Table

Minimum inhibitory concentrations of various antimicrobial agents against isolated bacteria from a hospitalised patient, Greece, July 2011

Isolate (type of sample)	Etest results for the antimicrobial agents (mg/L and interpretation[a])											
	IMP	MEM	ERT	CTX	CAZ	FEP	ATM	COL	TIG	CIP	GM	AN
Citrobacter koseri (bronchoalveolar lavage) n=1	0.75 S	0.19 S	8 R	4 R	2 NS	1.5 NS	4 R	0.25 S	0.25 S	0.25 S	0.19 S	2 S
Klebsiella pneumoniae (blood) n=2	32 R	16 R	32 R	64 R	256 R	32 R	64 R	16 R	0.5 S	16 R	1 S	12 NS
K. pneumoniae (vein catheter) n=1	32 R	16 R	32 R	64 R	256 R	32 R	64 R	16 R	0.5 S	16 R	1 S	12 NS
K. pneumoniae (faecal) n=1	32 R	16 R	32 R	64 R	256 R	32 R	64 R	16 R	0.5 S	16 R	1 S	12 NS

AN: amikacin; ATM: aztreonam; CAZ: ceftazidime; CIP: ciprofloxacin; COL: colistin; CTX: cefotaxime; ERT: ertapenem; FEP: cefepime; GM: gentamicin; IMP: imipenem; MEM: meropenem; TIG: tigecycline.

[a] R: resistant; NS: non-susceptible; S: sensitive.

The fact that the patient in this report was colonised by a KPC-positive *K. pneumoniae* in his gastrointestinal tract suggests the in vivo transfer of bla_{KPC-2} to *C. koseri*. Given that *K. pneumoniae* was not isolated from bronchoalveolar lavage cultures, it is most likely that the transmission could have occurred in the gastrointestinal tract. Bronchoalveolar lavage and sputum cultures during the patient's first hospitalisation did not reveal the presence of *C. koseri* or *K. pneumoniae* or other bacteria. It could be hypothesised that, during his first hospitalisation, he was colonised in his gastrointestinal tract by a *K. pneumoniae* of ST147, which predominates in this setting (unpublished data). A probable scenario is that the bla_{KPC-2} gene was transmitted from *K. pneumoniae* to *C. koseri*, since both are part of the gastrointestinal flora. Identification of a KPC-encoding *C. koseri* strain from faecal samples would provide support for this hypothesis. No such strain was isolated, but given the low minimum inhibitory concentration of imipenem against the *C. koseri* isolate, a likely explanation is that the imipenem concentration used for screening of faecal samples (1 mg/L) suppressed the growth of *C. koseri*.

Rapid spread of carbapenemase-producing *Enterobacteriaceae* is a serious concern in clinical patient care in Greece. The finding of an additional enterobacterial species, *C. koseri*, producing KPC underscores the increasing clinical importance of carbapenemase-positive microorganisms in this country.

*Authors' correction:

At the request of the authors, the word 'anaerobic' was deleted from the sentence '*C. koseri*, an environmental, anaerobic, Gram-negative bacterium, is occasionally found as a coloniser of the human gastrointestinal tract'. This change was made on 24 October 2011.

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Invasive Group A Streptococcal Disease in Ireland, 2004 to 2010

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Invasive group A streptococcal infections (iGAS) are a major clinical and public health challenge. iGAS is a notifiable disease in Ireland since 2004. The aim of this paper is to describe the epidemiology of iGAS in Ireland for the first time over the seven-year period from 2004 to 2010. The Irish national electronic infectious disease reporting system was used by laboratories to enter the source of iGAS isolates, and by departments of public health to enter clinical and epidemiological details. We extracted and analysed data from 1 January 2004 to 31 December 2010. Over the study period, 400 iGAS cases were notified. The annual incidence of iGAS doubled, from 0.8 per 100,000 population in 2004 to 1.6 in 2008, and then remained the same in 2009 and 2010. The reported average annual incidence rates were highest among children up to five years of age (2.3/100,000) and adults aged over 60 years (3.2/100,000). The most common risk factors associated with iGAS were skin lesions or wounds. Of the 174 people for whom clinical syndrome information was available, 28 (16%) cases presented with streptococcal toxic shock syndrome and 19 (11%) with necrotising fasciitis. Of the 141 cases for whom seven-day outcomes were recorded, 11 people died with iGAS identified as the main cause of death (seven-day case fatality rate 8%). The notification rate of iGAS in Ireland was lower than that reported in the United Kingdom, Nordic countries and North America but higher than southern and eastern European countries. The reasons for lower notification rates in Ireland compared with other countries may be due to a real difference in incidence, possibly due to prescribing practices, or due to artefacts resulting from the specific Irish case definition and/or low reporting in the early stages of a new surveillance system. iGAS disease remains an uncommon but potentially severe disease in Ireland. Ongoing surveillance is required in order to undertake appropriate control measures and gain a greater understanding of this disease.

Introduction

Invasive group A streptococcal infection (iGAS) occurs when *Streptococcus pyogenes* invades a normally sterile site, e.g. blood, cerebrospinal fluid (CSF) or pleural fluid, and is associated with severe disease including necrotising fasciitis (NF), meningitis and streptococcal toxic shock syndrome (STSS) [1].

Although iGAS is relatively uncommon, the rapidity with which patients deteriorate, its occurrence in otherwise healthy people and the difficulties in the differential diagnosis underlie the importance of surveillance of this disease. Surveillance enables early detection of clusters/outbreaks to ensure prompt implementation of infection prevention, and control precautions and appropriate management of contacts. In addition, it allows trends in iGAS to be monitored, to inform healthcare planning and to support ongoing scientific research into, transmission, risk factors, pathogenesis and control of iGAS.

In Ireland, iGAS is a notifiable disease under the Infectious Diseases Regulations 1981. Under Section 14 of these regulations, as amended by S.I. No. 707 of 2003, a medical practitioner and a clinical director of a diagnostic laboratory, on suspecting or identifying a case of the infection, is obliged to send a written or electronic notification to a medical officer of health (MOH) [1]. The MOH will then undertake/delegate an investigation to identify contacts in order to provide information and prescribe chemoprophylaxis if indicated. Indications are (i) close contacts if they have symptoms suggestive of localised group A streptococcal (GAS) infection or (ii) mother and baby if either develops iGAS in the neonatal period (first 28 days of life). The MOH investigation is also to identify outbreaks.

Following a report of a cluster of cases in the west of the country in early 2005 [2], enhanced surveillance, which includes collection of information on isolate site, clinical presentation, risk factors and patient outcome, has been conducted on iGAS cases, on a voluntary basis, by departments of public health and microbiology laboratories since 2005. The national electronic infectious disease reporting system (Computerised Infectious

Diseases Reporting system, CIDR), which allows real-time exchange of information between laboratories, regional departments of public health and the national centre for communicable disease surveillance (Health Protection Surveillance Centre, HPSC), is used to notify iGAS and record enhanced surveillance findings.

Collection of antimicrobial susceptibility data commenced in 2008. These data are collected separately via the national antimicrobial resistance surveillance system.

The aim of this paper is to describe the epidemiology of iGAS in Ireland for the first time over the seven-year period from 2004 to 2010 in order to improve the understanding of iGAS in Ireland and to compare the epidemiology in Ireland with other countries.

Methods

Case definition

Confirmed iGAS cases are defined as patients with *S. pyogenes* isolated from a normally sterile site (e.g. blood, CSF, pleural fluid). Probable cases are defined as patients with *S. pyogenes* isolated from a non-sterile site (e.g. throat, vagina) combined with a clinical presentation compatible with STSS.

STSS is defined as hypotension (fifth percentile of systolic blood pressure in children, or ‹90mmHg systolic pressure in adolescents and adults) and two or more of the following: renal impairment (creatinine greater than twice the upper limit of normal for age), coagulopathy (platelets ‹100,000x10^6/l or evidence of disseminated intravascular coagulation), liver dysfunction (alanine transaminase, aspartate aminotransferase or bilirubin more than twice the upper limit of normal for age), adult respiratory distress syndrome (pulmonary infiltrates and hypoxaemia without cardiac failure or generalised oedema), generalised erythematous rash that may desquamate or soft tissue necrosis (necrotising fasciitis, myositis or gangrene).

Dataset and data processing

The iGAS isolate site was entered into CIDR by microbiology laboratories. Clinical details, including seven-day outcome data, and epidemiological details, including clusters of infection, were collected by public health staff and microbiologists through contact with the clinicians caring for the cases, or the cases themselves if they were well enough. Where death occurred, iGAS was attributed as main cause or contributory cause based on clinician's assessment. A cluster was defined as two or more epidemiologically linked iGAS cases or where the observed number of iGAS cases exceeds the expected number [1]. Information was entered into CIDR by public health staff using the national iGAS infection enhanced data form [1]. For laboratories and departments of public health not on CIDR, data were sent to the HPSC where they were entered into the system.

Antimicrobial susceptibility data were collected separately via the national antimicrobial resistance surveillance system.

Table 1

Number of cases of invasive group A streptococcal infection, and Irish age-specific incidence rates per 100,000 aged-matched population, by five year age groups, and calendar year, Ireland, 2004–2010 (n=400)

Age interval in years	Number of cases (age-specific incidence rate per 100,000 age-matched population)							
	2004	2005	2006	2007	2008	2009	2010	2004–2010
0–4	4 (1.3)	4 (1.3)	7 (2.3)	13 (4.3)	5 (1.7)	9 (3)	6 (2)	48 (2.3)
5–9	3 (1)	2 (0.7)	1 (0.3)	4 (1.4)	7 (2.4)	1 (0.3)	4 (1.4)	22 (1.1)
10–14	0 (0)	2 (0.7)	4 (1.5)	1 (0.4)	3 (1.1)	3 (1.1)	0 (0)	13 (0.7)
15–19	1 (0.3)	3 (1)	2 (0.7)	0 (0)	1 (0.3)	0 (0)	2 (0.7)	9 (0.4)
20–24	1 (0.3)	2 (0.6)	4 (1.2)	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)	12 (0.5)
25–29	3 (0.8)	3 (0.8)	3 (0.8)	2 (0.5)	4 (1.1)	2 (0.5)	2 (0.5)	19 (0.7)
30–34	4 (1.1)	2 (0.6)	6 (1.7)	6 (1.7)	5 (1.4)	4 (1.1)	3 (0.9)	30 (1.2)
35–39	2 (0.6)	4 (1.2)	5 (1.6)	3 (0.9)	3 (0.9)	4 (1.2)	10 (3.1)	31 (1.4)
40–44	1 (0.3)	1 (0.3)	2 (0.7)	2 (0.7)	4 (1.3)	3 (1)	3 (1)	16 (0.8)
45–49	0 (0)	2 (0.7)	4 (1.5)	1 (0.4)	4 (1.5)	5 (1.8)	3 (1.1)	19 (1.0)
50–54	0 (0)	1 (0.4)	2 (0.8)	2 (0.8)	2 (0.8)	1 (0.4)	4 (1.6)	12 (0.7)
55–59	1 (0.4)	3 (1.3)	2 (0.9)	5 (2.2)	3 (1.3)	2 (0.9)	3 (1.3)	19 (1.2)
60–64	2 (1.1)	4 (2.2)	3 (1.7)	1 (0.6)	9 (5)	4 (2.2)	4 (2.2)	27 (2.1)
65–69	3 (2.1)	3 (2.1)	4 (2.8)	4 (2.8)	2 (1.4)	2 (1.4)	3 (2.1)	21 (2.1)
70–74	6 (5)	3 (2.5)	1 (0.8)	2 (1.7)	0 (0)	6 (5)	5 (4.2)	23 (2.8)
≥75	4 (1.9)	9 (4.4)	11 (5.4)	9 (4.4)	16 (7.8)	13 (6.3)	14 (6.8)	76 (5.3)
Unknown	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)	1 (0)	0 (NA)
Total	**35 (0.8)**	**49 (1.2)**	**61 (1.4)**	**57 (1.3)**	**70 (1.7)**	**60 (1.4)**	**68 (1.6)**	**400 (1.3)**

NA: not applicable.

Information on iGAS isolate site and patient demographics were collected from 1 January 2004, while data on clinical presentation, risk factors, and outcomes were collected from 1 January 2005. Antimicrobial susceptibility results were collected from 1 January 2008. Typing of isolates was not routinely performed. We extracted and analysed data from 1 January 2004 to 31 December 2010.

Monthly, yearly and average annual incidence was calculated for males and females by five-year age groups using the matched age and sex population enumerated in 2006 census as the denominator [3].

A regression against time model was fit to test for trend in incidence of iGAS over time.

Results

Over the seven year period, 400 cases of iGAS (390 confirmed cases, five probable and five not specified) were notified. No iGAS clusters were notified over the period from 2005 to 2010, for which enhanced data were available. There was a significant increase in iGAS incidence from 2004: 0.8 per 100,000 population to 2008: 1.6 per 100,000 population (R^2=0.85) and in 2009 and 2010 there was no further increase (Table 1). The highest incidence annually was between late December and late August but this was not statistically significant by individual year or when averaged over seven years (p>0.05), hence seasonal trends could not be inferred by this study.

Demographics

A total of 205 males (average annual incidence of 1.38/100,000 males) and 195 females (average annual incidence of 1.31/100,000 females) were notified as cases (ratio: 1.05, 95% Confidence Interval (CI): 0.89–1.24).

Cases occurred in all age groups (median age: 44 years, range: 0–97) but children up to five years of age and adults aged 60 years and over had the highest age-specific incidence rates (Table 1). In 2010, there was also a peak in adults aged 35 to 39 (three of whom were intravenous drug users). No meaningful differences between average annual incidences for males versus females could be observed in any age group.

Characteristics of *Streptococcus pyogenes* isolates

Of the 390 confirmed cases with *S. pyogenes* isolated from a normally sterile site, the site/s from which the isolate was/were obtained was recorded in 225 cases. Of these, the most frequently recorded site was blood (n=198, 88%). *S. pyogenes* was also isolated from deep tissue (n=15), joint (n=3), abscess (n=6), pleural fluid (n=3), CSF (n=2), peritoneal fluid (n=1), periorbital haematoma or tissue (n=2), aspirate (n=1), bone (n=1), ventriculoperitoneal (VP) shunt tip (n=1) and wounds (n=2). *S. pyogenes* was isolated from more than one site in 11% of cases (25/225) with blood and another site being the most common combination.

Antimicrobial susceptibility data were available on 149 isolates between 2008 and 2010. Of isolates tested against each of the following, all were susceptible to penicillin (n=147) and vancomycin (n=117). Erythromycin resistance was reported in 13 of 140 (9.3%) isolates; clindamycin resistance in two of 57 isolates and tetracycline resistance in seven of 69 isolates.

Clinical presentation

Clinical syndromes associated with iGAS were recorded in 44% (174/400) of cases. Bacteraemia was the most commonly recorded presentation (n=115, 66%), followed by cellulitis (n=70, 40%), STSS (n=28, 16%), pneumonia (n=27, 16%), and necrotising fasciitis (n=19, 11%) (Table 2). Some cases had more than

Table 2

Clinical presentation for cases of invasive group A streptococcal infection, Ireland, 2005–2010 (n=174)

Clinical diagnosis	Number of cases (%) n=174	Number of cases with STSS diagnosis (%) n=28	Number of cases of bacteraemia diagnosis (%) n=115
Bacteraemia	115 (66)	21 (75)	115 (100)
Cellulitis	70 (40)	8 (29)	41 (36)
Streptococcal toxic shock syndrome	28 (16)	28 (100)	21 (18)
Pneumonia	27 (16)	6 (21)	20 (17)
Necrotising fasciitis	19 (11)	7 (25)	8 (7)
Septic arthritis	11 (6)	2 (7)	5 (4)
Puerperal sepsis	9 (5)	1 (4)	3 (3)
Myositis	7 (4)	2 (7)	5 (4)
Meningitis	5 (3)	1 (4)	2 (2)
Peritonitis	3 (2)	1 (4)	1 (1)
Erysipelas	1 (1)	1 (4)	1 (1)

STSS: streptococcal toxic shock syndrome.
A case may have more than one clinical diagnosis recorded.

one clinical presentation. In 66% (76/115) of patients with bacteraemia, at least one other presentation was also recorded, with cellulitis being the most common. In 89% (25/28) of cases where STSS was recorded, another presentation was also recorded, with bacteraemia being the most common, followed by cellulitis (Table 2).

Underlying risk factors

Of the 158 cases (158/400, 40%), including nine deaths (9/11) where invasive group A streptococcal infection was main the cause, and for whom underlying risk factor information was reported, skin lesions or surgical wounds were the most frequently recorded (n=58, 37%). Intravenous drug use, steroid therapy, childbirth, diabetes mellitus, malignancy, nonsteroidal anti-inflammatory drug (NSAID) use, alcohol abuse and varicella infection were recorded as underlying risk factor in less than one percent to 13% of cases (Table 3).

Mortality

Over the seven year period, outcome data at seven days were provided for 141 of 400 cases (35%). Sixteen deaths occurred; iGAS was identified as the main cause of death for eleven cases (seven-day case fatality rate (CFR), 8%) and as a contributory cause of death for three cases. For the two remaining cases, it was not specified whether iGAS was the main or a contributory cause of death. The majority of deaths occurred in people aged 65 years and over (nine of 16). There were equal numbers of deaths in men and women. Of the cases with STSS where outcome was recorded, six deaths occurred giving a CFR of 21% (6/28). Of the 11 deaths directly attributable to iGAS (seven females, four males), six occurred in people aged 65 years of age and over. Risk factor data were available for nine of the eleven deaths where iGAS was the main cause. Skin lesions or surgical wounds and NSAID use were the most commonly recorded risk factor, with small numbers of other risk factors recorded (Table 3). Clinical presentation was recorded for 10 of the 11 cases, with two or more clinical syndromes recorded in seven cases. Six presented with bacteraemia (an additional four had GAS isolated from their blood), four with STSS, three with pneumonia, three with myositis, two with necrotising fasciitis and two with cellulitis.

Table 3

Underlying risk factors for cases of invasive group A streptococcal infection, including nine deaths at seven days, where invasive group A streptococcal infection was the main cause, Ireland, 2005–2010 (n=158)

Underlying risk factor	Number of cases (%) n=158	Number of deaths n=9
Skin lesion/surgical wound	58 (37)	3
Intravenous drug use	20 (13)	2
Malignancy	18 (11)	1
Diabetes	17 (11)	1
Childbirth	15 (9)	0
Steroids	11 (7)	1
Nonsteroidal anti-inflammatory drugs	10 (6)	3
Alcohol abuse	8 (5)	0
Varicella	1 (1)	0
No identified risk factor	39 (25)	3

Cases could have more than one risk factor.

Discussion

This study provides an overview of the first seven years of iGAS surveillance in Ireland. The incidence of iGAS increased from 0.8 per 100,000 population in 2004 to 1.6 in 2008, after which it stabilised, with the highest age-specific incidence rates seen in children less than five years of age and adults aged 60 years and over. Like other countries, there appears to be slightly more men than women infected and more cases occurring in late winter/spring, however, these patterns are not statistically significant, which may be due to small numbers or some other unknown factor. Eleven people died with iGAS identified as the main cause of death (seven-day case fatality rate, 8%). Most deaths occurred in people aged 65 years and over.

The incidence of iGAS reported in Ireland was lower than that reported in the United Kingdom (UK), Nordic countries and North America but higher than southern and eastern European countries [4-14]. In 2009, the rate of GAS bacteraemia for England, Wales and Northern Ireland was 2.6 per 100,000 population, with regional rates ranging from 2.1 in the East Midlands to 3.2 in the North (UK figures here only include data from bacteraemia) [13]. In the United States (US) in 2009, the estimated rate of iGAS disease was 3.6 per 100,000 population [12] (normally sterile site or wound plus NF or STSS). In Sweden and Finland, the incidence rates in 2010 were 3.8 and 3.3 per 100,000, respectively (Sweden: no definition on website; Finland: *S. pyogenes* isolated from blood or cerebrospinal fluid) [5,10]. The clinical presentations of iGAS in Ireland were similar to that reported in other countries [6,7,15,16], however mortality due to iGAS was lower than that found in the Strep-EURO study [6], though similar to the North American continent [7-9,15].

It is difficult to be certain what accounts for these differences in iGAS incidence. It is possible that there is a real difference in incidence rates due to some unknown environmental reason, such as population density or climate. It is more likely that empiric antibiotic prescribing practices in Ireland, which are relatively high, may account for some of the difference between Ireland and elsewhere. For example, in 2008, outpatient penicillin use was higher in Ireland at 11.34 Defined Daily Dose (DDD) per 1,000 inhabitants per day than Finland at 6.11 DDD, Sweden at 7.37 DDD and the UK 7.95 DDD per 1,000 inhabitants per day [17].

However, it may be the case that difference in incidence of iGAS in Ireland is due to notification rather than a

real difference in incidence. It is also likely that as a newly notifiable disease, not all practitioners notified cases of iGAS initially. There was an increase in notifications between 2006 and 2008, followed by a stabilising of rates in 2009 and 2010, which indicates that at least some of the difference in incidence in Ireland compared with other countries was due to practice with respect to notifications. In addition, the number of microbiology laboratories using the national electronic infectious disease reporting system, CIDR, increased over the study period. While every effort was made to collect the same data by other methods from laboratories not on CIDR, it is possible that some data from these laboratories were not collected. As more laboratories came online, this may have accounted for some of the observed increase.

A small number of cases may go unreported as a result of Ireland's current case definition, where confirmed cases of iGAS include only cases where *S. pyogenes* is isolated from a normally sterile site and probable cases include only patients presenting with STSS and *S. pyogenes* isolated from a non-sterile site. Other countries have broader case definitions. In the Strep-EURO study confirmed cases included patients with *S. pyogenes* isolated from a normally sterile site, or non-sterile site in combination with clinical signs of STSS [6]. The UK case definition includes patients with non-sterile site isolates with one of the following severe presentations: pneumonia, necrotising fasciitis, puerperal sepsis, meningitis or septic arthritis [13] and the US case definition includes patients with a wound culture accompanied by necrotising fasciitis or STSS [12]. This may lead to a probably very small number of cases (e.g. post-varicella iGAS with necrotising fasciitis and *S. pyogenes* cultured from wound swab) not being counted in Ireland that would be counted in other countries.

Microbiological findings confirm that iGAS remains susceptible to penicillin and that penicillin should continue to be the first line treatment where iGAS is suspected.

Our study has a number of limitations. Of the 244 enhanced surveillance forms completed between January 2005 and December 2010 (representing 68% of cases over this period, n=359), 94% contained data on the site of the isolate, 71% on the clinical presentation and 65% on risk factors. It is possible that the cases on which more complete data were obtained were not representative of the full dataset. This may impact on data validity and introduce bias.

A further limitation is lack of data on *emm*/M-protein gene types. Certain *emm*/M-types of *S. pyogenes* are known to be more virulent than others, e.g. *emm* 1 and 3 [7,15]. However, as there is no Irish streptococcal reference laboratory, no typing data were collated nationally to investigate whether more virulent *emm*/M-types were associated with more severe disease or whether there was any change in iGAS types circulating over time.

In conclusion, the addition of iGAS to the list of notifiable diseases in Ireland has yielded useful information in the understanding of iGAS in Ireland. However, there continue to be constraints, most notably the absence of a national reference laboratory, the incomplete information collected on enhanced surveillance data and the lack of a universal or at least European standardised case definition for iGAS.

The authors recommend continued collection of enhanced surveillance data on cases of iGAS and efforts to improve completeness of data collected on enhanced surveillance forms. We also recommend an international review of the case definition with a view to the establishment of a consistent case definition across all countries, thereby enabling standardised international comparisons. Finally, the authors believe that the establishment of a national streptococcal reference laboratory is essential to enable a better understanding of iGAS in Ireland.

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Mumps epidemic in orthodox religious low-vaccination communities in the Netherlands and Canada, 2007 to 2009

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We assessed the epidemiological characteristics of a mumps virus epidemic (genotype D) that occurred in the Netherlands between August 2007 and May 2009 and its association with a subsequent mumps outbreak in Canada. In the Netherlands, five data sources were used: notifications (only mandatory since the end of 2008) (56 cases), laboratory confirmation data (177 cases), a sentinel general practitioner (GP) database (275 cases), hospitalisation data (29 cases) and weekly virological reports (96 cases). The median age of cases in the notification, laboratory and GP databases ranged from 13 to 15 years. The proportion of cases that were unvaccinated ranged from 65% to 85% in the notification, laboratory and GP databases. Having orthodox Protestant beliefs was the main reason for not being vaccinated. In Canada, a mumps virus strain indistinguishable from the Dutch epidemic strain was detected between February and October 2008 in an orthodox Protestant community with historical and family links to the affected community in the Netherlands, suggesting that spread to Canada had occurred. Prevention and control of vaccine-preventable diseases among population subgroups with low vaccination coverage remains a priority.

Introduction

Mumps (parotitis epidemica) is a vaccine-preventable viral infection characterised by inflammation of the salivary glands. Complications include aseptic meningitis, deafness, encephalitis, orchitis and oophoritis [1]. In the Netherlands, the disease had been notifiable between 1976 and 1998, and became notifiable again in 2008 [2], following a review of the criteria for notification of infections.

In 1987, the combination vaccine against measles, mumps and rubella (MMR) was introduced in the Dutch National Immunisation Programme for all children aged 14 months and nine years. Since 1995, the estimated nationwide MMR coverage (measured by registration of the vaccination status for each Dutch child individually) for one dose has not been below 95% (in two-year-olds); for the second dose, the coverage is slightly lower, around 93% (in nine-year-olds) [3]. The mumps vaccine used contains the Jeryl Lynn mumps JL2 and JL5 vaccine strains [2]. The high coverage for the entire country, however, is not reached in areas where a part of the population refuses vaccination based on their orthodox Protestant beliefs [3,4]. In one of the municipalities where these groups reside, coverage for the first dose of the MMR vaccine in 2009 was as low as 62% [5]. About 1.5% of the Dutch population belongs to this minority of an estimated 250,000 persons [6].

Between August 2007 and May 2009, a mumps epidemic in the country was detected through laboratory surveillance [2,7], but assessment of the extent and characteristics of the epidemic was hampered by the absence of mandatory notification between January 1999 and December 2008 [8]. A subsequent mumps outbreak (in February to October 2008) was observed in Canada, with the first case identified in July 2008, nearly a year after the epidemic started in the Netherlands.

Mumps is a notifiable disease in Canada (notifiable during 1924 to 1959 and from 1986 onwards) [9]. The estimated MMR vaccine coverage for one dose in two-year-old children has not been below 93% since 2002 [10]. However, similar to the Netherlands, this overall figure conceals areas of lower coverage in

geographically clustered communities in Canada (in south-western Ontario) who refuse vaccination for orthodox Protestant reasons (population estimate unavailable). Historically, members of this Canadian community have had close family relationships with the orthodox Protestants in the Netherlands. Several outbreaks of vaccine-preventable diseases have spread from the Netherlands to these Canadian communities in the past, including poliomyelitis, measles and rubella [11-14]. Spread of an outbreak of a vaccine-preventable disease from Canada to the Netherlands, however, has never been documented.

The aim of our study was to assess the epidemiological characteristics of the mumps epidemic in 2007 to 2009 in the Netherlands and to study its association with the subsequent mumps outbreak in Canada.

Data sources in the Netherlands

To describe the epidemiological characteristics associated with the mumps outbreak in the Netherlands, five data sources were used. As there was no common identifier, unfortunately, these databases could not be linked.

Notification database (Osiris)

From 1 December 2008, mumps became again a notifiable disease in the Netherlands. Data of patients registered in the nationwide mandatory notification system, Osiris, with a date of symptom onset from 1 December 2008 up to 31 May 2009 were available (date of sampling was used when date of onset was unknown).

The case definition for notification was a person with at least one of the following three symptoms: (i) acute onset and painful swelling of the parotid or other salivary gland, (ii) orchitis and (iii) meningitis (clinical criteria for orchitis and meningitis were not specified); in addition, at least one of the two following criteria was met: laboratory-confirmed infection with mumps virus or contact (less than four weeks ago) with a person who had laboratory-confirmed mumps. Laboratory confirmation of infection with mumps virus included detection of mumps virus-specific IgM antibody in serum, detection of mumps virus RNA in oral fluid, oropharyngeal swab or urine specimens by reverse transcription (RT)-PCR or by virus culture. People who had been vaccinated less than four weeks before symptom onset were not notified, unless wild-type mumps virus RNA was detected.

Laboratory database

The Centre for Infectious Disease Control Netherlands at the National Institute for Public Health and the Environment (RIVM) serves as a reference laboratory for mumps. Early in the epidemic, municipal health services were asked to encourage physicians to send samples from mumps cases who had been vaccinated. This meant that unvaccinated cases were under-represented in the laboratory data.

A case was defined on basis of laboratory confirmation, which was either detection of mumps virus RNA in throat swabs, oral fluid or urine specimens by RT-PCR or detection of mumps virus-specific IgM in serum or dried blood spot specimens or, occasionally, on the basis of a fourfold rise in mumps virus-specific IgG titre [15]. The laboratory database contained information on sex, age, mumps virus genotype, date of symptom onset, vaccination status, reason for non-vaccination and PCR, IgM, IgG test results.

Data from all laboratory-confirmed cases with a date of symptom onset between 22 August 2007 (the date symptoms of the first case began) and 31 May 2009 were available.

General practitioners (GP) database

Enhanced sentinel surveillance was carried out in 11 GP practices situated in low vaccine coverage areas between 1 September 2007 and 31 December 2008. Cases were defined as patients with a clinical or laboratory-confirmed diagnosis of mumps (the clinical criteria for meningitis, orchitis or encephalitis were not specified and the requirements for laboratory confirmation were not specified in the database). The monthly incidence of the disease reported through this system was determined for three periods (September 2007 to March 2008, April to June 2008 and July to December 2008), as not all GPs participated during the entire study period.

National Medical Registry

We analysed the number of hospitalisations in 2006 to 2009 due to mumps or mumps-related complications from the National Medical Registry, to which all academic and general (and almost all specialised) hospitals supplied data. We included data from 2006 to show the number of diagnoses before the epidemic. Admissions from hospitals with incomplete reporting

Table

International Classification of Diseases codes used for analysis of hospital diagnoses related to mumps, the Netherlands, 2006–2009

Diagnosis	ICD-9-CM code
Mumps	072
Mumps orchitis	072.0
Mumps meningitis	072.1
Mumps encephalitis	072.2
Mumps pancreatitis	072.3
Mumps with other specified complications	072.7
Mumps hepatitis	072.71
Mumps polyneuropathy	072.72
Mumps with other complication	072.79
Mumps with unspecified complication	072.8
Mumps without complications	072.9

ICD-9-CM: International Classification of Diseases, ninth revision, clinical modification [16].

were excluded from the analysis, leaving data from approximately 75% of all hospitals in the Netherlands.

The diagnoses in the hospitals were defined according to the International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) [16]. The Table shows all the ICD-9-CM diagnoses that were considered. The National Medical Registry database also contains information on age, sex, date of hospital admission and discharge, main diagnosis and minor diagnoses.

Weekly virological reports

Since 1989, 21 medical microbiological laboratories in the country have reported their weekly number of positive virological test results, including detection of mumps virus, to the laboratory surveillance system (the reference laboratory is not included). Reporting is voluntary, but it is constant and complete. Only the number of positive samples is reported: no information about the number of samples tested or clinical information about the cases is available. This data source is particularly useful to detect trends over time. We used the reports from 2006 to 2009 (data from 2006 were included to show the number of diagnoses in a year without an epidemic).

Description of the epidemic in the Netherlands

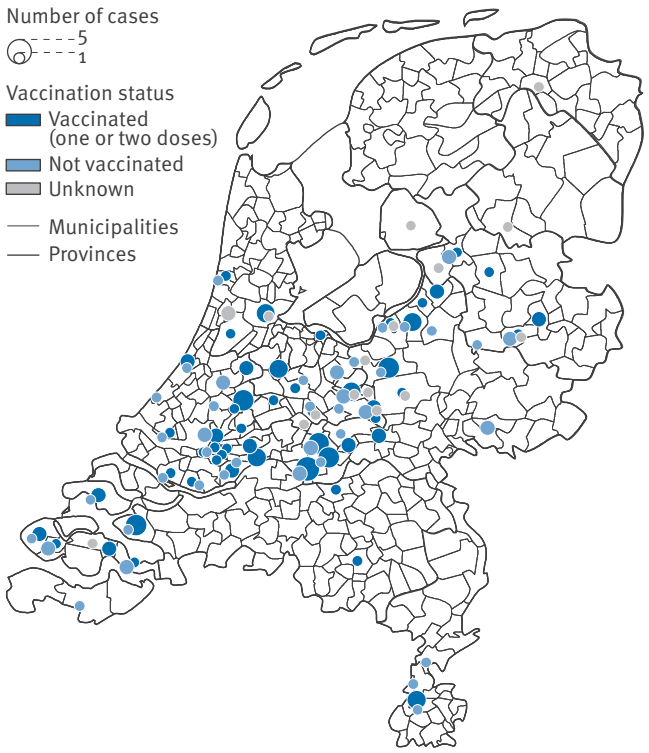
Notification database (Osiris)

A total of 56 cases with a date of symptom onset between 1 December 2008 and 31 May 2009 were registered in the national mandatory notification system, Osiris. The cases had a median age of 15 years (range: 1–56); 29 were male. For 10 cases, complications due to mumps were reported: seven of these had orchitis. The seven cases with orchitis were all unvaccinated; the three remaining cases with complications had received one dose of MMR vaccine (two cases had been vaccinated six months before diagnosis and one case had been vaccinated three years before diagnosis). Three of the 56 cases were hospitalised due to their complications (two because of orchitis, one had an abscess): the case with the abscess had received one dose of MMR vaccine and the other two cases were unvaccinated.

Vaccination status was known for 55 of the 56 cases: 40 had not been vaccinated. Of the 15 that had been vaccinated, nine had received one dose, five had received two doses and for one case, the number of doses was unknown. The median age of the unvaccinated cases was 17 years (range: 1–56); for cases vaccinated at least once, it was 9 years (range: 1–26) (p=0.02). For 32 of the 40 unvaccinated cases, a reason for

Figure 1

Laboratory-confirmed mumps cases diagnosed by the national reference laboratory at RIVM, by municipality and vaccination status, the Netherlands, August 2007–May 2009 (n=165)[a]



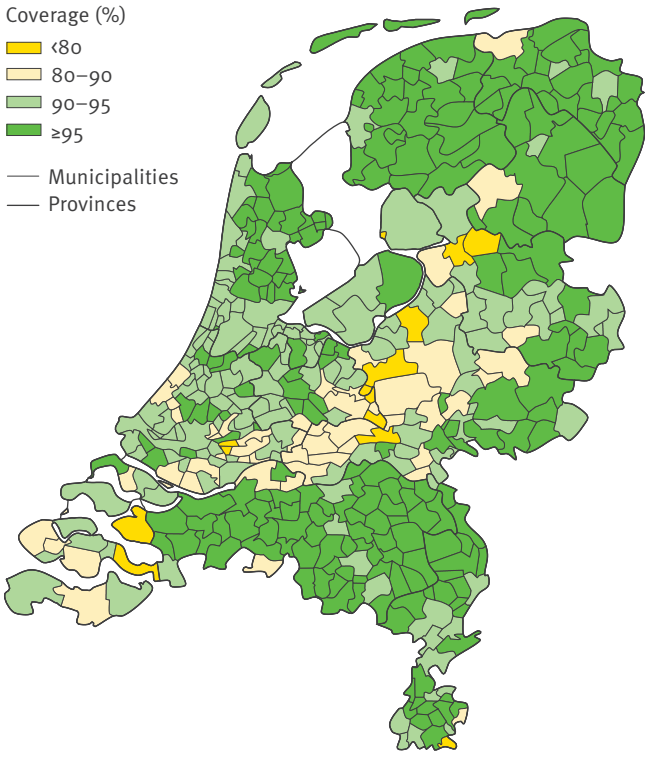
RIVM: National Institute for Public Health and the Environment.

[a] 12 cases were not included because of missing information.

Source: RIVM.

Figure 2

Measles-mumps-rubella vaccination coverage at the age of 10 years, by municipality, the Netherlands, 2006[a]



[a] 1995 birth cohort, completed vaccination at the age of 10 years.

Source: De Nationale Atlas Volksgezondheid [The Dutch National Atlas of Public Health].

non-vaccination was reported. The most frequent reason was having orthodox Protestant beliefs (n=27) and five cases had a critical attitude towards vaccination.

Laboratory database

The national reference laboratory received samples from 409 suspected cases with a date of onset symptoms between 22 August 2007 and 31 May 2009. In total, 43% (n=177) were confirmed as mumps cases. Most of these patients were not notified since mandatory notification started only in December 2008. The median age of the confirmed cases was 13 years (range: 1 month–56 years). Vaccination status was known for 156 (88%) of the confirmed cases. Some (35%; n=55) of these cases were vaccinated: 26 had been vaccinated once, 29 twice and 101 cases were unvaccinated. The median age of unvaccinated cases was 14 years (range: 1 month–56 years); for vaccinated cases, it was nine years (range: 1–29 years), p=0.00.

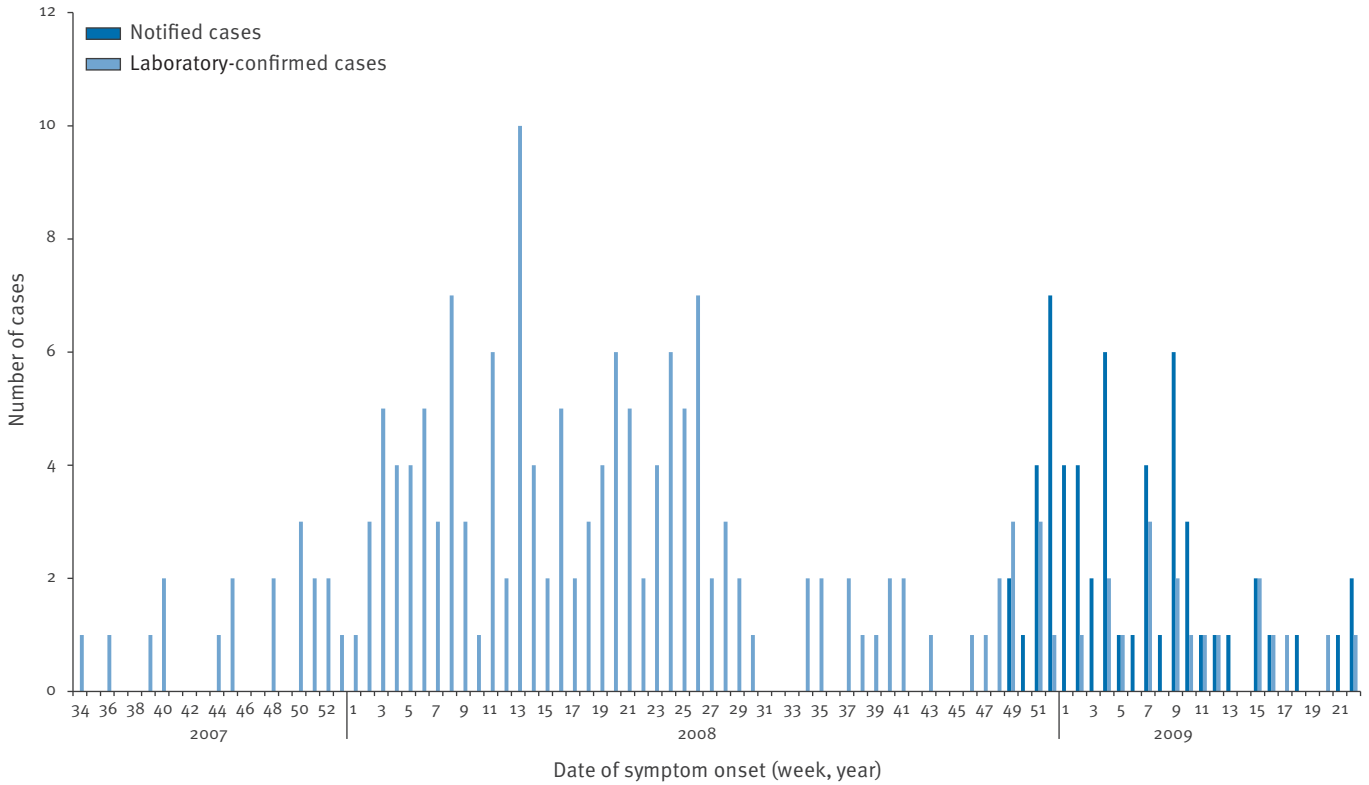
For 72 of the 101 unvaccinated cases, a reason for non-vaccination was reported. The reasons were religious beliefs (n=52), the age of the case (n=13, of which four were too young to be eligible for vaccination) and nine cases were born before vaccination against mumps had been introduced in the Netherlands), four had a critical attitude towards vaccination, and three had an anthroposophical lifestyle. Figure 1 shows the geographical distribution of laboratory-confirmed cases in the Netherlands from August 2007 to May 2009 by vaccination status and Figure 2 illustrates the MMR vaccination coverage in 2006 (having received two doses at the age of 10 years) of the 1995 birth cohort.

Figure 3 shows an epidemic curve of the mumps cases recorded through the notification and laboratory databases.

Virus genotyping results were available for 158 (89%) of the 177 laboratory-confirmed cases. The most frequent genotype was D (n=145; 92%); the remaining samples were genotype G (n=13; 8%). The 13 patients with genotype G had a date of symptom onset between February 2008 and April 2009. Of these, vaccination status was known for 10 patients: eight had been vaccinated (three had been vaccinated once, five had been vaccinated twice) and two were unvaccinated. Cases with genotype G were predominantly living in areas with higher vaccination coverage. There was one orthodox Protestant among the unvaccinated cases

Figure 3

Mumps cases registered through mandatory notification (n=56)[a] and laboratory-confirmed cases (n=177), by week of symptom onset[b], the Netherlands, 2007–2009[c]



[a] Mumps was not notifiable between January 1999 and December 2008.

[b] When the date of onset of symptoms was unknown, date of sampling was used.

[c] For the notified cases, 1 December 2008–31 May 2009 (week 49 2008–week 22 2009). For the laboratory-confirmed cases, 22 August 2007–31 May 2009 (week 34 2007–week 22 2009).

with genotype G and one case was too young to be vaccinated.

General practitioners database

The enhanced sentinel surveillance in 11 GP practices situated in low vaccine coverage areas resulted in detection of 275 mumps cases from 1 September 2007 to 31 December 2008. Their median age was 14 years (range: 1–67). The age distribution of cases from the notification, laboratory and GP databases is shown in Figure 4.

Of the 275 cases detected through the enhanced sentinel surveillance, 59% (n=163) were male. After excluding cases for whom only age and sex were recorded (n=69, reported by one GP), a total of 206 cases were included in our analysis. GPs reported whether there had been laboratory confirmation of the infection and decided whether to send samples for testing. Mumps diagnosis was confirmed by laboratory testing for 16 of the 206 cases (8%).

From September 2007 to December 2008, the 11 sentinel GP practices covered 38,281 people: in September 2007 to March 2008, the population covered was 34,981, in April to June 2008, it was 29,281 and in July to December 2008, it was 6,150. The estimated monthly incidence of mumps in these GP practices was 34.6 (95% CI: 27.9–42.5) per 100,000 population per month in September 2007 to March 2008 (n=92), 102.9 (95% CI: 82.1–127.1) per 100,000 population per month in April to June 2008 (n=85) and 180.1 (95% CI: 139.7–228.4) per 100,000 population per month between July and December 2008 (n=67). As not all GP practices reported throughout the study period, an epidemic curve would not be meaningful.

Of the 206 cases analysed, 85% (n=176) were unvaccinated. Their median age was 14 years (range: 1–67). The median age of the vaccinated cases (n=30) was 13 years (range: 4–31), p=0.44). Three had been vaccinated once, 10 had been vaccinated twice and five had been vaccinated either once or twice, while for 12, the number of vaccinations was unknown. Orthodox Protestant beliefs were the main reason for not being vaccinated (held by 163 (93%) of the 176 unvaccinated cases).

The median number of household members of the 206 cases analysed was six (range: 1–11). The median attack rate in their households was 50% (range: 13–100). Complications of mumps were reported in 33 (16%) cases. Of the 123 cases who were male, 25 (20%) had orchitis. Seven (3.4%) of all 206 cases had meningitis (including one case for whom meningitis was not confirmed) and one (0.5%) had encephalitis.

National Medical Registry

The number of hospitalisations due to mumps or mumps-related complications in 2006 to 2009 is presented in Figure 5. The outbreak peaked in May 2008, as documented from mumps related hospitalisations and weekly virological reports. The duration of the epidemic can be clearly seen from the hospitalisation data, with its peak in May 2008. During the epidemic, 29 patients were hospitalised due to mumps or a mumps-related complication: they accounted for 78% of all hospitalisations due to mumps during 2006 to 2009 in the Netherlands (n=37). A peak of seven admissions was observed in May 2008. There was another hospitalisation in June 2009, but as no new mumps cases with genotype D virus had been diagnosed in the laboratory database after 31 May 2009, we did not consider this case as part of the epidemic.

Weekly virological reports

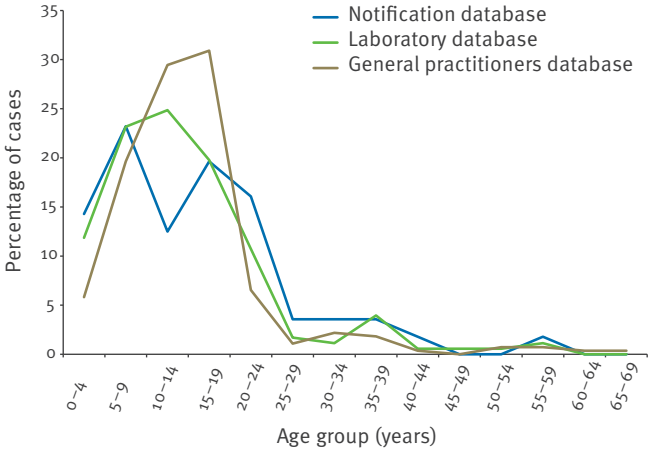
The number of tests that were positive for mumps virus from the weekly virological reports from 2006 to 2009 is shown in Figure 5. The peak number of positive tests was observed in May 2008 (n=13), which coincided with the peak in hospitalisations due to mumps or mumps-related complications. Of all positive tests in 2006 to 2009 (n=120), 80% (n=96) were observed during the epidemic (August 2007 to May 2009).

Spread to Canada

The Ontario Ministry of Health and Long-Term Care was notified by the regional health unit on 1 August 2008 about an outbreak of mumps. Outbreak-associated cases were identified retrospectively to 24 February 2008. The date of symptom onset of the last case of the outbreak was 26 October 2008; the majority of cases (n=288/324; 88%) had symptom onset between June and August 2008 and were mainly school-age children, with 77% (250/324) between the ages of 5 and 19

Figure 4

Age distribution of mumps cases registered in the notification database (n=56), laboratory database (n=177) and general practitioners database (n=275), the Netherlands, 2007–2009[a]



[a] Notification database: 1 December 2008–31 May 2009; laboratory database: 22 August 2007–31 May 2009; general practitioners database: 1 September 2007–31 December 2008.

years. The cases were all from Ontario [17], mainly in the south-west of the province in a community with low immunisation coverage.

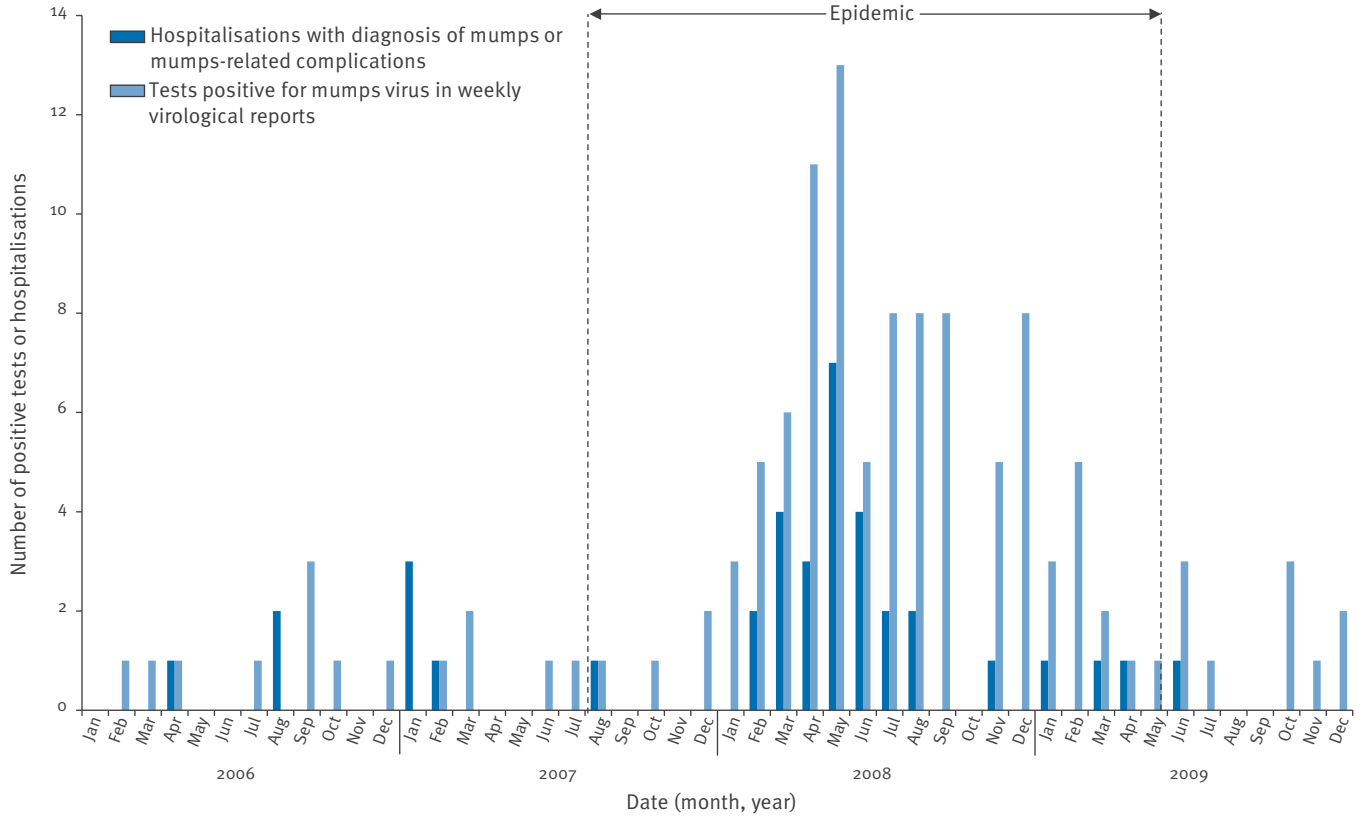
A confirmed outbreak case was defined as a person having any of the following, in the absence of mumps vaccination in the previous 28 days: (i) a positive serological test for mumps-specific IgM, with an acute onset of unilateral or bilateral parotitis lasting longer than two days without other apparent cause, (ii) demonstrated seroconversion or a fourfold increase in the titre of mumps virus-specific IgG between the acute and convalescent sera titres, or (iii) the detection of mumps virus RNA from urine or buccal swabs [18]. Symptomatic people who had an epidemiological link to a laboratory-confirmed case were also considered as confirmed outbreak cases.

All case and laboratory data were entered into Ontario's integrated Public Health Information System. There were 324 outbreak-associated cases reported, of which 289 (89.1%) were confirmed cases. Samples from nine of the confirmed cases were received at the National Microbiology Laboratory of the Public Health Agency of Canada between 30 July and 12 September 2008. Mumps virus genotyping was done as per the internationally accepted standard [19]. The sequences of the mumps virus strains from the samples were compared with the sequence of the Dutch outbreak strain and were submitted to GenBank. Phylogenetic analysis of the different mumps viruses was based on nucleotide sequencing of the coding region of the small hydrophobic (SH) gene of mumps virus RNA (317 base pairs) using the neighbour-joining method for phylogenetic comparison and using a set of reference genotypes obtained from GenBank [20].

All nine viral sequences were 100% identical and were indistinguishable from the Dutch genotype D epidemic strain, based on the same 317 bp sequence of the SH gene. Figure 6 shows the phylogenetic tree of Dutch (n=5) and Canadian (n=1) isolates and reference genotypes. A tenth sample was found to contain genotype G (importation from British Columbia), a genotype that has circulated in mumps outbreaks in North America since 2006 [21-24]. This sample had been taken from a member of the religious community with symptom onset on 8 September 2008, who had been originally thought to be part of the outbreak. As only a few samples were sent for genotyping, other people with mumps may also have been infected with a genotype G strain. This illustrates how people with the disease may appear to be part of the same cluster, as they appear linked in time and place, while they may in fact have been exposed to different sources of the virus and are thus not part of the cluster.

Figure 5

Monthly hospitalisations due to mumps or mumps-related complications recorded in the National Medical Registry and the number of tests positive for mumps virus in the weekly virological reports, the Netherlands, 2006–2009



Discussion and conclusion

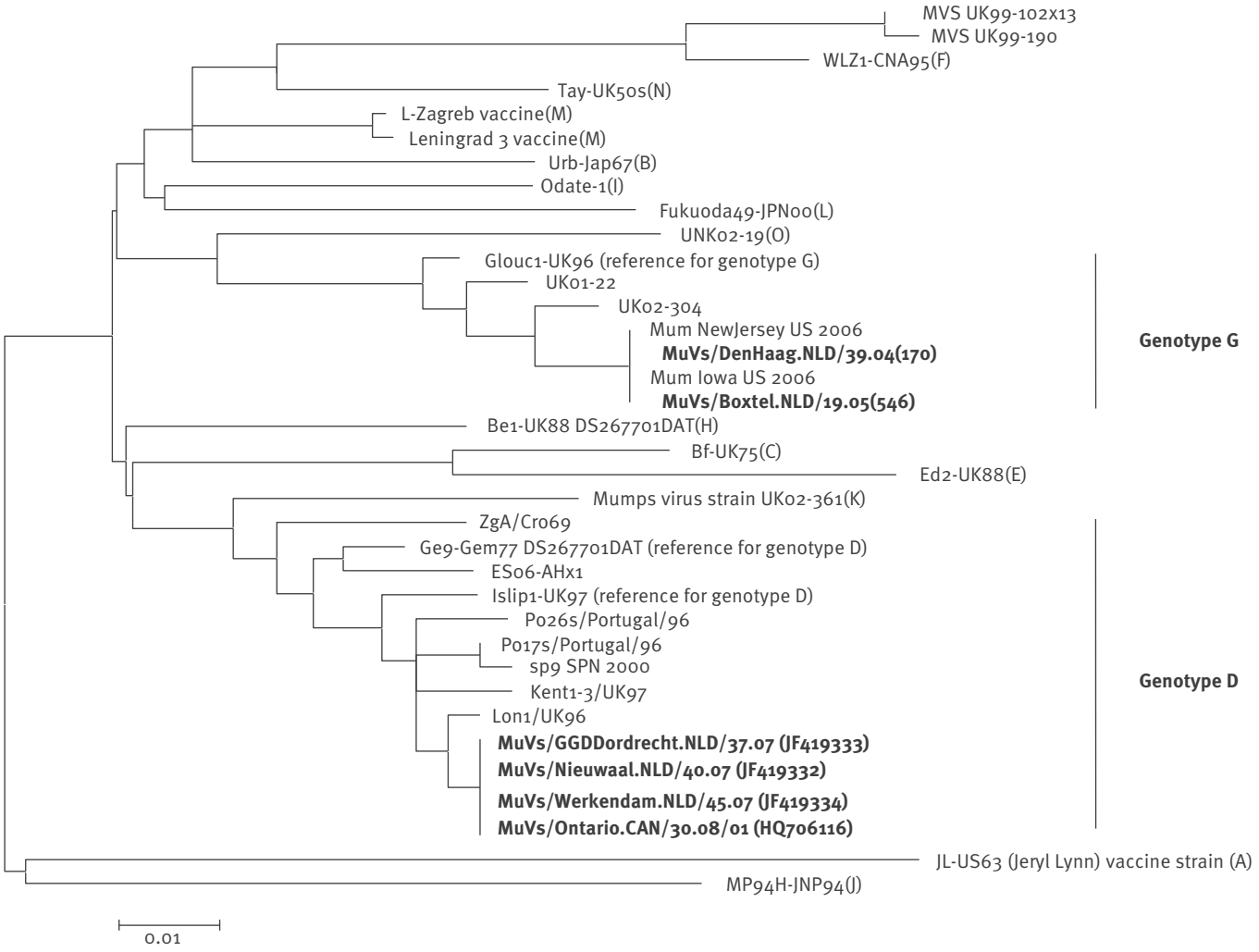
In this mumps epidemic in the Netherlands, most cases were living in low vaccination coverage areas and were unvaccinated, orthodox Protestant children. The orthodox Protestant population has been affected by several outbreaks of vaccine-preventable diseases, including poliomyelitis in 1978 and in 1992 to 1993 [25,26], measles in 1999 to 2000 [14] and rubella in 2004 to 2005 [12].

We believe that the vaccination status of cases can most reliably be estimated from the mandatory notification system. On the basis of the notification data, an estimated 27% of cases (n=15) had been vaccinated. Mumps among vaccinated individuals has been described in the literature [27-30]: possible causes are primary vaccine failure, secondary vaccine failure or waning immunity, and a mismatch between vaccine-induced immunity and the wild-type mumps virus strain [27,29-34].

The proportion of cases with a complication ranged from 16% (33/206) in the GP database to 18% (10/56) in the notification database. As patients with complications are likely to be overrepresented among those visiting a GP and those notified, both proportions are likely to be overestimates. Three of the 56 notified cases required hospital admission. The hospitalisation database, which covers approximately 75% of the Netherlands, registered 29 mumps-related hospitalisations during the epidemic. Compared with previous outbreaks of rubella and measles in the Netherlands, with 2% and 1% of cases admitted to hospital, respectively [12,14], the percentage of hospitalisations during the mumps epidemic was higher.

Figure 6

Phylogenetic tree of reference mumps virus genotypes and genotype D and G branches harbouring the reference strains and the Dutch (n=5) and Canadian (n=1) isolates, 2007–2009



Evolutionary distances are reflected as branch lengths. The distance indicator (length) reflects the fraction of nucleotide difference. The Dutch (NLD) and Canadian (CAN) isolates are shown in bold.

The spread of the mumps outbreak to Canada was not unexpected, as previous outbreaks of vaccine-preventable diseases had also spread to Canada [11-14]. The first case with mumps virus genotype D that was indistinguishable from the Dutch epidemic strain was identified in July 2008, nearly a year after the outbreak started in the Netherlands. This indicates that the virus had spread from the Netherlands to Canada and not vice versa. We suppose that close family relationships and subsequent visits of relatives caused the spread to Canada. We do not have any information about the occurrence of the Dutch epidemic strain in other countries.

There were several limitations in our study. Firstly, there was no single data source available that had complete information on all cases during the mumps epidemic in the Netherlands. Mumps was not a notifiable disease in the country up to December 2008. The laboratory database included cases diagnosed during the whole epidemic; however, due to increased awareness of the possible emergence of outbreaks among vaccinated persons, physicians were particularly encouraged to send samples of vaccinated mumps patients, so these data are not representative for the epidemic. Further, the laboratory database mostly includes data obtained from the national reference laboratory and very few from the peripheral laboratories in the Netherlands. It was, however, the only data source for genotype results. The GP database included data from GPs in low vaccination coverage areas, which results in estimates that are not representative. However, with the five data sources used in this study, we were able to give the best available description of the epidemic. Secondly, we were not able to link data sources as there was no unique identifier. Therefore it is possible that some cases were present in one or more data sources. Since we did not merge any of the data sets, this should not have affected our conclusions. Finally, the fact that different time periods were covered in the data sources is also a limitation.

At present, a new mumps outbreak is ongoing in the Netherlands mainly among students [35]. This outbreak started in December 2009, caused by mumps virus genotype G. Genotype G strains were also found in 2008, mainly among vaccinated individuals (data not shown). In contrast to the 2007 to 2009 epidemic, the majority of the students with mumps had been vaccinated: 80% had received at least one dose and 75% had been vaccinated at least twice [35]. The spread of this outbreak is being monitored closely and a study into risk factors has been initiated.

In conclusion, our study of a mumps epidemic mainly among unvaccinated orthodox Protestant individuals demonstrates that a focus on interventions to prevent and control vaccine-preventable diseases in population subgroups with low or intermediate vaccination coverage remains necessary, in the Netherlands and elsewhere. i.

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Letter to the editor: HIV-1 outbreak among injecting drug users in Greece, 2011: a preliminary report

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To the editor: I read with great interest the article by Paraskevis et al. on the approximately 10-fold increase in reported cases of HIV-1 among injecting drug users (IDUs) in Greece, recently published in *Eurosurveillance* [1]. The authors conclude that the increase reflects a recent outbreak among users. They use data collected through the systematic case reporting surveillance system and specialised laboratory studies (mainly sequencing based cluster or phylogenetic analysis) to further suggest that the root cause of the outbreak is transmission from HIV-positive migrants to native Greek drug users.

The conclusions of the study could be interpreted as suggesting that migration constitutes an external threat to the health of the native population. I think that this is an over-interpretation of the results. Such over-interpretation is not uncommon to epidemiological studies primarily reliant on high-resolution molecular typing, often also called molecular epidemiological studies.

High-resolution molecular typing relies on the sequencing and comparison of parts of or entire genomes of microbes. It allows classification of a microbial isolate or sample sequence according to its genetic relatedness to sets of potentially related sequences stored in research or reference databases. While the approach has potential for epidemiological analysis, it also has several limitations, insufficiently discussed in the report by Paraskevis et al. A thorough discussion of these limitations would be necessary and further research on the value of high-resolution typing for epidemiological studies is still needed.

Paraskevis et al. have compared HIV sequences sampled from newly reported cases among IDUs to sequences isolated from HIV cases in Greece in a large database (n=2,337), which were collected mainly through analyses of HIV drug resistance for clinical monitoring [2]. While relatively large, the representativeness of this database in relation to the HIV epidemic in Greece is difficult to assess. Furthermore, data collected through clinical monitoring are usually under-represented for IDUs.

The data that the authors show are not described in a way that would demonstrate representativeness of the sampled population (IDUs in Greece). The analysis is based on a total of 34 cases and only limited socio-demographic data are shown for the cases analysed and none for the reference population (the large database of sequences) it is compared with. Biased inclusion of cases in the reference database could easily result in masking an existing epidemic and enhanced sampling due to rising awareness could result in a false impression of a 'new' outbreak.

The authors state that: 'This finding supports a recent introduction from migrating population [...] and 'viral sources for the different networks were mainly originated from globally circulating viruses (CRF14_BG, subtype A) suggesting a potential role of migrant IDUs for the initiation of the recent outbreak'. While the authors acknowledge that another interpretation is possible, the conclusion that the outbreak was of migrant origin is reiterated as the main finding. Examination of the phylogenies presented in the report shows that there have been multiple introductions of HIV and sub-epidemics among IDUs in Greece in the past and this is evident even in the sample set analysed for this study. The authors miss the most important public health message highlighted by the outbreak: that the risks of HIV transmission by injecting drug use have not been properly addressed through prevention and therefore an outbreak was possible. The message should be that the prevention programme for this vulnerable group has failed.

From a prevention perspective, the origin of the outbreak virus (or its host) makes little difference and is likely to be a stochastic event that has mainly an academic interest. Prior examples of such stochastic events are common among IDUs [3, 4]. It is obviously important not to stigmatise migrants as being responsible for an HIV epidemic among IDUs, rather, it

is important to identify risks and then take appropriate preventive public health action. As pointed out by the authors, there is a need for an integrated and combined prevention initiative addressing infection risks among IDUs as a response to the increasing number of HIV cases in this vulnerable group.

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Authors' reply: HIV-1 outbreak among injecting drug users in Greece, 2011: a preliminary report

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To the editors: We read with interest the letter from M Salminen commenting on our paper about an outbreak of HIV infections in intravenous drug users (IDUs) in the first seven months of 2011 in Greece and the preliminary results from molecular epidemiological analysis, recently published in *Eurosurveillance* [1,2].

We hereby reply to the points made and thank the author for the opportunity to clarify and discuss some aspects of our work not included in the preliminary epidemiological report.

The letter comments that high resolution molecular typing is currently not an appropriate analytical method and that more research is needed on its value for epidemiological studies. The aim of our preliminary analysis was to present early findings of the outbreak and not to review and to thoroughly discuss advantages and limitations of high resolution molecular typing for epidemiological studies. However, we would like to point out that molecular epidemiological methods are widely used for the understanding of origin and spread of infectious agents [3, 4] and molecular typing was applied in different investigations in HIV epidemics among IDUs across Europe [5-7].

As concerns the representativeness of the Greek HIV sequence database and our cases, we can confirm that the database is representative for age, sex and transmission group distribution of the HIV epidemic in Greece according to earlier analyses [8, 9]. It includes sequences from 2,327 cases, one fourth of the total reported HIV cases in this country since the beginning of the HIV/AIDS epidemic in 1981. Even if the substance of our analysis was not representativeness, our database is sufficiently large to provide preliminary indication that the sequences from the majority of clustered IDU cases were not recognised previously in Greece. Moreover, as shown in Table 1 of our original communication, we compared our data with the reference population.

Since the epidemic is ongoing any clue on possible underlying risk factors might have implications for prevention. We acknowledge and agree with the author of the letter that scientific information may face the risk of political exploitation and migrant populations represent historically one of the most vulnerable groups. However, our hypothesis about the role of migrants in this outbreak is important for prevention and is based on the fact that (i) the outbreak seems to be very recent according to surveillance data, (ii) it involves a "new" HIV strain which clusters with sequences originated from IDUs of a specific ethnic background and (iii) a high number of IDUs of the same ethnic background live in close vicinity in Athens. These represent a hint that migrant IDUs could potentially have a role in this outbreak. Therefore, the Greek public health authorities are conducting an awareness campaign specifically targeting migrant populations and at the same time they are prioritising migrant IDUs recruitment in opioid substitution programmes, antiretroviral treatment and other public health preventive measures designated as "Seek, Test, Treat and Retain" strategy [10-12].

We strongly disagree with M Salminen that the prevention programme for IDUs as a vulnerable group has failed in Greece. As pointed out in our paper, a distinctive characteristic of HIV-1 transmission in Greece, compared with other European countries, was the unusually low number of HIV-1 infections until 2011. Moreover, considering the present difficult economic situation in this country [13] and the huge influx of undocumented migrants, it seems counterproductive to blame public health authorities for potential recent failure of preventive programmes against HIV.

In our paper we did not state that migration would constitute an external threat to the health of the native population and we were careful not to over specify our findings. Far from blaming migrants, we are convinced that we were able to provide relevant information for public health action that will hopefully contribute to prevention and control of the current outbreak.

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ECDC and EMCDDA joint guidance report on reducing infections among people who inject drugs

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On 12 October 2011, the European Centre for Disease Prevention and Control (ECDC) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) published a joint guidance on the prevention and control of infectious diseases among people who inject drugs [1]. The two agencies of the European Union (EU) bring together know-how from the fields of drugs and infections, assess the evidence-base for interventions as well as European good practice and expert knowledge in the guidance document to inform the development, monitoring and evaluation of national and regional strategies to reduce and prevent infections among people who inject drugs.

Injecting drug use remains a major factor of vulnerability for acquiring blood-borne and other infectious diseases, including HIV, hepatitis B (HBV) and C (HCV), tuberculosis (TB), bacterial skin and soft tissue infections, and systemic infections. Estimates of the number of people who inject drugs suggest that there are significant populations at-risk for these infections in all European countries. Unaddressed, these infections result in a large burden on European health systems, significant individual suffering and health inequality, as well as high treatment costs.

The success of pragmatic public health approaches to HIV prevention in Europe shows that the spread of blood-borne infections among people who inject drugs can effectively be reduced. Prevention is feasible and effective, if properly implemented, with close coordination between various sectors, including health, drugs and law enforcement authorities.

The guidance relies on a foundation of 'core values' guiding a set of 'principles of prevention and service provision'. Seven key interventions are identified, which, synergistically, have been shown by evidence and experience to be effective in the prevention and control of infectious diseases that affect people who inject drugs.

- **Injection equipment**: provision of, and legal access to, clean drug injection equipment, including sufficient supply of sterile needles and syringes free of charge, as part of a combined multi-component approach, implemented through harm-reduction, counselling and treatment programmes.
- **Vaccination**: hepatitis A and B, tetanus, influenza vaccines, and, in particular for HIV-positive individuals, pneumococcal vaccine.
- **Drug dependence treatment**: opioid substitution treatment and other effective forms of drug dependence treatment.
- **Testing**: voluntary and confidential testing with informed consent for HIV, HCV (HBV for unvaccinated) and other infections including TB and referral to treatment.
- **Infectious disease treatment**: antiviral treatment based on clinical indications for those who are HIV, HBV or HCV infected, anti-tuberculosis treatment for active TB cases, TB prophylactic therapy for latent TB cases, treatment for other infectious diseases as clinically indicated.
- **Health promotion**: health promotion focused on safer injecting behaviour, sexual health, including condom use; and disease prevention, testing and treatment.
- **Targeted delivery of services**: services combined, organised and delivered according to user needs and local conditions; provision of services through outreach and fixed site settings offering drug treatment, harm reduction, counselling and testing, and referrals to general primary health and specialist medical services.

The guidance is accompanied by an 'In Brief' version and by two technical reports that provide the evidence base for this guidance.

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