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Increased prevalence of influenza B/Victoria lineage viruses during early stages of the 2015 influenza season in New South Wales, Australia: implications for vaccination and planning

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During the early weeks of the 2015 Australian influenza season, influenza B accounted for 67% (821/1,234) of all positive influenza tests in New South Wales. Of 81 successive influenza B viruses characterised, 33 (41%) were from children aged < 16 years; 23/81 (28%) belonged to the B/Victoria lineage. This lineage is not contained in the southern hemisphere's 2015 trivalent influenza vaccine. The significant B/Victoria lineage activity in the southern hemisphere suggests that the quadrivalent vaccine should be considered for the northern hemisphere.

The first four weeks of the 2015 influenza season in New South Wales, Australia (15 June to 12 July) have shown substantial early influenza B activity, with frequent detection of influenza B/Victoria lineage viruses, including in children (aged under 16 years). This lineage is not contained in the southern hemisphere's 2015 [1] or the northern hemisphere's 2015/16 trivalent influenza vaccine [2].

Prevalence of influenza B viruses in New South Wales, Australia

Data from 13 sentinel laboratories in New South Wales, Australia's most populous state, showed that influenza B viruses accounted for 67% (821/1,234) of positive influenza tests from 15 June to 12 July 2015 [1]. Of the 1,234 subjects with laboratory-confirmed influenza, 35% (432/1,234) were children (aged under 16 years). Of the 821 influenza B cases, 336 (41%) were children (Robin Gilmour, personal communication, 4 August 2015). This is significantly greater than the overall rate of influenza in children (41% vs 35%; p = 0.007, Fisher's exact test). Influenza B viruses detected from samples collected from individuals with an influenza-like illness were then characterised at our laboratory (one of three World Health Organization National Influenza Centres in Australia). Of the first successive 81 influenza B viruses characterised, 58 (72%) belonged to the B/Yamagata lineage. Half of 28 influenza B viruses that we characterised from 1 to 14 July belonged to the B/Yamagata lineage. This is significantly lower than the 89/94 (95%) ($p<0.0001$, Fisher's exact test) observed globally for influenza B viruses characterised from 29 June to 12 July 2015 [3].

Of the 81 characterised influenza B viruses, 33 (41%) were collected from children under 16 years of age (median age: 4 years; range: 0–13) and 13 of the infections in this age group were caused by B/Victoria lineage viruses. The ages of cases from whom the virus was characterised were representative of the age distribution of all cases of confirmed influenza infection. The median age for those aged 16 or older was 56 years (range: 17–94).

We have no data on the proportion vaccinated among the cases reported in this study.

At four predominantly adult hospitals within our local health district in western Sydney, there were 88 emergency department presentations with laboratory-confirmed influenza from 1 April to 18 July 2015. Of the 88 patients, 82 (93%) were adults and six (7%) were children. A total of 41 (47%) infections were caused by influenza B; 19 (22%) were due to influenza A(H1N1), 9 (10%) to A(H3) and 19 (22%) were untyped A. Influenza B virus was detected in 37 adults and four children.

A total of 26 patients (30%) required hospital admission (22 adults and four children), including seven into high-dependency or intensive-care units. Of the 26, 16 had influenza A (including four A(H1N1), six A(H3) and six that were not subtyped) and 10 had influenza B (five B/Victoria, three B/Yamagata and two that were not characterised). Of the seven patients admitted to high-dependency or intensive-care units, five had influenza A (including two A(H1N1), one A(H3) and two untyped) and two had influenza B/Yamagata. There has been one death (due to A(H3)), and as at 23 July, three patients (two B/Yamagata and one influenza A (not subtyped)) remain mechanically ventilated. Outbreaks of influenza B virus infection belonging to both the B/Yamagata and B/Victoria lineages have also been observed in care facilities for elderly people in New South Wales [1].

This early influenza B activity in New South Wales (the Australian influenza season generally runs from June to September and peaks in August) is in contrast to the 2014/15 northern hemisphere influenza season. In Europe, influenza B occurred later in the season and was detected in 168/810 (21%) of characterised viruses: B/Victoria lineage was identified in 3/168 (2%) of influenza B viruses [4]. In the United States, influenza B viruses also appeared late in the 2014/15 season, were detected in 810/2,193 (37%) of viruses and 228/810 (28%) of the influenza B viruses typed as B/Victoria lineage [5]. This is similar to our data before but not after 1 July, although the sample size (n = 28) after that date is small.

Background

Influenza B virus infection causes considerable morbidity and mortality, including acute respiratory distress syndrome, encephalopathy, acute renal failure and myocarditis [6,7]. Two antigenically distinct influenza B virus lineages, B/Yamagata and B/Victoria, are currently co-circulating globally [3-5]. Although clinical studies have not demonstrated any major differences in disease outcomes or antiviral susceptibility [8], in vitro studies have found up to 1,000-fold difference in neuraminidase inhibitor susceptibility in viruses of the two lineages (substantially greater in B/Victoria compared with B/Yamagata lineage) [9].

Vaccination remains key in protecting the general population against influenza virus infection. Seasonal trivalent influenza vaccines contain two influenza A virus subtypes and one influenza B virus. The southern hemisphere's trivalent influenza vaccine for the 2015 season contains A/California/7/2009 (H1N1)-like, A/Switzerland/9715293/2013 (H3N2)-like and influenza B/Phuket/3073/2013-like (B/Yamagata lineage) viruses [1]. For the first time, a quadrivalent influenza vaccine that also contains the B/Brisbane/60/2008-like virus (B/Victoria lineage) is available for the 2015 Australian influenza season [1] (but not through the Australian Government's National Immunisation Program).

Discussion

Several hypotheses may explain the early increased detection of B/Victoria lineage viruses in Australia. There may be an absence of cross-protective antibodies against B/Victoria lineage viruses in those who have received the trivalent influenza vaccine, and there may be reduced population immunity given that B/Yamagata lineage viruses have been the predominant circulating lineage in the World Health Organization Western Pacific Region in the past few years [10]. We observed a significant proportion of influenza B virus infection in children in our study. It has been reported that children accumulate natural immunity to influenza B more slowly than to influenza A [11]. In the same seroprevalence study [11], antibodies against only a single influenza B lineage were detected in young children, suggesting that they were susceptible to viruses of the other B lineage in the absence of protective antibodies. The high proportion of B/Victoria lineage infections detected in children in New South Wales (13/33) may amplify community transmission of influenza B virus as children shed more virus and for longer periods of time than do adults [12].

The predominant circulating influenza B lineage has been different from that chosen in the trivalent vaccine in five of 10 influenza seasons from 2001 to 2010 [13]. Reduced vaccine effectiveness during influenza seasons where there has been vaccine mismatch has resulted in a greater burden of influenza B virus infection (including influenza illness, influenza-associated hospitalisations and deaths) [13]. The quadrivalent influenza vaccine has demonstrated superior immunogenicity for the influenza B lineage not contained in the trivalent influenza vaccine in children and adults [14,15], and has been shown to be cost-effective [16,17]. It remains unclear if vaccination with the trivalent vaccine offers cross-protection against the influenza B virus lineage not contained in the vaccine. Some studies, including a meta-analysis, have shown significant cross-lineage protection [18-20], while others have found little or no cross-lineage protection [21]. The methods employed to estimate vaccine effectiveness and the participants included have varied in previous studies in several ways including the following: use of different influenza vaccines (inactivated and live attenuated); use of test-negative or people with other virus diseases as controls; inclusion of individuals previously vaccinated against the other influenza B lineage not currently contained in the present season's trivalent vaccine; and the exclusion of children. Data on influenza B lineages were not available for all participants in the studies above [19-21].

Although the sample size of the present study is small, our preliminary data suggest early and significant B/Victoria lineage virus activity in children and adults in New South Wales. The recommended influenza B component of the 2015/16 northern hemisphere's trivalent influenza vaccine is the B/Phuket/3073/2013-like virus (B/Yamagata lineage). As there may be incomplete

protection against B/Victoria lineage infection for those receiving the trivalent vaccine, our early data would suggest that a quadrivalent vaccine should be considered for the upcoming northern hemisphere influenza season (and for travellers to the southern hemisphere). This will be especially relevant if the northern hemisphere experiences early and widespread influenza B/Victoria activity similar to that being observed in the current southern hemisphere winter.

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Conflict of interest

None declared.

Authors' contributions

ZJ, JK, DED: data analysis, preparation and editing of manuscript; IC: characterised influenza B viruses; KM: data analysis.

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Ross River virus disease in two Dutch travellers returning from Australia, February to April 2015

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We report two cases of Ross River virus (RRV) infection in Dutch travellers who visited Australia during February to April 2015. These cases coincided with the largest recorded outbreak of RRV disease in Australia since 1996. This report serves to create awareness among physicians to consider travel-related RRV disease in differential diagnosis of patients with fever, arthralgia and/or rash returning from the South Pacific area, and to promote awareness among professionals advising travellers to this region.

Case presentation

Case 1

A woman in her early 50s with a history of polymyalgia rheumatica visited the outpatient department of a hospital in Rotterdam because of persistent joint pains after travel to Australia. She had stayed in Australia from 30 January until 5 March, where she mainly stayed in the surroundings of Perth. From 7 February, she stayed in Cairns for six days. She recalled having had multiple mosquito bites during her stay in Cairns. Seven days after her return to Perth (on 20 February), she developed fever, fatigue, frontal headache, muscle aches and arthralgia of her hands, wrists, feet and ankles. In addition, she noticed an itchy papular rash on her face, neck and trunk. She was treated with prednisone by a local general practitioner for a presumed recurrence of her polymyalgia, pending the results of serological investigations. Serology for RRV was IgM positive, therefore treatment with prednisone was discontinued.

Two months after returning to the Netherlands, she still experienced debilitating arthralgia and an unsteady gait, frequently necessitating the use of a walking aid. In addition, she reported a subfebrile temperature and sweating. On physical examination, no abnormalities were seen. She had a normal body temperature of 36.9 °C and her joints did not show any sign of arthritis. Laboratory investigation revealed an elevated erythrocyte sedimentation rate (ESR) of 32 mm/hr, a normal leukocyte count of 6.6 x 10^9/L, no abnormalities in the differential morphology of the leukocytes and a C-reactive protein (CRP) level of 6 mg/L (norm: ‹10 mg/L). Serological testing for RRV on convalescent serum (taken 7 April) showed the presence of IgM and seroconversion for IgG antibodies specific for RRV (Table). RRV aetiology was further confirmed by comparative indirect immunofluorescence assay (IIFA) for RRV, Barmah Forest virus (BFV), chikungunya virus (CHIKV) and Sindbis virus (SINV), and virus neutralization (Table). BFV, CHIKV and SINV are alphaviruses causing symptoms comparable to those caused by RRV, which are endemic to the region.

Case 2

A woman in her late 60s visited her general practitioner on 11 May 2015 with complaints of fatigue, myalgia, arthralgia and a maculopapular rash but no fever. The patient had visited Australia from 29 March to 9 May 2015, where she stayed in New South Wales (in Sydney, Armidale and a mangrove forest near Coff Harbour). She recalled having been bitten by mosquitoes during a trip on 14 April. The first symptoms of wrist pains appeared around 21 April, followed by a rash a few days later. The patient visited a local physician on 27 April and treatment with meloxicam was initiated. Laboratory investigation revealed a normal erythrocyte sedimentation rate of 5 mm/hr. Diagnostics for RRV,

Table

Differential diagnostics for two Dutch travellers returning from Australia with Ross River virus disease, February–April 2015

Antibody tested	Test results	
	Case 1 Sample taken 46 days after symptom onset	Case 2 Sample taken 30 days after symptom onset
Anti-RRV-IgG[a]	2.23	3.64
Anti-RRV-IgM[a]	4.81	6.33
Anti-RRV-IgG[b]	1:10,240	1:2,560
Anti-RRV-IgM[b]	1:640	1:5,120
RRV NAb[c]	1:40	1:40
Anti-BFV-IgG/IgM[a,b]	neg	neg
Anti-CHIKV-IgG[b]	1:160	1:1,280
Anti-CHIKV-IgM[b]	1:320	neg
CHIKV NAb[c]	neg	neg
Anti-SINV-IgG/IgM[b]	neg	neg

BFV: Barmah Forest virus; CHIKV: chikungunya virus; NAb: neutralising antibodies; neg: negative; RRV: Ross River virus; SINV: Sindbis virus.

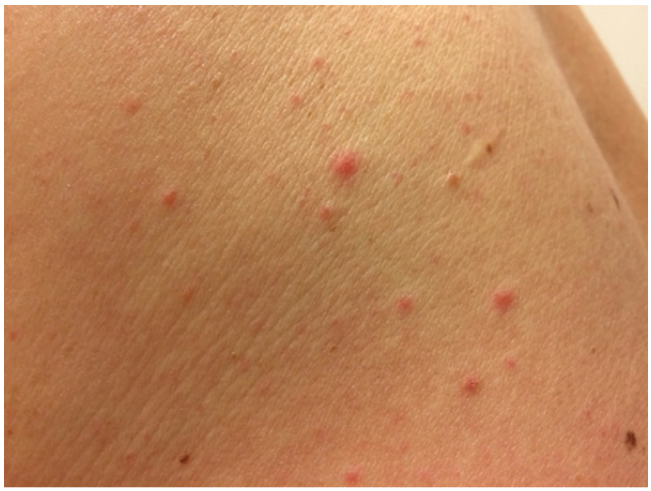
[a] Enzyme-linked immunosorbent assay (PanBio ELISA) values < 1.0 were considered negative.

[b] Indirect immunofluorescence assay titres < 1:20 for serum were considered negative [9].

[c] Virus neutralisation test titres < 1:20 for serum were considered negative [9].

Figure

Rash in a traveller (Case 2) returning from Australia with Ross River virus disease, 19 May 2015, 29 days post symptom onset



BFV, Epstein–Barr virus, B19 parvovirus and connective tissue disease were negative.

Upon the patient's return to the Netherlands, the rash reappeared (Figure) and the joint pains in her hands and knees increased. Treatment with naproxen was started. Serology for *Borrelia burgdorferi* showed IgM but no IgG; however, this diagnosis remained inconclusive as it was not confirmed by analysis of a second serum sample. Serological testing for RRV and BFV on a convalescent serum taken on 20 May showed the presence of IgM and IgG antibodies specific for RRV (Table). A second serum sample taken on 24 June showed decreasing IgM and increasing IgG titres. RRV aetiology was further confirmed by comparative IIFA for RRV, BFV, CHIKV and SINV, and by virus neutralisation (Table).

Background

RRV, an alphavirus transmitted by mosquitoes, is endemic in Australia and Papua New Guinea, with occasional epidemics in island countries in the Asia-Pacific region. The virus is maintained in an enzootic cycle between mosquitoes and marsupials, such as kangaroos and wallabies, as primary reservoirs. Rodents, rabbits, fruit bats, possums, horses, cats and dogs have been implicated as well [1-3]. Human-to-human transmission has been described in epidemic situations, and viraemic travellers from Australia have been linked to epidemics in the Cook Islands, Fiji, New Caledonia and Samoa [3]. Unnoticed circulation of RRV has been described in French Polynesia [4]. Recent evidence supports RRV transmission through blood donation [5]. Mosquitoes belonging to the genera *Aedes* and *Culex* are considered the main vector species and vertical transmission has been described as a way for the virus to persist during adverse conditions in desiccation-resistant eggs [6].

RRV is endemic in tropical and subtropical Australia (Northern Territory and Queensland) with year-round notification of human cases, while in temperate Australia (New South Wales and Victoria) human cases occur seasonally and in epidemics [3,6]. According to the Australian Department of Health, by 23 June 2015, a total of 7,552 RRV disease cases had been reported this year, which is the largest number of annual reported cases since 1996 [7]. Most cases up to 23 June were reported in Queensland (n = 5,075) and New-South Wales (n = 1,292) and peak incidences were in February to April.

The incubation period for RRV disease (also called epidemic polyarthritis) is typically 7–9 days, ranging from 3 to 21 days [1]. In 55–75% of infections, the individuals are asymptomatic. Symptomatic disease typically includes arthralgia, myalgia and fatigue.

Low-grade fever (37.5–38.5 °C) and maculopapular rash on the torso and limbs (sometimes palms, soles and face) occur in 50–60% of clinical cases [1]. Joint pain, stiffness and swelling are usually symmetrical, affecting wrists, hands, fingers, ankles and knees. Additional manifestations may include headache, diarrhoea and nausea. Symptoms most often resolve

within 3–6 months; permanent sequelae have not been described.

Treatment of symptomatic cases is supportive. Analgesics and nonsteroidal anti-inflammatory drugs may be helpful in the treatment of arthritis and arthralgia. No vaccine is available [1,3].

Laboratory findings are non-specific. Leukocyte counts and CRP levels are usually normal, ESR elevated. Diagnostics are most often based on serology as the viraemic stage is very short (typically fewer than seven days post symptom onset for alphaviruses) and molecular diagnostics are not considered useful on samples taken more than a week after symptom onset. Serology is complicated by putative cross-reactivity with other alphaviruses, especially CHIKV, which belongs to the same serogroup [1,3,8].

Discussion

Diagnosis of RRV disease in travellers returning to Europe is very rare [8-11]. A history of mosquito bites and stay in RRV-affected areas are epidemiological parameters supportive of a confirmative diagnosis based on RRV IgM and IgG responses. Based on these criteria, only three cases of RRV disease have been confirmed between 1 January 2009 and 30 June 2015 in the Netherlands, including the two cases in 2015 reported here, who had additional confirmation by gold-standard serology (virus neutralisation). In this period, a total of 56 diagnostic requests for RRV were submitted to the Dutch national arbovirus reference centre in Rotterdam. Of these, 20 requests indicated the travel destination as Australia and/or Asia-Pacific; for 30 requests, the travel destination was unknown. Although local circulation of RRV is unknown, travel to Indonesia, Thailand, Malaysia and the Philippines triggered diagnostic requests as well. Febrile disease and/or arthralgia were the most common symptoms (in 21 of 35 diagnostic requests with clinical data), leading to RRV disease being considered.

The cases presented here highlight the importance of considering RRV in differential diagnosis for travellers presenting with acute arthritis returning from Australia and the Asia-Pacific region. The two cases we describe were related to travel to risk areas in Australia in February/March and March–May 2015. Other arboviruses circulating in Australia and causing polyarthritis that should be included in differential diagnosis are the alphaviruses BFV and SINV, and the flaviviruses West Nile virus (Kunjin virus, KUNV) and Kokobera virus (KOKV). Depending on other travel destinations in the Asia-Pacific region, chikungunya virus, dengue virus and Zika virus should be considered as well [3,12]. The annual incidence of RRV disease in Australia ranges from 2,000 to 8,000 cases; for BFV disease, from 500 to 2800. Human cases of KUNV or KOKV disease are rare, while the occurrence of human infections with the Oceania lineage of SINV is under debate [3,12].

Although RRV-viraemic travellers have been linked to the spread and epidemics with RRV in the Asia-Pacific region, it is highly unlikely that return of viraemic travellers to Europe will result in autochthonous transmission. As the duration of viraemia is short, the likelihood that a traveller will be viraemic on their return is small. More importantly, the three main vectors for RRV transmission based on field isolations and competence studies are either strictly confined to Australia (*Ae. vigilax* and *Ae. camptorhynchus*, both invasive but not established in New Zealand) or the Asia-Pacific region (*C. annulirostri*) [1].

This report underlines the need for awareness of RRV-related risks among physicians, professionals advising travellers and travellers themselves. Australia is a popular travel destination for Europeans, especially for German, British and French tourists [13]. The number of leisure travellers from the Netherlands to Australia and/or New Zealand has been stable during 2002 to 2011, averaging to 52,000 travellers per year [14]. In January to March 2015, a total of 459,700 Europeans, including 12,600 from the Netherlands, had travelled to Australia [13]. Infection is preventable using common mosquito-prevention measures such as wearing long trousers, long sleeves, light-coloured clothes and insect repellents.

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Conflict of interest

None declared.

Authors' contributions

Chantal Reusken: coordination, data analysis, wrote article. Natalie Cleton: data analysis. Mariana Medonça Melo: treating physician. Chantal Visser: treating physician. Corine Geurts van Kessel: case medical microbiologist. Peter Bloembergen: case medical microbiologist. Marion Koopmans: co-wrote article. Jonas Schmidt-Chanasit: reference testing, co-wrote article. Perry van Genderen: treating physician, co-wrote article.

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Detection of influenza A(H3N2) virus in children with suspected mumps during winter 2014/15 in England

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Influenza A(H3N2) virus was detected in oral fluid from 16/107 children (aged 2 to 12 years) with a clinical diagnosis of mumps, who were sampled between December 2014 and February 2015 in England, during the peak of the 2014/15 influenza season. Sequence analysis of an A(H3N2) virus from a child with suspected mumps showed the virus was similar to other circulating A(H3N2) viruses detected in winter 2014/15, which were antigenically drifted from the A(H3N2) vaccine strain.

During winter 2014/15, clinical parotitis in children with confirmed influenza A(H3) infection was reported in North America [1]. In contrast, however, neither clinical nor virological surveillance for influenza-like illness (ILI) through sentinel general practitioners (GPs) in England detected an association between parotitis and influenza virus infection in the 2014/15 winter. In light of the observations from North America, gingival crevicular fluid (oral fluids) submitted for mumps surveillance in England were examined for influenza virus. Analysis of samples from 107 children (aged 2 to 12 years) with a clinical diagnosis of mumps but negative for mumps virus, sampled between December 2014 and February 2015, during the peak of the 2014/15 influenza season, showed that 16 (15%) were infected with influenza A(H3N2) virus.

Testing oral fluid samples from mumps surveillance for the presence of respiratory viruses

Of 116 residual oral fluids tested for mumps virus, a panel of 107 samples that were mumps virus negative was selected for testing for respiratory viruses based on age (2–12 years), sample taken between 1 and 5 days post onset of clinical parotitis between December 2014 and February 2015. Anonymised specimens were screened for respiratory viruses including influenza A(H1N1)pdm09 and A(H3N2), influenza B, respiratory syncytial virus A and B (RSV-A and RSV-B) and human metapneumovirus A and B (hMPV-A and hMPV-B) by real-time reverse transcription (RT) PCR using previously described assays [2-4] (Table 1). A total of 16 (15%) oral fluids tested were positive for influenza A(H3N2) virus in the mumps virus negative cohort (Table 2). One sample was found to contain a coinfection of influenza A(H3N2) virus and RSV-A.

As a control group, nine mumps virus positive oral fluids were screened using the same protocols and no respiratory viruses were detected. A further 63 control oral fluids were selected from the same age group (2–12 years) presenting with a different syndrome (suspected measles): only two (3%) of the measles virus positive samples were found to be positive for influenza A(H3N2) virus (Table 2). Two further separate coinfections of measles virus with RSV-A and hMPV-A were found.

Phylogenetic analysis of isolated influenza A(H3N2) virus haemagglutinin gene

Nucleotide sequencing of the haemagglutinin (HA) and neuraminidase (NA) genes of A(H3N2) viruses from influenza virus positive oral fluid samples by PCR (cycle threshold (Ct) values ‹ 33 (4/16) was undertaken (primer sequences available on request). Full-length HA and NA sequence was obtained from one oral fluid, Sample 69 (A/England/Sample69/2015), and an HA phylogenetic tree constructed as described previously [5] (Figure), using HA sequences from A(H3N2) viruses isolated in the 2014/15 influenza season in the United Kingdom, selected to be representative of the range of patient's age (2–12 years) and date of sample collection (between December 2014 and February 2015). Other reference virus sequences were obtained from the Global Initiative on Sharing All Influenza Data (GISAID) EpiFlu database (Table 3).

Analysis of the HA gene from A/England/Sample69/2015 showed that it fell into the A(H3N2) HA 3C.2a clade, as did the majority of A(H3N2) influenza viruses genetically characterised in the United Kingdom (UK) in 2014/15 (Figure) [6,7]. Similarly, phylogenetic analysis of the NA gene from A/England/Sample69/2015

Table 1

Oral fluid samples from mumps and measles surveillance selected for respiratory virus study, England, December 2014–February 2015 (n = 179)

Characteristic	Mumps surveillance		Measles surveillance
	Mumps virus negative	Mumps virus positive	Measles virus positive
Number of samples	107	9	63
Date sample taken	2 Dec 2014 to 26 Feb 2015	13 Jan 2014 to 9 Feb 2015	5 Dec 2014 to 5 Mar 2015
Number of days symptomatic before sampling (median)	1–5 (4)	2–10 (4)[a]	1–5 (4)
Patient age in years (median)	2–12 (6)	2–12 (8)	2–12 (4)

[a] Number of days symptomatic before sampling unknown for one sample.

Table 2

Detection of respiratory viruses in oral fluid samples from children with suspected mumps or measles, England, December 2014–February 2015 (n = 179)

Respiratory virus target	Mumps surveillance		Measles surveillance
	Mumps virus negative n = 107	Mumps virus positive n = 9	Measles positive n = 63
	Number of positive samples (%)	Number of positive samples	Number of positive samples (%)
Influenza A(H1N1)pdm09	0	0	0
Influenza A(H3N2)	16 (15%)	0	2 (3%)
Influenza B	0	0	0
Respiratory syncytial virus A	1 (1%)	0	1 (2%)
Respiratory syncytial virus B	0	0	0
Human metapneumovirus A	0	0	1 (2%)
Human metapneumovirus B	0	0	0

showed that it clustered with other 3C.2a clade viruses from 2014/15 (data not shown). Viruses from this clade are typically antigenically drifted from the 2014/15 northern hemisphere vaccine virus A/Texas/50/2102 and are more similar to A/Switzerland/9715293/2013, the A(H3N2) virus selected for the 2015/16 northern hemisphere influenza vaccine [8].

Discussion

Mumps is a notifiable disease in the UK, which is characterised by bilateral or unilateral inflammation of the parotid salivary glands. Mumps virus is the most common viral agent associated with parotitis, although other viral aetiologies have been investigated [9-11]. Surveillance for mumps virus infection is carried out widely in primary care through oral fluid testing of suspect cases of parotitis [12]. All oral fluid samples from throughout England are sent to the Public Health England (PHE) Virus Reference Department, Colindale, for testing. Recent infection is confirmed by detection of mumps virus-specific IgM antibodies and/or by detection of viral RNA by RT-PCR. Laboratory-confirmed positive cases are followed up to determine vaccination status.

An association between acute parotitis and influenza A virus has only rarely been made during previous epidemic periods in North America [13,14] and influenza is not often considered as part of differential diagnosis for this syndrome, and as a consequence oral fluid is not tested in England for the presence of influenza viruses [9,15].

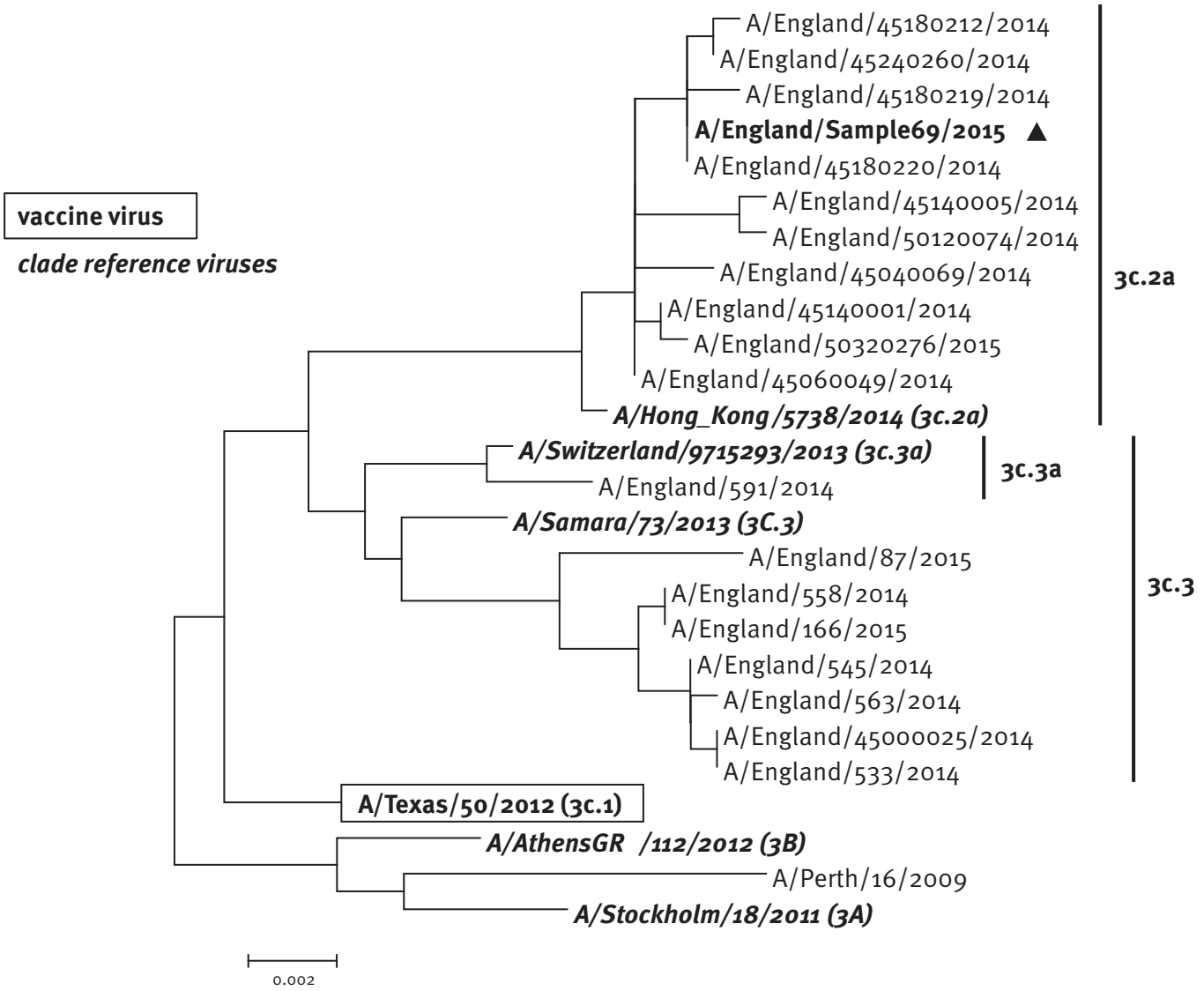
In the presence of a well-performing measles-mumps-rubella vaccination and surveillance programme in England, mumps infection is rarely confirmed in children aged under 12 years, with less than 10% of samples submitted from this age group being positive. During the last quarter of 2014, only 2% of samples submitted to the PHE Virus Reference Department were positive.

Systematic surveillance for influenza-associated parotitis using optimised specimen types, sensitive RT-PCR technology and appropriately timed studies during periods of heightened influenza virus circulation has, to the best of our knowledge, not hitherto been performed. This study, using oral fluid, provides evidence that a proportion of children presenting with suspected mumps during winter 2014/15 had influenza A(H3N2) virus infections. Mumps virus negative oral fluids were tested as a proxy for sampling for parotitis due to non-mumps aetiology. Although the oral fluids were not specifically collected for respiratory virus detection, the study selection criteria included only those that were taken within five days of symptom onset, to optimise detection of respiratory viruses during the period of greatest virus shedding [16]. Furthermore, analysis of oral fluid samples that were from patients without parotitis (i.e. measles virus positive) also found evidence of coinfections with respiratory viruses including influenza A(H3N2), RSV-A and hMPV-A.

Influenza A(H3N2) was the predominant virus circulating during the 2014/15 influenza season in the UK [6]. Genetic characterisation of an A(H3N2) virus

Figure

Phylogenetic analysis of influenza A(H3N2) virus haemagglutinin gene sequence from an oral fluid sample from a child with suspected mumps, England, December 2014–February 2015



The haemagglutinin gene sequence from the child's sample (A/England/Sample69/2015, marked with ▲) was analysed with HA sequences from A(H3N2) viruses isolated in the 2014/15 influenza season in the United Kingdom, selected to be representative of the range of patient's age (2–12 years) and date of sample collection (between December 2014 and February 2015). These representative gene sequences were deposited in the EpiFlu sequence database of the Global Initiative on Sharing All Influenza Data (GISAID) (accession numbers provided in Table 3). Other reference virus sequences were obtained from the GISAID EpiFlu database (Table 3). The phylogenetic tree was constructed with a neighbour-joining algorithm available in the Mega 6 software [5,24]. Branch lengths are drawn to scale.

from a child with parotitis found the viral HA and NA sequences were from the 3C.2a genetic subgroup, which is antigenically distinguishable from the vaccine strain, and similar to other A(H3N2) viruses detected through ILI surveillance [7]. Previous studies have found very limited sporadic evidence of seasonal influenza A(H3N2) or zoonotic virus infection with swine influenza A(H3N2) in children with parotitis [14,17] or occasionally in adults [18]. Former seasonal influenza A(H1N1) or A(H1N1)pdm09 viruses in patients with parotitis has not been described, to the best of our knowledge, although influenza A subtyping has not always been performed [9,15].

Information on influenza vaccination status in our study population was not collected so it is not possible to determine whether this could have affected the positivity rate for detection of influenza virus. The recent introduction of routine live-attenuated influenza vaccine (LAIV) for children aged 2–4 years in the UK may change the influenza positivity rate compared with that in an unvaccinated population [19] and further work to determine LAIV vaccine effectiveness against parotitis could be considered in future seasons.

Influenza virus as an atypical cause of acute viral parotitis should be considered especially during epidemic

Table 3

Origin of influenza A(H3N2) virus haemagglutinin sequences used in the phylogenetic analysis

Segment ID	Segment	Country	Collection date	Virus isolate name	Originating laboratory	Submitting laboratory
EPI539806	HA	China	2014-Apr-30	A/Hong Kong/5738/2014	Government Virus Unit, Hong Kong (SAR)	National Institute for Medical Research, London, UK
EPI530687	HA	Switzerland	2013-Dec-06	A/Switzerland/9715293/2013	Hopital Cantonal Universitaire de Geneves, Switzerland	National Institute for Medical Research, London, UK
EPI460558	HA	Russian Federation	2013-Mar-12	A/Samara/73/2013	WHO National Influenza Centre, Saint Petersburg, Russian Federation	National Institute for Medical Research, London, UK
EPI391247	HA	United States	2012-Apr-15	A/Texas/50/2012	Texas Department of State Health Services, Austin, US	Centers for Disease Control and Prevention, Atlanta, US
EPI358885	HA	Greece	2012-Feb-01	A/AthensGR/112/2012	Hellenic Pasteur Institute, Athens, Greece	National Institute for Medical Research, London, UK
EPI326139	HA	Sweden	2011-Mar-28	A/Stockholm/18/2011	Swedish Institute for Infectious Disease Control, Solna, Sweden	National Institute for Medical Research, London, UK
EPI211334	HA	Australia/ Western Australia	2009-unknown	A/Perth/16/2009	WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia	Centers for Disease Control and Prevention, Atlanta, US
EPI611914	HA	England, UK	2014-Dec-23	A/England/50120074/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI611874	HA	England, UK	2014-Dec-24	A/England/563/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI611826	HA	England, UK	2014-Dec-22	A/England/45240260/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI611810	HA	England, UK	2014-Dec-23	A/England/558/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI611714	HA	England, UK	2014-Dec-16	A/England/545/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI611698	HA	England, UK	2014-Dec-17	A/England/45180220/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI611690	HA	England, UK	2014-Dec-17	A/England/45180219/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI611674	HA	England, UK	2014-Dec-16	A/England/45180212/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI611626	HA	England, UK	2014-Dec-15	A/England/45140005/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI611618	HA	England, UK	2014-Dec-16	A/England/45140001/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI611528	HA	England, UK	2014-Dec-09	A/England/45060049/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI611520	HA	England, UK	2014-Dec-09	A/England/45040069/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI611496	HA	England, UK	2014-Dec-01	A/England/533/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI611488	HA	England, UK	2014-Dec-01	A/England/45000025/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI608041	HA	England, UK	2015-Feb-12	A/England/166/2015	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI607881	HA	England, UK	2015-Jan-22	A/England/87/2015	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI607785	HA	England, UK	2015-Jan-12	A/England/50320276/2015	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI607601	HA	England, UK	2014-Dec-23	A/England/591/2014	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale
EPI612846	HA	England, UK	NA	A/England/Sample69/2015	Public Health England, Reference Microbiology - Colindale	Public Health England, Reference Microbiology - Colindale

HA: haemagglutinin; NA: not available; SAR: Special Administrative Region; UK: United Kingdom; US: United States.

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seasons with drifted A(H3N2) strains, such as in 2014/15, or when zoonotic exposure has occurred.

Influenza A(H3N2) viruses from the 3C.2a clade that have predominantly circulated in the UK during winter 2014/15 show reduced agglutination of red blood cells used in laboratory tests suggestive of a change in binding specificity or avidity for sialic acid receptors [20]. Both mumps and influenza viruses bind sialic acid receptors on cells in the upper respiratory tract [21]. The unusual clinical presentation of parotitis during the 2014/15 season in conjunction with a change in virus receptor binding properties warrants further investigation.

In England, oral fluid sampling is routine for suspected mumps. Young adults (between 15 and 30 years) are the expected demographic for true mumps infection [22,23]. The target population for our study was younger children, where non-mumps parotitis is likely to be more common than true mumps infection.

Oral fluid sampling for detection of influenza virus should be further explored with appropriately timed studies in different age groups. Systematic collection of oral fluids alongside conventional nose/throat swabs during sentinel ILI surveillance would be a useful source of oral fluids for validation of detection of respiratory viruses. This would be a mechanism both for exploring less invasive sampling for influenza virus infection and also investigation of the incidence of influenza virus infection in uncommon clinical presentations such as parotitis. Oral fluids are not typically used as clinical samples for the detection of influenza and their utility for conducting influenza virological surveillance remains uncertain. The specific detection of influenza A(H3N2), and not influenza B or A(H1N1) pdm09 in this sample set, in combination with the clinical syndrome reporting from North America, suggests that influenza should be considered as part of the differential diagnosis for parotitis at the time when influenza virus is circulating, but this conclusion requires evaluation with different circulating influenza virus strains. The question of whether 3C.2a A(H3N2) influenza virus strains have an unusual tissue distribution compared with other A(H3N2) viruses or whether a subset of children infected with any influenza strain experience parotitis remains to be determined. Our conclusions would be strengthened by evaluation of further studies during future influenza seasons where oral fluids are taken in parallel with nasal swabs from children with influenza, with and without parotitis. Nevertheless, greater awareness of influenza virus as a potential cause of parotitis especially during epidemic periods associated with a drifted A(H3N2) strain is an important clinical and public health message.

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Conflict of interest

None declared.

Authors' contributions

CT was involved in acquisition and analysis of laboratory data, and wrote the manuscript. JE was involved in acquisition and analysis of laboratory data, and reviewed the manuscript. MG provided phylogenetic analysis, and reviewed the manuscript. MR reviewed the manuscript. KB was involved in study design, analysis of surveillance data, and reviewed the manuscript. MZ initiated the study, was involved in study design, and revision of the manuscript. All authors read and approved the final manuscript.

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Risk factors for sporadic listeriosis in the Netherlands, 2008 to 2013

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Although the disease burden of listeriosis on population level is low, on individual level the impact is high, largely due to severe illness and a high case fatality. Identification of risk factors supports and specifies public health actions needed for prevention. We performed a case–control study to determine host- and food-related risk factors for non-perinatal listeriosis in the Netherlands. Patients with non-perinatal listeriosis reported between July 2008 and December 2013 were compared with controls from a periodic control survey who completed a questionnaire in the same period. Higher age, male sex, underlying disease, especially cancer and kidney disease, and use of immunosuppressive medicine were strong risk factors for acquiring non-perinatal listeriosis. Analysis of the food consumption in the group of cases and controls with underlying diseases did not reveal any high-risk food products. Information and advice should continue to be given to persons at risk of severe listeriosis. Univariate analyses indicate that patients using gastric acid inhibitors are at risk. It is worth adding these patients to the group of susceptible persons.

Introduction

Listeria monocytogenes is widespread in nature, but human illness is almost always food-borne. Listeriosis is a rare but serious illness, mainly affecting elderly people, pregnant women and their unborn fetuses or newborn babies, and people with serious underlying disease [1-4]. The three most common clinical manifestations of listeriosis are febrile gastroenteritis, invasive illness (manifesting as bacteraemia, sepsis and/or meningitis) and maternal-fetal/neonatal listeriosis [2]. The disease burden of 14 food-borne pathogens in the Netherlands was assessed for 2009 [5]. The disease burden of listeriosis on population level was low (12th place; 96 disability adjusted life years (DALY) per year) but ranked second on individual level (1,220 DALY per 1,000 cases of illness), after toxoplasmosis and higher than for example salmonellosis and campylobacteriosis.

Identification of food products associated with listeriosis is difficult, because of the ubiquitous and psychrotrophic (cold-tolerant) nature of *L. monocytogenes*, the long and varying incubation period, and because severe illness is mainly restricted to vulnerable populations [6,7]. Outbreak investigations can provide information about risk products. In the case of listeriosis, outbreaks are often associated with errors during food production, such as contaminated slicing machines followed by opportunities for growth of the pathogen [8,9]. However, outbreak-related cases comprise only a small percentage of all listeriosis cases. In the Netherlands, no outbreak of listeriosis has been identified yet. Case–control studies of sporadic cases are useful for identifying risk factors, although it is more difficult to detect sources, as the cases do not necessarily share a single common source or food product [10].

Identification of risk factors for sporadic cases of listeriosis can help direct public health actions to prevent listeriosis, such as improved food safety messages for specific groups at risk. Here we performed a case–control study to determine host- and food-related risk factors for non-perinatal listeriosis in the Netherlands.

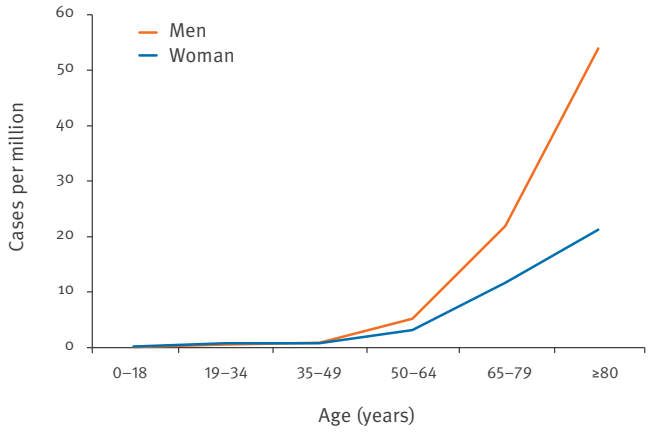
Methods

Listeriosis surveillance

In 2005, voluntary surveillance for human listeriosis was started in the Netherlands. Clinical microbiological laboratories were asked to report positive cultures of *L. monocytogenes* to the municipal health services. The health authorities contacted these patients with a questionnaire, and when possible interviewing them. If the patient had died or was too ill to be interviewed, spouses were interviewed when

Figure

Incidence of non-perinatal listeriosis, by age group and sex, the Netherlands, July 2008–December 2013 (n = 404)



possible. The questionnaire contained items about underlying diseases and exposure to possible risk factors in the 30 days before the date of onset of the listeriosis. Listeriosis became a notifiable disease in the Netherlands in December 2008 and the procedure for voluntary surveillance was formalised. Unfortunately, the notification questionnaire with a focus on underlying disease and food consumption was shortened and now contains fewer food items.

Since 2005, clinical microbiological laboratories have been sending *Listeria* isolates from patients with invasive disease to the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM), which forwards the isolates to the National Institute for Public Health and the Environment (RIVM) for pulsed-field gel electrophoresis (PFGE) and serotyping. The laboratories can also send *Listeria* isolates from patients with other symptoms directly to the RIVM. This procedure did not change when voluntary surveillance became surveillance based on notifications in 2008.

Control survey

In July 2008, a periodic control survey with a self-administered questionnaire was started in the Netherlands targeting the general population. The aim was to obtain data for identifying risk factors for several gastrointestinal, food-borne and respiratory infections. Three to four times a year, a random sample of the population is drawn and approached. The questionnaire comprises items about food consumption, contact with animals, travel and outdoor activities, health and underlying diseases and some demographic details. Only items phrased exactly the same as in the questionnaire used for the listeria case and administered in the same time period were included in the analyses. For a more detailed description of this control survey, see [11].

Case–control study

Cases and controls were included in the case–control study when they became ill or completed the questionnaire, respectively, between 1 July 2008 and 31 December 2013. This means that almost all listeriosis cases were reported via mandatory notification. Because the focus of the study was on non-perinatal listeriosis, pregnant women were excluded. Further exclusions applied to cases and controls were: (i) age 18 years or younger, as this group rarely develops listeriosis, (ii) travel abroad in the four weeks before illness or before completing the questionnaire, (iii) missing data on underlying disease or on use of immunosuppressants.

Case–case comparison

Also a case–case comparison was done, comparing infections with *L. monocytogenes* serotype 4b with those with serotype 1/2a. The two groups of cases were analysed for differences in underlying disease and food products eaten.

Data analysis

Logistic analyses in the case–control study were done in two phases. Firstly, underlying diseases and use of medicines were analysed, adjusted for sex, age group (five categories), season (four categories) and level of urbanisation (five categories). All variables with p values$<$0.1 were included in a multivariable model for further assessment, using backward selection. At each step, the least significant variable was removed from the model, until all variables in the model had reached significance ($p<0.05$) and the model was significant. At every step, the estimated odds ratio (OR) for the remaining exposure(s) was checked for major changes compared with the previous step. If removal of a variable had led to a major change, the exposure would have been retained in the model. In the second phase of the logistic analyses, the food consumption of cases and controls was analysed only including persons with the underlying diseases and/or medicines used that remained in the final model of phase 1. Food consumption consisted of 10 variables of meat products, eight fish and seafood products and five dairy products. Also, a variable was added about how often the respondent normally cleaned their refrigerator.

In the case–case comparison, underlying disease and food consumption were analysed together in one model, instead of the two phases that were applied in the case–control analyses. All analyses were done using SAS software, version 9.3 (SAS Institute).

Results

Between July 2008 and December 2013, 406 patients with non-perinatal listeriosis were reported, of whom 241 were men (59%), 163 women (40%) and two of unknown sex (0.5%). Incidence of non-perinatal listeriosis increased with age, but the increase was more pronounced in men than in women (Figure). Incidence remained below 1 per million inhabitants up to the age of 50 years, and then increased to almost 54 (men) and 21 (women) per million inhabitants 80 years or older. Forty-one of 345 cases with known status died (12%),

Table 1

Characteristics of listeriosis patients (n = 279) and control subjects (n = 1,733), the Netherlands, July 2008–December 2013

Characteristic	Number of cases (%)	Number of controls (%)
n	279	1,733
Sex		
Male	174 (62)	732 (42)
Female	105 (38)	1,001 (58)
Age group		
19–34 years	10 (4)	154 (9)
35–49 years	9 (3)	350 (20)
50–64 years	59 (21)	598 (35)
65–79 years	118 (42)	503 (29)
80 or older	83 (30)	128 (7)
Season		
Winter (Dec-Feb)	63 (23)	287 (17)
Spring (Mar-May)	48 (17)	429 (25)
Summer (Jun-Aug)	83 (30)	430 (25)
Autumn (Sep-Nov)	85 (30)	587 (34)
Level of urbanisation		
≥ 2,500 addresses/km²	47 (17)	294 (17)
1,500–2,499 addresses/km²	80 (29)	329 (19)
1,000–1,499 addresses/km²	59 (21)	367 (21)
500–999 addresses/km²	57 (20)	396 (23)
< 500 addresses/km²	36 (13)	347 (20)

for 61 cases this was unknown. More men (28/205; 14%) than women (13/140; 9%) died due to listeriosis (not statistically significant).

A total of 2,363 controls completed the questionnaire in the specified period. Three of the 406 patients and 287 controls were 18 years or younger, and were excluded from the case–control analyses. Furthermore, 19 cases and 267 controls had been abroad, and for a further 105 cases and 76 controls, no medical history was available. The case–control analysis therefore comprised 279 cases and 1,733 controls. Infection with *L. monocytogenes* serotype 4b was most common (n = 98; 35%), followed by serotype 1/2a (n = 67; 24%) and serotype 1/2b (n = 33; 12%); serotype 1/2c (n = 5; 2%) and 3b (n = 1; < 1%) were rarely seen, and for 75 patients (27%) no serotype was available. Thirty-one of the 273 listeriosis cases included in the case–control analyses died (11%), for six cases the outcome was unknown.

Characteristics of the patients and controls included in the case–control analyses are given in Table 1. Cases were more often male (62%) than controls (42%) and were older, with a median age of 72 years compared with 59 years.

Only a small number of cases (8%) had no underlying disease, in contrast to the controls of whom 70% had no underlying disease (Table 2). Of the diseases included in the analyses, only diabetes, rheumatism and other underlying disease did not reach significance in the univariate analyses. Organ transplantation was not included in the multivariable analysis, as it showed high collinearity with immunosuppressants. In the final model, immunosuppressant use was the strongest risk factor (OR 53.7; 95% CI: 31.0–93.0), followed by cancer (OR 26.8; 95% CI: 14.4–49.8) and chronic kidney disease (OR 21.8; 95% CI: 9.0–52.5).

A total of 246 cases (88%) and 288 controls (17%) had one of the underlying diseases from the final model or used immunosuppressants. Analysis of the food consumption in this group of cases and controls did not reveal any risk products. Eight of the 10 meat products, two of eight fish and seafood products and all five dairy products were eaten significantly less often by the cases than by the controls. The remaining eight products were eaten as often. No difference was seen in the frequency of cleaning the refrigerator.

Comparison of the cases with the two most commonly found serotypes, 4b and 1/2a, did not reveal any differences in underlying diseases or food consumption.

Discussion

In the present study, high age, male sex, underlying disease, especially cancer and kidney disease, and immunosuppressive medicine use were strong independent risk factors for acquiring non-perinatal listeriosis. These factors have been described before [7,12,13]. In a case–control study in Australia, usage of gastric acid inhibitors was identified as risk factor [14]. In the present study, gastric acid inhibitors were found a significant risk factor in the univariable analysis; in the multivariable model, it was no longer significant. This can be due to stronger effects of the comorbid factors that did remain in the final model. Bavishi and DuPont [15] concluded in their systematic review that the use of proton pump inhibitors can lead to bacterial colonisation and increased susceptibility to enteric bacterial infection. Although the evidence may still be weak for listeriosis, the biological plausibility of the effect of gastric acid inhibitors on the gastrointestinal system warrants caution in the use of these drugs, especially in already immunocompromised persons.

To exclude the impact of these host factors when examining high-risk food products, food consumption was analysed including only highly susceptible cases and controls (with underlying diseases or taking immunosuppressants). None of the food products could be labelled as risky food. This could be due to similar food advice given to both cases and controls; however, we had not asked about received food advice. Overall, identification of high-risk foods in a case–control study with sporadic cases can be difficult due to the ubiquity of the microorganism in the environment and fluctuating rates of contamination of food products, but also because some risky food products are frequently consumed in the control population, and

Table 2

Underlying diseases and use of medicines in listeriosis patients (n = 279) and control subjects (n = 1,733), the Netherlands, July 2008–December 2013

Characteristic	Number of cases (%)	Number of controls (%)	Univariate OR (95% CI) [a]	Multivariable OR (95% CI)[a]
Underlying disease				
Diabetes	50 (18)	158 (9)	1.4 (1.0–2.1)	
Cardiovascular disease	68 (24)	164 (9)	1.7 (1.2–2.4)	2.0 (1.2–3.3)
Immune disorder	28 (10)	19 (1)	14.7 (7.4–29.1)	3.3 (1.3–8.6)
Cancer	92 (33)	31 (2)	24.8 (15.4–40.0)	26.8 (14.4–49.8)
Chronic liver disease	13 (5)	5 (0.3)	22.1 (6.9–71.1)	9.7 (2.3–41.1)
Lung disease	40 (14)	93 (5)	2.1 (1.3–3.2)	-[b]
Gastrointestinal disease	32 (11)	64 (4)	4.2 (2.5–7.0)	2.1 (1.0–4.3)
Chronic kidney disease	38 (14)	13 (1)	18.2 (8.8–37.7)	21.8 (9.0–52.5)
Rheumatism	26 (9)	78 (5)	1.5 (0.9–2.6)	-[b]
Organ transplant	12 (4)	1 (0.1)	138.9 (15.7–∞)	ND
Other underlying disease	7 (3)	38 (2)	1.3 (0.5–3.1)	-[b]
No underlying disease	22 (8)	1,217 (70)	ND	ND
Medicine use				
Immunosuppressants	162 (58)	41 (2)	80.3 (49.8–129.7)	53.7 (31.0–93.0)
Gastric acid inhibitors; ‹missing values›	94 (43); ‹60›	232 (14); ‹57›	3.8 (2.7–5.3)	-[b]

CI: confidence interval; OR: odds ratio; ND: not determined

[a] OR adjusted for sex, age group, season and level of urbanisation.

[b] Not included in final multivariable model.

the varying incubation period [7,10,13,14]. Besides host and environmental components, virulence of the pathogen is another important risk factor [7]. Dose–response data are based on different animal and in vitro models and on epidemiological data from outbreaks which are scarce and have limitations. Another possibility for establishing food products as high-risk is by subtyping and comparing *Listeria* isolates found in humans and in food products [14]. Although finding similar strains in humans and in food does not prove causality, it could provide information about possible sources of infection and help us understand observed trends in human cases [16].

In our analyses, some food products generally recognised as risk foods for *Listeria* were significantly less often eaten by cases than by controls with similar host susceptibility. This probably indicates that persons with underlying diseases (cases and controls) have some knowledge about high-risk food and to some extent avoid eating such products. However, other often mentioned explanations include bias through differential recall of exposure between cases and controls or association of the food product with other unmeasured factors, such as the way and how long a product is stored at home. Furthermore, controls could possibly be less susceptible because underlying diseases are less frequent or less severe, or acquired (partial) immunity following frequent exposure to the high-risk food products [10]. Although it is assumed that immunity to *L. monocytogenes* in humans is long-lived, it has only been shown in mice [17-19].

Case–control studies in sporadic cases are commonly complex and resource-intensive [10]. In the present study, almost all cases in the case–control study were derived from the notification system as listeriosis has been a mandatory disease since December 2008. The controls originated from an ongoing control survey carried out since July 2008 [11]. This reduced substantially the extra work of seeking and contacting controls. A bias may have been introduced as most cases were personally interviewed by telephone while the controls received a self-administered questionnaire by post. Furthermore, the questionnaires to controls were sent on three defined dates per year, whereas cases occur throughout the year. The overall response rate in the control survey was 36% between July 2008 and December 2013. Analysis of the response in the period July 2008 to December 2012 showed a small underrepresentation of men, young people, people living in large cities and persons with both parents born outside the Netherlands [11]. Questioning persons can lead to exposure misclassification and recall bias [14]. Recalling food consumption more than four weeks in the past is difficult, especially when questioning spouses, and can make the respondents more likely to report usual food preferences than exact exposures.

Because of the ubiquity of the microorganism in the environment and the psychrotrophic nature of the bacterium, a wide variety of food products can become contaminated with *L. monocytogenes* and, when prepared without heating just before consumption, can infect a susceptible person [4]. Measures to minimise

the chance of contamination at the time of consumption are use of high-quality ingredients, hygienic manufacturing practices, indication of appropriate shelf-life, correct refrigerated storage, education of food handlers and food service managers, and monitoring of food industry, catering and retail [8,20-22]. However, *L. monocytogenes* contamination cannot be entirely prevented. Thus, pregnant women, the elderly and persons with diseases and/or medications weakening the immune system should receive information about the presence of *L. monocytogenes* and advice about potential high-risk food products and how to handle food safely [13,20]. Due to the relatively high usage of gastric acid inhibitors and the biological plausibility of the effect on the gastrointestinal system, adding the group of users of gastric acid inhibitors to the high-risk groups should be considered.

Conflict of interest

None declared.

Authors' contributions

IF: collected and analysed the data from the epidemiological and molecular surveillance, coordinated the control survey and drafted the manuscript. AvdE / LS: contributed to the serotyping of the Listeria isolates received at the Netherlands Reference Laboratory for Bacterial Meningitis and sent the isolates to the National Institute for Public Health and the Environment, revised the manuscript and approved the final manuscript. SK / MH: contributed to the serotyping and PFGE of the Listeria isolates received at the National Institute for Public Health and the Environment, revised the manuscript and approved the final manuscript. WvP: supervised this study, contributed actively to the manuscript and approved the final manuscript.

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