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Protecting asplenic individuals from fulminant pneumococcal disease

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In this issue of *Eurosurveillance*, Chironna *et al.* report on an unfortunate death of an asplenic individual with fulminant pneumococcal sepsis [1]. Whether or not the death of this particular individual could have been avoided with active preventive interventions remains unanswered. It does, however, raise the alert to revisit the preventive guidelines of asplenic patients in general, and need for reminders both among practicing clinicians as well as asplenic patients.

Asplenia usually results from splenectomy, which is carried out for three main reasons: (i) rupture of the spleen, either because of trauma, during an operation or spontaneous, (ii) as a desired consequence of treatment of certain haematologic disorders, or (iii) because of treatment of neoplasm of the spleen or other organs close to it. Asplenic individuals are at increased risk of fulminant sepsis caused by encapsulated bacteria, especially by *Streptococcus pneumoniae*, but also by *H. influenzae* and *N. meningitidis*. Clinicians should consider recommending that asplenic individuals get vaccinated against the latter two as well. Depending on the underlying cause of asplenia, and the baseline incidence of invasive pneumococcal disease (IPD) in a given country, the risk of IPD in asplenic individuals can be as high as 25 times that of the general population [2]. Approximately half of all episodes of overwhelming post-splenectomy infection (OPSI) occur more than five years after splenectomy [3], and case-fatality rates are 50% or higher, as also demonstrated in the case report by Chironna *et al.* [1].

What is the best means to protect asplenic individuals from fulminant pneumococcal disease? In Europe, the presently available 23-valent polysaccharide pneumococcal vaccine (23PPV) has been recommended at five-year intervals or even more often to asplenic patients [4]. Evidence arising from sufficiently powered randomised controlled trials on the impact of 23PPV in the prevention of OPSI is not available. Concern has been raised about the potential induction of hyporesponse after multiple doses of 23PPV, also after priming with pneumococcal conjugate vaccine [5-6]. The immunological mechanisms behind the hyporesponse to subsequent doses of 23PPV and the clinical relevance of this

observation is not fully understood. Immunogenicity studies suggest, however, that certain asplenic individuals might gain protection against IPD even after multiple doses of 23PPV given at five-year intervals [7]. An observational, population-based study carried out in a cohort of asplenic individuals from Denmark is in line with this finding [8], and thus give support to the present clinical practices. On the other hand, there is a subgroup of splenectomised patients with underlying haematologic diseases who clearly do not benefit from 23PPV and who should be identified by measurement of pneumococcal antibodies after vaccination [9] in order to be provided with other means of protection, such as prophylactic or early antimicrobial treatment.

There is a clear need for the development of more broadly acting, protein-based pneumococcal vaccines, given (i) the limitations of 23PPV in the prevention of pneumococcal disease in several medical risk groups as summarised in a recent meta-analysis published by the World Health Organization [10], (ii) the lack of improved immunity provided by conjugated vaccines to risk groups [11] as well as (iii) the suboptimal coverage of the disease causing pneumococcal serotypes of the presently available pneumococcal conjugate vaccines in these groups combined with the observation of replacement of vaccine serotypes by nonvaccine serotypes [12] especially in risk groups. Proof of clinical efficacy of these new vaccines will be needed, not only in healthy individuals, but also in predefined, immunocompromised risk groups who are most in need of pneumococcal vaccination.

While it will take several years before such new vaccines are licensed, clinicians need to guide and protect their asplenic patients according to the best available knowledge. At this moment the combination of 23PPV, measurement of antibody concentrations induced by 23 PPV and early antimicrobial therapy for those whose protective levels remain low, are the best ways to prevent unnecessary deaths among splenectomised individuals.

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Case report: Fulminant pneumococcal sepsis in an unvaccinated asplenic patient in Italy

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We report a fatal case of overwhelming pneumococcal infection in an asplenic young adult not vaccinated against *Streptococcus pneumoniae* (*S. pneumoniae*). Post-mortem microbiological investigations revealed the presence of *S. pneumoniae* in blood samples and lungs. Serotyping by molecular methods identified the presence of a 6C serotype not comprised in the current 23-valent pneumococcal vaccine, highlighting that a risk of fatal infections may persist even in vaccinated splenectomised individuals.

Introduction

Streptococcus pneumoniae (*S. pneumoniae*) is an important cause of upper respiratory tract infections and of severe invasive pneumococcal diseases (IPD) that include pneumonia, meningitis and sepsis [1].

To prevent pneumococcal diseases, two new polysaccharide-protein conjugate vaccines (PCV) are now available for vaccination of children, including infants. The 10-valent pneumococcal nontypeable *Haemophilus influenzae* protein D conjugate vaccine, Synflorix, approved by the European Medicines Agency (EMA), is used to prevent invasive pneumococcal disease and acute otitis media caused by pneumococcus, in infants and children [2]. The 13-valent PCV vaccine, Prevenar, containing six additional serotypes (1, 3, 5, 6A, 7F and 19A), has also been approved by EMA for use in children from six months to five years old [4].

The 23-valent pneumococcal polysaccharide vaccine (PPV23) has been designed for older children and adults at risk of pneumococcal disease [5].

Immunocompromised and asplenic patients are known to be particularly at risk for contracting overwhelming postsplenectomy infection (OPSI) [6] and should therefore be vaccinated to avoid serious illness and even death. Asplenic patients are strongly recommended to get vaccinated with PPV23, a one-dose vaccine, since they need protection against the maximum number of serotypes possible [5]. They are further recommended to repeat the PPV23 vaccination every five years due to the increased rate of decline of antibody levels observed in these subjects [7]. Long-term or emergency

stand-by antibiotic prophylaxis is also recommended for asplenic patients because OPSI is a life-long risk for such individuals [8].

We describe a case of overwhelming pneumococcal disease with a fatal outcome.

Case report

A young male in his early thirties, with a history of post-traumatic splenectomy presented with symptoms of hyperpyrexia ($>41.5^{\circ}\text{C}$), nausea, vomiting and diarrhoea at the emergency department of our hospital. He was transferred to the intensive care unit the same day where he rapidly became dyspnoeic, developed cyanosis, tachypnea, went into shock and deteriorated continuously. Despite ventilatory support, administration of intravenous fluids, antibiotics and vasopressor agents, the patient died a few hours following presentation. There was no history *S. pneumoniae* vaccination for the asplenic patient.

A chest X-ray taken upon admission demonstrated mild interstitial shadows; no apparent consolidation was observed in either lung. Because of the ongoing 2009 influenza A(H1N1) pandemic, real-time PCR was performed to determine whether the patient was infected with the influenza A(H1N1) virus. The test yielded a negative result for influenza A virus, including the pandemic A(H1N1) virus. Initial laboratory results revealed acidosis, marked leukopenia ($2.0 \times 10^3 \mu\text{l}^{-1}$ leukocytes), thrombocytopenia ($6.0 \times 10^3 \mu\text{l}^{-1}$ platelets) and considerably altered coagulation values consistent with the presence of disseminated intravascular coagulation. The coagulation values were out of measurable range.

Microbiological investigations on post-mortem biological samples revealed the presence of *S. pneumoniae* in blood samples and lungs. Serotyping of *S. pneumoniae* by molecular methods [9, 10] identified the presence of a 6C serotype.

Discussion

Fulminant, potential life-threatening infection due to *S. pneumoniae* is a major well-known risk after

splenectomy. Strategies to prevent OPSI include immunisation, antibiotic prophylaxis and education. Several studies have shown the effectiveness of vaccination with PPV23 in preventing IPD and recently it has been suggested that asplenic and hyposplenic individuals would benefit from vaccination against pneumococcae [11].

The serotype of *S. pneumoniae* strain isolated from the patient (6C) is not comprised in the current available 23-valent pneumococcal vaccine. Pneumococcal vaccines contain serotype 6B and patients vaccinated with PCV7 and PPV23 show poor immune response against serotype 6C [12]. Therefore, the patient may not have avoided IPD even after having been immunised. This highlights that a residual risk of contracting fatal infections may persist in splenectomised individuals even if vaccinated.

Various studies have provided conflicting evidence on the immune response to pneumococcal polysaccharide antigens in asplenic individuals [13, 14]. A recent study did not provide evidence to recommend routine PCV7 immunisation over PPV23 immunisation in adult asplenic individuals [7]. In the future, higher valent pneumococcal conjugate vaccines should be tested in this group to better address this issue.

In Puglia, the PPV coverage among patients affected by a chronic disease is quite low and estimated to be about 20% [15]. Until further knowledge is gained regarding the protective concentration of serotype-specific antibody concentrations and the impact of PCV on adults, vaccination and regular revaccination, at least every five years, in combination with education of patients and healthcare professionals may be effective for patients at risk for OPSI. This case serves as a reminder that new immunisation strategies and practices should be implemented to also cover subjects at risk for OPSI and to increase PPV coverage. The goal should be to vaccinate at risk subjects through the National Health System, not only through general practitioners.

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Syndromic surveillance to assess the potential public health impact of the Icelandic volcanic ash plume across the United Kingdom, April 2010

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The Eyjafjallajökull volcano in Iceland erupted on 14 April 2010 emitting a volcanic ash plume that spread across the United Kingdom and mainland Europe. The Health Protection Agency and Health Protection Scotland used existing syndromic surveillance systems to monitor community health during the incident: there were no particularly unusual increases in any of the monitored conditions. This incident has again demonstrated the use of syndromic surveillance systems for monitoring community health in real time.

Introduction

The Eyjafjallajökull volcano in Iceland began erupting on 14 April 2010. Due to the prevailing weather conditions the resulting plume of volcanic ash spread towards the United Kingdom (UK) and mainland Europe. On 16 April the ash cloud was located over the UK and air travel restrictions were introduced initially across Scotland and then the rest of the UK due to the threat the ash posed to aircraft safety. Restrictions were lifted on 20 April.

Weather conditions meant that most of the ash cloud remained at high altitude but some light ash falls were reported in Scotland and other parts of the UK. There were also anecdotal reports of the detection of various sorts of sulphurous odours in parts of Scotland (particularly in Shetland during the initial days following the eruption). As part of a public health risk assessment, the Health Protection Agency (HPA) in England and Health Protection Scotland (HPS) both used existing syndromic surveillance systems to establish whether there was any evidence of a population-based impact on public health.

The HPA and HPS both have syndromic surveillance systems that are routinely used to monitor seasonal

outbreaks of disease, e.g. influenza and norovirus infection, and provide surveillance support during incidents and events where there could be a potential impact on local community health, e.g. flooding, industrial fires, large-scale chemical releases and geopolitical meetings [1-4].

During the period the volcanic ash cloud was over the UK, these syndromic surveillance systems were used to monitor a range of symptoms and clinical indicators, chosen for their association with the potential health effects of exposure to volcanic ash, such as irritation of the eyes and upper respiratory tract.

Air quality and syndromic surveillance systems in the United Kingdom

Air quality monitoring data

UK air quality is monitored by the Automatic Urban and Rural Network (AURN), in more than 100 sites within designated urban and rural areas. These automatic air quality monitoring stations measure a range of pollutants including nitrogen oxides, sulphur dioxide, ozone, carbon monoxide and particles of diameter of less than 10µm (PM₁₀). An air quality banding system is used to estimate the levels of air pollution and the potential effect on public health ranging from Low, when effects of air pollution are unlikely to have any health effects, to Moderate, when mild effects may be noticed by sensitive individuals, to High and Very High, when sensitive individuals may experience significant effects requiring intervention to relieve the effects [5].

Other than the reports of light ash falls and anecdotal reports of sulphurous smells over parts of Scotland, provisional air quality monitoring data from AURN showed no evidence of pollution associated with the eruption. Levels of PM₁₀ and sulphur dioxide

were typically normal and there was no evidence of increased pollutant levels that could be attributed to the volcano [6,7].

Data from the Health Protection Agency for England

The HPA Real-time Syndromic Surveillance Team leads the production and development of information to guide public health action through syndromic surveillance systems that use data from a telephone health advice service of the National Health Service, NHS Direct, and two general practitioner surveillance systems, the HPA/QSurveillance and the Royal College of General Practitioners Weekly Returns Service systems [8-10]. Data from the three systems were routinely monitored; however, data from the HPA/QSurveillance system were predominantly used to produce the analyses and interpretations required during the volcanic ash incident and are therefore presented in this report.

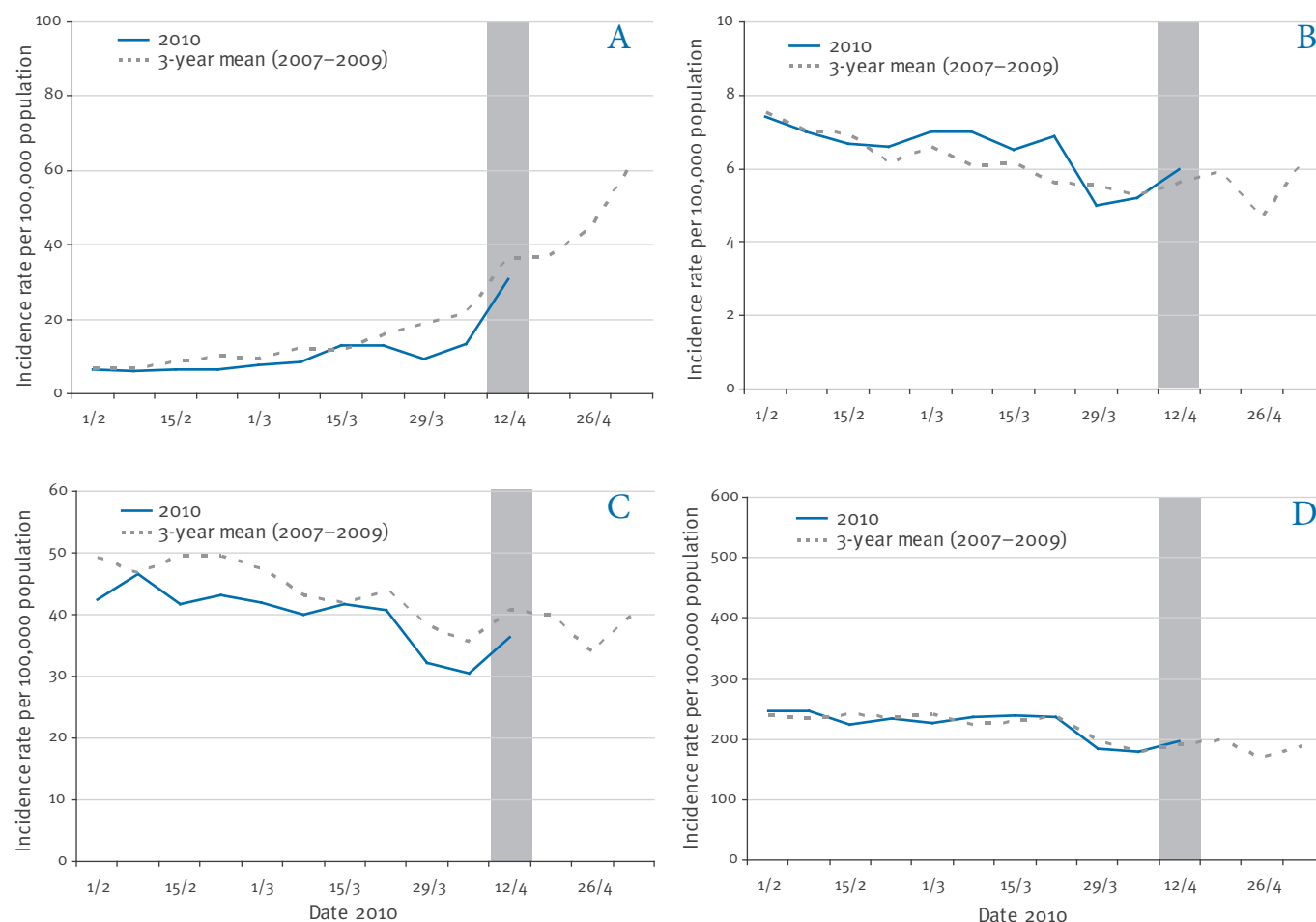
The HPA/QSurveillance syndromic surveillance system is a large, general practice-based network comprising

more than 3,500 practices and a weekly patient population of more than 23 million. The system covers the UK, but as there is currently no coverage available in Scotland and limited coverage across Wales and Northern Ireland, the system has maximal population representation across England, which has an estimated population of 51.5 million. Weekly incidence rates per 100,000 practice population were monitored for a range of clinical indicators and standardised incidence ratios calculated to identify countries and regions within the UK with unusually high incidence rates. The clinical indicators monitored during the volcanic ash cloud incident were:

- asthma
- conjunctivitis
- allergic rhinitis
- wheeze
- lower respiratory tract infection
- upper respiratory tract infection.

FIGURE 1

Weekly incidence rate of selected clinical indicators, 1 February – 3 May 2010 (weeks 6–18) against a three-year mean weekly incidence rate, United Kingdom



A: allergic rhinitis; B: asthma; C: conjunctivitis; D: upper respiratory tract infections.

The week during which the Icelandic volcanic ash cloud was located over the United Kingdom (16–20 April 2010) is illustrated by a vertical grey bar. For presentational purposes, historical data have been adjusted by incorporating a two-week lag to compensate for differences in calendar dates and public holiday periods between 2010 and previous years included within the three-year (2007–2009) mean incidence rate.

Source: Health Protection Agency/QSurveillance system.

During the week commencing 12 April 2010 (epidemiological week 15) all indicators increased in incidence (Figure 1). In the UK, weeks 13 and 14 (weeks commencing 29 March and 5 April 2010 respectively) contained public holidays, when access to general practitioner services is limited. This affects consulting behaviour and therefore incidence rates are artificially low. Routine statistical analysis of the HPA/QSurveillance data illustrated several statistically significant standardised incidence ratios. However, on further analysis, taking into account previous weeks' data and historical seasonal and public holiday trends, these were not considered unusual for the time of the year. There were no unusual rises detected in indicators in the HPA/NHS Direct and Weekly Returns Service surveillance systems routinely used throughout the incident.

Data from Health Protection Scotland

The respiratory team within HPS similarly leads the production and development of information to guide public health action through a syndromic surveillance system that uses data from NHS 24, a telephone health advice and treatment service. NHS 24 covers all of Scotland, which has an estimated population of 5.2 million, and data can be analysed by area of residence to determine the number and proportion of calls recording relevant symptoms. Daily data from this dataset were used to produce analyses and interpretations during the volcanic ash incident. The key symptoms monitored were:

- difficulty breathing
- eye problems
- cough
- rash.

Daily data were examined for the absolute number of NHS 24 calls allocated to specific syndrome categories. During 16–20 April 2010, when the ash cloud was located over the UK, there were no national exceedances for any of the key syndromes (Figure 2). During the period before the ash cloud there were a number of small daily exceedances in calls for difficulty breathing and eye problems compared with those expected for the period. These were evident at either an all Scotland or administrative healthcare area (NHS board) level, exceeding the upper limit of the 99% confidence interval for the number of calls received. Data for call proportions (percentage of total calls) were also examined for the same syndromes taking into account comparisons with historical syndrome baselines: there were no unusual rises in these proportions during the incident.

Discussion

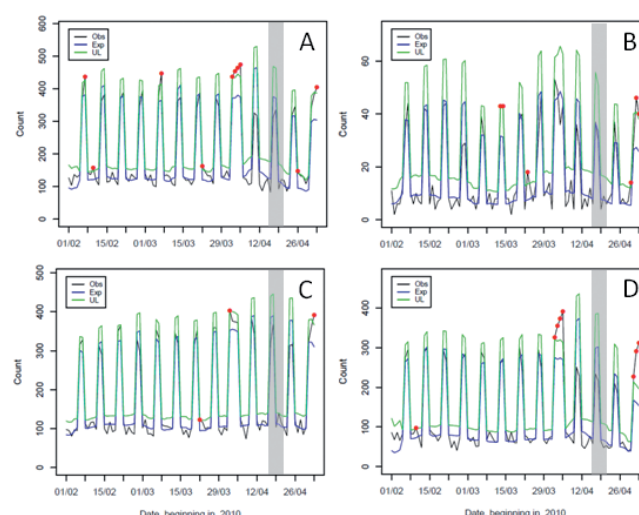
During the volcanic ash incident, a variety of data sources were analysed and interpreted to determine if there were any unusual increases in any of the symptoms or indicators. We detected rises in general practitioner-based diagnoses of asthma, allergic rhinitis, conjunctivitis and respiratory conditions (Figure 1); however, these increases were to be expected at that time of year, most probably because of increasing

pollen levels and possibly elevated ozone levels that were not associated with the volcanic eruption [11]. Despite the anecdotal reports of various sorts of sulphurous odours in parts of Scotland, extensive environmental monitoring of ambient air, rainwater, snow and grass also demonstrated that the eruption had little measureable impact on the UK and that any exposure would have been low and not likely to have had a significant impact on health. For example, air quality monitoring stations around UK did not show any increase in pollutants that could be associated with the eruption (e.g. PM₁₀ and sulphur dioxide) [6,7]. The incident also followed a series of public holidays (occurring during weeks 13 and 14) during which access to general practitioner services was limited, which is known to artificially lower the incidence rates of a range of general practitioner-based diagnoses recorded by the HPA/QSurveillance system. We used historical baseline data to determine that the reported trends (and effects of public holidays) were similar to previous years (Figure 1). These non-volcano-related factors led to an expected rise in several indicators during week 15. Despite these complexities in interpreting the data, the ability to use statistical methods to detect unexpected trends in the data ensured that we were confident that there were no population-based increases in morbidity associated with the ash cloud.

During this incident syndromic surveillance systems were the only sources of real-time health data. These syndromic data were used in conjunction with other

FIGURE 2

Daily number of telephone calls received for selected clinical indicators, 1 February – 3 May 2010 (weeks 6–18), Scotland



A: difficulty breathing; B: eye problems; C: rash; D: cough.

Data are displayed as counts of observed calls (Obs) and expected calls (Exp), upper 99% confidence limit (UL) and 99% confidence limit exceedances (red dots).

The period during which the Icelandic volcanic ash cloud was located over the United Kingdom (16–20 April 2010) is illustrated by a vertical grey bar.

Source: Health Protection Scotland/NHS 24.

data sources including environmental monitoring data to provide reassurance that there were no population-level adverse health effects caused by exposure to the volcanic ash cloud. During such a high-profile and uncertain situation, there is great value in having health effect data to complement available environmental monitoring and exposure data. This approach provides triangulation of data sources and adds further confidence to the public health risk assessment. It is also very valuable to be able to give the public appropriately reassuring messages in real time about the likely impact on health [12,13].

In Scotland, NHS 24 call data were examined on a daily basis for the absolute number of calls and call proportion (percentage of total calls) allocated into specific syndrome categories (Figure 2). Call patterns (e.g. a peak in total number of calls over the weekend and during public holidays) were considered when assessing whether call volumes were at normal levels or in excess of that normally observed. The observed daily exceedances in calls reporting difficulty breathing and eye problems were examined in respect of the nature of the call, including age, sex and location of the patient, temporal distribution and call disposition (whether the patient was just reassured, referred for further routine medical attention or sent to hospital urgently by ambulance). We concluded that these calls were not indicative of an unusual pattern and were in keeping with the expected pattern from previous seasons.

Syndromic surveillance systems have previously been shown to provide real-time tracking of disease outbreaks and they can provide earlier warning of community-based activity compared with traditional laboratory-based reporting systems. A potential limitation of these syndromic systems is a lack of specificity; however, it has previously been shown that there is a good association between syndromic surveillance data and laboratory data [2,14].

A potential confounder in this incident was increasing pollen levels commonly experienced at that time of year [11], as the generic indicators selected for their association with exposure to ash are equally sensitive for monitoring hay fever, e.g. wheeze, allergic rhinitis, eye problems and difficulty breathing. However, the rise in these indicators was as expected for the time of year. If the rate or magnitude of rise had been significantly above the expected level we may have been able to attribute it to the ash. This lack of detectable health effect is also supported by environmental monitoring data, which demonstrated that exposure to volcanic ash would have been very low and not likely to have had a significant effect on health.

Syndromic surveillance systems have previously been used to track events of major public health impact including influenza pandemics, heat waves and flooding. This incident has further demonstrated the benefit of using national syndromic surveillance systems for monitoring community health in real-time to assess the

impact of unforeseen circumstances and help develop clear evidence-based health protection messages.

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Upsurge of infections caused by *Salmonella* Concord among Ethiopian adoptees in Denmark, 2009

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Multidrug-resistant (MDR) *Salmonella* Concord has been associated with adoptees from Ethiopia. In 2009, Denmark saw an increase in MDR *S. Concord* infections: all eight cases reported in 2009 were among Ethiopian adoptees. The upsurge was linked to an increased number of infants adopted from Ethiopia. Data from other European countries suggests that they may face a similar problem.

Introduction

Two studies from seven European countries and the United States (US) have shown an increased number of infections with *Salmonella* Concord from 2003 to 2007 among mainly Ethiopian adoptees [1, 2]. Isolates associated with patients of Ethiopian origin were all multidrug-resistant to antimicrobials including third generation cephalosporins.

In 2009, we recognised an increase in *S. Concord* infections in Denmark by querying the central *Salmonella* database at Statens Serum Institut. The recent investigation of this upsurge indicates that multidrug-resistant *S. Concord* continues to be imported from Ethiopia and therefore represents a concern for international public health. Additionally, we wanted to compare the upsurge of this specific pheno-/geno-type observed in Denmark with what has been reported in the rest of Europe through data from the European Surveillance System (TESSy) database at the European Centre for Disease Prevention and Control (ECDC).

Methods

A previously published study had indicated that in the US, the occurrence of *S. Concord* followed the number of Ethiopian infants adopted [1]. In 2009, an increased number of Ethiopian children adopted to Denmark were observed why this study was initiated to investigate if the same correlation between Ethiopian adoptees and the number of *S. Concord* cases were present in Denmark. In Denmark, all *Salmonella* cases are notified by the general practitioners to the Statens Serum Institut and archived in a central database; "Det Tarmbakteriobiologiske Register". By querying this

database, the data on *S. Concord* were retrieved and the isolates further characterised. The patients or the parents of patients were interviewed to determine if the patients were adopted from Ethiopia, had travelled internationally or had any association with Ethiopians before onset of illness. Information about adoptions from Ethiopia was sought from national adoption agencies in Denmark [4, 5]. Serotyping and testing for susceptibility to antimicrobial agents was performed at Statens Serum Institut as minimum inhibitory concentration (MIC) determinations according to previously described methods [6], but with resistance (R) cut-off values for cefotaxime at $R \geq 2$ mg/ml. Confirmatory testing for extended-spectrum beta-lactamases (ESBL) was applied on the eight isolates of Danish Ethiopian adoptees conferring resistance to cefotaxime and cefixime [1].

To get an overview of the situation in other European countries, we obtained data from the TESSy database at ECDC for 2006-2008 [3]. Case-based data on *S. Concord* serotype, importation status, probable country of infection and resistance against 11 antimicrobials were analysed from European Union (EU) and European Economic Area (EEA) countries. Country specific details are not included in the study.

Results

In Denmark, the number of *S. Concord* infections increased from none in 2007, two in 2008 and eight in 2009 (Figure).

Eight patients were female and age ranged from less than one year up to 30 years. Eight patients were infants less than one year of age and all were Ethiopian adoptees. The two adult patients were a 30 year old male who had been infected during a visit to Africa (country not specified) and a 23 year old female who had neither history of recent international travel nor contact with children or adults arriving from Ethiopia. General practitioners and parents of seven infants and the two adults were interviewed. Four infant patients were asymptomatic and were examined due to underweight,

relatives with diarrhoea and for general screening purposes. Five patients including both adults were suffering from non-bloody diarrhoea and one infant from urinary tract infection (UTI). Two infants, including the one suffering from a UTI were hospitalised. The link between the Ethiopian adoptees and the respective orphanages were not investigated. However, a previously published study reveal that the adoptees often originate from multiple orphanages or transit centres [1].

Laboratory investigations

The eight *S. Concord* isolates originating from Ethiopian adoptees all conferred resistance to ampicillin, cefotaxime, ceftiofur, chloramphenicol, gentamicin, streptomycin, sulfamethoxazole, tetracycline, and trimethoprim respectively. Additionally, resistance to colistin (n=1), florfenicol (n=6) and reduced susceptibility to ciprofloxacin (n=6) was observed in the samples. The strains were all susceptible to apramycin, amoxicillin+clavulanic acid, nalidixic acid, neomycin and spectinomycin. All eight isolates were confirmed as ESBL-producing according to the phenotypic characterisation.

The two strains belonging to patients older than one year of age and without association to Ethiopia were both pansusceptible.

A total of 256 children were adopted from Ethiopia to Denmark from 2007 to 2009. During this period, the number of Ethiopian adoptees increased by 220% from 39 adoptions in 2007 to 125 in 2009 (Figure).

Data from other European countries

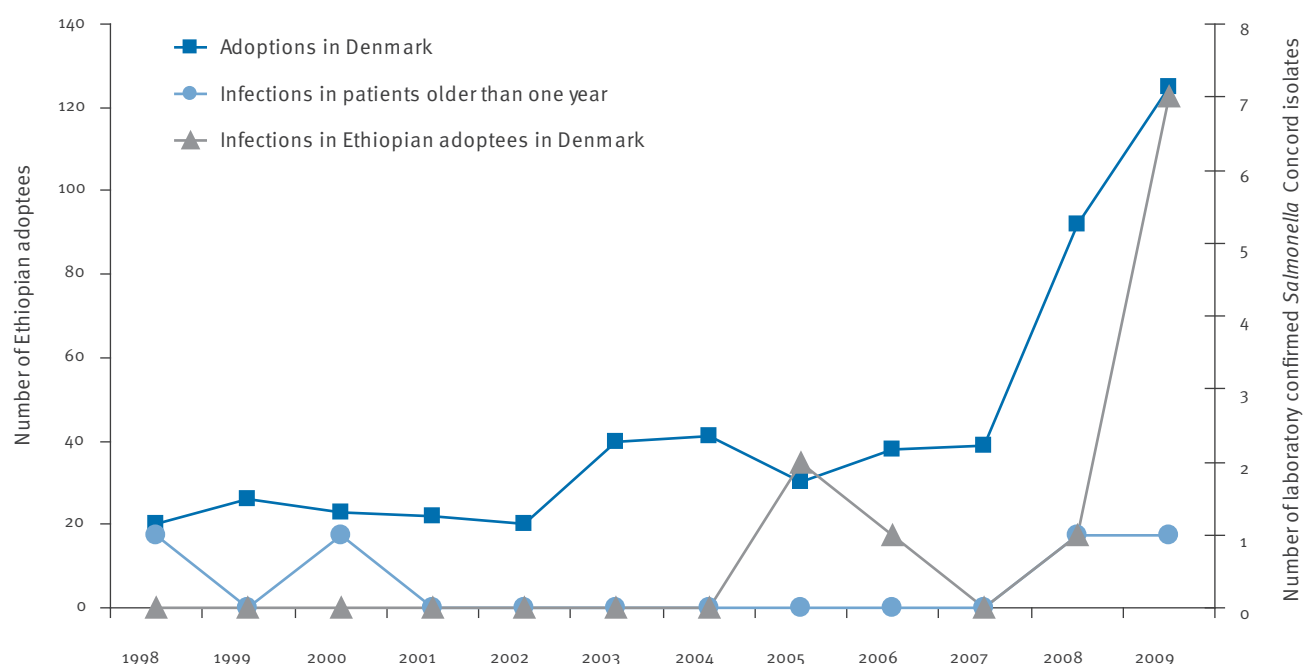
Data for 91 *S. Concord* patients were retrieved, as of 28 July 2009, from the TESSy database (2006: 21 patients from five EU/EEA countries; 2007: 37 from six EU/EEA countries; 2008: 33 from eight EU/EEA countries). In a pooled dataset from 2006-2008, 44 cases (48%) were reported in children under two years of age and 15 (16%) *S. Concord* cases were reported as acquired from outside of EU/EEA countries. The low proportion of isolates acquired from outside of EU/EEA are most likely biased due to the fact that many cases do not have the information on the country where the infection was contracted. Ethiopia was indicated as country of origin for eight cases in four countries and Kenya for one case. All eight cases originating from Ethiopia were below or one year of age. The one case with infection acquired in Kenya was a 24 year old male. Antimicrobial resistance data were available for 10 confirmed cases only, of which seven and four isolates conferred resistance to cefotaxime and ciprofloxacin, respectively; two of these cases were linked to Ethiopia.

Discussion

In Denmark and from a European perspective, *S. Concord* is a rarely reported serotype. From 2007 to 2009, an increased incidence of *S. Concord* infections among Ethiopian adoptees, most likely caused by the same multidrug-resistant clones from Ethiopia, was noted in Denmark [1, 2]. The increasing number of countries reporting cases of *S. Concord* and the suggested link between very young children and Ethiopia may be indicative of a noteworthy health problem in Ethiopia and an important route for the importation of *S. Concord* to Europe.

FIGURE

Number of children adopted from Ethiopia and the number of laboratory confirmed *Salmonella* Concord cases in Denmark, 1998 – 2009



In Denmark, the recent incidence of *S. Concord* has not earlier followed the adoption rate of Ethiopian infants as was described previously in the US [1]. There may be several explanations for this, one of which may be an increased awareness in Denmark of Ethiopian children being infected with *S. Concord* resulting in more testing. Another possibility could be an increased incidence of *S. Concord* in Ethiopian children.

In this study, the antimicrobial susceptibility data are consistent with the multidrug-resistant *S. Concord* widely spread among Ethiopian adoptees, whereas susceptible strains often can be traced to other parts of east Africa. It appears that the Danish strains from year 2009 are more resistant than previously observed, with six of seven strains from Ethiopian adoptees showing reduced susceptibility to fluoroquinolones. Previous studies of *S. Concord* isolates from Ethiopian adoptees have found that the strains harboured the following genes; *bla*_{CTX-M-15} and *bla*_{SHV-12} and *qnrA* and *qnrB*, respectively encoding resistance to third generation cephalosporins and reduced susceptibility to fluoroquinolones. Antimicrobial treatment of *S. Concord* from Ethiopian adoptees is hampered by the nature of the resistance pattern, which limits the options for treatment with traditional antimicrobials - including fluoroquinolones, which are not recommended for children [1].

Conclusions

The present study highlights the emergence of *S. Concord* isolates resistant to third generation cephalosporins among Ethiopian adoptees in Denmark during 2007 to 2009, and suggests that *S. Concord* continues to be a concern for international public health.

We recommend that physicians assess the health status of international adoptees, with special attention to Ethiopian adoptees, on arrival into the country of destination. If the health examination indicates that the child may have salmonellosis, specimens should be submitted for culture and subsequently for antimicrobial susceptibility testing if *Salmonella* is isolated. Unfortunately, it remains poorly understood why this *Salmonella* serovar seems to be linked in particular to Ethiopia, why the problem continues several years after its recognition, and how important this *Salmonella* serovar is for east African public health.

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Mumps outbreak in the former Yugoslav Republic of Macedonia, January 2008 – June 2009: epidemiology and control measures

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Mumps is a mandatorily notifiable disease in the former Yugoslav Republic of Macedonia. Routine vaccination with one dose of measles-mumps-rubella (MMR) vaccine at the age of 13 months started in 1983 and a two-dose vaccination schedule, with the second dose at the age of seven years, was implemented in 1997. The previous mumps outbreak in the country was reported in 1996, with 4,321 registered cases. In October 2007, an increase in mumps notifications was observed. Between January 2008 and June 2009, the Institute of Public Health received 16,352 notifications of mumps cases through the routine surveillance system. Young people aged 15–19 years ($n=7,876$, 48.2%) were most affected; more males (61.2%, $n=10,013$) were reported than females. Of the cases whose vaccination status was checked ($n=14,178$, 86.7%), 19.5% had not been vaccinated, 37% had been vaccinated with one MMR dose, 34.4% had received two doses, 0.6% had been vaccinated during catch-up vaccination (with MMR vaccine for people aged 15–26 years) and for 8.5% there were no records of vaccination. For 13.3% ($n=2,174$) of reported cases, their vaccination status was not checked. In February 2009, biological specimens (serum, saliva and urine) from 20 cases aged 15–19 years were sent to the National Institute for Public Health and the Environment (RIVM) in the Netherlands for genotyping. Of the 20, nine had been vaccinated with two doses of MMR vaccine, five with one dose, one had not been vaccinated and five had no records of vaccination). Mumps viral RNA was detected in samples from 17 patients: the sequence of the amplified small hydrophobic gene from all 17 showed that the mumps virus was genotype G5.

Introduction

Mumps, caused by a paramyxovirus, is generally a mild disease with fever, headache and swelling of the salivary glands (parotitis). It is spread directly from infected to susceptible people by respiratory droplets. The infection can be asymptomatic in up to 20% of cases; 40–50% of cases can have nonspecific or

primarily respiratory symptoms [1]. Parotitis occurs in 30–40% of infected people [1], but complications such as meningitis (in up to 15% of cases), encephalitis or orchitis may occur [2]. Permanent sequelae occur in about 25% of encephalitis cases, with an overall mortality of 1 per 10,000 cases [2]. In children, deafness caused by mumps affects approximately 5 per 100,000 cases [1,2]. Mumps infection during the first 12 weeks of pregnancy is associated with a 25% incidence of spontaneous abortion, although malformations following mumps virus infection during pregnancy have not been found [1].

Mumps is a mandatorily notifiable disease in the former Yugoslav Republic of Macedonia. Routine vaccination with one dose of measles-mumps-rubella (MMR) vaccine at the age of 13 months started in 1983 and a two-dose vaccination schedule, with the second dose at the age of seven years (or the year the child first starts school), was implemented in 1997. In 1969 to 1982, before mandatory mumps vaccination was introduced, the number of mumps cases in the country ranged from 2,143 (in 1969) to 8,436 (in 1979) (Figure 1). After the introduction in 1983 of mandatory single-dose MMR vaccination, the incidence of mumps decreased until 1996, with notifications falling from a high of 5,161 (in 1986) to 1,016 (in 1988). Until the outbreak described here, the last reported outbreak occurred in 1996, with 4,321 cases.

From 1997, when vaccination with a second dose of MMR vaccine was introduced in the country, the number of reported mumps cases decreased substantially, with a mean of 218 notifications per year during 1997 to 2006. The number of notifications fell from a high of 441 (in 2001) to 49 (in 2006).

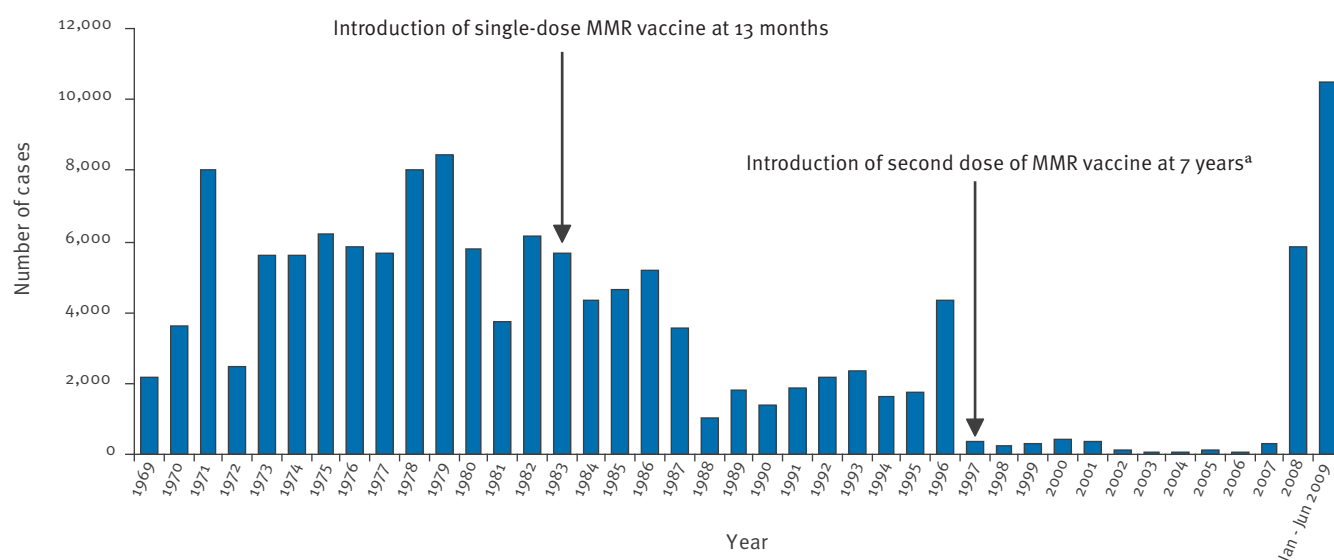
During 1969 to 1983, 94.8% of mumps cases were in children aged 0–14 years. The most affected age group was 0–6 years, comprising 49.5% of all cases, followed by the 7–9 years age group (28.8%) and 10–14 years

age group (16.5%). After the introduction of a single dose of MMR vaccine, during 1984 to 1996 the age distribution of cases shifted to slightly older age groups: the age group 0–6 years accounted for 28.4% of notified cases, 7–9 years for 25.8%, 10–14 years for 30.6% and 15–19 years for 12%. In the previously reported outbreak in 1996, 52.6% of notified mumps cases were aged 15–19 years.

In October 2007, the number of reported mumps cases began to increase (n=25). The number rose substantially in 2008 (with 5,865 cases that year) and continued to increase until February 2009 (in January – February 2009, there had been 4,561 cases). The number of reported cases then began to fall. In this report, we analyse the outbreak from January 2008 to June 2009 (during which time 16,352 cases had been reported).

FIGURE 1

Annual notification of mumps cases, former Yugoslav Republic of Macedonia, January 1969 – June 2009 (n=137,993)

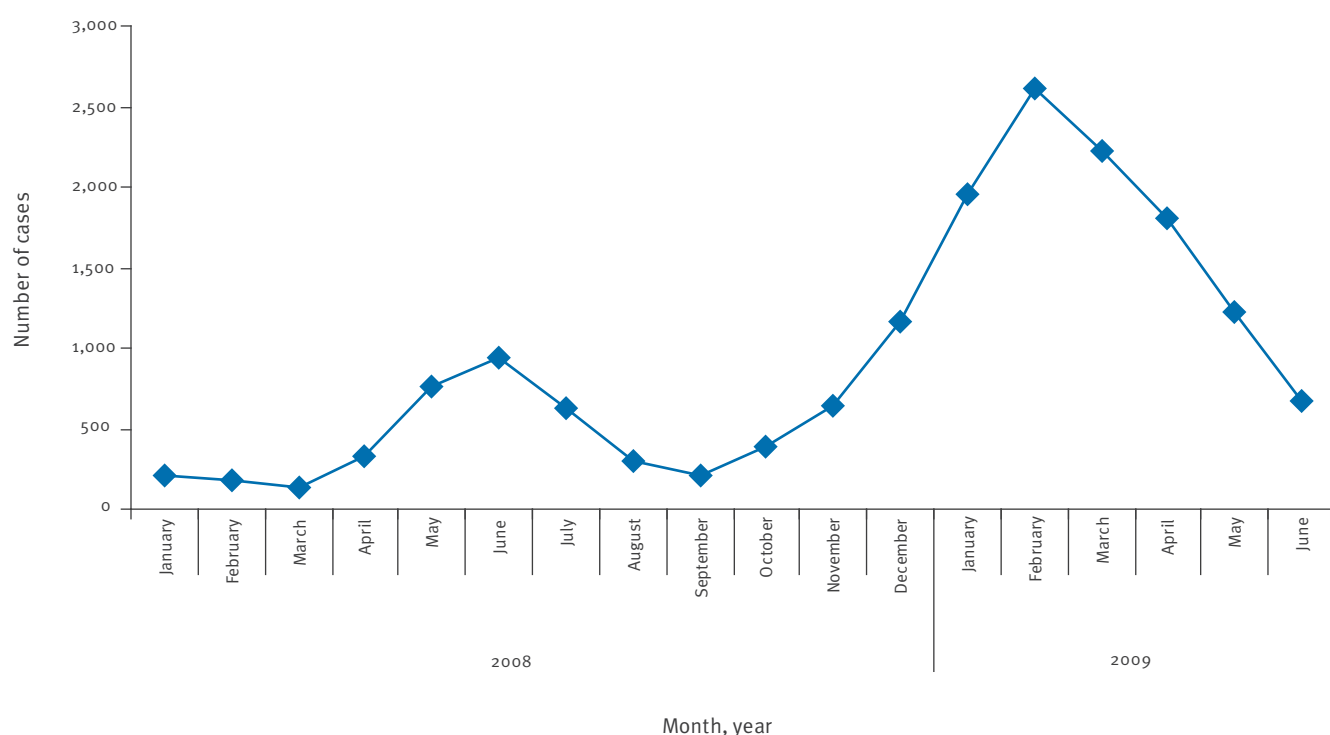


Jan: January; Jun: June; MMR: measles-mumps-rubella.

^a Or the year the child starts school.

FIGURE 2

Monthly notification of mumps cases, former Yugoslav Republic of Macedonia, January 2008 – June 2009 (n=16,352)



Methods

Mumps surveillance in the former Yugoslav Republic of Macedonia

Notifications from general practitioners and hospital clinicians are collected by public health centres. The country's surveillance system for communicable diseases requires each of the 10 regional public health centres to notify the national Institute of Public Health of mumps cases that meet the clinical classification, are laboratory confirmed or are epidemiologically linked with a laboratory-confirmed case. The Institute of Public Health then enters the details into a national database.

As a result of the increased number of reported mumps cases, the Ministry of Health issued an order in December 2007 for enhanced mumps surveillance in the country, as recommended by the Commission for Communicable Diseases. Enhanced surveillance included strengthening the control of mumps case reporting (by increasing the number of visits of the Health Inspectorate to general practitioners to ensure timely and complete reporting) and field visits of

epidemiologists to find and vaccinate susceptible children (i.e. those who had not been vaccinated with MMR vaccine or had been partially vaccinated or those who had no record of MMR vaccination and had no medical record of previous mumps infection). School absence, was also monitored. In addition, on entry into primary or secondary school, children had to have proof of MMR vaccination, or medical proof of previous mumps infection.

In January 2008, as part of the country's enhanced surveillance of mumps, the Institute of Public Health recommended that epidemiologists and public health workers from the public health centres examine the vaccination records of each notified mumps case. These records were the cases' personal vaccination cards and vaccination registers, both of which were kept at the vaccination sites.

In addition to regular notification, from January 2008 to September 2009, public health centres also reported mumps cases on separate forms, which were then sent

TABLE 1

Notified mumps cases and incidence by health region, former Yugoslav Republic of Macedonia, January 2008 – June 2009 (n=16,352)

Health region	2008		2009	
	Incidence/100,000 population	Number of notified cases	Incidence/100,000 population	Number of notified cases
Bitola	167	313	177	331
Kocani	646	728	473	533
Ohrid	10	15	53	82
Prilep	223	262	1,016	1,193
Kumanovo	318	553	416	723
Skopje	112	659	626	3,698
Stip	606	608	660	662
Strumica	1,267	1,332	472	496
Tetovo	6	20	578	1,799
Veles	728	1,375	513	970
Total	287	5,865	514	10,487

TABLE 2

Mumps cases by age group and sex, former Yugoslav Republic of Macedonia, January 2008 – June 2009 (n=16,352)

Age (years)	Number of cases (%)	Cumulative incidence/ 100,000 population	Sex	
			Male	Female
0–4	283 (1.7)	231	170	113
5–9	805 (4.9)	562	493	312
10–14	3,080 (18.8)	1,921	1,869	1,211
15–19	7,876 (48.2)	4,761	4,764	3,112
20–24	2,220 (13.6)	1,371	1,460	760
25–34	1,381 (8.4)	458	891	490
35–44	392 (2.4)	132	192	200
45–54	220 (1.3)	81	128	92
55–64	60 (0.4)	32	25	35
≥65	35 (0.2)	16	21	14
Total	16,352 (100)	809	10,013	6,339

to the Epidemiology Department at the Institute of Public Health as aggregate weekly numbers, showing year of birth and vaccination status.

Data on cases notified through the regular surveillance system and enhanced surveillance of mumps cases were analysed using Microsoft Excel and SPSS v16.

Coverage data for MMR vaccination were obtained from the archives of the Institute of Public Health and from annual coverage reports from the Department for Monitoring of Immunization at the Institute of Public Health. The data come from vaccination sites on the number of children eligible for vaccination and the number vaccinated in the calendar year. The information collected by the public health centres is sent to the Institute of Public Health, where national, regional and subregional coverage is then estimated for each vaccine in the calendar year, for inclusion in a national database.

Results

In October 2007, a substantial rise in the number of mumps notifications was seen, compared with the means for the previous five years. A total of 284 cases were registered in 2007; 71.8% of these (n=204) were registered in the last three months of the year. The first cases reported were young Roma adolescents and, in November 2007, cases were reported among young adults in the general population by the regional public health centres in Bitola and Prilep, where the first two local outbreaks were reported. The cases reported in 2007 were not included in our analysis, as we had very limited information on their vaccination status.

In 2008, a total of 12 local outbreaks were reported from six health regions, with a total of 5,865 cases. The peak of the first wave of the outbreak was observed in June 2008 (n=942). The number of notifications then started to decrease in July and August 2008, possibly because of schools' summer vacation. With the start of the following school year, the number of mumps notifications started to rise again, with a mean monthly increase of 66.8% until February 2009, when the highest number of monthly notifications was received (n=2,602).

By the end of June 2009, nine of the 10 regional public health centres had reported outbreaks, with a total of 10,487 cases – exceeding previous annual numbers of mumps cases in the country (Figure 1).

From March to June 2009, the number of new notifications decreased each month: 2,231 in March, 1,802 in April, 1,223 in May and 670 in June (Figure 2).

Geographical distribution of mumps cases

Of the mumps cases reported between January 2008 and June 2009, 89.5% (n=14,635) were from urban areas and 10.5% (n=1,717) from rural regions. In 2008, the highest mumps incidence (1,267 per 100,000

population) was registered in the health region of Strumica in the east and central part of the country, followed by Veles (728 per 100,000 population), Kocani (646 per 100,000 population) and Stip (606 per 100,000 population). In 2009, the epidemic shifted to the north-west of the country, with the highest incidence registered in Prilep (1,016 per 100,000 population), Stip (659 per 100,000 population), Skopje, the capital city (626 per 100,000 population) and Tetovo (578 per 100,000 population) (Table 1).

Age and sex distribution of mumps cases

Some 61.2% (n=10,013) of all notified mumps cases in the January 2008 to June 2009 outbreak were male; 38.8% (n=6,339) were female (Table 2). Their ages ranged from 0 to 89 years (mean: 18 years; median: 17 years). The most affected age group (15–19 years) accounted for 48.2% of all mumps cases in the outbreak and had the highest cumulative incidence (4,761 per 100,000 population). Patients aged 10–14 years accounted for 18.8% of cases, with a cumulative incidence of 1,921 per 100,000 population and the 20–24 years age group had 13.6% of cases, with a cumulative incidence of 1371 per 100,000 population (Table 2).

Vaccination status of mumps cases

From regional and local public health centres, the Institute of Public Health received information on vaccination status for 86.7% (n=14,178) of all notified mumps cases (n=16,352). Of cases whose vaccination status had been checked, 19.5% (n=2,764) had not been vaccinated, 37.0% (n=5,243) had been vaccinated with one dose of MMR or other mumps-containing vaccine, 34.4% (n=4,880) had been fully vaccinated with two doses of MMR or other mumps-containing vaccine, 0.6% (n=85) had been vaccinated with MMR in the catch-up vaccination for 15–26-year-olds and there were no vaccination records for 8.5% (n=1,206) (Table 3). For 13.3% (n=2,174) of all notified cases, the Institute of Public Health did not receive any information regarding vaccination status.

Of the cases who had been eligible for two-dose MMR vaccination (i.e. those born from 1990 to 2001) and whose vaccination status had been checked (n=9,693), 7% (n=680) had not been vaccinated, 35.2% (n=3,411) had been vaccinated with one dose of MMR or other mumps-containing vaccine, 48.9% (n=4,745) had been vaccinated with two doses of MMR or other mumps-containing vaccine, 0.8% (n=75) were vaccinated in the MMR catch-up vaccination and for 7.8% (n=761) there were no data on vaccination status (Table 3).

Of the cases with checked vaccination status, 44.7% (n=3,157) of those born from 1990 to 1994 (i.e. aged 15–19 years) received both doses and 39.2% (n=2,764) received only one dose, while of cases born from 1995 to 1999 (i.e. aged 10–14 years), 62.2% (n=1,481) received both doses and 23.1% (n=550) received one dose. Of the cases born from 1982 to 1989 – who had

been eligible for only one dose of MMR vaccine – 53.3% (n=1,413) had been vaccinated (Table 3).

The January 2008 to June 2009 outbreak started and incidence was highest among people born in 1991 to 1994: of the cases whose vaccination status was checked (n=14,178), 45.6% (n=6,466) were born in this period; people born in 1992 alone accounted for 15.6% (n=2,216) (Table 3). The lowest coverage with MMR or

other mumps-containing vaccine (35.1%) was registered in 1993 (i.e. coverage of people born in 1992) and in 1992 (52.9% coverage, of people born in 1991), as a result of vaccine shortages.

As a result of shortage of MMR vaccine in 1993, monovalent measles vaccine was used in most of the country; only in some parts were a bivalent measles–mumps vaccine or monovalent mumps and measles

TABLE 3

Vaccination status of mumps cases^a with checked vaccination records by year of birth, former Yugoslav Republic of Macedonia, January 2008 – June 2009 (n=14,178)

Year of birth	Number of cases vaccinated with two doses of MMR vaccine ^{b, c}	Number of cases vaccinated with one dose of MMR vaccine ^b	Number of cases vaccinated in catch-up MMR vaccination	Number of cases not vaccinated	Number of cases with no vaccination records	Total (%)
≤1978	0	7	0	864	29	900 (6.3)
1979	1	2	0	91	5	99 (0.7)
1980	1	4	0	125	9	139 (1.0)
1981	3	12	0	134	7	156 (1.1)
1982	2	70	0	74	21	167 (1.2)
1983	6	73	1	65	28	173 (1.2)
1984	10	121	0	76	41	248 (1.7)
1985	11	165	0	86	50	312 (2.2)
1986	9	173	0	77	40	299 (2.1)
1987	12	223	0	113	54	402 (2.8)
1988	21	299	0	124	63	507 (3.6)
1989	50	289	9	133	62	543 (3.8)
1990	131	285	3	101	69	589 (4.2)
1991	550	710	19	120	116	1,515 (10.7)
1992	846	1,025	35	158	152	2,216 (15.6)
1993	858	491	14	104	130	1,597 (11.3)
1994	772	253	3	40	70	1,138 (8.0)
1995	553	167	0	49	61	830 (5.9)
1996	359	145	0	31	56	591 (4.2)
1997	252	104	1	29	28	414 (2.9)
1998	182	76	0	14	34	306 (2.2)
1999	135	58	0	22	26	241 (1.7)
2000	70	44	0	12	9	135 (1.0)
2001	37	53	0	21	10	121 (0.9)
2002	6	109	0	20	13	148 (1.0)
2003	1	96	0	14	10	121 (0.9)
2004	1	77	0	12	9	99 (0.7)
2005	1	55	0	12	1	69 (0.5)
2006	0	37	0	11	3	51 (0.4)
2007	0	19	0	20	0	39 (0.3)
2008	0	1	0	12	0	13 (0.1)
Total (%)	4,880 (34.42)	5,243 (36.98)	85 (0.60)	2,764 (19.49)	1,206 (8.51)	14,178 (100.0)

MMR: measles-mumps-rubella.

^a Only mumps cases for which the Institute of Public Health received information regarding vaccination status.

^b Or other mumps-containing vaccine.

^c Some of the cases born in 1979 to 1989 are reported to have received two doses since in some parts of the country, single dose MMR vaccination started before 1983 and introduction of a second dose started before 1997. Some of the cases born in 2002, started school earlier than usual (at the age of six years), and so were vaccinated with two doses. Some cases born in 2003 to 2005 are reported to have received two doses of MMR vaccine: the reason for this is unknown.

vaccines used. Children who did not receive MMR vaccine in 1992 were scheduled for vaccination (and thus eligible) in 1993, so the denominator was much higher than usual. In order to estimate the coverage of vaccination with a mumps-containing vaccine in 1993, we took as denominator all children eligible for MMR vaccine (including those not vaccinated in 1992 and scheduled for vaccination in 1993) and as nominator only those who had received a mumps-containing vaccine. This calculation leads to a very low vaccination coverage of 35.1%.

Coverage of MMR or other mumps-containing vaccine was also low (75.6%) in 1994 (in people born in 1993) and in 1996 (in people born in 1995), with coverage of 88% (Figure 3). However, the number of mumps cases was also high in people born in 1995–1999 ($n=2,382$ with checked vaccination status), despite high vaccination coverage (mean for the first dose: 95.0%; mean for the second dose: 95.5%).

During the field visits conducted in the affected regions in 2008 and 2009, the team from the Institute of Public Health identified some oversights in immunisation records from the years in which there had been a shortage of MMR vaccine (1992–1997). It was

recorded on some cases' vaccination cards that they had received MMR vaccine when in fact they had not. In the vaccination card, the date of vaccination and vaccine serial number are recorded (in the MMR field of the card). However, in some cases, the serial number corresponded to a monovalent measles vaccine or a bivalent measles–mumps vaccine. The extent of these oversights is hard to quantify, but it is possible that, for people born in 1991 to 1996, the proportion of mumps cases vaccinated with one or two doses of MMR or other mumps-containing vaccine could be smaller than reported and could therefore lead to overestimates of the proportion of cases vaccinated against mumps.

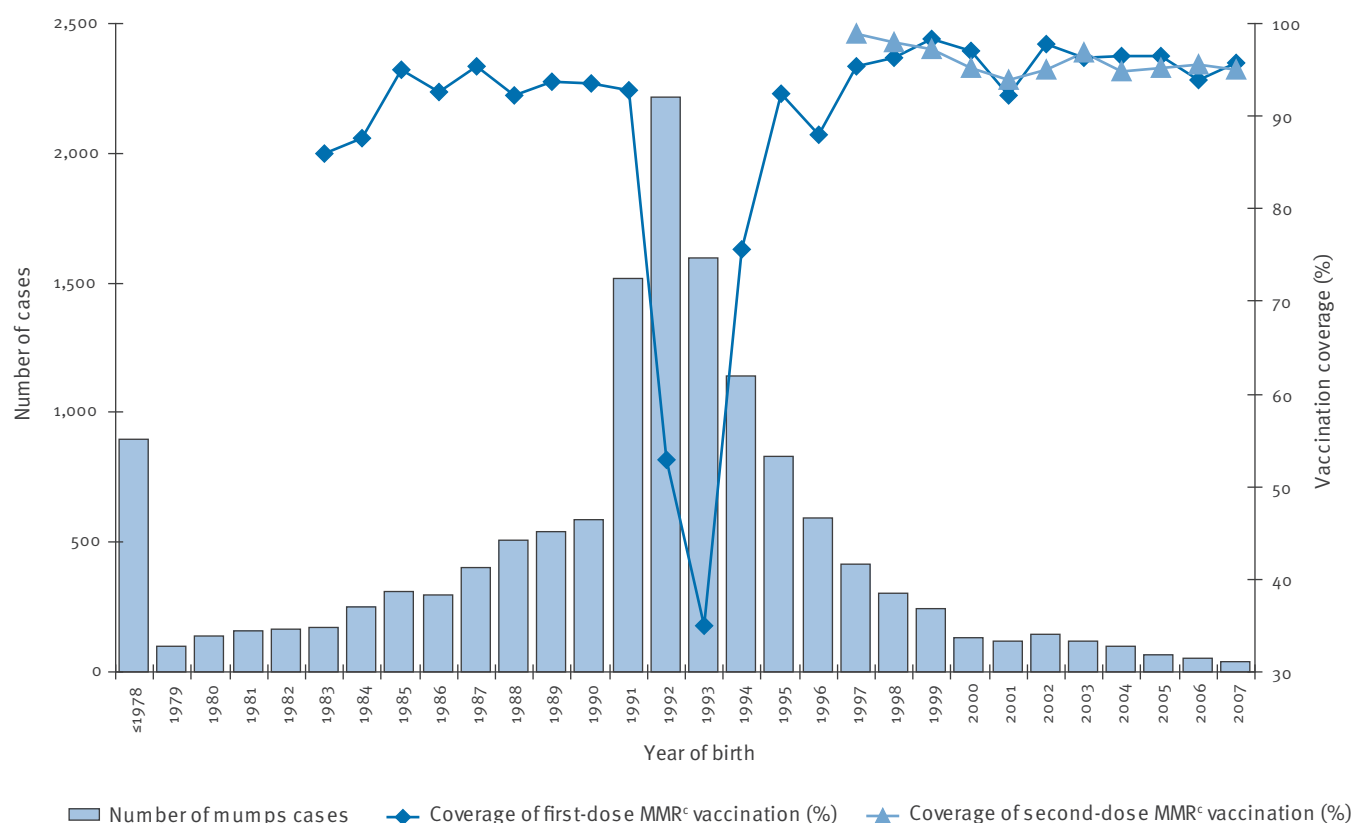
Catch-up MMR vaccination

The Ministry of Health ordered that from December 2007 susceptible children aged up to 14 years should be found and vaccinated with two doses of MMR vaccine in accordance with the country's immunisation requirements. As part of the anti-epidemic measures, children entering primary or secondary school had to have evidence of vaccination against mumps or medical records of past mumps infection.

In March 2008, the Institute of Public Health recommended MMR catch-up vaccination to the Committee

FIGURE 3

Vaccination coverage^a and number of mumps cases^b, former Yugoslav Republic of Macedonia, January 2008 – June 2009 ($n=14,178$)



MMR: measles-mumps-rubella.

^a Vaccination coverage is presented by calendar year. For example, coverage with the first MMR dose in 1993 refers to the 1992 birth cohort, etc.; coverage with the second MMR dose in 2008 refers to the 2001 birth cohort, etc.

^b Only mumps cases for which the Institute of Public Health received information regarding vaccination status.

for Communicable Diseases at the Ministry of Health. In February 2009, the Ministry of Health ordered mandatory additional, catch-up vaccination of susceptible people (those unvaccinated, vaccinated with one dose of a mumps-containing vaccine, or with no record of vaccination) aged 15–19 years. In March 2009, non-mandatory MMR vaccination was offered free of charge to people aged 20–26 years.

During 2 February to 31 May 2009, 58,351 people were vaccinated with MMR through this catch-up vaccination; 90.5% of them (n=52,795) were aged 15–19 years (Table 4).

After the start of the catch-up vaccination, the number of new mumps notifications started to decrease especially among people in the 15–19 years and 20–29 years age groups. However, mumps incidence among children aged 10–14 years remained at same level until June 2009, when the number of mumps notification in

this age group decreased by 34.3% compared with the previous month (Figure 4).

Clinical complications in mumps cases

In January to June 2009, clinical complications from mumps infection were reported in 6.1% (n=641) of all registered cases. Of these, 39% (n=250) had manifestations of orchitis, 4.7% (n=30) were diagnosed with meningitis, pancreatitis occurred in 0.8% (n=5), while 55.5% (n=356) were hospitalised due to more severe manifestation of mumps infection.

Mumps virus genotype

In February 2009, 68 biological specimens (serum, saliva and urine) from 20 mumps cases aged 15–19 years were sent to the National Institute for Public Health and the Environment, (RIVM) in the Netherlands for genotyping. Of these, 45% nine had received two doses of MMR vaccine, five had one dose, one had not been vaccinated and for five, there were no records of vaccination. Mumps viral RNA was detected in the specimens from 17 cases. Sequencing of the amplified small hydrophobic gene showed that all 17 viral isolates were genotype G5.

Discussion

As in many other European countries [3-7], the former Yugoslav Republic of Macedonia has experienced an increase in mumps notifications, particularly among young age groups (15–26 years). The first such increase was registered in October 2007 and continued in 2008 and 2009. In the first six months of 2009, mumps incidence was highest in people aged 15–19 years (birth cohort 1990–1994), accounting for almost half of the cases notified during the outbreak.

TABLE 4

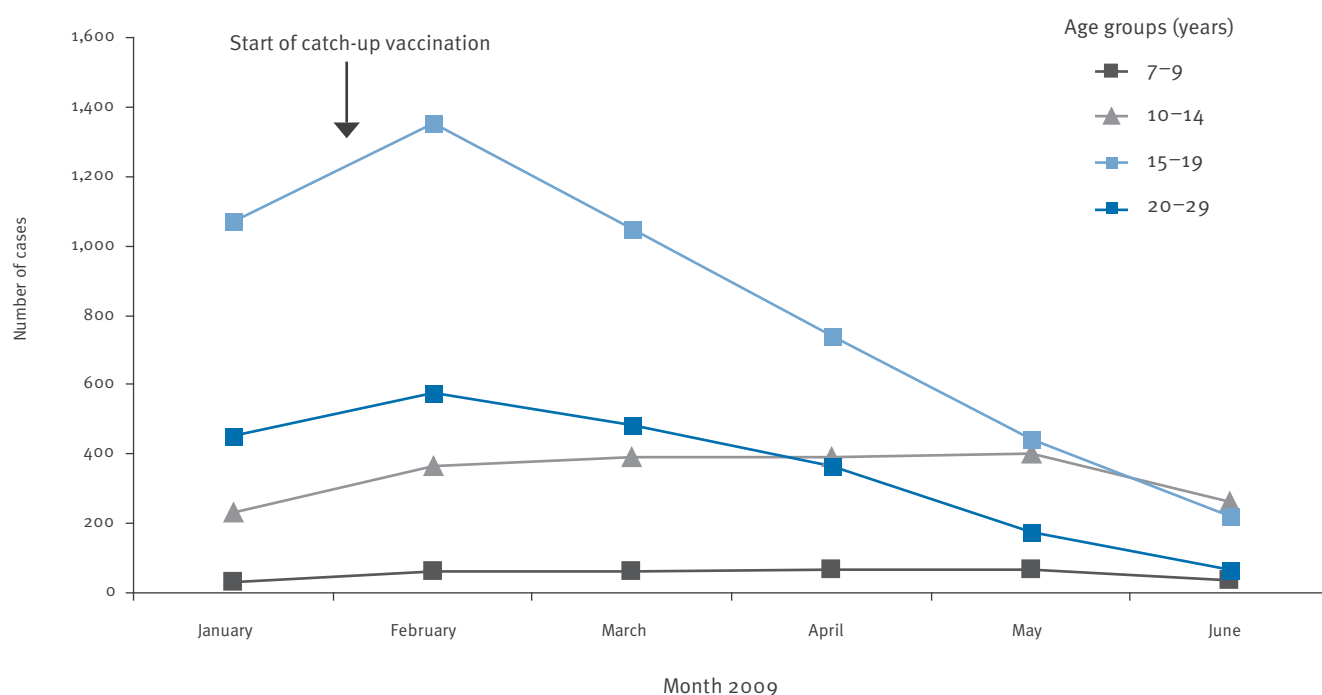
Number of people vaccinated in the catch-up MMR vaccination by age group, former Yugoslav Republic of Macedonia, 2 February – 30 May 2009 (n=58,351)

Age group (years)	Number of people vaccinated
8–9	508
10–14	2,071
15–19	52,795
20–26	2,977
Total	86,592

MMR: measles-mumps-rubella.

FIGURE 4

Monthly number of mumps cases by age group, former Yugoslav Republic of Macedonia, January – June 2009 (n=10,487)



Several factors may have contributed to the clustering of cases in this age group. The first is the low vaccination coverage in this cohort (mean: 69.8% for the first dose of MMR or other mumps-containing vaccine).

Another factor might be extended close contacts between young adults (in classrooms and dormitories, etc.), which could facilitate the transmission of mumps, which is spread by direct contact or airborne droplets [10]. Late implementation of the catch-up MMR vaccination for people aged 15–26 years may also have contributed to case clustering.

Waning immunity [8, 9] cannot be excluded. In the cases aged 15–19 years (born 1990–1994) – the most affected age group – the time from the last dose of mumps-containing vaccine to infection was 8–12 years. Waning immunity might also be relevant in cases born between 1982 and 1989, who had been eligible for only one dose of MMR vaccine. For these people, the time from the last dose of MMR vaccine was 19–26 years. Additionally, in this group, 53.3% (n=1,413) (of cases with checked vaccination status) had been vaccinated, but as demonstrated elsewhere [10], protection after one dose of MMR vaccine varies from 65% to 90%.

In the epidemic, 18.8% (n=3,080) of cases were people aged 10–14 years (birth cohort 1995–1999). Of those with checked vaccination status, 1,481 (62.2%) had been vaccinated with two doses of MMR vaccine. The reasons for the outbreak in this age group are unknown.

Possible failures in the vaccine cold chain could also have contributed to lower vaccine efficacy in the affected age groups eligible for one or two doses of MMR vaccine.

Virus genotype

Viral isolates from 17 cases were shown to be genotype G5: viruses of this genotype had been responsible for mumps outbreaks in the United Kingdom (in 2003–2008), United States, Canada (in 2005–2006) and Moldova (in 2008) [4].

Type of mumps vaccine

Data on the vaccine types used during 1982 to 1999 were incomplete, making it impossible to correlate the vaccine type and number of cases. Before 2000, each public health centre was responsible for the procurement of vaccines. However, records of the manufacturers and vaccine types used during 1982 to 1999 were incomplete. Only three public health centres could show records of the vaccine type used: an MMR vaccine manufactured by the Institute of Immunology in Zagreb, Croatia. From 1992, due to conflicts in the Balkans, vaccines were largely supplied through humanitarian aid; however, records on vaccine types used were again partial. From 2000, the Ministry of Health became responsible for the procurement and

distribution of vaccines to all public health centres in the country.

Conclusion

What remains to be explained is the high incidence of cases in people aged 10–14 years (born from 1995 to 1999), despite high coverage of two-dose MMR vaccination, especially as the time to their second dose of MMR vaccine would have been no longer than seven years. Further studies are needed to measure seroconversion rates after MMR vaccination among different age groups, as are other studies to analyse possible vaccination failure.

In order to prevent future outbreaks of vaccine-preventable diseases, high vaccine coverage must be maintained and timely catch-up vaccination carried out if gaps in vaccination coverage are identified.

In order to improve surveillance of communicable diseases, especially vaccine-preventable diseases, in the former Yugoslav Republic of Macedonia, further training of health workers regarding recording and reporting of vaccinations is necessary. In addition, data on communicable diseases and vaccination history should be recorded electronically.

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Cross-reactivity of antibodies to viruses belonging to the Semliki forest serocomplex

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To the editor: We read with interest the paper by Receveur *et al.* describing an infection with Mayaro virus in a French traveller returning from the Amazon region [1]. We agree that this communication is of clinical relevance because Mayaro virus infections are relatively unknown and easily misdiagnosed on clinical grounds as dengue fever.

Although Mayaro virus has been reported to be a member of the Semliki forest serocomplex [2] – clustering with old world alphaviruses such as Chikungunya virus, with their clinical manifestations of fever and arthralgias – Mayaro virus infections are as yet confined to South America. The other alphaviruses that occur in South America belong to the so-called new world alphaviruses such as eastern equine encephalitis virus, western equine encephalitis virus, Venezuelan equine encephalitis virus. The clinical manifestations are characterised by central nervous system manifestations but not by arthralgias.

Small outbreaks of Mayaro virus infection have been registered in areas near tropical rain forests in various South American countries including Brazil and Suriname [3] but infections outside these endemic foci are rare, particularly in travellers. In 1966, Metselaar described a Mayaro virus infection in a son of a Dutch military man, living in the Coronie District in Suriname [4]. In January 2008, we diagnosed Mayaro virus infection in a Dutch couple who presented with intractable arthralgias after visiting the interior of Suriname (manuscript submitted). In serological tests using enzyme-linked immunosorbent assay (ELISA), we detected cross-reactivity of antibodies for Chikungunya virus and Mayaro virus. As mentioned earlier, both alphaviruses belong to the same antigenic complex, the Semliki forest serocomplex. Seroneutralization tests were therefore necessary to demonstrate the specificity of the antibody for Mayaro virus. Receveur *et al.* seem not to have used these seroneutralization tests. Currently, cross-reactivity in serological tests does not seem to be of major importance for diagnosis since Chikungunya viral infections do not occur in South

America. However, with the increase of international travel and the spread of potential vectors as a consequence of global warming and intensification of trade, infections caused by arthropod-borne viruses are likely to expand on a global scale and may result in overlapping regions of endemicity. This cross-reactivity between alphaviruses should be borne in mind, in particular when ELISA is used for serological diagnosis of the causative virus. Additional seroneutralisation tests should be carried out to establish the virus specificity of the antibody.

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