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Ongoing mumps outbreak in Novi Sad, the autonomous province of Vojvodina, Serbia, January to April 2012

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From 16 January to 30 April 2012, a total of 119 cases of mumps were notified in Novi Sad, Serbia. Of these cases, 89 (75%), were among students. The average age of cases was 22 years-old (range 3-37). The outbreak is still ongoing in Novi Sad and is spreading to other parts of the Vojvodina province. As of 30 April, 209 cases have been notified in the province among those 119 from Novi Sad.

Resurgent outbreaks of mumps have recently been reported from several European Union and neighbouring countries [1-7]. Here we report on an ongoing mumps outbreak in Novi Sad, capital of the Autonomous Province of Vojvodina, Serbia. Similarly to outbreaks in England, Netherlands and Israel in recent years, the present one affects mainly young adults [8-10].

Mumps is a vaccine-preventable disease caused by a paramyxovirus. The typical clinical picture comprises fever, headache, malaise, painful unilateral or bilateral parotid swelling and complications such as orchitis, meningitis and encephalitis occur. Mumps is a notifiable disease in Serbia.

Outbreak description

On 16 January 2012, the Institute for Student Health Care in Novi Sad reported two cases of mumps among students who study at University of Novi Sad, to the Institute of Public Health of Vojvodina. These students had spent the Christmas and New Year holidays in Bosnia and Herzegovina, where a large outbreak of mumps is ongoing [7,11,12].

Novi Sad is the second largest city in Serbia, capital of the northern Serbian province of Vojvodina, and the administrative centre of the South Bačka district. The urban area has a population of 221,854, while its municipal area has a population of 335,701 [13].

Since 25 January, the Public Health Service in Novi Sad has been registering further cases of mumps among students and residents of the town. These had not travelled during the maximum length of the incubation period, 25 days. Here we provide detailed information about cases up to 30 April.

Case definition

An imported case of mumps is defined as any person in Novi Sad with a history of painful swelling of one or both parotid glands without any other apparent cause, epidemiologically linked with a case of mumps in Bosnia and Herzegovina within the maximum length of the incubation period.

A possible case is defined as a case with a clinical picture compatible with mumps diagnosed by a physician after 16 January 2012, in Novi Sad.

An epidemiologically linked case is defined as any person in Novi Sad meeting the clinical criteria and epidemiologically linked with a confirmed or imported case of mumps.

A confirmed case is defined as a case with symptoms compatible with mumps and with serological confirmation of IgM mumps antibodies and/or verification by PCR from throat swabs in any person not vaccinated in the previous two months.

By 30 April, a total of 119 cases had been reported from Novi Sad to the Institute of Public Health of Vojvodina of which 25 were considered as imported (Figure). In total, 32 cases were laboratory-confirmed (IgM or PCR-positive), genotyping was not performed. 87 cases were clinically diagnosed as either possible cases (n=45) or epidemiologically linked cases (n=42).

The average age of cases was 22 years. The youngest case was three years old and the oldest was 37 years

of age. Cases occurred most frequently in the 20 to 29 year-olds age group (n=91; 76%). There were more male (n=70) than female (n=49) cases. Thirteen cases were hospitalised with complications, nine with orchitis and four with pancreatitis. In total 13% of males over 15 years old contracted orchitis.
For 86 cases, there was no information or data about previous mumps vaccination. The remaining 33 cases were vaccinated, among which 29 had received two doses of measles-mumps-rubella (MMR) vaccine. Four were vaccinated with only one dose of MMR.

Public health response

The public health authorities of Vojvodina, advised the paediatric health services to revisit immunisation records of all children between one and 14 years of age and to call-in and vaccinate children who had not received the recommended MMR vaccine for temporary reasons, as soon as possible.

Other epidemic control measures include, disseminating information to health services and the general public about the mumps outbreak by the public health authorities, isolating infected persons and limiting contact with them. Furthermore, persons who had been in contact with those infected, are placed under medical surveillance and receive information about the disease.

Discussion and conclusion

Immunisation against mumps was introduced in Serbia in 1986. Between 1996 and 2006, a combined MMR vaccine was administered according to a two-dose schedule at the ages of 12 months and 12 years but no later than 14 years of age. In 2006, the schedule was changed and the second dose is now administered at the age of seven.

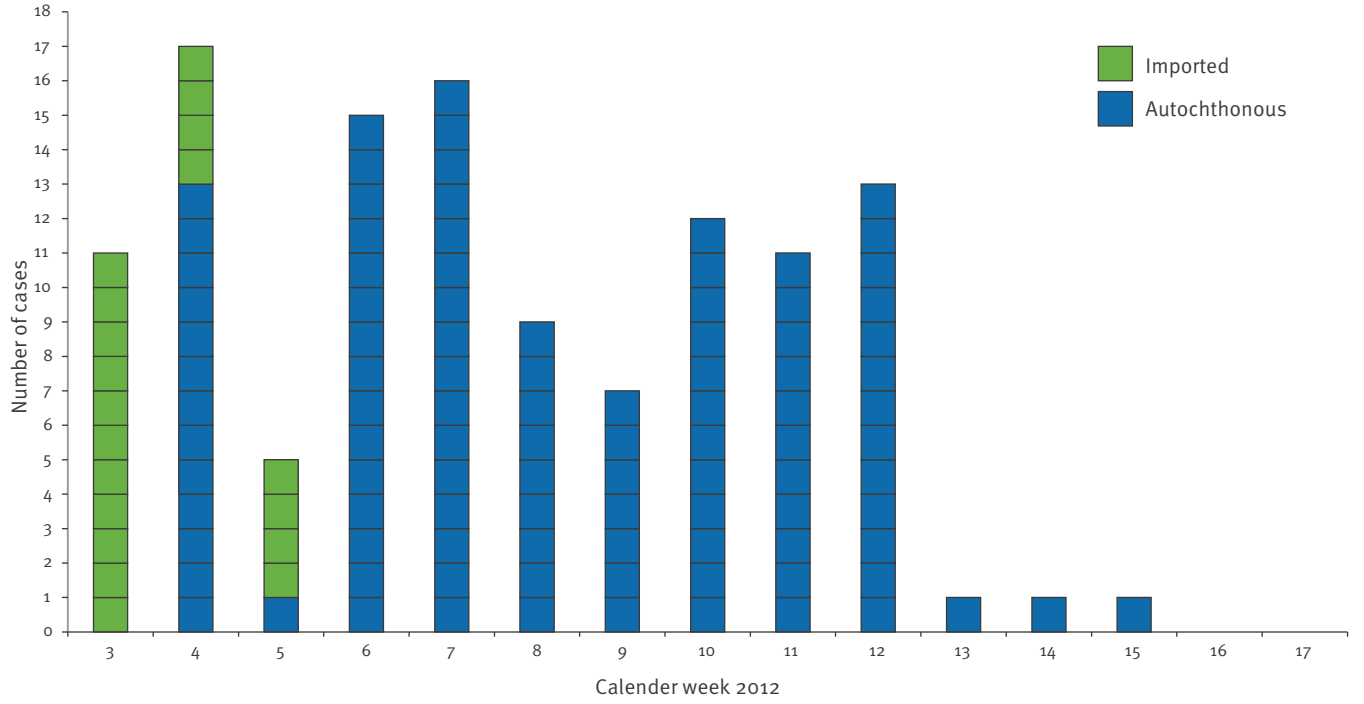
In Serbia, before vaccination against mumps became part of the Serbian childhood vaccination schedule, mumps occurred frequently among children 5 to 9 years of age. Since the introduction of mumps vaccine into the routine childhood immunisation schedule, the number of cases has declined dramatically from 240 in 1982, to 30 in 1994 [14-16].

In Novi Sad, after introduction of the MMR vaccine into the national schedule in 1996, a total of 36 cases of mumps were registered between 1996 and 2011. The incidence rate was low and ranged from zero per 100,000 population in the period from 2007 to 2009 to 3.3 per 100,000 population in 2003 [17].

The importation of mumps cases from Bosnia and Herzegovina contributes to the epidemic spread of mumps in 2012 in Novi Sad and further on in Vojvodina. Ill students infected in Novi Sad probably represent a

Figure

Cases of mumps by calendar week of symptom onset, Novi Sad, Serbia 2012 (n=119)



source for the further spread of the outbreak to other towns, all over Vojvodina Province, where there are a number of susceptible people in age groups that were not targeted for mumps vaccination as children and adolescents. In total, from 16 January to 30 April 2012, 209 cases of mumps were registered in Vojvodina among those 119 from Novi Sad, with the majority of cases in 20 to 29 year-olds.

The fact that new outbreaks of mumps take place decades after vaccine introduction, and the occurrence of cases among young adults and previously immunised persons, indicate the need for further improvement of prevention strategies. The complication rate early in this outbreak of 13% is slightly higher than that in the literature and also highlights the need for attention [18,19].

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Age-dependent prevalence of antibodies cross-reactive to the influenza A(H3N2) variant virus in sera collected in Norway in 2011

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Antibody cross-reactivity to the influenza A(H3N2) variant virus recently reported in the United States, was investigated in Norwegian sera. Seroprevalence was 40% overall, and 71% in people born between 1977 and 1993. The most susceptible age groups were children and people aged around 50 years. The high immunity in young adults is likely to be due to strong priming infection with similar viruses in the 1990s. More research is needed to explain the poor immunity in 45–54 year-olds.

Introduction

From August 2011 to April 2012, 13 cases of human infection were identified in the United States (US) with a variant of influenza A(H3N2) virus that had been circulating in pigs in North America. The variant has been designated as A(H3N2)v by the World Health Organization (WHO) [1]. Almost all cases have been in children, some of them with no recognised exposure to pigs, and limited human-to-human transmission appears to have occurred [2-5]. These viruses have not been shown to circulate in European swine, and until now no human influenza A(H3N2)v cases have been reported in Europe.

The haemagglutinin of these H3N2v viruses is descended from H3N2 viruses that were circulating worldwide in humans in the mid-1990s [6], with A/Wuhan/359/1995(H3N2)-like viruses the most similar vaccine strain [7].

In order to assess the risk and possible impact of further spread of influenza A(H3N2)v viruses in the human population, we need to clarify whether prior exposure to earlier antigenic variants of human H3N2 viruses, either through infection or through vaccination, may have resulted in persisting immunity that could protect segments of the population today against the current H3N2v virus.

Although the genetic similarities to previously circulating viruses suggest that pre-existing immunity may exist, it is important to corroborate this with seroepidemiological evidence. This study presents a first analysis of antibodies reactive to the H3N2v virus in a panel of human sera collected in Norway in August 2011.

Methods

In August each year, The Norwegian Annual Influenza Seroepidemiology Programme collects a panel of anonymised convenience sera representative geographically and for all age groups (about 2,200 sera per year) [8]. In the present study, we used a sub-panel (n=253) of the serum collection from August 2011 containing sera from hospital laboratories in three counties representing different geographic areas of Norway (Bodø, Stavanger and Oslo). The collection and testing of these serum samples for influenza seroepidemiology has been approved by the local research ethics board.

Serum antibody titres were determined using the haemagglutination inhibition (HI) assay, testing sera in serial two-fold dilutions starting at dilution 1:10, with turkey red blood cells (RBC) as indicator cells [8] and taking as the HI titre the serum dilution factor that produced complete inhibition in the assay. An HI titre of 40 or higher against a particular influenza virus is widely considered to be associated with reduced risk for infection [9]. Our experience is that turkey RBC give more stable results when compared to RBC from other species. We have not used other RBCs in this study. For calculations of geometric mean titres, sera with titres <10 were assigned an HI titre of 5. Differences by age group in the proportion of sera with protective HI antibody titres were analysed for statistical significance using the chi-square and Fisher's exact test. Differences in titres between age groups were analysed using the non-parametric Kruskal–Wallis test. All statistical analyses were undertaken in PASW Statistics 17 (version 17.0.2; SPSS Inc, Chicago).

The influenza A/Indiana/08/2011(H3N2)v virus was provided by the WHO Collaborating Centre for Reference

and Research on Influenza at the National Institute for Medical Research in London (WHO CC/UK) through the WHO Global Influenza Surveillance and Response System (GISRS) under terms applying to the sharing of Pandemic Influenza Preparedness Biological Materials [10]. The virus was grown in Madin-Darby canine kidney (MDCK) cells and used non-inactivated as antigen in the HI assay. All work with the A(H3N2)v virus was performed in a biosafety level 2 facility employing biosafety level 3 procedures and precautions. A/Wuhan/359/1995(H3N2) has not been included in this study, but we plan a more comprehensive study using this virus.

Results

A considerable overall proportion, 40%, of the analysed sera contained antibody to the H3N2v virus with HI titres correlating with protection (HI titre ≥40) (Table 1).

A distinctive age-related pattern was observed. Very high proportions of approximately 71% were seen in people born between the late 1970s and the early 1990s (Figure, panel A). High proportions of 40 to 50% presumably seroprotective antibodies were also seen in the age group born between 1967 and 1976 as well as in persons born in the mid-1950s or earlier. In particular, in children born in 1999 or later, no protective HI titres to the H3N2v virus were seen. Children born in the latter part of the 1990s showed a seropositivity rate of 16%.

Remarkably, the prevalence of seroprotective antibodies to the H3N2v virus was low, with 14%, in people born in the last part of the 1950s and the first part of the 1960s. This low seroprevalence was significantly different from other adult age groups (Table 2). The seroprevalence results were in general also reflected by the pattern of geometric mean titres in the respective age groups (Figure, panel B and Table 1). Statistical significance was reached for many of the differences between age groups in seroprevalence and antibody levels (Table 2).

Discussion

We have investigated the occurrence of antibodies reactive to the influenza A(H3N2)v virus in a serum panel representing all age groups from 0 to 97 years. The finding of a considerable antibody prevalence in persons who were young in the 1990s i.e. those between 18 and 34 years old, is in good agreement with the fact that the haemagglutinin gene of the H3N2v viruses is descended from a human H3N2 antigenic variant that was circulating in the mid-1990s [7], represented by the vaccine virus A/Wuhan/359/1995.

That the young adults had persisting antibody-mediated immunity to virus variants that they presumably were exposed to during their childhood years is not unexpected and is in good agreement with previous observations that have led to or supported the 'original antigenic sin' concept [11].

Our findings are also in agreement with two other recent studies. In sera from a Canadian vaccine study in 2010 it has been demonstrated that antibodies to H3N2v increase with age in children and decreases with age in adults [12]. The subjects of that study, however, did not include children between 10 and 19 years of age or the elderly, and thus could not provide a full age profile of the seroprevalence. Similarly, in a recent study of sera from a US vaccine study in 2010–11 as well as sera from a 2007–08 health survey, children under the age of 10 years had little or no cross-reactive

TABLE 1

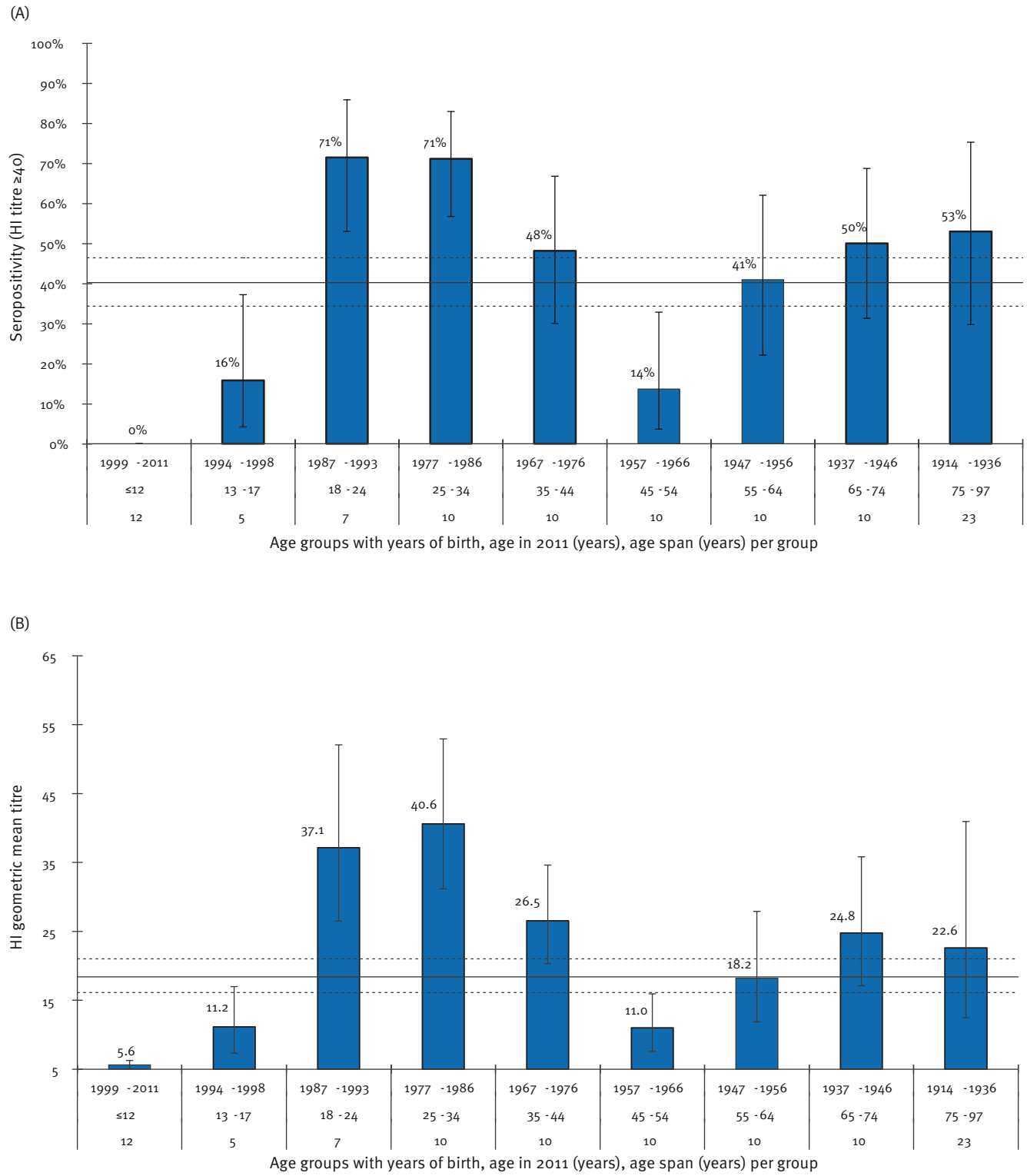
Cross-reactive antibodies to influenza A/Indiana/08/11(H3N2)v virus, by age group, Norway, sera collected in August 2011 (n=253)

Age group (years)	Age span in group	Birth years	n	Sera with HI titre ≥40			Geometric mean titre	
				n	%	95%CI	**Titre**	**95%CI**
0–12	12	2011–1999	47	0	0	–	5.6	(5.1–6.3)
13–17	5	1998–1994	19	3	16	(4–37)	11.2	(7.3–17.0)
18–24	7	1993–1987	28	20	71	(53–86)	37.1	(26.5–52.1)
25–34	10	1986–1977	45	32	71	(57–83)	40.6	(31.2–52.9)
35–44	10	1976–1967	27	13	48	(30–67)	26.5	(20.3–34.6)
45–54	10	1966–1957	22	3	14	(4–33)	11.0	(7.6–15.9)
55–64	10	1956–1947	22	9	41	(22–62)	18.2	(11.9–27.9)
65–74	10	1946–1937	26	13	50	(31–69)	24.8	(17.1–35.8)
75–97	23	1936–1914	17	9	53	(30–75)	22.6	(12.5–40.9)
All ages	–	1914–2011	253	102	40	(34–47)	18.4	(16.1–21.0)

CI: confidence interval; HI: haemagglutinin inhibition.

Figure

Cross-reactive antibodies to influenza A/Indiana/08/11(H3N2)v virus, Norway, sera collected in August 2011 (n=253)



CI: confidence interval; HI: haemagglutinin inhibition.

Panel A: Proportion of sera with HI titre ≥40 in the various age groups with 95%CI (vertical lines). Percent positivity for 'All ages' is shown (horizontal solid line) with 95% CI (dotted lines).

Panel B: geometric mean HI titres by age group. Annotations as for panel A.

antibodies, while some older children and adults had such antibodies [13]. This study did not investigate a continuous age series either, since sera from 50–64 year-old people were missing.

In our study, cross-reactive antibodies to H3N2v were virtually absent in children 12 years and younger, which is also in good agreement with the serological data from Canada and the US. This is consistent with the fact that the influenza A(H3N2) antigenic variant that was predominant in humans in the mid-1990s was, toward the end of the decade, replaced by an antigenically distinct drift variant (represented by A/Sydney/5/1997 and A/Moscow/10/1999) [14]. Individuals born in 1999 or later are thus not expected to have been exposed to the human H3N2 viruses that most closely resemble the current H3N2v virus. As noted by others, almost all recorded human H3N2v infections have occurred in this age group [5,12,13].

However, unexpectedly and not evident in the previous studies from Canada and the US, there was also increasing seroprevalence and increasing mean HI titre with age in the age group older than 50 years. Conversely, there appeared to be a distinct gap in immunity in persons born in the late 1950s or early1960s. We do not have a straightforward explanation for this finding. Persons born before the 1968–70 A(H3N2) pandemic would in general be expected to have a similar history of exposure to H3N2 antigenic variants, i.e. throughout the entire H3N2 era from the 1968 pandemic until today. One could speculate that there may be a certain age span during which individuals are more prone to mount vigorous immune responses to their first infection with a virus, which then dominate over and preclude effective responses against subsequent, antigenically related viruses. Conceivably, individuals who were past that age when they were first exposed to the H3N2 viruses during or after the 1968–70 pandemic

TABLE 2

Statistically significant differences between age groups in cross-reactive antibody titres to influenza A/Indiana/8/11(H3N2)v virus, Norway, sera collected in August 2011 (n=253)

Age in 2011 (years)		≤12	13–17	18–24	25–34	35–44	45–54	55–64	65–74	75–97	Comparison of proportions of sera with HI titre ≥40 between age groups[c]
	Year of birth	1999–2011	1994–1998	1987–1993	1977–1986	1967–1976	1957–1966	1947–1956	1937–1946	1914–1936	
≤12	1999–2011		0.021	<0.001	<0.001	<0.001	0.029	<0.001	<0.001	<0.001	
13–17	1994–1998	<0.001		<0.001	<0.001	0.031	-[a]	-	0.027	0.033	
18–24	1987–1993	<0.001	<0.001		-	-	<0.001	0.044	-	-	
25–34	1977–1986	<0.001	<0.001	-		-	<0.001	0.031	-	-	
35–44	1967–1976	<0.001	0.001	-	0.028		0.015	-	-	-	
45–54	1957–1966	<0.001	-	<0.001	<0.001	<0.001		0.042[b]	0.013	0.014	
55–64	1947–1956	<0.001	-	0.009	0.003	-	-		-	-	
65–74	1937–1946	<0.001	0.006	-	0.037	-	0.003	-		-	
75–97	1914–1936	<0.001	-	-	-	-	0.048	-	-		
	Comparison of HI titres between age groups[d]										

CI: confidence interval; HI: haemagglutinin inhibition.

p values are given for pairs where statistical significance was reached. These positions in the matrix have background colouring. The upper-right triangle contains data for differences in seroprevalence, while the lower-left triangle contains data for the differences in antibody levels.

[a] Not significant (-).

[b] As determined by chi-square test, p=0.088 by Fisher's exact test.

[c] Statistical significance (p values in light green cells) determined by Fisher's exact test.

[d] Statistical significance (p values in light blue cells) determined by Kruskal–Wallis test.

may have mounted a more restrained and adaptable response and thus gradually developed their immunological repertoire in pace with the evolution of the virus, either through adding new epitope specificities or through making antibodies against the most conserved epitopes. Clearly, more research is needed to confirm this observation and to better understand the mechanisms and conditions behind this pattern.

The findings reported here are subject to some limitations. We do not know to which extent the measured cross-reactive antibody in the various age groups correlates with actual protection against infection and illness. A recent study has suggested that the titre needed for protection might be higher for children than for adults [15]. Furthermore, it is widely recognised that the titres determined by the HI test are prone to considerable variation and the proportion of sera with titres above a certain cut-off thus should not be considered as an absolute measure. However, this is not expected to affect the quite substantial relative differences between age groups that are reported here. Finally, immune responses such as cell mediated immunity and antibody against other antigens than those measured by HI have not been assessed.

Conclusions and future work

Our observations provide further knowledge on the possible susceptibility in the population to the current influenza H3N2v viruses. The data support and further extend the previous findings by two recent seroepidemiological studies which did not study the complete range of age groups. The considerable prevalence of cross-reactive antibodies suggests that there may be a limit to the epidemic potential of these viruses in their current form. The highest seroprevalence to influenza A(H3N2)v virus is observed in young adults, consistent with persisting immunity caused by exposure in childhood to antigenically and genetically related viruses that were circulating in humans during the mid-1990s. Seroprevalence is very low in children and adolescents that are unlikely to have been exposed to H3N2 viruses before they had drifted antigenically away from the mid-1990s variant. However, we also find high seroprevalence in the elderly, while, surprisingly, adults born in the late 1950s or 1960s represent a group that appears to have limited immunity against the H3N2v virus. Further studies are warranted to better understand the nature of these differences in immunity between age groups that should have been exposed to the same range of H3N2 antigenic variants albeit at different stages in life.

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Fatal case of human rabies imported to Italy from India highlights the importance of adequate post-exposure prophylaxis, October 2011

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In October 2011, an Indian man resident in Italy was admitted to a hospital in Mantua, Italy with symptoms of acute encephalitis. Due to a recent history of bite by a suspected rabid dog in India, where he had received incomplete post-exposure treatment, rabies was suspected. The patient died after 22 days of intensive care treatment and rabies was confirmed post mortem. This report stresses the need of appropriate post-exposure prophylaxis in rabies-endemic countries.

Case report

An Indian man in his 40s, who had been resident in Italy for 10 years, was admitted to a public hospital in Mantua, Italy, on 23 October 2011, with fever (40.4 °C), malaise, headache, diplopia, unilateral ptosis (left eye), whole body paraesthesia, ataxia, myalgia and flaccid paresis of the arms, especially of the left one. His behaviour appeared abnormal, with signs of anxiety and agitation. While undergoing clinical evaluation and tests, he developed ventricular tachycardia and acute respiratory distress and was therefore intubated, sedated and put under assisted mechanical ventilation.

The patient reported an extensive biting on his left arm and right leg by a dog showing marked aggressiveness, on 28 September 2011 while he was in a suburban area of the city of Manpur, north-east India, visiting relatives and friends. One month after the bite and at the time of hospital admission in Italy, the lesions had become purulent. Immediately after the accident, he had received post-exposure prophylaxis (PEP) in India, consisting of four vaccine injections (on day 0, 3, 6 and 14) with a locally-produced purified duck embryo vaccine against rabies. However, rabies immunoglobulin was not administered. On 17 October, he left from India to Germany, where he visited his sister living in Hamburg. During his stay in Hamburg, until 23 October, he started to experience a generalised weakness.

On the first day of hospital admission, a lumbar puncture was performed and revealed a white blood cell count of 25/µl (normal value: <4/µl), 70% lymphocytes, 20% neutrophils and 10% monocytes, absence of red blood cells, glucose of 86 mg/dl (normal range: 40–70 mg/dl) and protein 97 mg/dl (normal range: 15–60 mg/dl). Complete blood count and routine chemistries revealed a slight increase of leucocytes (11.34; normal: 4.4–11.0 x10^3µl) and moderate hyperglycaemia (125; normal range: 75–100 mg/dl). Progressive metabolic acidosis was also revealed as the blood pH value had decreased from 7.429 to 7.074 within six hours.

Computed tomography (CT) of the head and thoracic radiography performed on the day of hospital admission were normal. The CT was repeated four days later and revealed substantial alteration of the basal nuclei (particularly in the left hemisphere), the thalamus and the cerebral peduncles.

Symptoms and findings from the cerebrospinal fluid (CSF) tests and from the CT were highly indicative of a viral encephalopathy. Due to the clinical findings and to the exposure history, rabies was immediately suspected and diagnostic samples (saliva, skin biopsy, CSF and blood serum) were submitted to the National Reference Laboratory for Rabies at the World Organisation for Animal Health (OIE) Collaborating Centre for Diseases at the Animal-Human Interface, Istituto Zooprofilattico Sperimentale delle Venezie (IZSVe) in Legnaro, Padua (Italy), on 25 October. In the meantime, CSF was tested for the presence of the following bacterial and viral pathogens, either using molecular methods or antigen agglutination: meningococcus, group B streptococcus, *Haemophilus*, pneumococcus, enteroviruses (poliovirus 1-3, Coxsackie A 2-12, 15-18, 20, 21 and 24, Coxsackie B 1-16, echovirus 1-9, 11-15, 17-21, 24-27, 29-33, enterovirus 68-71) JC

polyomavirus, herpes virus simplex 1 and 2, varicella-zoster virus. The presence of specific herpes virus 6 and 8, Epstein-Barr virus and cytomegalovirus DNA, as well as the presence of specific anti-echovirus antibodies were also investigated in the blood. Following all these investigations, the results were negative.

Serological tests performed on both blood serum and CSF at IZSVe gave positive results for specific anti-rabies IgG but results for IgM were unclear, due to the weak fluorescent signal obtained. Viral RNA or viral antigens were not detected in the skin biopsy and saliva specimens (Table).

However, the presence of specific rabies antibodies in the CSF was consistent with the initial suspicion of rabies. A second panel of samples were collected on 27 October and submitted to IZSVe for serological confirmation and viral detection. Tests on the second panel at IZSVe confirmed the previous findings. On 28 October, the patient developed severe coma (Glasgow Coma Scale 3) and was maintained alive by intensive care treatment and mechanical ventilation. The sample panels were sent to the World Health Organization (WHO) Collaborating Centre for Reference and Research on Rabies at the Centers for Disease Control and Prevention (CDC), Atlanta (USA) that confirmed the absence of viral RNA and antigen and the presence of specific IgG and IgM.

Neither rabies vaccine nor immunoglobulin was administered during the hospitalisation. The patient died on 14 November 2011 in hospital.

Post mortem, the entire central nervous system (CNS) was collected and tested for the presence of the virus. Fluorescent antibody testing performed on different portions of the CNS revealed the presence of viral antigen in all regions, and particularly in the cerebellum and thalamus and, to a lesser extent, in the medulla oblongata, the corpus callosum, the hippocampus and in the brain cortex. A similar pattern was revealed by immunohistochemistry on formalin fixed paraffin embedded tissues (Figure 1).

One step RT-PCR and sequencing analysis were performed as previously described [1] on brain tissues and the obtained viral sequences (GenBank accession number JQ845907) were aligned and compared with 92 sequences representative of rabies viruses available

TABLE

Laboratory diagnosis of rabies performed at Istituto Zooprofilattico Sperimentale delle Venezie on samples submitted ante mortem and post mortem, rabies case, Italy, October and December 2011

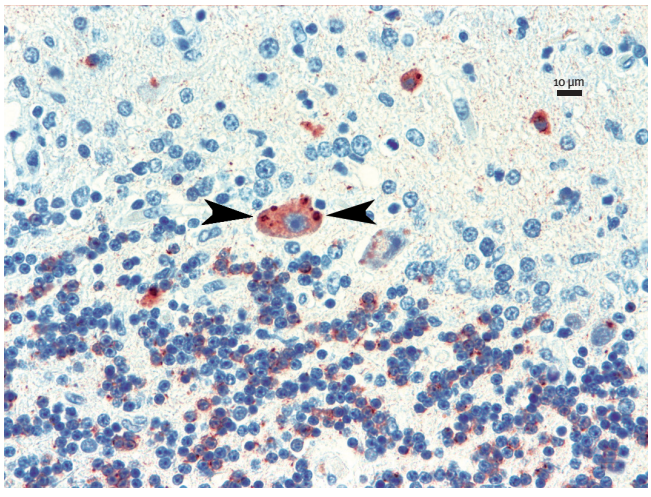
Sample	Method	Result
Samples submitted on 25 October 2011		
Skin	FAT	Negative
Skin	RT-PCR	Negative
Saliva	RT-PCR	Negative
CSF	IFA test for IgG	Positive
CSF	IFA test for IgM[a]	Positive
Blood serum	IFA test for IgG	Positive
Blood serum	IFA test for IgM[a]	Positive
Samples submitted on 27 October 2011		
Skin	FAT	Negative
Skin	RT-PCR	Negative
Saliva	RT-PCR	Negative
Saliva	RT-PCR	Negative
Saliva	RT-PCR	Negative
Saliva	RT-PCR	Negative
CSF	IFA test for IgG	Positive
CSF	IFA test for IgM[a]	Positive
Blood serum	IFA test for IgG	Positive
Blood serum	IFA test for IgM[a]	Positive
Samples submitted on 7 December 2011		
CNS	FAT	Positive
CNS	RT-PCR	Positive

CNS: central nervous system; CSF: cerebrospinal fluid; FAT: fluorescent antibody test; IFA: immunofluorescent-antibody.

[a] Serological tests were positive for specific anti-rabies IgG but unclear for IgM both in blood serum and CSF. Results obtained from samples submitted ante mortem were confirmed by further investigation at the Centers for Disease Control and Prevention (Atlanta, USA).

FIGURE 1

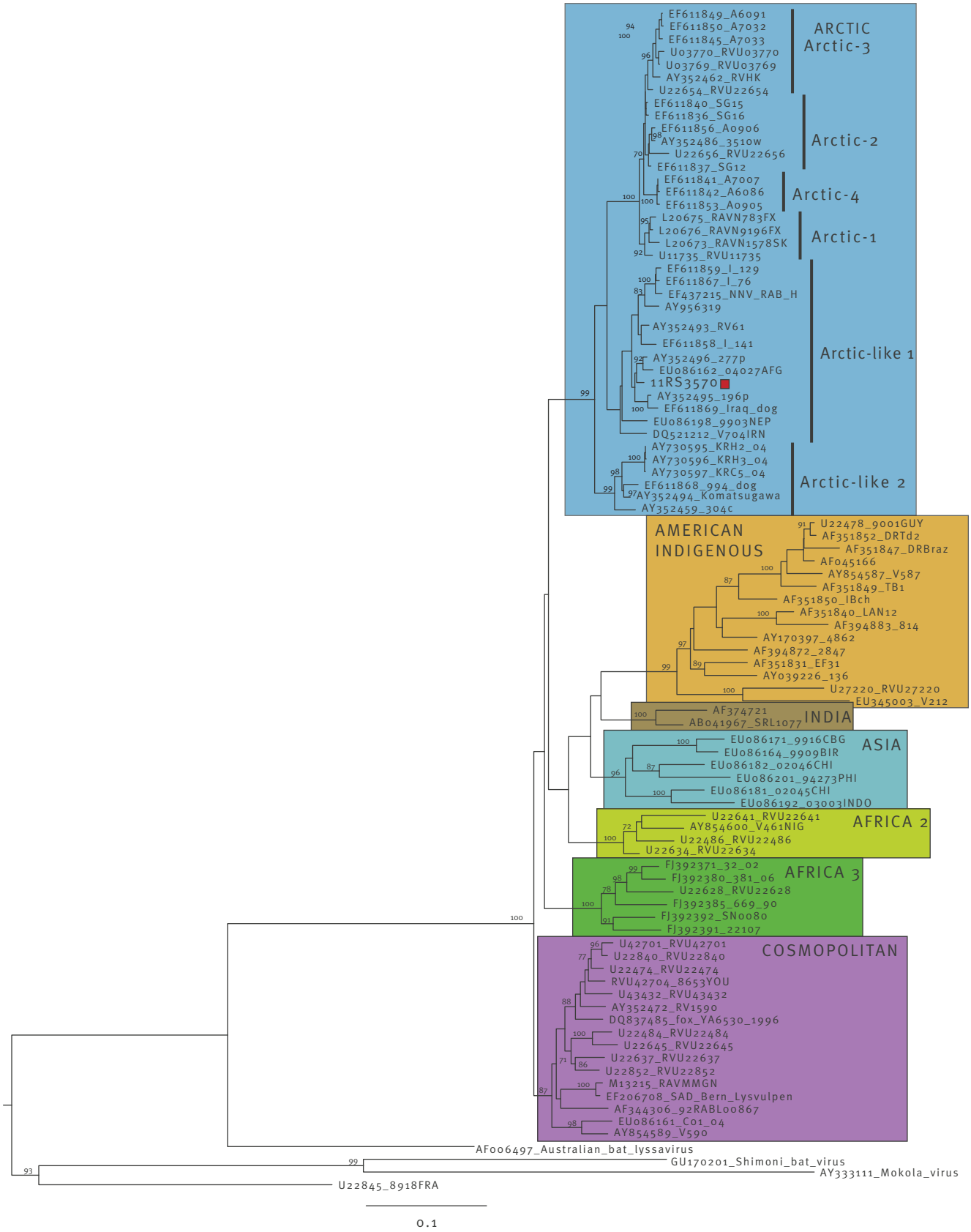
Fine granular staining and Negri bodies within the cytoplasm of a Purkinije cell in cerebellum positive for rabies viral antigen, rabies case, Italy, 2011



Fine positive staining is present also in the granular cell layer. Immunohistochemistry, EnVision FLEX/HRP, diaminobenzidine (DAB) as chromogen and hematoxylin counterstain.

Figure 2

Maximum likelihood phylogenetic tree[a] estimated for the partial N gene sequence of the imported human rabies case (11RS3570[b]) from India to Italy, October 2011



[a] Using PhyML version 3.0.

[b] GenBank accession number JQ845907.

The red square indicates the isolated strain.

A bootstrap re-sampling process (1,000 replications) employing the neighbour-joining method was used to assess the robustness of individual nodes of the phylogeny. Bootstrap values are indicated as numbers at the nodes.

in GenBank. The phylogenetic analysis confirmed that the virus causing the infection belonged to the Arctic-like 1 lineage of the rabies virus (RABV) circulating in southern Asia, northern India and the Middle East [2] (Figure 2).

Risk assessment for contacts

A risk assessment was carried out for health professionals who might have been in contact with the case. Although human-to-human transmission has never been documented in a healthcare setting, transmission of rabies virus could occur if open wounds or mucus membranes were contaminated with infected saliva or neural tissue. In the case described here, hospital staff had adhered to standard infection control procedures and did not require the administration of PEP.

The sister of the patient living in Hamburg was contacted and, following a risk assessment, she undertook PEP.

Conclusions

Laboratory diagnosis of rabies ante mortem is generally based on the detection of the viral antigen or RNA in a skin biopsy from the neck base, or from saliva and by detecting specific rabies antibodies in serum and CSF. However, viral antigen and RNA are rarely detected intra vitam because of low viral replication in peripheral nerves and intermittent excretion in saliva. Detection of specific rabies antibodies in serum samples can be a result of previous vaccine administration or of exposure to any lyssavirus, and thus, cannot be considered alone as confirmatory diagnostic tool. In this case, ante mortem laboratory diagnosis was complicated by the administration of post-exposure vaccine, which inevitably yields the production of specific antibodies. However, the detection of specific immunoglobulins in CSF, IgG and particularly IgM, was strongly indicative of rabies, if combined with anamnestic and clinical data. Diagnosis was performed post-mortem and was conclusive of fatal rabies. A summary of this case was reported through ProMED-mail on 6 February 2012 [3].

This is the 23rd case of imported human rabies in the European Union (EU) in the last 20 years (since 1992 [4,5]), and the fourth in Italy since 1975. The most recent infection in the EU was reported in August 2011 in a woman who was bitten by a dog in Guinea Bissau three months before developing symptoms while in Portugal [5]. In Italy, the most recent cases were imported from Asia, specifically from India and Nepal [6-8]. According to WHO data, the Indian subcontinent is affected by a high number of human deaths caused by rabies, most of them following the bite of a domestic dog (from about 1.7 to 3.3 per 100,000 population and more than 20,000 deaths per year) [9,10]. Efforts in raising public awareness and improving medical infrastructures are being carried out in several rabies-endemic countries including India [10], and it is also essential to ensure that the full range of products for PEP is available for residents and travellers.

Travellers should be informed of the risks before travelling in an area endemic for rabies. Pre-travel advice and further decision to apply preventive vaccination are based on several factors including: a risk assessment based on the duration of stay, the likelihood of engagement in risky activities, the age of the traveller, the rabies endemicity and access to appropriate medical care in the country of destination. However, information on the latter two is generally poorly available for endemic countries [11]. In the case described here, the patient likely lacked of pre-travel consultation, nevertheless he sought and underwent immediate PEP in India. Unfortunately, PEP was incomplete as rabies immunoglobulin was not administered. This was likely the cause of spread to the CNS, which resulted in the patient's death. In most cases, appropriate PEP is successful and can prevent infection and death of the patient. However, a recent publication reviewing the management of PEP in injured travellers indicates that vaccine and immunoglobulin are often unavailable or improperly administered abroad [11], as the case presented herein may confirm.

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Case registry systems for pandemic influenza A(H1N1) pdm09 in Europe: are there lessons for the future?

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Countries across Europe developed a range of database systems to register pandemic influenza A(H1N1) pdm09 cases. Anecdotal reports indicate that some systems were not as useful as expected. This was a cross-sectional, semi-structured survey of health professionals who collected and reported pandemic influenza A(H1N1)pdm09 cases in 23 countries within the 27 European Union (EU) Member States plus Norway. We describe here the experiences of using pandemic case register systems developed before and during the pandemic, whether the systems were used as intended and, what problems, if any, were encountered. We conducted the survey to identify improvements that could be made to future pandemic case registers at national and EU level. Despite many inter-country differences, 17 respondents felt that a standardised case register template incorporating a limited number of simple standard variables specified in advance and agreed between the World Health Organization and the European Centre for Disease Prevention and Control could be useful. Intra- and inter-country working groups could facilitate information exchange, clearer system objectives and improved interoperability between systems.

Introduction

After the Single European Act of 1986, the European Commission pushed for better collaboration between national sentinel systems for infectious disease surveillance, establishing 'Eurosentinel' in 1989 [1]. This international sentinel network of general practitioners included surveillance of influenza-like-illness (ILI) and acute respiratory infection (ARI). Since then, ILI and ARI surveillance have become well established in Europe and many European Union (EU) Member States have developed sophisticated surveillance systems for influenza and other infectious diseases [2-4]. Since September 2008, national ILI/ARI data, virological data and other indicators from all 27 EU Member States plus Iceland and Norway have been reported on a weekly basis to the European Centre for Disease Prevention and Control (ECDC). The novel influenza A(H1N1)pdm09 pandemic of 2009 posed a range of new challenges, however [5], and evaluations of pandemic preparedness and response are still ongoing at regional, national and multinational level. Many focus on the high-level strategic management aspects of the pandemic, while others look more specifically at vaccination and antiviral strategies, surveillance, communications and cross-sectoral working [6]. In this survey, we focus on the challenges encountered with both new and established pandemic influenza case registration systems by the professionals within public health institutions of EU Member States and Norway, who were charged with collecting, analysing and reporting on the 94,512 influenza A(H1N1)pdm09 cases in the first three months of the pandemic [7] (and many more thereafter).

The rationale for this study was the experience with case registration in the Netherlands, heretofore undescribed: at the onset of the pandemic, a newly developed data warehouse known as Pandora (Pandemic Research Application) was trialled as a pandemic case register. Pandora was originally developed in response to the avian influenza A(H7N7) outbreak that occurred in the Netherlands in 2003 [8]. It was designed to facilitate outbreak control and research through comprehensive data collection from clinical, laboratory, hospital, public health and agricultural sources and also to facilitate data linkage at an individual level. It was not fully operational at the onset of the influenza A(H1N1)pdm09 pandemic and the operating system failed when it was used as a real-time case registration system. It had to be abandoned in the early phase of the outbreak, but was later used successfully to record hospitalisation data during the pandemic and is now operational and on standby for avian influenza outbreaks, as originally intended.

Anecdotal reports indicate that in some other European countries, complex database systems were also developed to register influenza cases that were subsequently not used at all, not used immediately, or did not provide the necessary information during the pandemic. We hypothesised that countries using case registers that were well established pre-pandemic

were less likely to experience problems scaling them up than those that developed new systems. Our aim was to ascertain whether other countries successfully managed comprehensive data linkage within their pandemic case register and whether a single system could successfully meet the competing information needs of stakeholders. Our objectives were to describe – from the perspective of the system user – experiences of using pandemic case register systems developed before and during the pandemic, whether the systems were used as intended during the pandemic and what problems, if any, were encountered. The survey was conducted with a view to identifying improvements that could be made to future pandemic case registers at national and EU level.

Methods

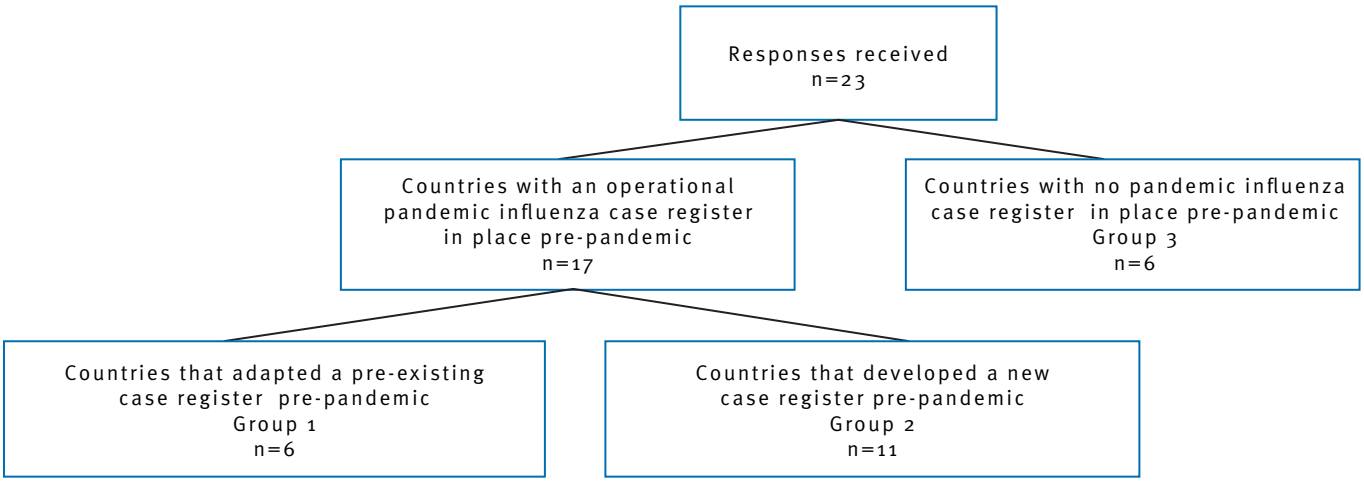
A cross-sectional survey was conducted in June and July 2010, which included 30 countries within 27 EU Member States (England, Wales, Scotland and Northern Ireland were approached separately) plus Norway. Fellows who were training with the European Programme for Intervention Epidemiology Training (EPIET), placed at national centres for surveillance and control of communicable diseases across the EU, identified one senior person in their institute with direct experience of the pandemic case registration system in that country. Following initial email contact, two follow-up reminder emails were sent, and if no response was received, the EPIET fellow recommended an alternative contact person. Respondents were guaranteed anonymity, unless the respondent gave permission for their country to be named.

The survey was conducted by electronic questionnaire using QuestBack software [9]. Questions, in English, related to the purpose and content of the case registration system (objectives, data sources, data collected and means of collection), professional groups involved (in developing the system and data collection, aggregation and reporting), necessary adaptations and ultimately a description of the systems used, problems encountered and lessons learnt. The questionnaire was first piloted with four senior, multilingual health professionals working in national public health institutes across Europe for whom English is not their first language. It was semi-structured and divided into two sections: (i) relating to the pandemic influenza case register in place before pandemic phase 4 was declared by the World Health Organization (WHO) on 27 April 2009 and before the first case of influenza A(H1N1)pdm09 was confirmed in their country (hereafter referred to as 'pre-pandemic') and (ii) relating to the pandemic influenza case register or other additional/supporting systems or software used after the first case was confirmed. Sections i and ii comprised 15 and 10 questions, respectively, and the questionnaire took approximately 10 minutes to complete. Response options were dichotomous (yes/no), Likert-type scales and open-text fields. Descriptive analysis was conducted on qualitative data.

Using the approach of Baker et al. [10], case register objectives were classified as control focused or strategy focused. They were considered control focused if they were necessary for the monitoring and management of healthcare systems and other services

Figure

Flow chart of 23 respondent countries[a] in survey on case registry systems for pandemic influenza A(H1N1)pdm09 in Europe and their status regarding having a pandemic influenza case register pre-pandemic[b], June–July 2010



[a] Belgium, Bulgaria, Cyprus, England, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Romania, Scotland, Slovakia and Sweden.

[b] 'Pre-pandemic' refers to before pandemic phase 4 was declared by the World Health Organization on 27 April 2009 and before the first case of influenza A(H1N1)pdm09 was confirmed in their country.

internally within the country. Objectives were classed as strategy focused if they supported prevention strategies to reduce population health risk. Control-focused and strategy-focused objectives are, of course, not mutually exclusive and one can inform the other.

Univariable analysis (using Pearson chi-square test) was conducted using Stata 11.1. Probability of p≤0.05 was considered statistically significant.

Results

Of the 31 countries contacted, 23 responded to the questionnaire: Belgium, Bulgaria, Cyprus, England, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Romania, Scotland, Slovakia and Sweden. Six respondents were heads of department (at an epidemiology or surveillance of infectious diseases unit) nationally or at state level, seven were epidemiologists and four were public health doctors or medical officers. Nine described their principle role as one of coordination or management within their department, and about half of the respondents (n=12) had a responsibility in relation to surveillance, data analysis and reporting. Only one respondent reported a role in making recommendations and one described a role in public relations.

A total of 17 responding countries reported having an operational pandemic influenza case registration system in place pre-pandemic, of which 11 developed a new system in advance and six adapted an existing register, including the seasonal influenza registration system (n=3) and other infectious disease surveillance systems (n=2). Six countries did not have a pandemic influenza case register prepared pre-pandemic (Figure). We divided responding countries into terciles based on per capita gross domestic product, but did not find any difference in countries' state of readiness whether they had a system in place pre-pandemic or not (data not shown).

Countries with an operational pandemic influenza case register in place pre-pandemic (n=17)

Countries with a pandemic influenza case register in place pre-pandemic were divided into those that adapted an existing system (n=6, Group 1) and those that developed a new one (n=11, Group 2). All 17 of these countries reported that clear objectives were defined in advance (Table 1). All respondents reported at least one control-focused objective and one strategy-focused objective, but Group 1 countries were more likely than those in Group 2 to report 'to inform strategies to prevent/reduce mortality and morbidity' as an objective (Pearson chi-square statistic: 3.61; p=0.05).

Involvement of experts in the development of the register was variable (Table 1) and no statistically significant

TABLE 1

Respondent countries with a pandemic influenza case register developed pre-pandemic[a] (n=17): objectives and professional groups involved in its development, survey on case registry systems for pandemic influenza A(H1N1) pdm09 in Europe, June–July 2010

Objectives of case register and professional groups involved in its development	Number of respondent countries n=17
Objectives specified (answered by the 17 countries)[b]	
Control-focused objectives	
To count cases and track the number of cases occurring over time	16
To track cases geographically	15
To follow individual cases over time, documenting outcome (death, hospitalisation, etc.)	15
To conduct contact tracing	11
Strategy-focused objectives	
To inform strategies to prevent/ reduce mortality and morbidity	13
To maintain virological surveillance	12
To record detailed information about all cases	11
To record detailed information about early cases only	9
Other[c]	3
No clear objectives specified	0
Professional groups involved in developing the register (answered by the 17 countries)[b]	
Epidemiologists	16
Information technology specialists (health-/public health-focused)	12
Health/public health specialists (e.g. physicians, nurses)	10
Laboratory experts (e.g. virologists)	8
Infectious disease doctors	8
Health service managers/planners	6
Information technology specialists (non-health related)	4
General practitioners	4
Other	0

[a] Pre-pandemic refers to before pandemic phase 4 was declared by the World Health Organization on 27 April 2009 and before the first case of influenza A(H1N1)pdm09 was confirmed in their country.

[b] Multiple answers were possible.

[c] Other objectives were: to collect symptoms, travel history, demographics and treatment provided, to record detailed information about fatal cases with influenza A(H1N1)pdm09, and to monitor antiviral therapies and vaccination status among cases and to estimate transmission parameters and effectiveness of interventions.

difference was found between the involvement of the various professional groups.

Data sources and data collection

Data sources used, means of data entry and state of readiness for use are reported by group in Table 2. There was no statistically significant difference between Groups 1 and 2 in the number or nature of data sources accessed or the means of data entry. Where data were entered manually, software used included EpiData (n=2), Microsoft Excel (n=2), Microsoft Access (n=2), dBase (n=1) and MySQL open source database [11] (n=2).

Four respondents in Group 1 provided details of their country's register (Box 1). Brief descriptions provided by respondents in Group 2 are in Box 2.

System readiness pre-pandemic

In five of the six respondent countries that adapted a pre-existing case register before the pandemic (Group 1), the systems were live and ready for use pre-pandemic. In countries where the system was not ready for use immediately on confirmation of the first case in the country, the system was ready within five days in one country, within 30 days in two countries (paper records were kept until the system was ready in one country) and within two months and six months for recording of cases and deaths, respectively in one country.

Necessary system modifications

Overall, 16 of the 17 countries with an operational pandemic influenza case register in place pre-pandemic reported that they used their new or adapted system during the pandemic (one country had to abandon their

TABLE 2

Development of case registers pre-pandemic[a] by 17 respondent countries (Groups 1 and 2) during the influenza pandemic, survey on case registry systems for pandemic influenza A(H1N1)pdm09 in Europe, June–July 2010, June–July 2010

Development of case registers		Number of respondent countries n=17	
		Group 1 Adapted pre-existing case register before pandemic (n=6)	Group 2 Developed new case register before pandemic (n=11)
Data sources used[b]			
Laboratory reports		6	10
National notifiable infectious disease database		6	6
Hospital admission information		5	7
Regional case reports		3	6
Sentinel network of physicians		4	4
Other		0	2
Means of data entry			
Entered automatically		1	3
Entered manually		2	1
A combination of both of the above		3	7
State of readiness			
Was the system live and ready for use before the World Health Organization declared pandemic phase 4 (27 April 2009)?	Yes	5	2
	No	1	6
Was the system live and ready for use before the first influenza A(H1N1)pdm09 case was confirmed in your country?	Yes	5	8
	No	1	3
Modification of the register			
Was the case register modified at any point?	Yes	1	7
	No	5	3

[a] Pre-pandemic refers to before pandemic phase 4 was declared by the World Health Organization on 27 April 2009 and before the first case of influenza A(H1N1)pdm09 was confirmed in their country.

[b] Multiple answers were possible.

Box 1

Overview of case registration systems, provided by four respondent countries in Group 1[a], survey on case registry systems for pandemic influenza A(H1N1)pdm09 in Europe, June–July 2010

Germany
In Germany, the multistate electronic reporting system for communicable diseases (SurvNet [12]) was used. This is a physically distributed, dynamic database used by all local health departments, state health departments and the Robert Koch Institute, the national agency for infectious disease epidemiology. The database is characterised by a number of highly standardised, core questions, but it incorporates responses to questions in free-text format in order to obtain additional information about risk factors, therapy, etc. from cases.

Sweden
A detailed description of pandemic influenza A(H1N1) pdm09 surveillance in Sweden is available [13]. Briefly, a comprehensive regional/national system for communicable disease surveillance called SmiNet-2 has been developed [2]. This web-based system allows for reporting from physicians (via an online form) and laboratories (directly from the laboratory data system). Random, population-based reporting was also conducted in Stockholm via a telephone- or Internet-administered cohort study ('SickReport', described in detail elsewhere [3]), in which approximately 5,500 people participated during the pandemic. Surveillance of influenza-related web queries on a medical advice website [14] was conducted via an automated system that used statistical modelling to estimate the proportion of patients with influenza-like illness also described in detail elsewhere [15,16]). Other systems used in Sweden included aggregated voluntary laboratory reporting of the number of samples analysed for influenza virus infection and the proportion positive, voluntary reporting of severity of influenza illness from a register within intensive care departments called 'Intensive care of influenza cases in Sweden' (IRIS), reports of deaths from pathologists and the official death registry, and weekly reports on use of antivirals and vaccine coverage from the county medical officers (Smittskyddsläkarna) of the Swedish Institute for Communicable Disease Control (SMI) .

Ireland
In Ireland, the web-based 'Computerised Infectious Disease Reporting' (CIDR) information system was used [4]. This is a shared national information system for the regional health departments, the Ministry of Health, the Health Protection Surveillance Centre and other partners.

Finland
In Finland, several surveillance systems were used [17]. These included the national infectious disease register, notifications of clusters of influenza (via doctors responsible for communicable disease control in healthcare districts); influenza-like or influenza-related illnesses reported by selected primary healthcare centres in all healthcare districts, case-based surveillance (including details of symptoms and recent travel), hospital surveillance (daily number of patients hospitalised and total number of inpatients in general wards and in intensive care units with confirmed or suspected Influenza A(H1N1)pdm09 infection), virological surveillance and mortality surveillance.

[a] Respondent countries that adapted a pre-existing case register before the influenza pandemic.

new system during the pandemic because it could not be adapted to the new situation in time). In Group 1 (countries that adapted a pre-existing case register before the pandemic), five of the six respondent countries were able to use their system effectively without modification. In Group 2 (countries that developed a new case register before the pandemic), seven of the 11 respondent countries had to modify the system after a variable number of cases were confirmed (mean: 418 cases; range: 1–1,200). Reasons for modifying or abandoning the system are in Box 3. There was no statistically significant difference between the professional groups involved in system development and successful implementation of the system.

Of the 17 countries with an operational pandemic influenza case register in place pre-pandemic, 12 reported using more than just the case register. Other systems used in tandem with the case register were Microsoft Excel (n=4, which one respondent reported was used to record the very earliest cases before switching

Box 2

Overview of case registration systems, provided by five respondents in Group 2[a], survey on case registry systems for pandemic influenza A(H1N1)pdm09 in Europe, June–July 2010

We collected individual data on everyone who was swabbed in our country during the pandemic. We had a separate database for those who required antivirals and those who took the influenza vaccine and also for our sentinel surveillance.

We connected our notification system with the (central and peripheral) laboratory systems, together with the questionnaires that were developed for studies among patients and contacts.

We had several systems for different purposes and times. The First Few 100 (FF100) database was for detailed follow-up of 392 cases and their contacts (this was an online Postgre SQL database [18]). Along side this, we had a less detailed national dataset (the 'Whiteboard') of all confirmed cases which occurred (e.g. all FF100 cases were on the Whiteboard but not vice versa), this was initially an Excel spreadsheet until an online SQL database could be built. This housed data until 1 July 2009 when we stopped our containment phase. Case data was also on another on-line system (which had been developed and rolled out to local health protection teams during the containment phase so ran in parallel to the Whiteboard for a while). This included discarded (negative) cases and was also used for case management locally.

Our case tracking system consisted of (a) notification of laboratory-confirmed severe cases who were hospitalised (b) laboratory reporting of influenza A(H1N1)pdm09 cases, (c) sentinel surveillance of influenza-like illness, including a clinical and a laboratory component.

Multiple sources for the first 200 cases: communicable disease web-based reporting system NAKIS. Laboratory reporting system, sentinel providers reporting system and hospital admission system were additional.

[a] Respondent countries that developed a new case register before the pandemic.

to the national case register database, and another reported using for cases of severe acute respiratory infections), Microsoft Access (n=2, which was reportedly used for collecting data on enhanced surveillance of pandemic cases in intensive care units, for monitoring all cause deaths, pneumonia and influenza deaths, and for monitoring sentinel general practice ILI and virological surveillance), Microsoft Word (n=1) and a paper-based system (n=3), which one country reported for a few weeks at the very outset of the pandemic in their country.

Countries with no pandemic influenza case register pre-pandemic (n=6)

Six countries had no pandemic influenza case register in place before the first case of influenza A(H1N1) pdm09 was confirmed in their country. The systems used instead included Microsoft Word (n=3), Microsoft SQL (n=1), a paper-based system (n=3), Microsoft Access (n=1) and Voozano [19] (n=1). Respondents' brief descriptions of the systems used are shown in Box 4.

Suggestions for future pandemic case registers

Respondents were asked what they would change about the way cases were tracked when developing a system for a future pandemic. In countries where an existing national system was adapted (n=6) there were few suggestions for improvement, but one comment was *'Incorporate a contact tracing functionality for early cases in the containment phase'*. In countries developed a new system pre-pandemic (n=11), comments predominantly related to simplification of the reporting forms and automatic data collection (Box 5).

Usefulness of a standardised case register developed at EU level

Finally, respondents were asked if they would find it useful if a standardised case register template was developed at the European level for use in future pandemics. Of the 23 respondents, 17 thought that this could be useful, with one respondent noting that it would allow comparison of information between countries and evaluation at EU level, and another that if such a register was also compliant with WHO requirements, it could avoid double reporting. However, some respondents expressed reservations (Box 6).

Box 3

Reasons for modifying or abandoning the case registration systems in place before the pandemic, provided by seven respondents in Groups 1 and 2[a], survey on case registry systems for pandemic influenza A(H1N1)pdm09 in Europe, June–July 2010

The system was too complex to use, users were not familiar enough with system.

The system crashed after the inclusion of around 20 suspect cases (so actually before the first confirmed case). Problem was that it had been tested for around 10 cases, that worked fine, but after 20 it technically shut down due to the overload of information. Too complex, too slow.

It was not flexible to changing demands.

At the beginning of the pandemic we developed a system for epidemiological investigation of every confirmed case. After the first 1,000 cases it was impossible to manage contact tracing of all confirmed cases and we adopted a more simple form to be filled in only for confirmed cases that were to be a fraction of ILI cases diagnosed by hospitals and GPs.

The continuation of enhanced surveillance of influenza A(H1N1)pdm09, including contact tracing around cases, would be inadvisable as case counts increased. Under such circumstances it was exceedingly difficult to maintain this practice, and its public health benefit was doubtful. On 15 July 2009 we moved to a mitigation phase, which was communicated as 'patient protection phase'. In this phase, contact tracing was discontinued and the recommendation for chemoprophylaxis of all close contacts was withdrawn. Surveillance shifted to: a) notification of laboratory-confirmed severe cases who were hospitalised, b) laboratory reporting of influenza A(H1N1)pdm09 cases, (c) sentinel surveillance of influenza-like illness, including a clinical and a laboratory component.

Modifications had to be made due to the gap of reporting demands of WHO and ECDC.

The necessity to include additional indicators.

ECDC: European Centre for Disease Prevention and Control; GP: general practitioner; WHO: World Health Organization.

[a] Group 1: respondent countries that adapted a pre-existing case register before the influenza pandemic. Group 2: respondent countries that developed a new case register before the pandemic.

Discussion

In this paper, we describe the case registers developed before and during the influenza pandemic in European countries in order to support planning for case registry systems for future pandemics. Not surprisingly, countries that made use of a pre-existing, standardised national computerised surveillance tool that was pretested, live and ready for use before the pandemic reported relatively few problems and five of six such countries used their system without modification. In countries that started to develop a new system before the pandemic, five were live and ready for use by the time WHO declared a pandemic and a further five were ready by the time the first case was confirmed in their country.

All countries with an operational system in place pre-pandemic reported that the system was designed to meet a variety of control and strategic objectives, with a clear emphasis on national monitoring. Countries that developed a new system were less likely to report prevention or reduction of morbidity and mortality as a strategic objective than countries with a well-established surveillance system, although we were unable to investigate this further.

Even at national level, the process seems to have been complicated, with new systems incorporating data from multiple sources in multiple formats. Seven countries had to modify their system, mainly because it was

Box 4

Brief description of case registration system provided by four respondents in Group 3[a], survey on case registry systems for pandemic influenza A(H1N1)pdm09 in Europe, June–July 2010

We had no system - we could not succeed in developing a common tool … The questionnaire was based on [that provided by] WHO (not adapted to the situation) and was too long. When it was ready it was no longer useful. Instead we used Excel and then relied on sentinel surveillance.

Primary health centres reported to the regional Public Health centres, which further reported to the national level.

Before the pandemic, we worked on a tracking system and were waiting for funds to set it up. It helped us to set up a system in few days. The database could then be shared by national and local representatives of the institute and with major partners. Therefore management of cases and analysis in real time could be done with the same tools.

We did not have a case tracking system during the pandemic. To register the cases we used the WHO form for case-based data collection. This form was filled in by hand and was sent back by fax from Ministry of Health.

WHO: World Health Organization.

[a] Respondent countries with no pandemic influenza case register in place pre-pandemic.

too complex, difficult to manage, inflexible or system users were not familiar with it. In one country, the new system was abandoned due to its incapacity to handle large amounts of case data. In some countries where the recording systems had not been developed before the pandemic, attempts were made to develop a common tool, but time and financial pressures seem to have been a limiting factor.

Clear themes emerged as to how international monitoring and communication could be improved and 17 respondents agreed that a standardised case register template developed at European level would be useful. The respondents suggested firstly, use of a limited number of simple standard variables, specified in advance and agreed between WHO and ECDC (to ease data collection requirements) and secondly, a distributed or web-based data collection tool (to facilitate data transfer to WHO and ECDC and inter-country comparison).

The efficiency of electronic data transmission during the international severe acute respiratory syndrome (SARS) outbreak in 2003 has previously been described [20]. Krause et al. also advocate (and respondents in our survey largely agreed) that flexible, scalable systems, capable of coping with large quantities of data must be available to deal with new global epidemics as the characteristics of the disease, the organism and

Box 5

Suggestions for improving case registration systems in countries that experienced difficulty with their system during the influenza pandemic, provided by 15 respondents in Groups 2 and 3[a], survey on case registry systems for pandemic influenza A(H1N1)pdm09 in Europe, June–July 2010

Simplify the form at the beginning.

Develop a separate simpler system (fewer variables), different from the one we used.

Develop a much simpler system, because it's very likely that you have to adapt your system anyway. MS Access will probably be enough. Merging of datasets can be done as you go along, you don't have to prepare all this automatically in advance.

It will be useful to use [a] standardised case register template.

Standard variables with in-built validation rules, easier linkage between systems.

It would be better to have had a dedicated outbreak database already in existence. Setting up a database for use at such short notice was not ideal.

Making it automatically fed, not manually.

What would have helped if the information could have just been transported to WHO/ECDC data bases with just a click of a button.

We would use web based system only (not paper based).

We need to have the national legal basis in place beforehand. We would want to integrate a system for surveillance of serious cases, including hospital admissions and deaths.

I would design a standard tool for the whole country – I would not record cases in Excel again.

Reporting forms should be ready beforehand. Population based surveillance to get data must be more firmly established beforehand. A vaccination register for continuous follow up of efficacy and side-effects is a must.

In our small country our system worked efficiently enough for tracking the cases, just the computer-based data transfer would be simpler. There are plans to include the creation and introduction of computerised data flow system for influenza to the national influenza plan.

It would be better to have had a dedicated outbreak database already in existence. Setting up a database for use at such short notice was not ideal.

I would like to use a web based information system for tracking the cases.

ECDC: European Centre for Disease Prevention and Control; MS: Microsoft; WHO: World Health Organization.

[a] Group 2: Countries that developed a new case register pre-pandemic. Group 3: countries with no pandemic influenza case register in place pre-pandemic.

the outbreak emerge. Not all respondents in our survey, however, were convinced that a common register would be easily implementable, pointing to the different requirements and capacities of countries' healthcare systems locally and nationally, and at EU level, and the lack of data comparability between countries within existing systems.

There were a number of limitations in this study: firstly, the questionnaire was distributed in English, and there may have been issues with interpretation and response (although the questionnaire was pretested with a number of colleagues across Europe for whom English is not their first language). Secondly, it would have been useful to define direct and indirect costs related to staffing and resources required to operate and maintain different systems, but given the lack of any standard measure, we were unable to obtain this information. Finally, it remains unclear why countries internally experienced such surveillance difficulties. These could have been due to pressure on staff, as other essential services had to be maintained. Or there may have been excessive or unclear expectations by local or national managers and decision-makers, or it may reflect inherent deficiencies within the case-register system. Also, in relation to international monitoring and communication, although respondents clearly felt the process needed to be simplified, we did not ascertain what their expectations at the European level would be and why. These are clearly issues that warrant further investigation.

Overall, respondents saw the value of pre-pandemic planning and standardisation of data collection and data linkage at the national level at the very least. Given the wealth of experience gained in this pandemic, intra- as well as inter-country working groups could facilitate information exchange and improved interoperability between systems in the future. Also, given the requirement under the International Health Regulations (2005) [21] that countries report certain disease outbreaks and public health events to WHO, and given the partnership between EU Member States, European Economic Area (EEA)/European Free Trade Association (EFTA) countries and ECDC [22], clear objectives for monitoring of influenza at EU level with a minimum set of indicators should be agreed.

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Box 6

Concerns expressed by eight respondents regarding development of a standardised case register at European Union level, survey on case registry systems for pandemic influenza A(H1N1)pdm09 in Europe, June–July 2010

Four respondents thought it could be useful

[It] depends on what it will contain. We don't need it but for EU standardisation we need case definitions and guidance as to data validation, to get comparable data.

Yes, potentially useful. However, it will need to be flexible to adapt rapidly and in a short space of time to the characteristics of the new emergent flu organism identified.

Yes but unfortunately, different administrative level authorities often demand more specific tools.

Yes, providing that it would be possible for us to adapt it.

Four respondents did not think it would be useful

Probably not. We want the system to be integrated with our already existing systems.

Personal opinion: generally preferred, but in reality not feasible, and at the end: you would not gain comparable data because of the different health systems.

Not totally convinced.

Not necessary, each country should develop its own depending on its capacity and local conditions.

EU: European Union.

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