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Group A streptococcal infections during the seasonal influenza outbreak 2010/11 in South East England

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We present a series of 19 cases of invasive Group A streptococcal (iGAS) infection reported to the Thames Valley Health Protection Unit from 1 December 2010 to 15 January 2011. Ten patients died and a prodrome of influenza-like illness was reported in 14 cases. Influenza B co-infection was confirmed in four cases, three of which were fatal. Our report provides further evidence that influenza B co-infection with iGAS has the potential to cause significant morbidity and mortality.

On 10 January 2011, the United Kingdom (UK) Chief Medical Officer issued a statement advising primary and secondary care doctors to remain vigilant to the possibility of severe bacterial co-infection in patients with influenza [1], because preliminary data indicated an increase in bacterial diseases known to cause co-infection with influenza.

Streptococcus pyogenes, a Lancefield group A streptococcus, is known to be one of the major pathogens causing severe systemic disease during seasonal and pandemic influenza outbreaks. Invasive group A streptococcal (iGAS) disease is notifiable in the UK, and the infection has become a public health issue since the resurgence of invasive disease in the late 1980s [2].

Because iGAS has an increased incidence in winter months, it has been suggested that this may be related to seasonal influenza [2]. As reported by the World Health Organization (WHO) on 14 January 2011 [3], the current seasonal influenza outbreak has resulted in increased consultation rates across northern and western Europe. The WHO sentinel practices reported that 44% of swabs were positive for influenza. Of these, 74% were influenza A and 26% influenza B.

Since the start of the influenza season, we have noted a marked increase in iGAS disease in the Thames Valley area (Oxfordshire, Buckinghamshire and Berkshire) of South East England, with a catchment population of 2.2 million people (Figure). At the same time, a similar rise in iGAS incidence was noted across the whole of England as described by Zakikhany *et al*. in this issue of *Eurosurveillance* [4].

Data collection

Data were collected during the routine investigation of iGAS cases reported to Thames Valley Health Protection Unit (TVHPU) from 1 December 2010 until 15 January 2011. The data gathered included demographic information, presence and nature of a prodromal illness, presence and nature of chronic conditions, influenza immunisation status, details on the hospital stay and reports from the Health Protection Agency (HPA) reference laboratory for *emm* typing of invasive isolates as well as viral swabbing. Where these data were incomplete, further information was obtained by telephone interview with the patient's treating hospital physician and general practitioner.

Further data on cases in the South East region (approximately 8 million inhabitants) were obtained through the national reference laboratory and regional epidemiology unit for the same time period. Clinical and demographic information was collected from the data entered routinely in the HPA case management database (HPZone).

Results

Table 1 shows the characteristics of the 19 iGAS cases reported to TVHPU during the reporting period.

Fourteen patients were female, and five were male. The average age was 43 years, ranging from 2 to 83 years. Fourteen patients had no significant past medical history, three had a chronic respiratory condition, two had a history of alcohol dependence, one was pregnant and one was post-partum. All 14 patients reported influenza-like symptoms lasting for a mean of six days prior to hospitalisation with iGAS. Influenza-like illness was defined as at least two of the following three symptoms: fever (included if reported as subjective symptom), cough and upper airway congestion. In 12 patients, influenza-like symptoms in the family were also elicited.

Respiratory infection with iGAS was predominant in 12 cases, followed by blood culture positive disease with no focus of infection in four cases, and septic arthritis in two cases. Only three patients received antivirals. All but one received antibiotics. Of the seven patients who had received seasonal influenza vaccinations, four had received trivalent seasonal influenza vaccine in each of the last two years, two patients had received the vaccination in late 2009 and one only in late 2010. For those vaccinated in 2009, information was not available about the type of vaccine given and if it included vaccination against influenza A(H1N1)2009.

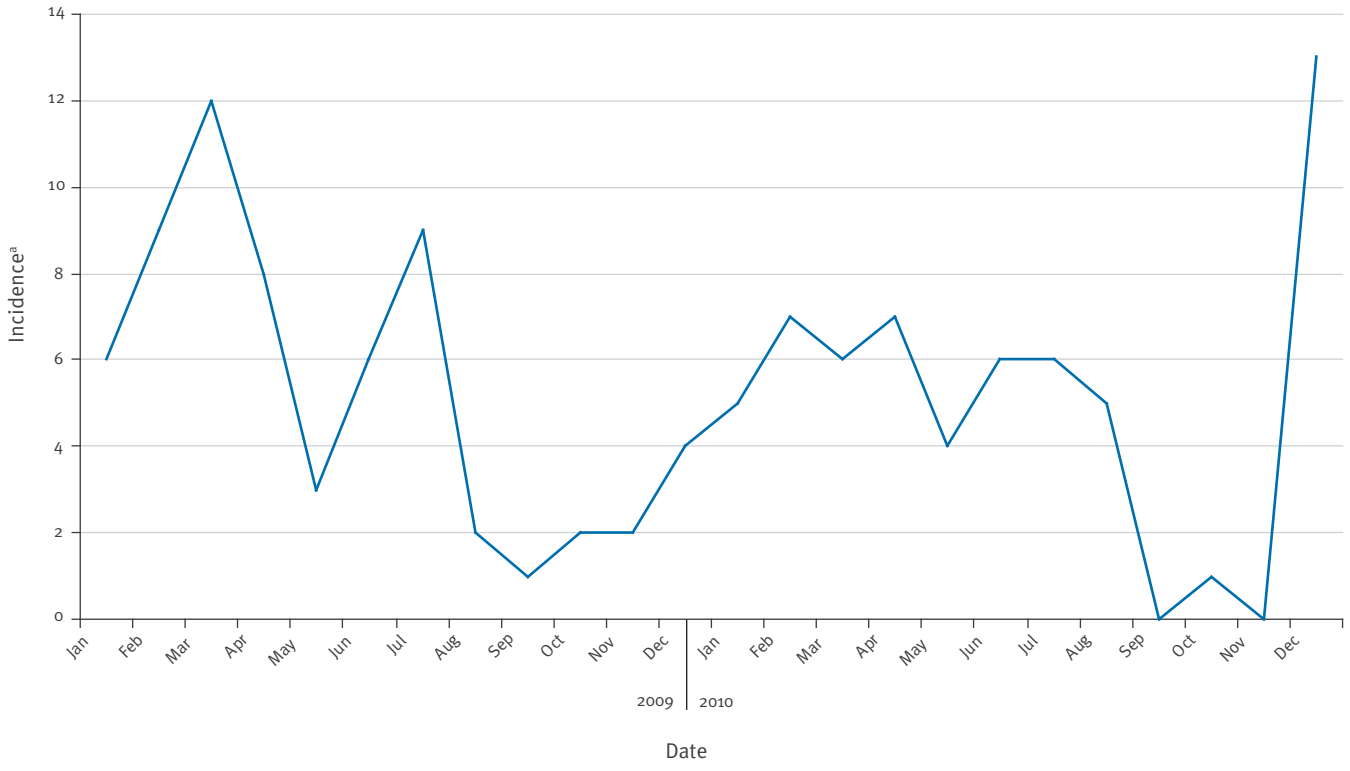
All 10 patients who died had been admitted to hospital and died within two days of admission. These patients were older than the patients who survived (55 versus 29), but had a similar duration of prodromal illness.

Viral swabs were taken from 10 patients, of which six were positive. There were four co-infections with influenza B, one with influenza A(H1N1)2009 and one with human metapneumovirus. None of the cases with proven influenza co-infection had received vaccination against influenza. The predominant iGAS *emm* type was st1.0, which was isolated from eight patients. This was followed by st89.0 with three cases and st1.52 with two cases and corresponded to the dominant types in the UK as mentioned in the most recent Health Protection Report [5].

Three of the four cases with confirmed influenza B died. These patients had a mean age of 26 years (range 10–47 years). They were previously healthy, and none had received influenza vaccination. All four cases had a prodrome of influenza-like illness and iGAS disease

Figure

Incidence of invasive group A streptococcal disease in Thames Valley Health Protection Unit area, United Kingdom, 2009–10



[a] Number of cases per month in the population of Thames Valley (2.2 million people).

Table 2

Comparison of Thames Valley Health Protection Unit with other Health Protection Units in South East England, 2010/11

	Thames Valley Health Protection Unit	South East England Health Protection Units including TVHPU
Population covered	2.2 million	8 million
Number of iGAS cases reported	19	57
Deaths reported	10	12
Influenza co-infection cases reported	4 influenza B, 1 influenza A(H1N1)2009	No further co-infections identified
Sex	26% male, 74% female	49% male, 51% female
ICU admission	52%	44%

ICU: intensive care unit; iGAS: invasive group A streptococcus; TVHPU: Thames Valley Health Protection Unit.

Table 1

Cases of invasive group A streptococcal disease, Thames Valley, United Kingdom, 1 December 2010–15 January 2011 (n=19)

No	Age group (years)	Sex	Comorbidities[a]	Seasonal influenza vaccination	Prodrome	Time from onset to admission (days)	ILI in close contacts[b]	iGAS disease	*emm* type	ICU admission	Intubated	Death	Length of stay in hospital (days)	Antivirals received	Antibiotic received	Viral swab result
1	10-19	F	None	No	ILI	6	Yes	Bilateral empyema	st1.0	Yes	Yes	No	>32	Yes	Yes	Lost
2	10-19	M	None	No	ILI	14	Yes	Splenic, laryngo-tracheobronchitis	st89.0	No	Yes	Yes	<1	No	No	Influenza B
3	80-89	F	None	No	None	N/A	No	Pneumonia	st89.0	No	No	Yes	<1	No	Yes	Not taken
4	30-39	F	None	No	ILI	3	Yes	Pneumonia	st1.0	Yes	Yes	Yes	2	No	Yes	Influenza B
5	0-9	M	None	No	ILI	7	No	Septic arthritis	st12.0	No	No	No	1	No	Yes	Not taken
6	80-89	M	Type 2 diabetes mellitus, gout	2010 and 2009	None	1	No	Pneumonia	st1.0	Yes	Yes	Yes	<1	No	Yes	Not taken
7	10-19	F	None	No	ILI	7	Yes	Pneumonia	st1.0	Yes	Yes	No	>20	Yes	Yes	Influenza B
8	30-39	F	None	No	ILI	5	Yes	Pneumonia	st1.52	No	No	No	3	No	Yes	Influenza A(H1N1)2009
9	50-59	F	Alcoholism	2009	ILI	4	Yes	Pneumonia	N/A	Yes	Yes	Yes	2	No	Yes	Negative
10	40-49	F	Post-partum	No	None	N/A	Yes	Endometritis	st28.0	No	No	No	5	No	Yes	Not taken
11	0-9	F	None	N/A	Fever, joint pain	5	No	Septicaemia	st3.1	No	No	No	>14	No	Yes	Not taken
12	70-79	F	None	2010 and 2009	ILI	3	No	Pneumonia	st1.0	Yes	Yes	Yes	2	No	Yes	Not taken
13	30-39	M	Alcoholism, lung lobectomy	No	ILI	7	Yes	Pneumonia	st1.0	Yes	Yes	Yes	1	No	Yes	Not taken
14	50-59	F	Bedbound due to back pain, asthma	2010 and 2009	ILI	14	Yes	Pneumonia	st1.52	Yes	Yes	Yes	<1	No	Yes	Negative
15	40-49	F	Asthma, cerebral artery aneurysm	No	Diarrhoea and ILI	10	Yes	Septic arthritis	N/A	No	No	No	>9	No	Yes	Negative
16	70-79	M	None	2010 and 2009	Diarrhoea and ILI	3	No	Septicaemia	st1.0	Yes	Yes	Yes	1	No	Yes	hMPV
17	30-39	F	Pregnant	2010	ILI	7	Yes	Bacteraemia	st3.4	No	No	No	>10	No	Yes	Negative
18	40-49	F	None	No	ILI	6	Yes	Pneumonia	st1.0	Yes	Yes	Yes	1	Yes	Yes	Influenza B
19	80-89	F	None	2010	None	N/A	No	Septicaemia	st89.0	No	No	No	1	No	Yes	Not taken

F: female; hMPV: human metapneumovirus; ICU: intensive care unit; iGAS: invasive group A streptococcus; ILI: influenza-like illness; M: male; N/A: not available.

[a] Conditions likely to affect outcome.

[b] Close contacts defined as someone who has had prolonged close contact (includes at least one overnight stay) with the case in a household type setting during the seven days before onset of illness.

affecting the respiratory system. The patient who survived had a prolonged stay in an intensive care unit (ICU) and has been in hospital for more than 20 days.

The increase in iGAS infections in the Thames Valley catchment area was only partially reflected in the reporting for South East England. Other surveillance units in our area also noted an increase in cases of iGAS disease, from a background rate of 12 cases per month between January and November 2010. However, the severity of iGAS infection was not replicated in the iGAS outbreak in South East England. Table 2 shows the data from TVHPU on the background of regional data. This includes all patients with a sample date on or after 1 December 2010 received by the national reference laboratory by 15 January 2011.

Discussion

The association and pathogenic synergism of influenza and bacterial disease is well known and has been best described for *S. pneumoniae* [6]. Co-infection with *S. pyogenes* is thought to be uncommon. Few case series have reported influenza A complicated by group A streptococcal infection, the largest of which was a series of 10 cases during the influenza A(H1N1)2009 pandemic [7] that reported a 70% mortality rate.

Our case series is notable for the high frequency of prodromal influenza-like illness preceding hospitalisation with iGAS and the high rate of respiratory involvement: a large German study reported that pneumonia only accounted for 5.6% of all iGAS disease manifestations [8]. We were able to provide microbiological evidence of concurrent viral infection in almost a third of our cases. We also note that all fatal cases died within two days after hospitalisation.

Influenza B virus is generally considered less pathogenic than influenza A and thought to cause less morbidity and mortality in previously healthy adults. Co-infection of influenza B and streptococci has only been reported once in a series of three previously healthy female cases aged 27, 40 and 61 years, one of whom died [9]. Two of those cases had tested positive for *S. pyogenes*, one for *S. pneumoniae*.

The high proportion of confirmed influenza B in our series is striking, considering the predominance of influenza A(H1N1)2009 in the UK during the report period. Similarly to the only other case series reported to date, our patients co-infected with influenza B and iGAS were young and did not fall into any risk group. In conclusion, our paper provides further evidence for the potential morbidity and mortality associated with influenza B virus in the context of co-infection with iGAS.

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Increase in invasive *Streptococcus pyogenes* and *Streptococcus pneumoniae* infections in England, December 2010 to January 2011

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Increases in invasive *Streptococcus pyogenes* and *S. pneumoniae* above the seasonally expected levels are currently being seen in England. Preliminary analyses suggest that the high level of influenza activity seen this winter may be contributing to an increased risk of concurrent invasive bacterial and influenza infections in children and young adults.

Following the early and rapidly escalating start of the 2010/11 influenza season in England [1,2] the Health Protection Agency (HPA) became aware of a number of anecdotal reports of invasive bacterial infections complicating seasonal influenza or influenza A(H1N1) 2009. In parallel, analyses of routine surveillance data identified increases in *Streptococcus pyogenes* and *S. pneumoniae* infections [3,4]. This triggered a cascaded alert from the United Kingdom (UK) Chief Medical Officer to healthcare professionals to be vigilant for bacterial co-infections complicating influenza cases [5].

The UK has experienced intense and widespread influenza activity this winter season due primarily to influenza A(H1N1)2009 virus with a significant contribution

Table 1

Cases of invasive *Streptococcus pyogenes, Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae* and *Neisseria meningitidis* infection diagnosed in England between 1 July and 14 January, 2007 to 2011

	Age (years)	2007/08	2008/09	2009/10	2010/11
S. pyogenes	<15	78	93	93	114
	15-44	137	159	122	140
	≥ 45	303	342	279	371
	Total	**518**	**594**	**494**	**625**
S. pneumoniae	<15	252	275	333	228
	15-44	456	470	434	526
	≥ 45	1,456	1,723	1,550	1,606
	Total	**2,164**	**2,468**	**2,317**	**2,360**
S. aureus	<15	1,077	956	1,177	1,114
	15-44	1,702	1,306	1,310	1,232
	≥ 45	6,134	5,137	4,787	4,509
	Total	**8,913**	**7,399**	**7,274**	**6,855**
H. influenzae	<15	55	58	43	55
	15-44	37	34	30	18
	≥ 45	134	200	141	174
	Total	**226**	**292**	**214**	**247**
N. meningitidis	<15	425	427	302	357
	15-44	137	102	89	94
	≥ 45	75	103	63	98
	Total	**637**	**632**	**454**	**549**

from influenza B. To rapidly estimate the potential contribution of influenza to incident cases of invasive bacterial infections, routine laboratory surveillance and information on isolate submission data were analysed for the 2010/11 influenza season and compared with historical data to identify patterns suggestive of a possible interaction with influenza.

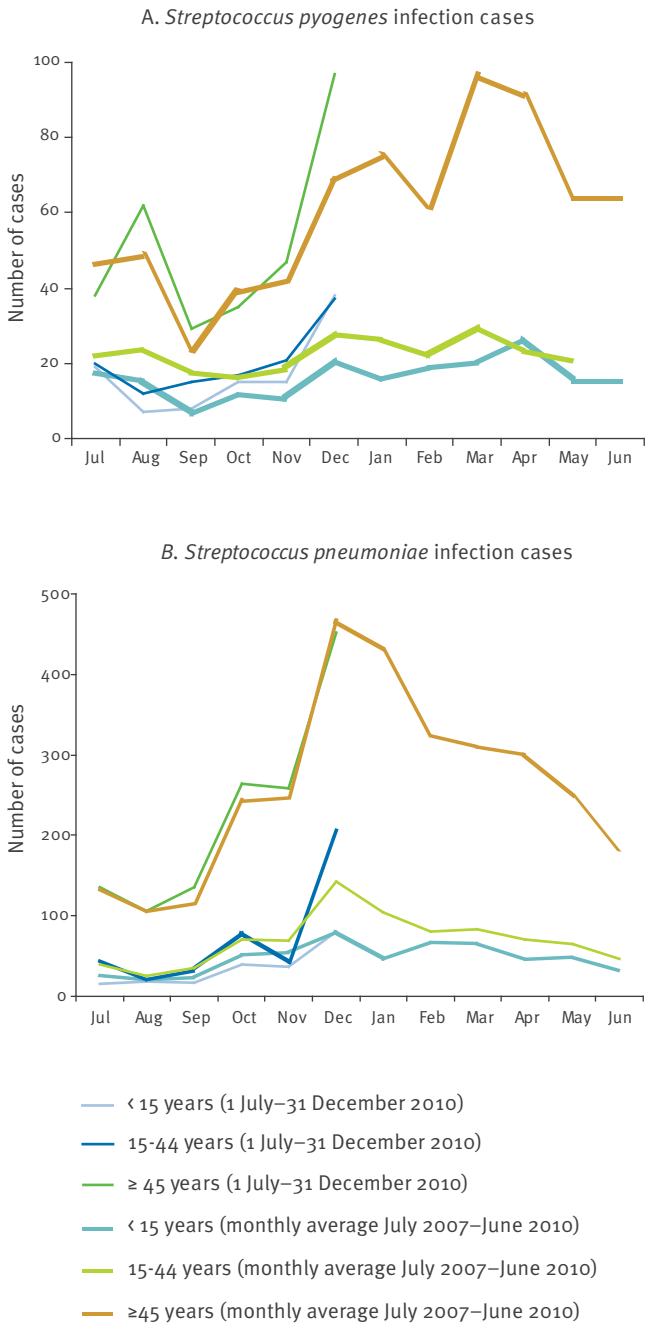
Identification of cases

Cases of invasive *S. pyogenes*, *S. pneumoniae*, and *Haemophilus influenzae* infection (defined through the isolation of these organisms from a normally sterile site) were identified through isolate referral to the national or regional reference laboratories. Cases of meningococcal infection included those with a clinically compatible illness where an isolate of *Neisseria meningitidis* was referred or where meningococcal DNA was detected in a clinical specimen at the national reference laboratory. Confirmed infections due to *Staphylococcus aureus* and *S. pyogenes* were derived from reports to the HPA from laboratories in England. Cases of influenza were defined as persons with influenza-like illness (ILI) with laboratory-confirmed influenza A or B infection reported by local or regional laboratories in England [6].

To obtain a minimum estimate of the potential importance of influenza as a risk factor for invasive bacterial infection, invasive bacterial surveillance data between 1 November 2010 and 14 January 2011 were matched on unique patient identifier (National Health Service (NHS) number, or name and date of birth if NHS number was unavailable) to laboratory-confirmed influenza diagnoses. Cases in both datasets with sample dates within two weeks of each other were considered as possible co-infections.

Figure 1

Age-specific reports of invasive *Streptococcus pyogenes* infection (n=532) (A) and referred *Streptococcus pneumoniae* isolates (n=1,983) (B) England, 1 July–31 December 2010, compared to monthly average (July 2007–June 2010)



Results

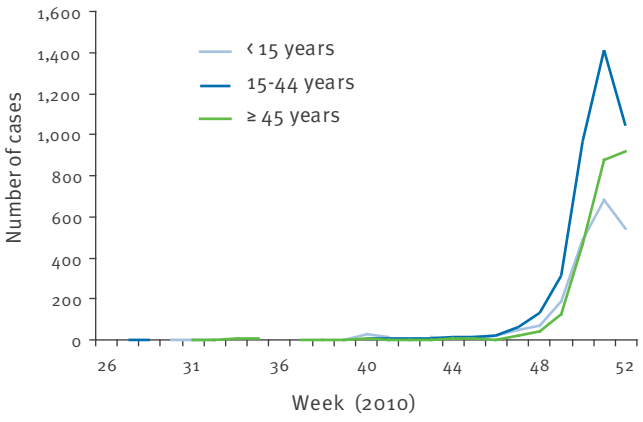
Invasive bacterial infections in England

When compared to the same period in the previous three years, surveillance data for 2010 and 2011 (1 July 2010 to 14 January 2011) do not indicate an overall increase in the number of invasive *S. pneumoniae*, *S. aureus*, *H. influenzae* or *N. meningitidis* infections (Table 1). In contrast, numbers of invasive *S. pyogenes* infections showed a slight elevation overall (Table 1), although more pronounced in December 2010 when 173 reports were received compared to an average of 99 for the same month in 2002–09 (range 68 to 147).

Increases in invasive *S. pyogenes* disease cases were noted in all age groups (Figure 1A) and were seen across all regions of England with the exception of Yorkshire and the Humber. Increases in invasive *S. pneumoniae* infections were seen exclusively in young adults (15-44

Figure 2

Confirmed cases of influenza A and B by sample date and age group, England, 1 July–31 December 2010, (n=8,645)



years) (Table 1), with numbers in December 2010 being much higher than the average for the same month of the previous three years (2007–09) (Figure 1B).

These increases coincided with increased influenza activity in December 2010, in particular in children (under 15 years-old) and young adults (15-44 years-old) (Figure 2).

Concurrent bacterial infections in seasonal influenza and influenza A (H1N1) 2009 cases in England

Linkage of influenza surveillance data to the 4,232 invasive bacterial surveillance records reported since the beginning of the 2011/11 influenza season (1 November 2010) to 14 January 2011, identified 144 (3.4%) cases co-infected with influenza (Table 2). Of the bacterial co-infections, the majority (85%) were diagnosed within the seven days after the date of laboratory-confirmed influenza diagnosis (122/143). Around three quarters (109/143) of identified co-infections were influenza A, 26% (37/143) were influenza B and 2% had both infections. *S. pyogenes* and *S. pneumoniae* had the highest proportion of confirmed influenza co-infections compared to the other bacterial infections. Cases of *S. pyogenes* under the age of 15 years had the highest likelihood of influenza co-infection (14%) followed by cases aged between 15 and 44 years (13%). Similarly, the highest proportion of co-infections with *S. pneumoniae* and influenza was found in the 15-44-year-olds (Table 2).

Discussion

Routine monitoring of surveillance data in England has identified a widespread increase in invasive *S. pyogenes* in December 2010 beyond the seasonally expected. A similar trend was not observed for other invasive bacterial pathogens where overall case numbers remained in line with previous seasons. Analysis of case fatality rates for all invasive bacterial pathogens studied were within the usual range.

Periodic upsurges in invasive *S. pyogenes* disease are reported by both European and non-European countries [7]. The drivers behind these increases are not fully understood but are likely to reflect both natural cycles governed by population susceptibility and heightened transmission in specific risk groups (e.g. injecting drug users). Our preliminary findings suggest that the heightened influenza activity this season has contributed to an increased risk of invasive *S. pyogenes* infection in children and young adults as co-infections with *S. pyogenes* and influenza were specifically observed in these age groups. This is in line with incidence rates of influenza and influenza-like illness (ILI) which were highest in December 2010 in children (1-4 year) (211.2 per 100,000 population) and young adults (15-44 years) (156.3 per 100,000 population) [2]. Similarly, the rise in invasive *S. pneumoniae* infections observed in young adults (15-44-year-olds age groups) may be partly attributable to concurrent influenza which was most commonly found in this age group. Increases in the numbers of *S. pneumoniae* infections in the younger age groups may have been prevented through the introduction of the 7-valent conjugate pneumococcal vaccine for children in 2006 [8], and the subsequent change to a 13-valent conjugate vaccine in 2010 [9]. Trends in older age groups, however, may have also been affected by recent changes in the vaccine programme.

As we were only able to match to laboratory-confirmed influenza, it is likely that we have underestimated the number of true cases of co-infections in the population, and influenza may be a more significant contributor to the overall rate of invasive infections. Furthermore, the importance of influenza as a risk factor for inva-

Table 2

Age distribution of invasive bacterial infections with concurrent influenza A or B infection in England, 1 November 2010–14 January 2011

	Total		<15 year-olds		15-44–year-olds		≥ 45–year-olds	
	Number	Cases of concurrent influenza infection (%)	Number	Cases of concurrent influenza infection (%)	Number	Cases of concurrent influenza infection (%)	Number	Cases of concurrent influenza infection (%)
Streptococcus pyogenes	302	27 (9)	58	8 (14)	62	8 (13)	182	11 (6)
Streptococcus pneumoniae	1,288	76 (6)	125	10 (8)	305	33 (11)	858	33 (4)
Staphylococcus aureus	2,063	31 (2)	332	10 (3)	376	8 (2)	1,355	13 (1)
Haemophilus influenzae	126	3 (2)	29	2 (7)	9	0 (0)	88	1 (1)
Neisseria meningitidis	449	6 (1)	269	3 (1.1)	101	3 (3)	79	0 (0)
All bacterial infections	4,232	143[a]	817	33	857	52	2,566	58

[a] A total of 144 bacterial cases co-infected with influenza were identified but no information on age was available for one case.

sive bacterial infection is likely to vary across different parts of the country [10].

The changes observed in invasive *S. pyogenes* infections may be due to factors other than influenza, in part supported by the observed increase in older age groups, such as the unusually cold weather experienced in England during December 2010. The latter suggestion is supported by the observation of increases in infections in older age groups, who have been relatively unaffected by influenza.

Given the on-going influenza activity in the UK, continued vigilance for changes in the incidence of *S. pyogenes* and *S. pneumoniae* infections is essential. As the start of the 2010/11 influenza season in the UK was ahead of other European countries and influenza transmission is now underway elsewhere in Europe, other national public health institutes should be alert to the possibility of similar observations.

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Continued emergence and changing epidemiology of oseltamivir-resistant influenza A(H1N1)2009 virus, United Kingdom, winter 2010/11

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During the winter period 2010/11 27 epidemiologically unlinked, confirmed cases of oseltamivir-resistant influenza A(H1N1)2009 virus infection have been detected in multiple, geographically dispersed settings. Three of these cases were in community settings, with no known exposure to oseltamivir. This suggests possible onward transmission of resistant strains and could be an indication of a possibility of changing epidemiology of oseltamivir-resistant influenza A(H1N1)2009 virus.

To date, during the winter period 2010/11, 27 confirmed cases of oseltamivir-resistant influenza A(H1N1)2009 virus infection have been detected. Three of these cases with resistant strains were in community settings. While the number of cases infected with a resistant strain who have been detected in the community is small, it is likely to have epidemiological significance given that no such cases were detected in 2009/10.

The 2010/11 winter season in the northern hemisphere has been characterised by co-circulation of different influenza strains, primarily influenza A(H1N1)2009, influenza B and, sporadically, influenza A(H3N2) [1]. Residual population susceptibility to influenza A(H1N1)2009 virus has led to severe and fatal illness among children and young adults, with many of the fatal cases having underlying risk factors associated with severe disease outcomes such as debilitating neurological conditions and chronic respiratory diseases. This emphasises the need for early antiviral therapy, which has proved successful in reducing viral shedding and severity of illness [2]. Neuraminidase inhibitors (NI) (oseltamivir and zanamivir), the most common antiviral drugs used for treatment and prophylaxis of patients with all influenza subtypes, were widely used in the first and second wave of the pandemic in the United Kingdom (UK) during 2009, and were available through the National Pandemic Flu Service (NPFS) telephone helpline [3] to all sections of the population, irrespective of whether the patient belonged to a risk group. In the winter of 2010/11 the use of NI has been restricted to those in recognised clinical risk groups, consistent with National Institute for Health and Clinical Excellence (NICE) guidance [4].

Resistance to NI is determined by mutations in the viral neuraminidase (NA) [5]. During the first 10 years post licensure, oseltamivir resistance, when it was observed and investigated, was associated with a loss of viral fitness and reduction in transmissibility [6]. Mutations giving rise to NI resistance are both influenza subtype-specific and drug-specific, with a histidine to tyrosine mutation at position 275 (H275Y) of the viral NA being the most common in influenza A(H1N1) viruses [5]. Unexpectedly, during the winter season 2007/08, the emergence of a transmissible, drug-resistant influenza A(H1N1) strain rendered the use of oseltamivir ineffective against this subtype [7,8]. This strain, with H275Y in the viral NA likely arose as a result of additional compensatory mutations elsewhere in the viral NA gene or elsewhere in the viral genome.

During the 2009 influenza A(H1N1) pandemic, oseltamivir was used extensively globally for both treatment and prophylaxis. A total of 319 cases infected with oseltamivir-resistant influenza viruses have been recognised globally, from more than 20,000 influenza-positive samples tested [9].

Resistance to oseltamivir was mainly detected in severely immunosuppressed individuals or hospitalised patients sampled post-treatment, although several clusters involving limited person-to-person

transmission were recognised. While this indicated a low prevalence of oseltamivir resistance, the continual evolution of influenza viruses emphasises the necessity for close surveillance of antiviral resistance. Here we report on our findings during winter 2010/11.

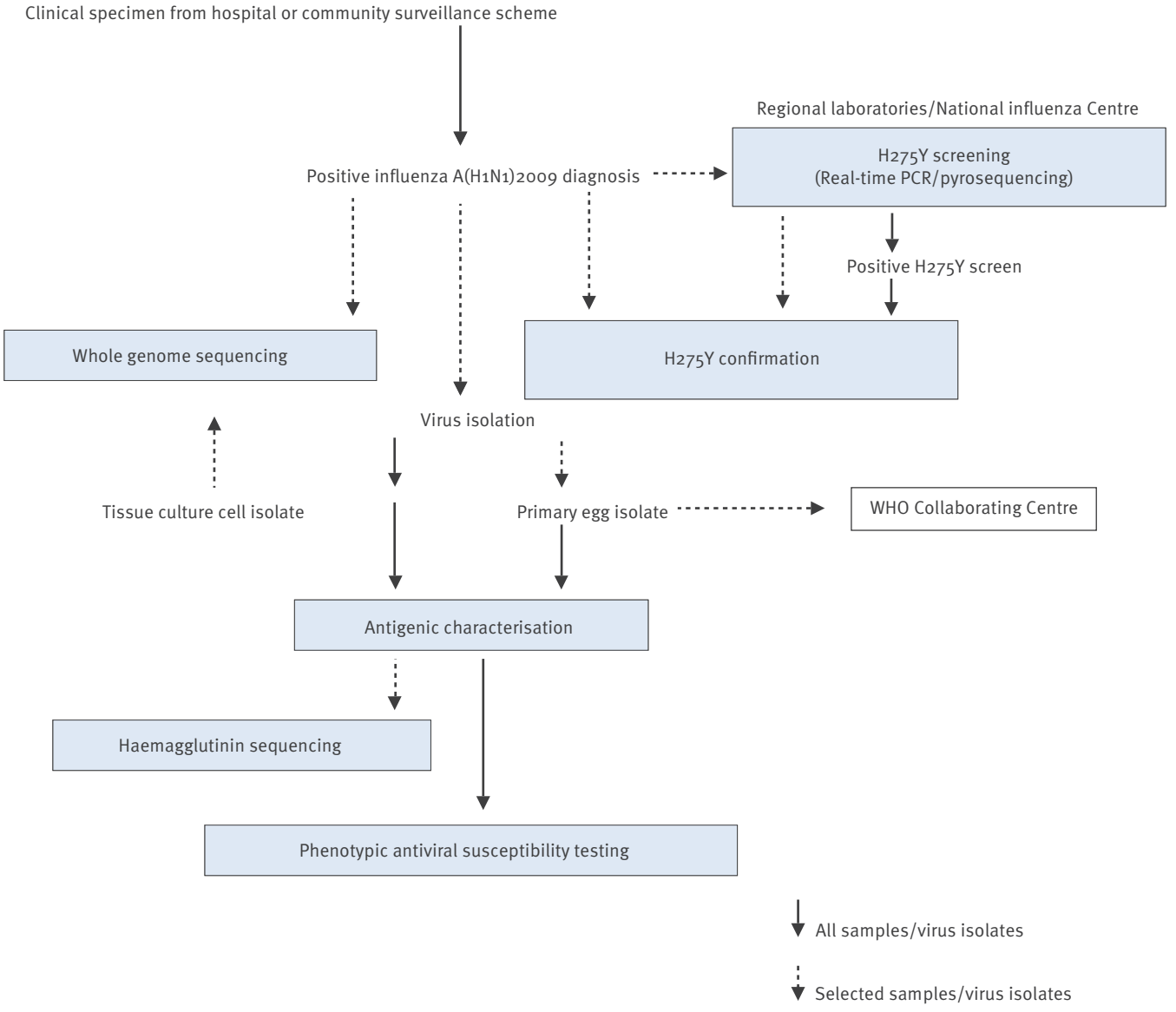
Methods

Monitoring of antiviral drug susceptibility in the UK circulating influenza strains, among hospitalised and primary care patients, is performed as part of influenza virological strain surveillance and is integrated with antigenic and genetic analyses at the National Influenza Centre (NIC) at the Health Protection Agency (HPA), Colindale (Figure 1) [1]. Rapid genotypic screening of influenza A(H1N1)2009 strains for the H275Y single-nucleotide polymorphism (SNP) by regional laboratories, beginning in England and Wales in October 2010 (and in Scotland in 2009), allows rapid detection of resistant strains closer to the point of care and supports a national enhanced surveillance programme for antiviral drug susceptibility. This screening is performed by SNP analysis on clinical specimens using a real-time polymerase chain reaction (PCR) method that differentiates between wild-type and resistant viruses. The HPA methodology is available on request, as the manuscript is in preparation. Resistance is confirmed by pyrosequencing at the NIC, where additional viral genotypic and phenotypic surveillance and characterisation is performed to identify additional alterations in drug susceptibility and any other associated mutations [10].

Clinically and epidemiologically relevant resistance (>50% of viral quasi-species in the original clinical material harbour the H275Y mutation) are reported weekly in HPA weekly influenza reports, to the

Figure 1

Influenza A(H1N1)2009 antiviral drug testing strategy in the United Kingdom



Source: Health Protection Agency, laboratories/National influenza Centre, United Kingdom.
PCR: polymerase chain reaction; WHO: World Health Organization.

European Centre for Disease Prevention and Control (ECDC) via the European Surveillance System (TESSy) and to the World Health Organization (WHO) headquarters and the WHO Regional Office for Europe. Clinical specimens with quasi-species harbouring <50% resistant virus are reported back to clinicians as resistant for patient management but not internationally, according to the agreed WHO strategy (Technical consultation meeting (8 September 2010) proceedings paper under preparation by the WHO).

Written informed consent and explicit ethical approval was not sought as this was an observational study undertaken as part of routine pandemic surveillance. It was carried out under UK legislation NHS Act 2006 (section 251), which provides statutory support for disclosure of data by the NHS, and their processing by the Health Protection Agency (HPA) for communicable disease control. Health Protection Scotland remains a constituent part of the NHS and coordinates the investigation and management of all national outbreaks in Scotland. Additional clinical and laboratory data on influenza cases with resistant strains were collected via national databases and by contacting attending physicians where appropriate. Frequencies were compared using the chi-square or Fisher's exact test as appropriate.

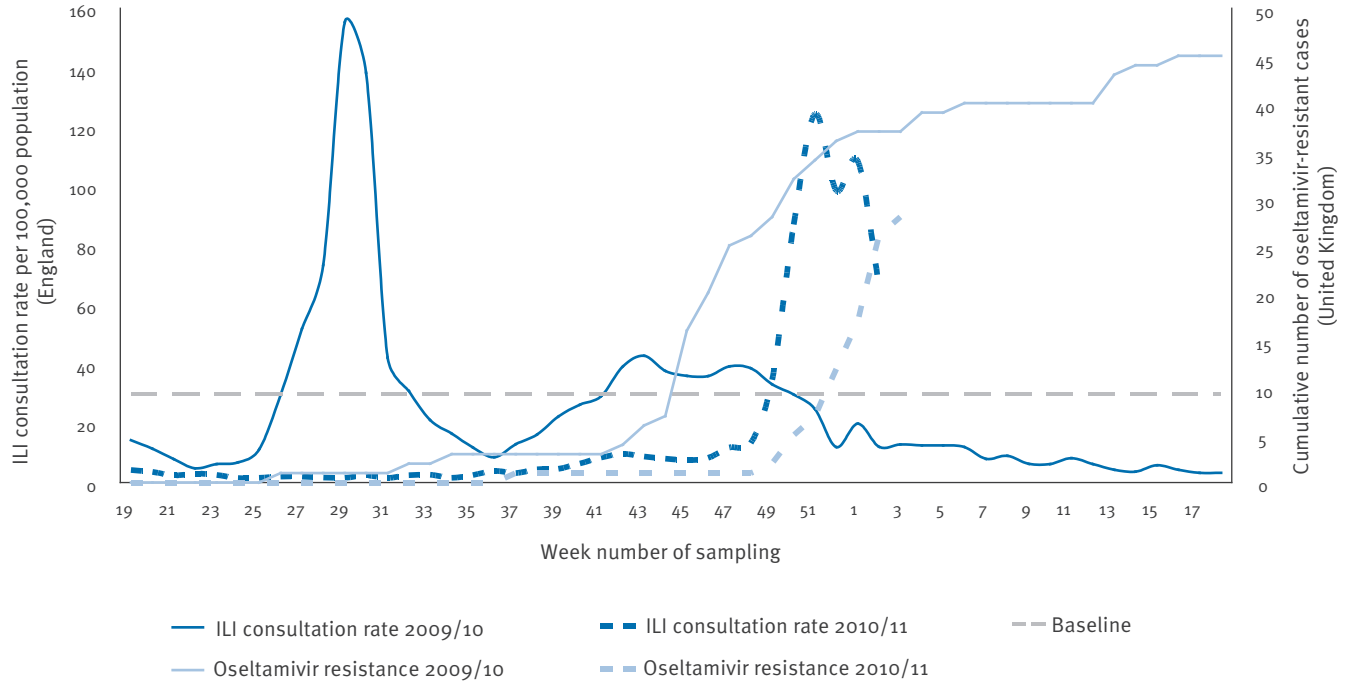
Virological findings

To date, during the winter period 2010/11, 27 confirmed cases of oseltamivir-resistant influenza A(H1N1)2009 virus infection have been detected up to week 3 of 2011 (Figure 2). Similar rates of oseltamivir resistance (1%) due to the H275Y mutation were detected in 2010/11 as in 2009/10 (Table 1). During 2009/10, resistance was detected exclusively from hospital-based surveillance. However, three of 27 cases with resistant strains detected in 2010/11 were in community settings, with no known exposure to oseltamivir (p=0.05). While the number of cases infected with a resistant strain who have been detected in the community is small, it is likely to have epidemiological significance given that no such cases have been previously detected in 2009/10 despite a large sample size (1,098 cases analysed).

All oseltamivir-resistant viruses in 2010/11 were wild type (isoleucine) at position 223 in NA, a site at which

Figure 2

Influenza-like illness consultation rates in primary care and cumulative cases infected with oseltamivir-resistant influenza A(H1N1)2009, United Kingdom, week 19 of 2009 to week 3 of 2011 [12]



ILI: influenza-like illness.

Table

Incidence rates of oseltamivir-resistant influenza A(H1N1)2009 virus infection, United Kingdom, 2009/10 (n=45) and 2010/11 (n=27)

Setting	May 2009-April 2010			May 2010-January 2011		
	Total tested	Number resistant	Percentage resistant	Total tested	Number resistant	Percentage resistant
Community	1,098	0	0.0	364	3	0.8
Hospital	4,489	45	1.0	2,500	24	1.0
Total	5,587	45	0.8	2,864	27	0.9

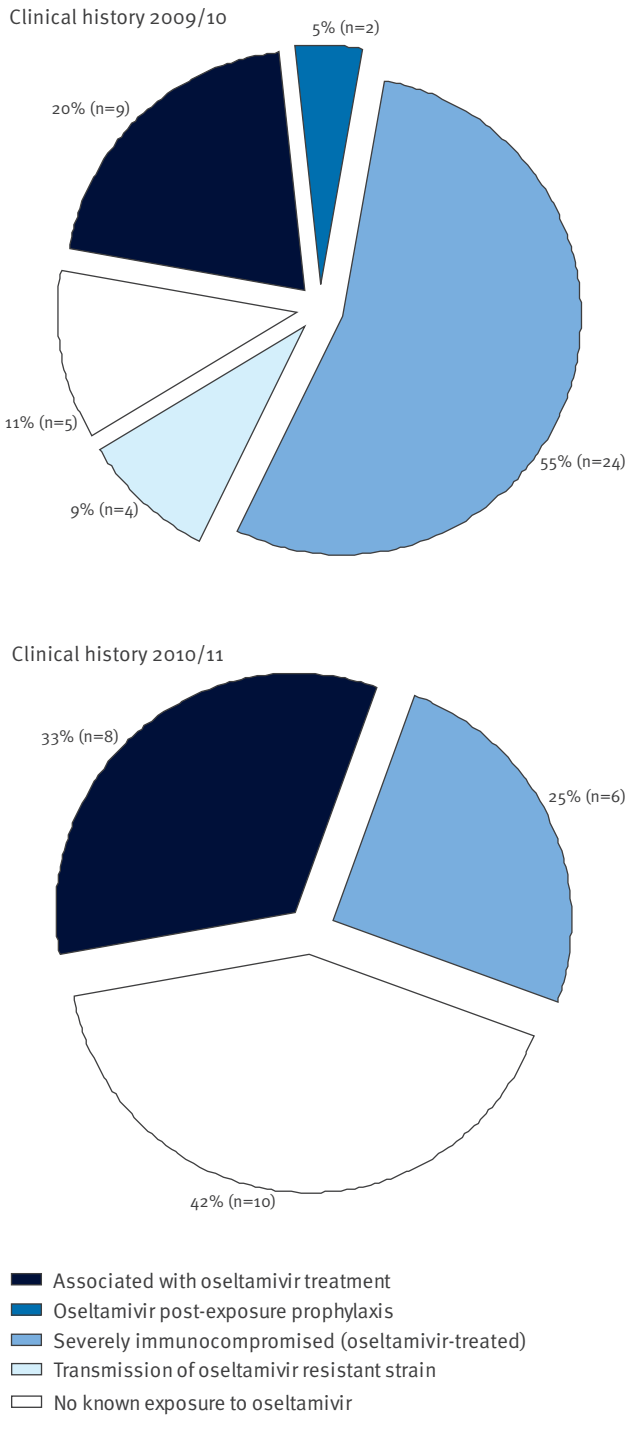
mutations can increase the phenotypic impact of resistance due to the H275Y mutation.

Analysis of influenza A(H1N1)2009-positive material taken from both hospitalised and community cases during the first and second waves of the pandemic in the UK found that the earliest UK detection of oseltamivir resistance due to the H275Y mutation occurred in June 2009. A total of 45 resistant cases were detected between week 19 of 2009 and week 18 of 2010 (Figure 2), eight of whom were associated with a nosocomial outbreak among severely immunocompromised individuals [11].

During 2009/10 the majority of sporadic resistance (80%) was detected in individuals with a history of exposure to antiviral drugs or immunosuppression (Figure 3). Whole genome sequencing of 10 of 45 resistant strains and phenotypic analysis of 15 of 45 resistant strains did not reveal any other known drug-resistant variants.

Figure 3

Patient characteristics associated with oseltamivir-resistant influenza A(H1N1)2009 virus infection in the United Kingdom during 2009/10 (n=44) and 2010/11 (n=24)



Clinical and epidemiological findings

In 2010/11, the mean age of all cases (n=27) infected with oseltamivir-resistant influenza A(H1N1)2009 virus was 32 years (median: 37; range: nine months to 75 years); in 2009/10, the mean age of such cases (n=45) was 38 years (median: 43 years; range: four months to 95 years). In 2010/11, 10 of the 27 cases were male and the corresponding figure for 2009/10 was 33 of the 45 cases (p=0.01).

Clinical and epidemiological features were available for 24 of 27 cases infected with oseltamivir-resistant influenza A(H1N1)2009 virus in 2010/11 and 44 of 45 such cases in 2009/10 (Figure 3).

Most notably, 10 of 24 of cases with resistant strains in 2010/11 had no known exposure to oseltamivir or contact with known cases of resistance (including three otherwise healthy individuals sampled in the community as part of virological surveillance) as compared with five cases of 44 in 2009/10 (p=0.01). The cases with resistant strains were distributed throughout England, Scotland and Wales. The frequency of these cases in both 2009/10 and 2010/11 increased with a 1–2-week delay (using sample date) of the increase in influenza-like illness (ILI) consultation rates (Figure 2), possibly reflecting that testing volume sufficient to detect infrequent resistance has been attained. ILI is defined as the presence of four of the following ICHPPC criteria i) sudden onset ii) cough iii) rigors/chills iv) fever v) prostration and weakness vi) myalgia vii) no significant respiratory physical signs other than redness of nasal mucous membrane and throat viii) influenza in a close contact.

Seven patients (of 24) in 2010/11 were immunosuppressed (six were treated with oseltamivir and one had no known oseltamivir exposure), compared with 34 of 44 immunosuppressed patients in 2009/10 (p=0.001). Of the 2009/10 cases, 24 were treated, two were given post-exposure prophylaxis, four were infected with the resistant strain and four had no known exposure to oseltamivir in 2010/11. To date in 2010/11, there has been no documented onward transmission of resistant strains, whereas in 2009/10, transmission was documented for four of 44 cases with resistant strains (p=0.3).

Conclusions

In 2010/11, cases infected with oseltamivir-resistant influenza A(H1N1)2009 virus have emerged sporadically in the community, some of whom have had no known exposure to oseltamivir, in addition to such cases occurring in hospitalised patients. Although clustering has not been formally ascertained, it is considered unlikely, which therefore suggests the likelihood of low-level onward transmission of resistant strains. In 2007/8 oseltamivir-resistant seasonal influenza A(H1N1) harbouring the H275Y mutation emerged, unrelated to antiviral drug use, and spread at varying rates globally, quickly becoming dominant over the sensitive strain in most countries by the end of 2008 [13]. The emergence of oseltamivir-resistant influenza A(H1N1)2009 virus is of concern and, despite the current low levels, requires vigilance.

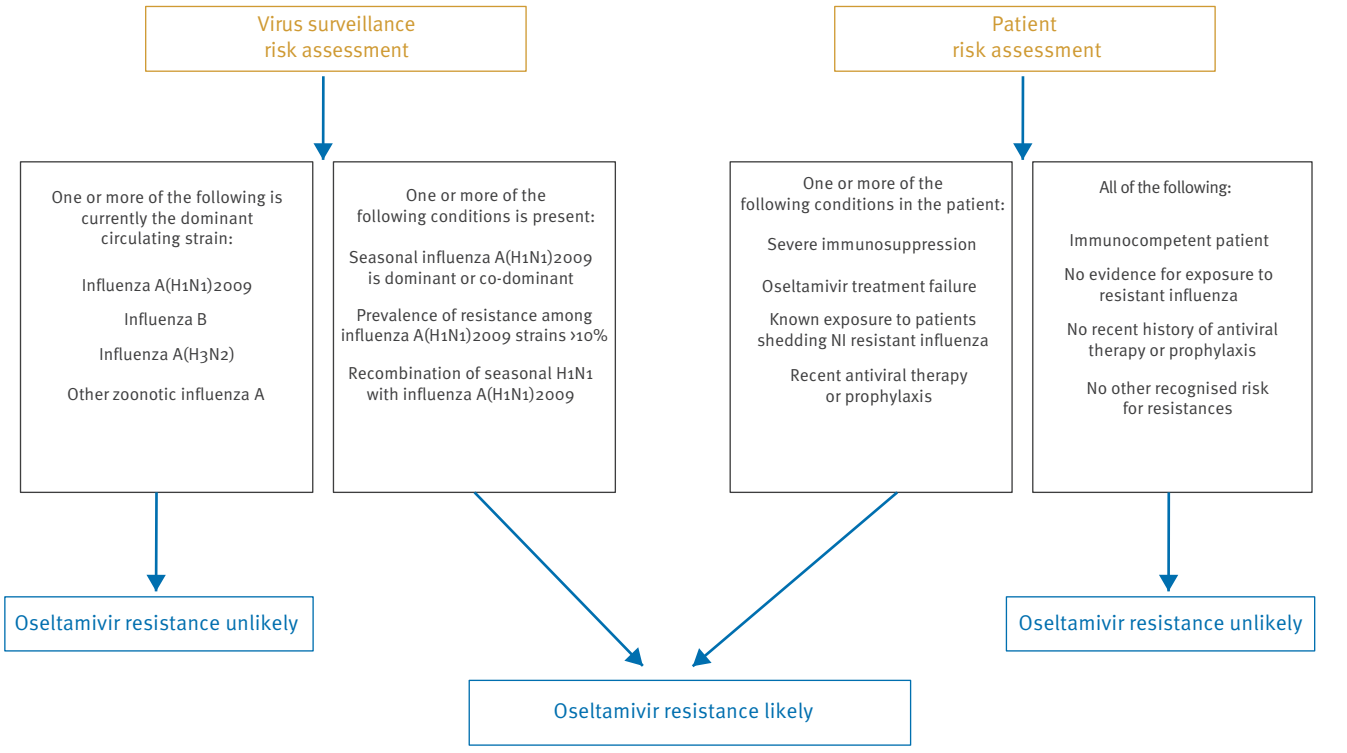
The frequency of immunosuppression as an underlying risk factor is lower among cases with resistant strains in 2010/11, which may be explained in part by the high index of suspicion for the emergence of resistance due to the H275Y mutation, resulting in increased and timely use of zanamivir in this patient population, as advocated by national UK guidance. The HPA revised guidance for managing influenza in the era of emerging oseltamivir resistance emphasises the necessity of active surveillance for antiviral drug resistance, particularly among high-risk groups such as those who are immunosuppressed [14,15].

In the light of the varying rates of oseltamivir resistance among different influenza subtypes and across geographical locales, the choice of antiviral agent is often difficult. Clinical decisions should therefore be based on the perceived risk for resistance both at the individual level and global (population) level, using current local virological and epidemiological data wherever possible. A proposed model for such risk assessment is outlined in Figure 4. Ongoing incidence of oseltamivir resistance in the community in patients without evident risk factors will influence antiviral prescribing recommendations if the overall frequency of resistance rises above 10%. Decisions about antiviral therapy for patient management will increasingly require risk assessment and national and international antiviral policies.

Observational data produced through surveillance provide the crude rates of oseltamivir resistance among currently circulating influenza subtypes. Assessing risk factors for antiviral resistance and propensity for onward transmission are also important and assist in recognition of new resistance mechanisms. Current *in vitro* and *in vivo* studies of the fitness of resistant influenza A(H1N1)2009 strains are conflicting. In human airway cultures the resistant variant was shown to have a fitness deficit in comparison to its wild-type counterpart [16] and Duan *et al*. found that the drug resistant virus only transmitted via the contact route, not the respiratory droplet route and was outgrown by its wild-type counterpart in co-infected animals [17]. In contrast however, Hamelin *et al*. found that oseltamivir-resistant A(H1N1) virus was equally virulent as its wild-type counterpart in mice and ferrets and did transmit [18].

Figure 4

A decision-support tool for guiding the choice of antivirals through risk assessment[a]



[a] For patients requiring prophylaxis or antiviral therapy for suspected or proven influenza A(H1N1)2009

Our surveillance findings imply the need for urgent studies to evaluate possible underlying compensatory mutations among resistant strains.

Acknowledgements

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Pertussis incidence among adolescents and adults surveyed in general practices in the Paris area, France, May 2008 to March 2009

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Since the introduction in 1998 of an adolescent pertussis vaccine booster (for persons aged 11–13 years) in France, the incidence of pertussis in adolescents and adults has been unknown. We therefore undertook a study to estimate the incidence of pertussis in these population groups and to evaluate the feasibility of a real-time electronic surveillance system for pertussis in general practices in France. The general practitioners selected for the study were located in Paris and the surrounding area. Polymerase chain reaction (PCR) or measurement of anti-pertussis toxin IgG levels by enzyme-linked immunosorbent assay (ELISA) was used to confirm the infection. Among the 204 patients enrolled in the study, 46 (23%) were diagnosed as having pertussis: 21 were confirmed cases, 24 were clinical cases and one was an epidemiological case. The median age of the 204 patients was 44 years and 134 (66%) were female. The median duration of the patients' cough at enrolment was 24 days. No clinical difference was observed between those with and without a pertussis diagnosis. The incidence of pertussis was estimated to be 145 (95% confidence interval: 121–168) per 100,000 population based on the results from the 10-month study period (calculated for 12 months). Problems in sample collection were identified: pertussis sentinel surveillance cannot be developed without training the staff of medical laboratories who take the biological samples. French health authorities were alerted and training procedures were developed.

Introduction

Bordetella pertussis remains in fifth place among the leading aetiologies of vaccine-preventable deaths in children around the world. The majority of hospitalisations, complications and deaths due to pertussis occurs in infants who are too young to have been fully vaccinated, predominantly those younger than two months of age [1,2].

In France, a paediatric hospital-based surveillance network (RENACOQ) was set up in 1996 to monitor the occurrence of pertussis among hospitalised infants and the age of the people who were the source of their infection. The national incidence rate of pertussis in infants younger than three months of age between April 1996 to December 2007 was estimated to be 257 per 100,000 population (95% confidence interval (CI): 213–300 per 100,000 population), with the incidence rate varying from 476 (95% CI: 418–535) per 100,000 population in 2000 to 117 (95% CI: 88–147) per 100,000 population in 2003 and 2007 [2]. Among pertussis cases who were aged younger than six months old and where contact with a pertussis case had been identified, the mean age of the persons who were the source of their infection increased from 19.6 years in 1996 to 31.9 years in 2007 [3]. Data on incidence of the disease in adolescents and adults are limited, as in 1986, pertussis was no longer a notifiable disease in France. The last study using the results of biological sampling to evaluate the incidence of the disease in adults, in those aged over 18 years, was carried out in 1999 in the Paris area, reporting an annual incidence rate of 866 (95% CI: 601–1,199) per 100,000 population [4]. Since then, it has been shown that adults are generally the source of infection of infants who are hospitalised with pertussis [3]. In addition, *B. pertussis* has been shown to be an important cause of nosocomial infection in different hospital services, including neonatal and maternity units [5,6].

Pertussis acellular vaccines were introduced in many developed countries more than 10 years ago, to replace whole-cell vaccines. The acellular vaccines are safer in that they cause substantially fewer side effects [7]. Thirty years after the introduction of pertussis vaccination for infants and young children, transmission of *B. pertussis* is still observed in France [3]. For this reason, an adolescent vaccine booster was introduced in

1998, for those aged 11–13 years and a cocooning strategy was implemented in 2004. This strategy aims to protect newborn infants from becoming infected with *B. pertussis* by administering pertussis booster vaccines to mothers, family members and other contacts of newborn infants, young adults, people who are planning to have children, and childcare and healthcare workers. In this way, mothers, other family members and contacts are protected from getting pertussis and passing *B. pertussis* on to the young infants. In 2008, a further vaccine booster was introduced (in parallel with the cocooning strategy), for adults who had not received a vaccine booster in the previous 10 years [8-10].

Given the lack of data on pertussis incidence in adolescents and adults, we carried out a pilot, prospective study to determine the incidence of the disease in these population groups and to evaluate the feasibility of adding pertussis to the health indicators currently surveyed by the French Sentinelles Network. This network comprises 1,294 volunteer general practitioners (GPs) located throughout France who participate in the ongoing surveillance of 10 health indicators and in *ad hoc* epidemiological studies [11]. GPs have individual access to a web-based platform, to declare the health indicators: seven infectious diseases (influenza-like illness, acute diarrhoea, mumps, varicella zoster virus infection, herpes zoster, male urethritis and Lyme disease), as well as three non-infectious conditions (asthma, suicide attempts and any-cause hospitalisations).

Methods

From May 2008 to March 2009, we carried out a survey of selected general practitioners (GPs) belonging to the French Sentinelles Network. As this was a pilot study, we involved only GPs in the Network who were located in Paris and surrounding areas. The 129 GPs located in this area were invited to participate in this study: of those who accepted (n=69), 44 were selected, in order to be representative of the GPs in the Paris area (according to the GP's sex, age and volume of activity in general practice). An independent ethics committee revised and authorised the study protocol. The survey was anonymous and all patients were informed by their GPs about the nature of the study. All enrolled patients agreed to give a biological sample.

An electronic form was specifically created in which GPs could enter data of pertussis patients. The GPs were asked to report patients with clinical suspicion of pertussis, as they do for the other health indicators. They were asked to: (i) include in the study all patients older than 13 years with a newly occurred cough that persisted more than seven days and with at least one specific sign of pertussis (whooping, paroxysmal cough, vomiting, increased coughing at night); (ii) record on the electronic form the patients' clinical data (age, date of onset of the cough, clinical symptoms, date of last pertussis vaccination or disease history, knowledge of close contact with a pertussis confirmed case, contact with a pet with respiratory symptoms or conjunctivitis (because of possible infection due to *B. bronchiseptica* [11]), whether the patient had asthma, and whether antibiotics were prescribed; (iii) send the patients to a laboratory to have a nasopharyngeal aspirate (NPA) taken if the cough lasted less than 21 days or a blood sample taken if the cough lasted 21 days or longer; and (iv) establish and record on the form their final diagnosis (after having received the laboratory results). If GPs did not enrol any patients, they were contacted regularly by telephone or email to find out why.

Samples were analysed at the Institut Pasteur in Paris, by real-time polymerase chain reaction (PCR) [12] or by measurement of anti-pertussis toxin (PT) IgG by enzyme-linked immunosorbent assay (ELISA) [12]. The minimum level of anti-PT IgG detection was 4 international units (IU)/mL. Infection with *B. pertussis* was confirmed if the PCR was positive or the anti-PT IgG titre was ≥100 IU/mL. Titres of anti-PT IgG of between 25 and 100 IU/mL were considered as intermediate. In such cases, GPs were asked to contact the patient in order for a second blood sample to be taken.

Case definition

A confirmed case was defined as a patient with at least one specific sign of pertussis (whooping, paroxysmal cough, vomiting, increased coughing at night), whose *B. pertussis* infection was confirmed by either PCR or ELISA.

A clinical case was defined as a patient with at least one specific sign of pertussis (whooping, paroxysmal cough, vomiting, increased coughing at night) whose disease was diagnosed clinically by a GP, without laboratory confirmation of *B. pertussis* infection.

An epidemiological case was a patient with at least one specific sign of pertussis (whooping, paroxysmal cough, vomiting, increased coughing at night), without laboratory confirmation of *B. pertussis* infection, but the person had had close contact with a confirmed case in the previous three weeks.

Data analysis

Electronic forms were filled in by the GPs in real time in their personal web-based platform. We monitored these weekly, in order to survey the data entry and match the GPs' data with test results from the Institut Pasteur (to obtain the number of recruited patients, number of samples received and final diagnosis reported by GPs). All the data collected electronically constituted the patient database, which was used for statistical analysis.

Pertussis incidence of the enrolled patients was estimated according to the method of the Sentinelles Network, i.e. multiplying the mean number of cases per participating GP by the total number of GPs in Paris area and then dividing the result by the number of

people older than 13 years in the Paris area (9,170,000, according to the national census data of 2007) [13]. As the study was performed during 10 months, the incidence was multiplied by 12 and divided by 10, to obtain a 12-month incidence. To calculate the 95% CI, it was assumed that the number of reported cases followed a Poisson distribution.

Data analyses were performed using the statistical package R, and all statistical analyses were conducted at the 5% level of significance.

Results

Characteristics of the general practitioners in the study

The participating GPs (n=44) had a mean age of 55 years and were mainly men (n=38). Of the participating GPs, 34 enrolled 230 eligible patients while 10 did not enrol any patients. No difference was found between those who enrolled patients and those who did not (by age, sex, years of experience and number of patients seen per year), except in their pertussis vaccination practices. Eight of the 10 GPs who did not recruit patients were following the recommended cocooning strategy, so their patients targeted by the cocooning strategy and in accordance with French guidelines were systematically vaccinated against pertussis.

Sampling results and diagnoses of enrolled patients

A biological sample was obtained for 204 (88.7%) of the 230 enrolled patients but was missing for 26 (11.3%) patients, for the following reasons: 22 patients never went to the laboratory, three samples were lost during the transport between the laboratory and the Institut Pasteur and a sample was not taken for one patient as NPAs were not standard practice in the laboratory.

The ELISA or PCR results were negative for 127 (62.2%) patients, intermediate for 19 (9.3%), and positive for 22 (10.8%) (Table 1). The results for 36 patients (17.6%) were not interpretable as serological tests were carried out by mistake for patients who had been coughing for less than 15 days (n=6) or because NPAs were incorrectly sampled (n=30).

A final diagnosis was made by GPs based on the laboratory results and the clinical characteristics of each patient. A total of 46 (22.5%) of the 204 enrolled patients were diagnosed as pertussis cases: 22 were laboratory confirmed, 23 were clinically diagnosed and one was epidemiologically diagnosed (Table 1).

Characteristics of enrolled patients

Characteristics of the patients enrolled in the study with or without a pertussis diagnosis are compared in Table 2.

The median age of patients enrolled in the study (n=204) was 44 years (range: 14–89 years) and the majority were female (66%). The median duration of the patients' cough at enrolment was 24 days, 18 (9%) patients had asthma and 16 (8%) had already had pertussis in infancy. Pertussis vaccination status was reported for 27 patients but was documented for only 12 (in the patient's vaccination booklet). Among those 12, three patients had been vaccinated in the last five years: these patients were diagnosed as not having pertussis by their GP.

The frequency of clinical symptoms (such as vomiting, increasing coughing at night, paroxysmal cough, fever) observed in patients with a diagnosis of pertussis (n=46) was similar to that observed in those who were not diagnosed as having pertussis (n=158).

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Estimated incidence of pertussis among enrolled patients

On the basis of the study data, we estimated that in the Paris area, 723 patients (95% CI: 678–785) per 100,000 population during the study period (calculated for 12 months) would meet the inclusion criteria, giving an incidence of all pertussis cases of 145 (95% CI: 121–168) per 100,000 population (Table 3). The estimated incidence of clinical, confirmed and epidemiological cases is also shown.

Feasibility of pertussis surveillance

Problems in sample collection were identified: (i) no sample was available for 26 patients (11.3%); (ii) some medical laboratories (n=30), which routinely collect samples, did not know how to collect an NPA. As a result, for 30 patients (14.7%), NPA samples were replaced by expectorations, or saliva or nasal swabs, for which the PCR results were non-interpretable; (iii) some GPs (n=8) arranged for measurement of anti-PT IgG levels too soon after the beginning of the patient's cough. Thus for eight patients, intermediate IgG results were obtained (levels between >25 and <100 IU/mL), which did not allow to a definitive diagnosis to be made. When the patients were asked later for a second blood sample, they did not go to the laboratory.

Discussion

Our study indicates that pertussis is still present among adolescents and adults with a persistent cough in the Paris area, despite the cocooning strategy having been recommended in France since 2004 and the adult booster since 2008 [9,10]. The estimated incidence was lower than that described in 1999 for the same area [4]: 145 cases versus 866 cases per 100,000 population, respectively. This decrease was also observed in a French national observational study conducted in 2006 among people older than 16 years, where the incidence of pertussis was estimated to be 110 cases per 100,000

Table 1

Test results and diagnoses of enrolled patients, Paris area, France, May 2008–March 2009 (n=204)

Test result	Final diagnosis by general practitioners				Total n (%)
	Not pertussis n (%)	Confirmed case n (%)	Clinical case n (%)	Epidemiological case n (%)	
Negative					
Negative PCR or anti-PT IgG <25 IU/mL	120	0	6	1	127 (62.2)
Positive					
PCR positive or anti-PT IgG ≥100 IU/mL	0	22	0	0	22 (10.8)
Intermediate					
Anti-PT IgG between >25 and <100 IU/mL	8	0	11	0	19 (9.3)
Not interpretable[a]	30	0	6	0	36 (17.6)
Total	**158 (77.5)**	**22 (10.8)**	**23 (11.3)**	**1 (0.5)**	**204 (100)**

PCR: polymerase chain reaction; PT: pertussis toxin; IU: international units.

[a] Serological tests were either carried out by mistake for patients who had been coughing for less than 15 days or because nasopharyngeal aspirates were incorrectly sampled.

Table 2

Characteristics of enrolled patients from whom suitable samples were obtained, Paris area, France, May 2008–March 2009 (n=204)

Characteristic	Patients without pertussis diagnosis n (%)[a]	Patients with pertussis diagnosis n (%)[a]	Enrolled patients from whom suitable samples were obtained n (%)[a]	P value
Median age	44 years	44 years	44 years	0.81
Female	102 (64.6)	33 (71.8)	135 (66.2)	0.37[b]
Asthma	12 (7.6)	6 (13.0)	18 (8.8)	0.21[c]
Median number of days of cough	25 days	22 days	24 days	0.08[d]
History of whooping cough in infancy	13 (8.2)	3 (6.5)	16 (7.8)	0.99[c]
Paroxysmal cough	141 (89.2)	44 (95.6)	185 (90.7)	0.15[b]
Whooping	32 (20.2)	10 (21.7)	42 (20.6)	0.83[b]
Increased coughing at night	105 (66.5)	33 (67.6)	138 (67.6)	0.5[b]
Fever (>38 °C)	21 (13.3)	6 (13.0)	27 (13.2)	0.96[b]
Contact with a sick pet[e]	10 (6.3)	1 (2.2)	11 (5.4)	0.46[c]
Contact with a confirmed pertussis case	2 (1.3)	2 (4.4)	4 (1.9)	0.22[c]
Cyanosis	11 (6.7)	1 (2.2)	12 (5.9)	0.46[c]
Vomiting	26 (16.5)	8 (17.4)	34 (16.7)	0.88[b]
Antibiotics prescribed	61 (38.6)	19 (41.3)	81 (39.7)	0.74[b]
Total	**158**	**46**	**204**	–

[a] Unless otherwise indicated.

[b] Chi-square test.

[c] Fisher's exact test.

[d] Wilcoxon test.

[e] Pet with respiratory symptoms or conjunctivitis.

Table 3

Estimated incidence of pertussis based on data on enrolled patients, Paris area, France, May 2008–March 2009[a]

Item	Number of patients	Estimated pertussis incidence per 100,000 population (95% confidence interval)
Type of patient		
All patients meeting the inclusion criteria	230	723 (678–785)
All patients meeting the inclusion criteria and from whom suitable samples obtained	204	641 (531–620)
Diagnosis		
All patients with a pertussis diagnosis	46	145 (121–168)
Confirmed cases	22	66 (46–76)
Clinical cases	23	75 (62–98)
Epidemiological cases	1	3 (0–7)

[a] The incidence estimates are for a 12-month period, based on the 10-month study results.

inhabitants per year [14]. A reduction in the number of pertussis cases was also reported by RENACOQ (the paediatric hospital-based surveillance network) in children below 16 years of age: in 2000, 467 laboratory-confirmed cases were reported, whereas in 2008, there were 138 cases. These observations of hospital-based surveillance indicate that pertussis has a cyclic variation in France (with the number of cases up in 2000 and down in 2008). But it is very difficult to ascertain whether this decrease is attributable to the pertussis cycle or whether it could also be due to the introduction of the adolescent booster (for those aged 11 to 13 years) since 1998 [3]. Surveillance in the coming years will help us to clarify this point. Patients were included in our study if older than 13 years: only four were less than 18 years old and were diagnosed as not having pertussis, suggesting that adolescents are probably more immune than adults.

Countries' case definitions, vaccination strategy and coverage, and surveillance systems differ, making incidence comparisons difficult [15-17]. In our study, 23% of enrolled patients from whom suitable samples were obtained were diagnosed by their GP as having pertussis. The incidence of pertussis in our study population could have been underestimated due to a number of unexpected problems that occurred during sample collection. A surveillance programme, as a part of Sentinelles Network, for pertussis in France will not be possible without training staff in medical laboratories on how to collect NPAs. Consequently, a letter describing the required procedures was sent by the Pasteur Institut to all French medical laboratories. In January 2010, a video demonstrating the procedures was posted on the website of the National Centre of Reference located at the Institut Pasteur, to help to train laboratory staff [18].

The epidemiology of pertussis in adolescents and adults is not well defined because of the broad spectrum of clinical manifestations. In our study, no clinical differences were observed between patients with and without a pertussis diagnosis. It has previously been reported that most (80%) adolescents and adults with pertussis had a cough that lasted more than 21 days and that many were still coughing at 90 days [19]. In our study, patients were not followed to record the number of days that they continued coughing after their visit to the GP, but three confirmed cases had been coughing for more than 40 days when they were enrolled in the study.

The gold standard treatment in French pertussis guidelines [21] is macrolides; however, in our study only 40% of the cases prescribed antibiotics received a prescription for a macrolide. Further medical education in antibiotic therapy is therefore needed.

Some limitations must be considered when interpreting the results of this study. There may have been selection bias because GPs who participated in this study might be more concerned about pertussis that non-responders and their practices might, therefore, differ. Some GPs (n=10) in the study were surveying their patients for pertussis, but did not enrol any patients with a cough. The principal reason given by these GPs for this was that they usually vaccinated all their patients against pertussis (according to the cocooning strategy and French guidelines), thus the chances of them seeing patients with pertussis in their practices were reduced. Eight of the 10 GPs who did not enrol any patients were following the recommended cocooning strategy. Similarly, the patients enrolled in the study may not be representative of the general population in the area. In addition, women were overrepresented in the study. The overrepresentation of women is often observed in studies conducted in general practices, probably because women visit their physician sooner than men [22].

Taking into account that there are 9,170,000 people older than 13 years in the Paris area, and that the incidence of pertussis is probably underestimated in this area because of the problems identified in this study, it is important to establish robust sentinel surveillance. In order to allow comparison of surveillance data, standardised biological sampling as well as standardised diagnostic techniques is urgently needed.

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Call for applications for EUPHEM fellows

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