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Differentiation of two distinct clusters among currently circulating influenza A(H1N1)v viruses, March-September 2009

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Analysis of all complete genome sequences of the pandemic influenza A(H1N1)v virus available as of 10 September 2009 revealed that two closely related but distinct clusters were circulating in most of the affected countries at the same time. The characteristic differences are located in genes encoding the two surface proteins - haemagglutinin and neuraminidase - and four internal proteins – the polymerase PB2 subunit, nucleoprotein, matrix protein M1 and the non-structural protein NS1. Phylogenetic inference was demonstrated by neighbour joining, maximum likelihood and Bayesian trees analyses of the involved genes and by tree construction of concatenated sequences.

Following the worldwide spread of the pandemic influenza A(H1N1)v virus after its emergence in the United States (US) and Mexico in March 2009, the World Health Organization (WHO) raised the influenza pandemic alert level to phase 6 on 11 June 2009. It is expected that this new influenza virus will continue to circulate and spread due to efficient human to human transmission. Data on the genetic composition of the virus became available very early in the pandemic [1], and until 10 September 2009, more than 3,500 individual gene sequences had been deposited in public databases such as GISAID and GenBank. The influenza A(H1N1)v virus, which is a unique combination of gene segments from both North American and Eurasian swine influenza viruses [2], has a high mean evolutionary rate for individual segments and the whole genome (3.66×10^{-3} substitutions per site per year) [3].

Analysis of all eight gene segments of more than 300 full-length influenza A(H1N1)v sequences available in the Genbank database (Figure 1; this figure is only available in the online version) enabled us to show that two closely related but distinct clusters of the virus were circulating in most of the affected countries at the same time. The two clusters could be differentiated clearly by nine nucleotide signatures. These were located in the genes for the two surface proteins haemagglutinin HA and neuraminidase NA and in the genes for four internal proteins, the polymerase PB2 subunit, the nucleoprotein NP, matrix protein M1 and the non-structural protein NS1. The polymerase genes PB1 and PA were identical in all isolates and no genetic signature was evident in these two segments. Four of the nine nucleotide changes, present on the HA, NA, NP and NS1 segments, were non-synonymous and lead to amino acid replacements (Table). Eight of the mutations were transition substitutions (seven of them A/G substitutions), and one change was a transversion substitution (A/T substitution). None of the changes in the sequences seemed to be located in regions of the genome responsible for known phenotypic differences or biological functions.

The differentiation of circulating influenza A(H1N1)v viruses into two clusters based on their nucleotide sequence differences was also supported by phylogenetic inference. Concatenated sequences were prepared using open reading frames of six viral segments (the ones included in the Table). Distance-based neighbour-joining trees were constructed using the Tamura 3-parameter model available in MEGA 4.0 [4]. Clustering of influenza A(H1N1)v viruses could be demonstrated by individual trees of the involved single genes (not shown) and with higher evidence by tree construction of concatenated sequences (Figure 2), despite the fact that the differences between the two clusters comprised only a few nucleotides. The analyses were supported by maximum likelihood using generalised time reversible substitution model (GTR) and Bayesian inference implemented in TOPALi v2 [5]. All phylogenetic analyses were conducted on all available sequences (Figures 3

Table

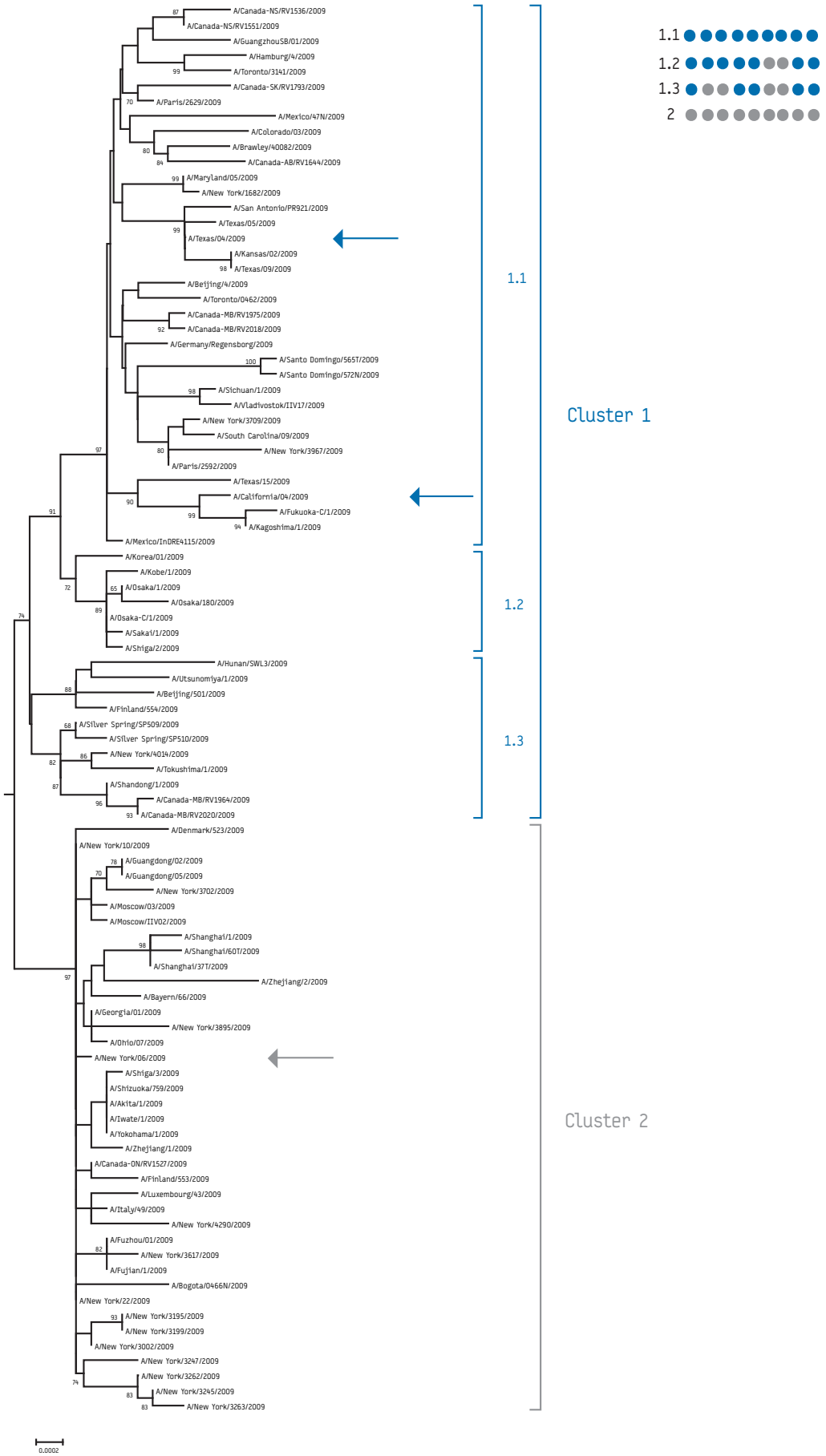
Nucleotide and amino acid residues located in six segments of the new H1N1 influenza viruses specific for the two clusters

	HA		NA	M		NP		NS	PB2
	658 (220)[a]	1,408 (470)	742 (248)	492 (164)	600 (200)	298 (100)	1,143 (381)	367 (123)	2,163 (721)
Cluster 1	T (S)	C (L)	A (N)	G (Q)	G (A)	G (V)	G (A)	A (I)	G (K)
Cluster 2	A (T)	T (L)	G (D)	A (Q)	A (A)	A (I)	A (A)	G (V)	A (K)

Nucleotide positions and amino acid positions (in brackets) for all genes are counted from the start codon.

Figure 2

Neighbour-joining phylogenetic tree of concatenated open reading frames of six viral segments of selected influenza A(H1N1)v viruses



The tree was rooted to influenza A/Michigan/01/09 and was calculated using 1,000 bootstrap values. The blue line marks cluster 1, including three sub-clusters, and the grey line marks cluster 2. The blue arrows show the two first isolates of cluster 1 and the grey arrow show the first isolate of cluster 2. The blue and grey circles stand (from left to right) for nucleotide replacements at HA T658A and C1408T, NA A742G, M G492A and G600A, NP G298A and G1143A, NS A367G, and PB2 G2163A.

and 4; these figures are only available in the online version) and representatives of each monophyletic group (Figure 2).

Taking into account the complete sequence data available from Mexico and the US, it is noteworthy that viruses of cluster 1 occurred earlier than those of cluster 2, with a time difference of about two weeks. Most sequences from Mexico, Texas and California belonged to cluster 1, whereas most sequences from New York belonged to cluster 2. Whether these differences were due to the geographical region, the date of isolation or other reasons needs to be elucidated in further epidemiological investigations. Virus sequences of both clusters have been reported from most countries on different continents. In Germany, influenza virus A/Regensburg/2009 was one of the first influenza A(H1N1)v isolates and belonged to cluster 1 [6]. This virus has been investigated by whole genome sequencing (GenBank accession numbers: FN401574–FN401581) and animal experiments in pigs and chickens [7]. Interestingly, viruses of both clusters could be detected in Germany although complete sequences of all eight segments were available only for four viruses at the time of this analysis (Figure 2).

All available full-length sequences for the six segments with cluster specific signatures were selected and duplicate sequences from identical isolates were removed. Of 305 viruses included in the analyses, 150 belonged to cluster 1 and 155 to cluster 2. All viruses in cluster 2 shared nine genetic signatures specific for this cluster. In cluster 1, three sub-clusters were identified. Most viruses in cluster 1 share all nine genetic signatures specific for this cluster (sub-cluster 1.1). In contrast, most viruses from Japan belonged to cluster 1 but had a cluster 2-like nucleoprotein sequence. These viruses constitute sub-cluster 1.2 (Japanese sub-cluster). A small group of sequences fit into cluster 1 when the concatenated sequences were analysed but shared the same four sequence features with cluster 2 (sub-cluster 1.3) (Figure 2), which may point to a reassortment event between the two clusters. The importance of these findings and epidemiological links between different clusters remains to be analysed.

Our findings allow the differentiation of the influenza A(H1N1)v viruses into distinct clusters among the currently circulating influenza A(H1N1)v viruses, contributing additional knowledge of the new pandemic virus and encouraging further research on this topic.

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"RAISIN" – a national programme for early warning, investigation and surveillance of healthcare-associated infection in France

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Surveillance is a key component of the French plan for prevention of healthcare-associated infection (HAI) and has progressively evolved in the past decades. We describe the development and current organisation of surveillance of HAI in France and summarise key achievements and results. Surveillance of HAI is under the auspice of the national institute for public health surveillance through a central coordinating structure, the Réseau d'alerte, d'investigation et de surveillance des infections nosocomiales (RAISIN), which consists of five regional coordinating structures, two national advisory committees of the Ministry of Health and public health agencies. Surveillance includes the performance of national prevalence surveys every five years (latest in 2006), specific surveillance networks to follow trends and characterise HAI that are national priority, and mandatory reporting of HAI that meet specific criteria for alert purposes. RAISIN prioritises activities, defines technical specifications of surveillance systems, coordinates their implementation, and supports response to alerts, emergences or outbreaks of HAI. We demonstrate that the French surveillance program of HAI has become comprehensive and contributes to evaluating the impact of control and prevention of HAI. Data from RAISIN indicate a general decrease in the risk of HAI in acute care in France. They show a decrease in HAI during recent years, particularly of those related to methicillin-resistant *Staphylococcus aureus* (MRSA) for which a drop of 38% was documented between 2001 and 2006. RAISIN is also integrated into European surveillance of HAI coordinated by the European Centre for Disease Control.

Background

Healthcare-associated infections (HAI) are leading causes of morbidity and mortality among hospitalised patients [1]. Five to 10 % of patients admitted to acute care hospitals acquire during their stay one or more infections according to recent European prevalence surveys [2-4].This proportion is greater in immuno-compromised patients and patients with underlying diseases, undergoing invasive procedures, admitted to an intensive care unit (ICU) and the elderly. In a multicenter study of tertiary-care hospitals, HAI contributed to the death of 2.8% of patients that died 48 hours after admission. Extrapolated nationwide this indicates that HAI may account for about 4,200 deaths per year in France [5]. Outbreaks of HAI are frequent and may spread between HCF through patient transfers [6]. Also HAI cause disability, reduce quality of life and create emotional stress [7, 8]. Effective infection control measures may prevent 20 to 30% HAI [9-11]. Surveillance is a key element of the control and prevention of HAI because it provides data relevant for appropriate intervention methods [10-13]. HAI have a growing social and political impact in many western countries with aging populations because the elderly are more susceptible to infections and require increasingly intensive healthcare [14,15]. In France, surveillance of HAI is integrated in the national HAI control and prevention program which was implemented more than two decades ago [16]. In this paper, we describe the organisation of HAI surveillance in France and its main outcomes.

Organisation of HAI control and prevention in France

The control, prevention and surveillance of HAI are based on interacting local, regional and national structures with complementary roles. Their organisation and coverage have developed progressively since 1988 and have been reinforced on several occasions All public HCF (since 1988) and private HCF

Figure

Nosocomial infection surveillance coordination structures and locations, France

(since 1999) are legally obliged to set up an infection control committee to define an HAI control program that is implemented by a control team. French authorities recommend one infection control nurse for 400 beds and one infection control practitioner for 800 beds; smaller HCF share infection control personal through networks. Five interregional infection control coordinating centers, Centre de coordination de la lutte contre les infections nosocomiales (CClin), were created in 1992 to coordinate control, prevention, counseling, surveillance and training activities and support hospitals in implementing the national program (Figure). Each CClin coordinate a network of regional antenna (n = 23), legally instituted in 2006. At the national level, two committees advise the Ministry of Health: one on strategic orientations, the other one is an expert committee that produces recommendations for the prevention of adverse health care events, including HAI.

Surveillance of HAI in France

A first survey of HAI was conducted in 46 hospitals in 1990 after this, the first large scale surveillance activity was a national prevalence survey in 1996 which was repeated in 2001and 2006 [18-21]. Surveillance HCF, participating on voluntary basis (hereafter referred to as voluntary HCF), targeting high priority HAI were developed by the CClin from 1993 onward. The system was completed in 2001 by a mandatory notification of HAI events, described in the section *Notification of HAI, alert and response to outbreaks*, to provide timely assistance to HCF for control purpose [22]. Surveillance of HAI was initially implemented through an interregional coordination level under the Ministry of Health. With the creation of a national institute for public health surveillance, Institut de Veille Sanitaire (InVS) in 1998, the coordination for HAI surveillance moved to the InVS. A coordinating structure that gathers in a contractual way the InVS, the five CClin, the Ministry of Health and its advisory committees and other public health agencies and bodies involved in HAI prevention was therefore set up: the Réseau d'Alerte, d'Investigation et de Surveillance des Infections Nosocomiales (RAISIN, nosocomial infection early warning, investigation and surveillance network). It prioritises surveillance activities, defines technical specifications of HAI surveillance, coordinates implementation of surveillance programs and studies and assists in investigating outbreaks [23].

Definitions for nosocomial infections

The definitions used for surveillance were adapted from the United States' Centers for Disease Control and Prevention (CDC) in 1992 [24,25] and further updated in 1999 to take into account long-term care patients [26] and surgical site infections (Table 1) [27,28]. In 2007, definitions for HAI were updated and expanded to outpatients care structures [29].

Surveillance activities

Prevalence surveys

Three national HAI prevalence surveys were performed in 1996, 2001 and 2006, to advocate and train HCF for HAI surveillance and control, to estimate the burden from HAI describe their characteristics and assess trends over time [19-21]. All public and private HCF were invited to participate. Participating HCF enrolled on a given day in June all inpatients present that day. Standardised questionnaires were used by trained investigators to collect data from medical records, microbiological laboratories, temperature charts and interviews with physicians or nurses. Data included characteristics of the participating HCF and patients: age, sex, admission date, individual risk factors including immunosupression, the Mac Cabe Score [30], extrinsic risk factors such as presence of a urinary or a vascular catheter and surgery within 30 days prior to the time of the survey. Up to three HAI were recorded for each patient. For each HAI, date of onset, infection site, microorganism and source were recorded. Each HCF entered data using dedicated software for validation, analysis and standardised reporting for feedback. Data were then transferred to CClin for aggregation and analysis at regional level, and to InVS, which managed the national database, analysis and report.

The number of HCF and patients included increased overtime. However, the number of patients per HCF decreased due the smaller size of newly recruited hospitals (Table 2). Results were relatively stable for most parameters in all three surveys, however, the prevalence of HAI, infected patients and methicillin-resistant *Staphylococcus aureus* (MRSA) decreased from 1996 to 2006, especially after 2001 (Table 2). Comparisons between 2001 and 2006 were restricted to 1,351 HCF that participated in both surveys, used similar case definitions and were adjusted for all available confounding variables to account for changes in methods in 2006 (exclusion of asymptomatic bacteriuria) and the inclusion of smaller hospitals in most recent survey. The multivariate analysis indicated a 12 % decrease in the prevalence of infected patients and of 38% for infection with MRSA [21].

Incidence surveillance networks

Since 1993, five incidence surveillance networks of voluntary HCF were set up: surgical site infections (SSI), intensive care units (ICU), blood and body fluids exposure (BBFE), bloodstream infections (BSI) and multidrug-resistant bacteria (MDRB) infections. The first two networks use the methodology proposed by the United States National Nosocomial Infections Surveillance System (NNIS) system and produce standardised indicators [72]. Denominator data collection is, however, patient-based and not aggregated by unit of care which allows adjustment on individual risk factors. Surveillance of BBFE uses the method proposed by the American National Surveillance System for Healthcare Workers (NaSH) [73]. The BSI and MDRB networks are laboratory-based. For each surveillance network, data are collected, entered and analysed by participating HCF using dedicated software. Data are sent to CClin for validation and aggregation into a regional database for analysis. Surveillance methods that were implemented through the five CClin were standardised nationwide between 1999 and 2003, and regional data are now aggregated into national databases [31]. Annual national HAI surveillance reports are available on the Raisin website [23]. Current efforts focus on facilitating data collection and on developing new indicators such as the standardised incidence ratio [32].

Surveillance of surgical site infections (SSI): the ISO-Raisin network

Since 1999, regional SSI surveillance data are aggregated into a national database. Each year, CClin include voluntary surgery wards for a two or three months survey of at least 200 surgical patients each (excluding re-interventions) with a post-operative 30 day-follow-up. Data include risk factors (age, sex, score of the American Society of Anesthesiologists, [33] pre- and post-operative hospital stay, type and duration of procedure, emergency/elective procedure, video-endoscopy and Altemeier wound class) and SSI, if any [34, 35]. Participation increased from 1999 to 2006. from 230 (8.2%) to 568 (20%) of the 2,804 public and private HCF (Table 3). The annual number of procedures rose from 79,803 in

Table 1

Definitions for Hospital-acquired infection (HAI) and Surgical site infections (SSI) in France

Definitions for Hospital-acquired infection (HAI) and Surgical site infections (SSI) in France	
Hospital-acquired infection (HAI)	Infections occurring at least 48 hours after the patient's admission.
Surgical site infections (SSI)	Infections occurring within 30 days after an operative procedure if no implant is left in place or within one year if an implant is in place and the infection appears to be related to the operative procedure.

Table 2

Participation and main results of nosocomial infection point prevalence surveys, France, 1996 to 2006

Year	Hospitals (n, % of all French hospitals beds)	Patients included (n)	Prevalence of HAI (%) all HAI [acquired only]	Prevalence of infected patients (%) all HAI [acquired only]	Proportion of MRSA among S. aureus (%)
1996	830 (77%*)	236,334	n.a [7.6]	n.a. [6.7]	57%
2001	1,533 (77%†)	305,656	7.5 [6.4]	6.9 [5.9]	64%
2006	2,337 (94%¶)	358,467	5.38 [4.34]	4.97 [4.01]	52%

HAI: healthcare-associated infections; MRSA: methicillin-resistant Staphylococccus aureus; n.a: not available
* for public hospitals only;
† 55% for private hospitals and 91% for public hospitals
¶ 84% for private hospitals and 99% for public hospitals
Note: the 1996 survey only collected data on HAI acquired in the reporting facility; the 2001 and 2006 surveys included HAI acquired in the reporting facility AND imported from another facility; both types of rates are given when available

Table 3

Annual participation and trends in healthcare-associated infections incidence through RAISIN (Réseau d'alerte, d'investigation et de surveillance des infections nosocomiales) incidence surveillance networks, France, 1999 – 2006

Surveillance Network	Year of Surveillance							
	1999	2000	2001	2002	2003	2004	2005	2006
ISO-Raisin (surgical site infections)								
Healthcare Facilities (n)	230	248	292	303	271	340	425	568
Surgical wards (n)						811	1,027	1,331
Procedures (n)	79,803	82,348	109,419	114,579	107,576	126,451	150,006	193,946
Overall SSI incidence (%) ¶	2.0	1.8	1.7	1.5	1.5	1.6 [1.59]	1.37 [1.24]	1.26 [1.26]
Overall SSI incidence (%) (NNIS-0) ¶	1.1	0.9	0.9	0.8	0.9	0.9 [0.93]	0.78 [0.73]	0.74 [0.58]
REA-Raisin (infections in intensive care units)								
Intensive care unit wards (n)						116	141	158
PNE per 1,000 intubation-days						17.1	17.4	16.1
COL per 1,000 catheter-days						5.86	5.56	4.87
BSI per 1,000 patient days						3.32	3.35	3.27
UTI per 1,000 urinary catheter-days						8.44	7.94	7.94
AES-Raisin (blood and body fluids exposures)								
Healthcare facilities (n)				228	228	371	385	518
BBFE per 100 beds ‡				6.9	7.5	8.9 [7.9]	8.8 [7.6]	8.0 [7.2]
BN-Raisin (bloodstream infections)								
Healthcare facilities (n)				268	137	286		
BSI per 1,000 patient days				0.60	0.62	0.45		
BMR-Raisin (multidrug-resistant bacteria)								
Healthcare facilities (n)				478	488	527	589	675
MRSA cases per 1,000 patient days *				0.63	0.68 [0.71]	0.62 [0.68]	0.58 [0.63]	0.55 [0.60]
ESBL cases per 1,000 patient days †				0.13	0.14 [0.17]	0.15 [0.18]	0.16 [0.20]	0.17 [0.19]

BBFE: blood and body fluids exposures; BSI: bloodstream infections; COL: central venous catheter colonisation with or without catheter-related infection/bacteraemia (CRI/CRB);
ESBL: extended-spectrum beta-lactamase, MRSA: methicillin-resistant Staphylococcus aureus; NNIS: National Nosocomial Infections Surveillance System [REF]; PNE: ventilator-associated pneumonia;
SSI: surgical site infections; UTI: urinary tract infections (UTI) associated with indwelling urinary catheter.
¶ Results within brackets calculated for cohort of 374 surgical wards participating in the SSI survey from 2004 to 2006.
‡ Results within brackets calculated for cohort of 173 healthcare facilities participating in the BBFE survey from 2004 to 2006.
* Results within brackets calculated for cohort of 255 healthcare facilities participating in the MRSA survey from 2003 to 2006.
† Results within brackets calculated for cohort of 228 healthcare facilities participating in the ESBL survey from 2003 to 2006.

1999 to 193,946 in 2006. Incidence of SSI varied according to NNIS score from 0.85% for the lowest risk patients (NNIS-0) to 12.92% for the highest risk patients (NNIS-3). In this group, SSI incidence decreased over time (Table 3). Among NISS-0 patients, SSI icidence significantly decreased for herniorraphy (-70%), cholecystectomy (-55%), appendicectomy (-53%), colon surgery (-33%), caesarean section (-56%), and breast surgery (-39%) [36-38-]. Surveillance of SSI is well accepted and provides standardised indicators to evaluate prevention. It suggests a positive impact of the French national HAI control program, at least in lower risk patients.

Surveillance of HAI in intensive care units (ICUs): the REA-Raisin network

The REA (Réanimation)-Raisin targets device related-infections in ICUs: ventilator-associated pneumonia (PNE), central venous catheter colonisation (COL) with or without catheter-related infection/bacteraemia (CRI/CRB), urinary tract infections (UTI) associated with indwelling urinary catheter and BSI. Six months per year, voluntary ICU collect for data for patients hospitalised more than two days in the ICU on patients' characteristics (age, sex, admission date), risk factors (trauma, antibiotic treatment, diagnosis category, immunosupression, new simplified acute physiology score -SAPS II [39], invasive devices) and infections. Incidence rates are adjusted per 1,000 device-days [40]. In 2006, 158 ICUs (accounting for about 25% of French ICU) included 22,090 patients, of whom 3,113 (14.1%) had at least one infection (5,284 nosocomial events). The most frequent micro-organisms were *Pseudomonas aeruginosa* (15.0%), *E. coli* (14.8%), *S. aureus* (14.0%), *Candida albicans* (5.7%) and *S. epidermidis* (5.5%) ; 39,5% of *S. aureus* strains were resistant to methicillin in 2006 (2004: 48.7%). Incidence rates decreased from 2004 to 2006 for PNE (-5.9%), COL (-16.9%), BSI (-1.5%) and UTI (5.9%) [40-42] which suggest an improvement for HAI in ICU (Table 2).

Surveillance of blood and body fluids (BBFE) exposure: the AES-Raisin network

The AES (Accident d'Exposition au Sang)-Raisin network monitors the incidence of reported occupational BBFE in French healthcare workers. Since 2002, a prospective national follow-up of healthcare workers has been set up in tertiary hospitals, local medical centers and specialised psychiatric centers [43]. All reported BBFE are documented by the occupational physician using an anonymous standardised questionnaire [44]. In 2006, 518 HCF, accounting for 18% of 2,804 French HCF and 43% of hospital beds, recorded 14,876 BBFE; the majority of these (72%) were needle-stick injuries. Around half (48.6%) of 12,123 percutaneous injuries were avoidable through adherence to standard precautions. The BBFE incidence rate was 8.0 per 100 hospital beds (Table 3), 1.5 per 100 full-time equivalent physicians, 6.5 per 100 full-time equivalent nurses and 1.8 per 100 full-time equivalent nurses 'aides. Human immunodeficiency virus (HIV) serology was unknown in 3,353 (22.5%) patients that were the source of a BBFE.

Extrapolating results nationwide, it was estimated that 35,418 BBFE occurred in 2006 in France. In 173 HCF that participated over all years, compliance to glove use increased from 60.6% in 2004 to 66.1% in 2006 and sharps disposal containers accessibility increased from 65.2% to 68.6%, while BBFE incidence decreased slightly (Table 3) [45].

Surveillance of bloodstream infections (BSI): the BN-Raisin network

Surveillance of BSI was conducted from 2002 to 2004 through the BN-Raisin network. It provided a reference for the incidence, microbial ecology and origin of acute invasive HAI to assess the impact of control measures for specific routes of infection [46]. The laboratory-based network included all wards of voluntary HCF for three months each year. In 2004, 286 HCF (10% of public and private HCF) participated. For each nosocomial BSI a standardised questionnaire documented patients' characteristics (age, sex, type of hospital and medical specialty), source of the bacteraemia, organisms and antibiotic susceptibility and follow-up for seven days after onset of bacteraemia. Incidence was calculated per 1,000 patient days (pd) [47]. In 2004, overall incidence was 0.45 (Table 3). Among identified sources, venous catheters and urinary tracts catheters were the most common (24.9 and 24.8% respectively). The main microorganisms isolated were *E. coli* (20.5% of isolated pathogens, 2.8% of which produced extended-spectrum beta-lactamase - ESBL), *S. aureus* (24.9%, 41.4% of which were MRSA) and coagulase-negative *Staphylococci* (24.8%). Death occurred in 11.8% patients with BSI and was more frequent in patients infected with *P. aeruginosa* (21.5%) than patients with BSI caused by other bacteria (11.22%). These results indicate that venous and urinary tract catheter-related bacteraemia should be targeted for prevention with priority.

Surveillance of hospital-acquired multidrug-resistant bacteria (MDRB): the BMR-Raisin network

France is one of the European countries mostly affected by MDRB, particularly MRSA [48]. The BMR (Bactériémie Multirésistante)-Raisin network assesses the impact of national efforts on the incidence of MDRB HAI. Data on MRSA and ESBL-producing *Enterobacteriaceae* are collected prospectively three months a year from all diagnostic specimens other than screening isolates; duplicates, strains with the same susceptibility profile per patient, are excluded and incidence rates per 1,000 pd are calculated and stratified by type of ward [49].

In 2006, 675 HCF participated (24% of the 2,804 public and private HCF) a 41% increase since 2002. The MRSA incidence was 0.55 per 1,000 pd and greater in acute (0.65) and in intensive care (1.91) than in rehabilitation and long term care facilities

Table 4

Mandatory notification criteria and cumulative number, France, 2001 – 2006

Notification criteria for healthcare-associated infections	N	%
1. Rare or noticeable HAI, due to …	2,644	63.8
1a. microorganism characteristics, including resistance	1,806	43.5
1b. infection site	746	18.0
1c. associated medical devices	353	8.5
1d. medical practices	167	4.0
2. Patient's death linked to HAI	823	19.8
3. Airborne or waterborne HAI	622	15.0
4. Otherwise mandatory notification (e.g., legionellosis)	466	11.2
5. Other (none of the above)	566	13.6
Total number of notifications	4,147	100.0

HAI: healthcare-associated infections.
Note: sum of all notification criteria is >100% as healthcare facilities can use one or more criteria
Source: Bulletin épidémiologique hebdomaire 51-52/2006 and 30-31/2008.

(0.37). In 255 HCF that participated from 2003 to 2006, MRSA incidence decreased by 15% (Table 3). The ESBL incidence was 0.17 per 1,000 pd in 2006; it was twice higher in acute care (0.20) compared to rehabilitation and long term care facilities (0.11). Among the 228 HCF that participated from 2003 to 2006 incidence of ESBL increased from 0.17 to 0.19 (+12%, Table 3) in line with a growing proportion of *Escherichia coli* among *Enterobacteriaceae* species (2003:25%; 2006: 43%). These results suggest a positive impact of the HAI national program on hospital-acquired MRSA [50]. In contrast, the emergence of ESBL, especially for *E. coli,* is of concern [50,51]. Similar trends have been observed by the National Observatory for the Study of Antimicrobial Resistance (Observatoire National de l'Etude de la Résistance Bactérienne aux Antibiotiques - Onerba), [52], an independent organisation that promotes standardisation of methodologies, conducts descriptive studies on antimicrobial resistance and contributes to the European Antimicrobial Resistance Surveillance System (EARSS) since 2001 [48,53].

Notification of HAI, alert and response to outbreaks

Prevalence or incidence surveys do not cover all hospitals and HAI and do not allow prompt detection of emerging HAI or outbreaks. Therefore, a national HAI infection notification system was implemented in 2001 to detect unusual events, promote early outbreak investigation and control and identify emerging problems. HCF have to notify HAI to CClin and the district health authority, which in turn inform the InVS. Notification criteria are:

- rare or severe infections, concerning microorganism characteristics (i.e. resistance), the infection site, a contaminated device/product or practice failure;
- infections leading to death;
- airborne or waterborne infection (e.g., legionellosis);
- otherwise reportable diseases (e.g., tuberculosis etc.).

As the system is designed to detect unusual events, there is no restrictive list of events to notify. The reporting form includes the nature of the event and main characteristics, investigations and control measures performed, and allows to request assistance [22,54,55]. At the national level, InVS provides support for outbreak investigation and analyses data to detect unusual trends.

From 8 January 2001 to 12 December 2006, the InVS received 4,117 notifications from 918 HCF (33% of all HCF in France), accounting for 12,561 HAI and 1,482 deaths (13%). Twenty-six percent notifications (1,059 out of 4,117) were related to clusters (ranging from 2 to 178 cases) and external assistance was requested for 8% (319). The average monthly notifications increased from 30 in 2001 to 80 in 2006. The median time between an event and notification to InVS decreased from 62 days in 2001 to 9 days in 2006. The most frequently used notification criteria were related to microorganisms (33%), deaths associated with HAI (15%), infection sites (13%), airborne/waterborne HAI (11%), contaminated devices (6%), or practice failures (3%). The most frequently notified microorganisms were *S. aureus* (15%, 47% of which were MRSA), *Enterobacteriaceae* (11%, 72% of which produced ESBL), *Acinetobacter* (9%, 28% of which were imipenem-resistant), *P. aeruginosa* (8%, 37% of which were imipenem-resistant and 27% ceftazidime-resistant), or *Legionella* (7%). *Enterococcus faecalis* or *E. faecium* accounted for 3% of all notifications, 91% of which were vancomycin-resistant (VRE) [55].

Today, the system is well accepted; it provides daily assistance in outbreak investigation and control to HCF, and allowed the early detection and control of outbreaks or emerging pathogens at local, regional or national level, such as an outbreak of hepatitis C in a hæmodialysis unit in 2001 [56], an outbreak of VEB-1 ESBL-producing *Acinetobacter baumannii* in northern France in 2003 [6], an outbreak of *Enterobacter sakazakii* associated with a contaminated powdered infant formula in 2004 [57], the national emergence of VRE in 2005 [58] or of 027/NAP1 *Clostridium difficile* in 2006) [59]. Following the detection and extensive investigation and follow-up of these major events, national recommendations were updated accordingly or issued where not available.

Specific studies through the RAISIN network

Specific studies are performed through Raisin to assess the impact of a particular threat or document and characterise a specific HAI issue. We illustrate the benefits of three such nation-wide public health oriented studies.

Survey to estimate the presence of glycopeptide intermediate S. aureus *(GISA)*

In 1999, following reports of clinical isolates of *S. aureus* with reduced susceptibility to glycopeptides (Glycopeptide intermediate *S. aureus* – GISA, being intermediately resistant to teicoplanin and susceptible to vancomycin) a survey was carried out in 2000 and 2001 to estimate the incidence of GISA and their proportion within MRSA strains. An optional GISA module was proposed to hospital laboratories participating in MDRB surveillance. During one month, each first MRSA strain isolated from a clinical sample was documented with a standardised questionnaire and then screened for GISA using recommendations from the French Society for Microbiology. One hundred and sixty-five volunteer hospitals included 2,066 patients with a clinical MRSA isolate, 254 (12%) of which were suspected to be GISA, however, only 45 (2.2%) were confirmed GISA, an incidence of GISA of 2.3 per 100,000 pd. Analysis of the antibiotic susceptibility profiles suggested that most strains were closely related to the gentamicin-resistant MRSA clone that was responsible for the MRSA epidemic in French hospitals until 1995 [60]. Although this study confirmed the presence of GISA strains in French hospitals in 2000-2001, such strains were rarely identified by French hospitals.

Survey on risk of bacterial pneumonia from defective bronchoscopes

In 2002, flexible bronchoscopes of the same brand were recalled after a defect (a loose biopsy-port cap in the bronchoscopes) that reduced the efficacy of disinfection procedures and might be responsible of transmitting infections from patients to patients was identified by the French Health products safety agency (Agence Française de Sécurité Sanitaire des Produits de Santé Afssaps). InVS and CClin assessed the risk of bacterial pneumonia among patients exposed to these medical devices in a retrospective study including the last 30 patients in each participating HCF exposed to the bronchoscopes before they were recalled. Of 347 HCF contacted, 211 (67%) participated in the survey and traced 4,112 patients for exposure to 97 (85%) of 114 defective bronchoscopes. One bacterial pneumonia (0.07%) was documented among exposed patients within 2 to 10 days after exposure. In addition we found that 16 (1.3%) patients were colonised or infected with a *Mycobacterium* on the day of bronchoscopy, in nine cases *Mycobacterium tuberculosis*. This demonstrated that tracing patients exposed to specific bronchoscopes was possible in French

hospitals, suggested that the risk of bacterial pneumonia associated with the defective bronchoscopes was low but that exposure of patients to transmission of mycobacterial infection was possible if the bronchoscopes were not adequately reprocessed after use [61].

National survey to assess the prevalence of hepatitis C virus and hygiene practices in dialysis units

Following a large outbreak of hepatitis C virus (HCV) infection in a dialysis unit in 2001 [56] a national survey was undertaken to assess the prevalence of HCV and of hygiene practices in dialysis units. Two complementary studies were carried out: one through Raisin and the French Nephrology Society who sent a standard mail questionnaire to all hæmodialysis units between October and December 2004 and a second was an observational audit of infection control practices on a 10% random sample of dialysis units. Of 873 hæmodialysis units, 477 (55 %) participated, 200 dialysis centers and 277 autodialysis units. HCV prevalence was 6.6 % in hæmodialysis centers and 5.9 % in autodialysis units. The audit of practices survey indicated a high level of compliance with infection control recommendations but identified breaches for which corrective actions were needed [62].

Laboratory support to surveillance

In France, laboratory support to surveillance (detection, typing and molecular epidemiology) is performed through a network of 47 national reference centers (NRC) funded by InVS and designated every four years through a call for tender. The list of NRC is revised regularly by a national committee and their specific missions and tasks are defined according to surveillance needs [63]. Several NRC provide an important contribution to surveillance and outbreak investigation of HAI caused by pathogens such as MRSA, *P. aeruginosa, Legionella*, hepatitis C virus, or glycopeptide-resistant *Enterococcus*. Following *C. difficile* 027 introduction in 2006 in France, a network of five regional laboratories (one in each CClin area) coordinated by a specific NRC was created to enhance the national capacity of typing of *C. difficile* strains isolated from patients suffering severe disease or outbreaks identified through the mandatory notification system. This close institutional interaction between routine surveillance activities, detection of new emerging infectious threats and the planning of reference laboratory resources greatly facilitated the response to 027 *C. difficile* spread in French hospitals [59]. A prospective surveillance of *C. difficile* infections has been implemented in 2009.

Discussion

The surveillance of HAI in France has gradually evolved over two decades to become comprehensive finally. It has documented encouraging results in recent years which probably reflect the positive impact of control and prevention efforts. The collegial management of a comprehensive system through Raisin allows standardisation of protocols and a close interaction between private and public hospitals, regional structures and national public health agencies. The very high level of participation of hospitals in the 2006 national prevalence survey illustrates the effectiveness of this three level - national, inter-regional and local- approach.

The surveillance activities in which Raisin is involved include planned surveys, surveillance networks and assistance to investigation of and response to unusual HAI events. These complementary activities allow each participating structure a comprehensive understanding and knowledge of the HAI epidemiology, which facilitate response and public health actions and finally promote the prevention of HAI. The generic and flexible early warning system for HAI has clearly and repeatedly shown a strong added value to prevalence studies and surveillance networks. It supports HCF in the control of outbreaks that may spread to other hospitals regionally or even nationally. Besides regional or national alerts described previously, it also allowed responding to recurrent outbreaks such as several outbreaks of hepatitis C transmission in health care settings [64,65].

Efficient surveillance is resource intensive. Because of reporting delays, often required complex analysis (including risk-adjustments), and the voluntary participation of HCF, HAI surveillance has been criticised and sometimes felt not linked enough with day-to-day action by consumers and policy planners. Pushed by a strong social demand, the French Ministry of Health has implemented a national program of mandatory patient care performance indicators in all HCF. The first published indicators are scores related to the HCF efforts to control and prevent nosocomial infection and of appropriate use of antibiotics [66,67]. Additional indicators are under consideration and include the rate of MRSA infection in HCF. The Raisin database on hospital-acquired multidrug-resistant bacteria (BMR-Raisin) was extensively used to help define and construct this last indicator. However, publicly reported performance data cannot replace surveillance because HAI, surveillance has a unique value in the evaluation of efforts to reduce the incidence and prevalence of HAI.

On a European level, Raisin, through its coordinating structure and its institutional integration with the InVS, has permitted to interact efficiently with European surveillance and early warning schemes, which since 2005 are part of the European Centre for Disease Control (ECDC) mandate. French SSI surveillance data are included from 2004 to 2006 in the Hospitals in Europe Link for Infection Control through Surveillance (HELICS) database, representing 86,434 (17%) of the 521,186 procedures included in HELICS-SSI database [38] and for 57,963 (41%) of the 142,558 patients included in the HELICS-ICU database [42]. France collaborates actively to the European Early Warning and Response System (EWRS) for HAI threats that may spread to other European Member States [68]. The link between the EWRS and the HAI notification system is made by InVS as part of its risk assessment of alerts. If an HAI event is severe and may spread to other Member States, the EWRS is used to inform all EU partners and ECDC about the nature of the event, its potential risk of spread and the measures taken to limit its spread [69]. This was done for several severe outbreaks such as the VEB-1-producing A. baumannii outbreak in hospitals in northern France [6], an international outbreak of *Klebsiella pneumoniae* infections in patients of an hepatic surgery centre [70], and the 027 *C. difficile* outbreak in 2006 [59]. The timely share of authoritative information between national public health authorities before it has been published and communicated via the media is extremely useful to national and EU public health authorities in order to anticipate and plan and coordinate response.

A European HAI surveillance scheme implies some adjustment of national systems with the commonly agreed European methodology. When this will be done in all Member States, the comparison of rates and of trends overtime by countries will become legitimate and may yield interesting insights regarding quality and structure of care across Europe. However, comparison of rates needs to be done carefully, as differences in healthcare systems, methodologies, and sample sizes may have a huge influence on rates and their significance [71]. In Europe, the methods, case definitions and data collected on HAI are not harmonized, which preclude comparison of results and burden of HAI between EU Member States. European harmonisation of surveillance schemes for HAI

such as prevalence surveys, SSI and ICU surveillance need further European consideration.

As France is now in its 2009-2012 plan for the prevention and control of HAI, surveillance will continue to be adjusted to new developments and challenges. Foreseen evolutions include the evaluation and adjustment of current surveillance networks, the move of the HAI notification system which is still done through paper forms to a fully electronic scheme and the extension of surveillance to HAI that occur in health care settings other than hospitals.

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Oseltamivir-resistant influenza A(H1N1) viruses detected in Europe during season 2007-8 had epidemiologic and clinical characteristics similar to co-circulating susceptible A(H1N1) viruses

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During the 2007-08 influenza season, high levels of oseltamivir resistance were detected among influenza A(H1N1) viruses in a number of European countries. We used surveillance data to describe influenza A(H1N1) cases for whom antiviral resistance testing was performed. We pooled data from national studies to identify possible risk factors for infection with a resistant virus and to ascertain whether such infections led to influenza illness of different severity. Information on demographic and clinical variables was obtained from patients or their physicians. Odds ratios for infection with an oseltamivir resistant virus and relative risks for developing certain clinical outcomes were computed and adjusted through multivariable analysis. Overall, 727 (24.3%) of 2,992 tested influenza A(H1N1) viruses from 22 of 30 European countries were oseltamivir-resistant. Levels of resistance ranged from 1% in Italy to 67% in Norway. Five countries provided detailed case-based data on 373 oseltamivir resistant and 796 susceptible cases. By multivariable analysis, none of the analysed factors was significantly associated with an increased risk of infection with an oseltamivir-resistant virus. Similarly, infection with an oseltamivir-resistant virus was not significantly associated with a different risk of pneumonia, hospitalisation or any clinical complication. The large-scale emergence of oseltamivir-resistant viruses in Europe calls for a review of guidelines for influenza treatment.

Introduction

In Europe, virological surveillance of antiviral susceptibility of influenza viruses has been performed since 2004 through the European Union (EU)-funded European Surveillance Network for Vigilance against Viral Resistance (VIRGIL), in collaboration with the European Influenza Surveillance Scheme (EISS), the World Health Organization (WHO) and national influenza centres (NICs) [1]. In January 2008 this surveillance system started to detect significant proportions of oseltamivir-resistant viruses among influenza A(H1N1) specimens collected in several European countries from November 2007 onwards [2]. This was associated with a histidine to tyrosine mutation at residue 275 of the neuraminidase protein (H275Y or H274Y in N2 numbering), which is known to confer high level resistance to the neuraminidase inhibitor oseltamivir [3]. Oseltamivir resistance was confirmed in most EU countries as more influenza A(H1N1) viruses were isolated and tested, although at very different levels ranging from under 2% of all influenza A(H1N1) viruses tested in Italy and Spain to over 40% in Belgium, Estonia, France and Norway by the end of the 2007-8 influenza season [4,5]. These differences, however, were also influenced by the time during the season when specimens were collected and the number of influenza A(H1N1) viruses tested for oseltamivir susceptibility in each country [6]. The wide circulation as well as outbreaks of oseltamivir-resistant viruses, together with a rise in resistance proportions throughout the season indicated that influenza A(H1N1) H275Y-mutated strains were fit and transmissible [6]. This was supported by the absence of correlation between oseltamivir resistance and exposure to oseltamivir at population level [7]. However, it was unclear whether there were any factors favouring infection with an oseltamivir-resistant virus and whether such an infection would affect the clinical course of influenza illness with or without treatment.

In order to obtain additional data on the characteristics of patients infected with influenza A(H1N1) viruses, the EISS and VIRGIL coordination centres rapidly set up an enhanced

surveillance system requesting the European NICs to report for confirmed influenza A(H1N1)-infected patients additional information (such as clinical outcome and exposure to antivirals) to that already routinely collected. Furthermore, a number of countries in the EU and European Economic Area (EEA) conducted specific epidemiological investigations based on a general protocol developed by the European Centre for Disease Prevention and Control (ECDC) in collaboration with some EU countries with the following objectives:

- To identify risk factors for infection with an oseltamivir-resistant versus an oseltamivir-susceptible influenza A(H1N1) virus during the 2007-8 influenza season.
- To assess whether patients infected by an oseltamivir-resistant influenza A(H1N1) virus had a different risk of a severe clinical outcome than patients infected by an oseltamivir-susceptible influenza A(H1N1) virus.

The study hypothesis was that oseltamivir-resistant influenza A(H1N1) viruses emerged during the 2007-8 season were different from co-circulating oseltamivir-susceptible influenza A(H1N1) viruses in terms of risk factors for infection and severity of illness.

This article reports on the descriptive analysis of data from the enhanced surveillance and on the analysis of the pooled data from the national epidemiological studies.

Methods

Surveillance data

The descriptive analysis of influenza surveillance data concerns information collected during the season 2007-8 from week 40/2007 to week 20/2008 in countries participating in EISS. National surveillance systems collect standard case-based epidemiological information for all patients undergoing clinical sampling for laboratory confirmation. However, this information is not routinely reported to EISS. Laboratory confirmation is carried out for surveillance purposes on a subset of individuals presenting with influenza-like illness (ILI) and/or symptoms of acute respiratory infection (ARI) to one of the sentinel physicians participating in the national influenza surveillance. The selection of patients with ILI or ARI undergoing virological testing can be either random/systematic, as recommended by EISS, or left to the physician's clinical judgement [8]. Virological testing is usually performed at the NICs, which are WHO-recognised laboratories for influenza and in Europe collaborate within the Community Network of Reference Laboratories (CNRL) for human influenza [9]. The sentinel physicians are part of national networks that intend to cover a representative sample of the general population. Moreover, case-based information is collected nationally on patients tested for influenza as part of the individual clinical management (non-sentinel samples). Such samples cover a heterogeneous group of individuals including hospitalised patients who are likely to have experienced a more severe influenza illness. In Norway, however, both non-sentinel and sentinel specimens are collected mainly from patients presenting to the primary healthcare system. Additional information on the organisation and functioning of virological influenza surveillance in Europe can be found elsewhere [10].

During the season 2007-8, when higher than expected levels of oseltamivir resistance were detected in influenza A(H1N1) viruses in many European countries, the data routinely collected by EISS and VIRGIL was expanded to include the following additional information: oseltamivir susceptibility, age, gender, geographic location, hospital or community-based, date of specimen collection, date of disease onset, exposure to antivirals of the patient or household contact (in the 14 days preceding onset of illness), influenza vaccination status, and whether complications, hospitalisations or death occurred in the 14 days following onset of illness. Oseltamivir susceptibility was determined phenotypically or by sequencing or by both, as described elsewhere [6]. Data were uploaded during the season and were downloaded on 19 August 2008. The descriptive virological surveillance data presented in this paper might differ slightly from those presented previously [6], as data for the present paper were downloaded one month later and countries could have updated the database since then. In addition, the weeks included in reference [6] (weeks 40-19) differed by one week from the data presented in this paper (weeks 40-20). A descriptive analysis was carried out and individual characteristics were assessed.

Some European countries experiencing high levels of oseltamivir resistance collected additional information on influenza A(H1N1) cases by retrospectively interviewing patients and/or their physicians. The ECDC supported and coordinated such studies by providing a study protocol and organising three meetings as well as regular teleconferences with the study group. To increase the efficiency and timeliness of a European study, only those countries were invited to participate in which at least 50 virus isolates had been tested for antiviral resistance and some level of oseltamivir resistance had been detected as of February 2008. Of the six countries that met this criterion for inclusion, five (Germany, Luxembourg, the Netherlands, Norway and the United Kingdom (UK)) agreed to participate and to provide their databases for a pooled analysis by ECDC.

Epidemiological studies

Questionnaires and study procedures developed by each of the five participating countries were submitted to the ECDC in order to identify common variables for the joint analysis. In all participating countries, the study population included all individuals diagnosed with an influenza A(H1N1) virus infection between week 40/2007 and week 20/2008 for whom antiviral susceptibility testing was performed and for whom it was clear whether the specimens came from sentinel or non-sentinel sources.

Analysis of risk factors for infection with resistant virus

To identify risk factors for infection with an oseltamivir-resistant influenza A(H1N1) virus, a nested case control approach was chosen within the cohort of subjects with laboratory-confirmed influenza A(H1N1) infection. Cases were defined as individuals with laboratory-confirmed influenza A(H1N1) infection whose isolates showed phenotypic (IC50 level) or genetic (H275Y mutation) markers of oseltamivir resistance, and controls were defined as individuals with laboratory-confirmed influenza A(H1N1) infection whose isolates were susceptible to oseltamivir by either phenotypic or genetic analysis. Information was collected for cases and controls on age, sex, country of residence, location of initial sampling (sentinel versus non-sentinel), pre-existing medical conditions, influenza vaccination status, antiviral exposure (i.e. prophylaxis or treatment in the 14 days preceding symptom onset) and travel history within 10 days before symptom onset.

Analysis of outcomes of infection with resistant virus

To assess whether patients infected by oseltamivir-resistant influenza A(H1N1) virus were at higher risk of a severe clinical outcome than patients infected by oseltamivir-susceptible influenza

A(H1N1) virus, a cohort approach was chosen, with cases and controls as the exposed and the unexposed subjects, respectively. The outcomes investigated were symptoms at presentation, hospitalisation for any cause related to influenza, pneumonia, death, and any other clinical complication attributable to influenza virus infection.

Data collection

Retrospective data for the case control analysis and follow-up information for the cohort analysis were collected using slightly different methods and data sources in the different countries. In Germany a subset and in Luxembourg all patients with a confirmed influenza A(H1N1) infection were contacted by local or national public health offices and administered a questionnaire by telephone (Germany) or mail (Luxembourg) in addition to the information already retrieved from the routine surveillance datasets. In the Netherlands, all sentinel physicians and virologists (and subsequently the treating clinicians in the hospitals) who had provided specimens positive for influenza A(H1N1) were contacted by the national public health institute and sent a questionnaire by mail. Those not responding were contacted by telephone. In Norway, general practitioners (GPs) and clinicians in hospitals who had reported an influenza A(H1N1) case to the NIC were contacted by the national public health institute and administered

Table 1

Influenza detections and oseltamivir resistance of influenza A(H1N1) viruses in countries reporting data to EISS and VIRGIL during the 2007-8 influenza season (surveillance database)

Country	Specimens tested positive for influenza virus	Influenza A detections; (% in brackets)	Influenza A(H1) virus detections[a] / subtyped viruses	Influenza A(H1N1) viruses tested for oseltamivir resistance[b]	InflluenzaA(H1N1) viruses resistant to oseltamivir[b]; (% in brackets)	Proportion of resistant viruses detected by sentinel sources	Case-based clinical data available in surveillance database (yes/no)
Austria	531	457 (86)	262/262	164	12 (7.3)	100	Yes
Belgium	918	596 (65)	312/318	32	17 (53.1)	100	Yes
Bulgaria	21	16 (76)	16/16	9	0	n.a.	n.a.
Croatia	176	113 (64)	91/91	6	0	n.a.	n.a.
Czech Republic	262	176 (67)	135/135	24	0	n.a.	n.a.
Denmark	306	203 (66)	182/196	45	2 (4.4)	n.a.	Yes
Estonia	244	207 (58)	137/198	7	3 (42.9)	100	Yes
Finland	209	165 (79)	69/138	13	3 (23.1)	n.a.	No
France	2,887	1,820 (63)	255/267	496	231 (46.6)	n.a.	No
Germany	2,199	1,098 (50)	1,002/1,042	505	66 (13.1)	79	Yes
Greece	213	140 (66)	136/136	65	7 (10.8)	80	Yes
Hungary	212	173 (82)	154/154	11	0	n.a.	n.a.
Ireland	211	110 (52)	74/81	63	7 (11.1)	100	Yes
Italy	210	111 (53)	49/62	106	1 (0.9)	0	Yes
Latvia	608	586 (96)	340/343	15	0	n.a.	n.a.
Luxembourg	463	264 (57)	18/18	227	59 (26.0)	78	Yes
Netherlands	443	232 (52)	165/191	171	46 (26.9)	30	Yes
Norway	856	466 (54)	296/313	273	184 (67.4)	20	Yes
Poland	88	53 (60)	24/24	10	1 (10.0)	n.a.	No
Portugal	118	52 (44)	52/52	29	6 (20.7)	n.a.	No
Romania	482	372 (77)	361/372	49	4 (8.2)	100	Yes
Serbia	63	60 (95)	60/60	18	0	n.a.	n.a.
Slovakia	198	159 (80)	119/120	14	0	n.a.	n.a.
Slovenia	269	252 (94)	173/174	28	1 (3.6)	n.a.	No
Spain	1,738	805 (46)	539/564	106	2 (1.9)	100	Yes
Sweden	1,318	487 (37)	71/82	36	4 (11.1)	0	Yes
Switzerland	620	394 (64)	128/135	53	10 (18.9)	90	Yes
Turkey	n.a.	n.a.	n.a.	3	0	n.a.	n.a.
Ukraine	128	85 (66)	35/35	67	23 (34.3)	n.a.	No
United Kingdom	1,887	1,044 (55)	475/545	347	38 (11.0)	29	Yes
Total	**17,878**	**10,471 (59)**	**5,765/6,003**	**2,992**	**727 (24.3)**		

Countries marked in bold were included in the analytical study.
EEA: European economic area; EFTA: European Free Trade Association; EU: European Union; n.a.: not available.
[a] Data available in EISS database on 8 July 2008.
[b] Data extracted 27 August 2008 from the EISS-VIRGIL. A number of countries tested all influenza A(H1N1) and influenza A viruses for oseltamivir resistance by pyro-sequencing. Some samples were not definitely proven to be H1 subtype, therefore the number of H1 virus detections can be lower than the number of tests for resistance.

TABLE 2

Risk factors for being infected with an oseltamivir-resistant virus, data from five EU and EEA/EFTA countries, 2007-8 influenza season (n=1,169)

Factor	Categories	% oseltamivir-resistant virus[a,b] N: 373 (1,169)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)[c,d]
Age in years	0-17	28 (572)	1	1
	18-64	43 (439)	1.93 (1.49-2.51)	1.39 (1.01-1.91)
	>65	60 (10)	3.76 (1.05-13.51)	2.33 (0.52-10.47)
Sex	Female	36 (536)	1	n.i.
	Male	32 (527)	0.82 (0.63-1.05)	
Sample source	Non-sentinel	45 (517)	1	1
	Sentinel	21 (652)	0.32 (0.25-0.42)	0.81 (0.55-1.20)
Seasonal influenza vaccination	No	35 (781)	1	n.i.
	Yes	25 (24)	0.61 (0.24-1.55)	
Any chronic underlying disease	No	48 (435)	1	n.i.
	Yes	69 (55)	2.42 (1.32-4.41)	
Diabetes	No	56 (362)	1	n.i.
	Yes	90 (11)	7.83 (0.99-61.82)	
Immunosuppression	No	49 (465)	1	n.i.
	Yes	78 (18)	3.61 (1.17-11.12)	
Cardiovascular disease	No	57 (366)	1	n.i.
	Yes	57 (7)	1.02 (0.23-4.64)	
Respiratory disease	No	72 (228)	1	n.i.
	Yes	80 (15)	1.53 (0.42-5.59)	

CI: confidence interval; EEA: European economic area; EFTA: European Free Trade Association; EU: European Union; n.i.: not included in the final model.
[a] Numbers in parentheses represent denominators for each category.
[b] Totals per each variable may be smaller than the total number of cases due to missing values.
[c] The final model included age, source of the sample and reporting country.
[d] P-value from likelihood ratio test comparing the model with and without age was <0.08.

TABLE 3

Effect of oseltamivir resistance on clinical outcomes, data from five EU and EEA/EFTA countries, 2007-8 influenza season, sentinel networks (n=790)

Outcome		% oseltamivir-resistant virus[a] N: 138	% oseltamivir-susceptible virus[a] N: 652	Crude risk ratios (95% CI)	Adjusted risk ratios (95% CI)[b]
Symptoms at presentation [c]	Sudden onset	97 (99)	96 (459)	1.01 (0.81-1.26)	n.i.
	Fever	97 (99)	96 (381)	1.01 (0.81-1.26)	n.i.
	Headache	82 (82)	65 (165)	1.25 (0.92-1.69)	n.i.
	Myalgia	85 (130)	83 (456)	1.01 (0.82-1.25)	n.i.
	Dry cough	92 (130)	90 (471)	1.03 (0.84-1.26)	n.i.
	Sore throat	66 (79)	53 (163)	1.23 (0.87-1.74)	n.i.
	Runny nose	56 (78)	59 (164)	0.95 (0.67-1.36)	n.i.
Complications [c]	Hospitalisation[d]	2 (123)	1 (247)	1.34 (0.22-8.01)	1.25 (0.21-7.58)
	Any clinical complication	8 (120)	5 (244)	1.69 (0.73-3.92)	1.59 (0.68-3.71)
	Pneumonia	2 (85)	1 (148)	3.48 (0.31-38.40)	3.98 (0.35-45.42)
	Otitis	3 (86)	4 (149)	0.87 (0.22-3.46)	0.94 (0.23-3.84)
	Death	0 (123)	0 (248)		n.i.

CI: confidence interval; EEA: European economic area; EFTA: European Free Trade Association; EU: European Union; n.i.: not included in the final model.
[a] Numbers in parentheses represent denominators for each category.
[b] Adjusted for age but not for the presence of chronic medical condition because of the high proportion of missing values for this variable.
[c] Each case may have presented multiple symptoms and developed multiple complications.
[d] Hospitalisation is included here for practical reasons but may have occurred for reasons other than clinical complications.

a questionnaire by mail or telephone. In the UK, information was collected only on oseltamivir-resistant cases and there were no controls. GPs and hospital clinicians who had reported a case were contacted by national or local public health staff by telephone, and details were collected using a structured interview. In cases where clinicians were unable to provide the information, the patients were contacted directly.

Data management and analysis

Country-specific databases were shared with the ECDC for the final analysis. The databases were first analysed separately to detect differences in the results that would have to be considered in the pooled analysis. This was not possible for the UK data, which only included information on oseltamivir-resistant cases; however, these contributed to the pooled dataset. For each country, the prevalence of the various exposures in cases and controls was compared using contingency tables and the chi-squared test to check for statistical significance. Crude odds ratios were also computed. For the cohort approach, the prevalence (risk) of any of the considered clinical outcomes was calculated in exposed and unexposed individuals and the chi-squared test was used to check for statistical significance. Crude risk ratios were also computed. In order to allow for a pooled analysis of the five databases, they were merged into a unique database converting data from Access and Excel into STATA 10 format. Only variables collected by at least four of the five countries were retained in the final database.

The univariable analysis of the pooled database was conducted by using the procedures described above for the country-specific databases. The analysis of risk factors for severe influenza disease (cohort approach) was restricted to the population reported by sentinel surveillance systems. This was because individuals identified through non-sentinel sources are generally more likely to represent cases with more severe influenza and are thus already selected for the outcome of interest. By contrast, the analysis of risk factors for oseltamivir resistance was conducted first separately by source of the sample and then by combining the two populations. Multivariable analyses were conducted by using logistic regression to obtain adjusted odds ratios for the risk of being a case, and Poisson regression to obtain adjusted risk ratios for developing the outcomes of interest in the cohort analysis. Variables significant in univariable analyses ($p<0.05$) were included in the initial multivariable models. The presence of effect modification between study country and each variable was checked, and in the absence of a significant interaction, country was treated as a potential confounder. A backward elimination procedure was used to build the final models. Despite the common protocol, covariates were not uniformly collected in the different studies. In order to determine the possible confounding effects of these variables, a sensitivity analysis was therefore conducted excluding studies one by one from the univariable analysis and the final multivariable models and comparing the results with those of all studies included.

Evaluation of resistance to neuraminidase inhibitors was carried out either at country level (when laboratory capacity was available) or by the Health Protection Agency (HPA) in London in collaboration with the WHO Collaborating Centre for Reference and Research on Influenza (WHO-CC). Assessment of resistance was through phenotypic analysis (IC50) or genotypic analysis (sequencing) for detection of the mutation H275Y. A subset of viruses tested for antiviral susceptibility both at HPA and NICs yielded 100% concordant results with respect to resistance status. IC50 and genetic testing performed on a subset of viruses were also 100% concordant [6].

Results

Surveillance data

The 2007-8 influenza season in Europe was initially dominated by type A influenza viruses, and 96% of subtyped type A influenza viruses were A(H1) [6]. Type B influenza viruses became dominant in week 8/2008. For 30 countries in EISS, data on susceptibility of influenza A(H1N1) viruses to oseltamivir were reported (Table 1). From week 40/2007 to 27 August 2008, a total of 2,992 influenza A(H1N1) viruses were tested for oseltamivir resistance. Of these, 727 (24.3%) were resistant to oseltamivir (Table 1). Resistance was reported in 22 countries and ranged from 1% (n=106) in Italy to 67% (n=274) in Norway (Table 1). No resistance was found in eight countries, most of which were located in the central and eastern part of Europe (Bulgaria, Croatia, Czech Republic, Hungary, Latvia, Serbia, Slovakia and Turkey). However the period of testing and numbers of viruses tested were not representative and might have resulted in an underestimation of the real proportion of resistant viruses [6]. Oseltamivir-resistant viruses were detected in sentinel and non-sentinel patients, and the distribution varied by country (e.g. 20-30% were reported from sentinel sources in the UK, the Netherlands and Norway, and around 80% in Germany and Luxembourg). Sixteen countries also reported case-based clinical information through the enhanced surveillance (Table 1) system as described in the methods section. However, the level of completeness of data was low in countries not conducting ad hoc epidemiological studies and therefore the analytical part of this article is based on the data provided by the five countries conducting such studies.

Epidemiological studies

Analysis by country

None of the main variables collected (age, sex, travel history, influenza vaccination, chronic medical condition) was significantly associated with an increased risk of infection with an oseltamivir-resistant virus. Some of the variables analysed showed some effects that, although not statistically significant, deserve to be mentioned: In the Netherlands, individuals suffering from any kind of immunosuppression were more likely to be infected with an oseltamivir-resistant virus (odds ratio (OR): 5.5, 95% confidence interval (CI): 0.95 to 32; p=0.056). In addition, individuals reported through the sentinel system were less likely to be infected with a resistant virus (OR: 0.51, 95% CI: 0.25 to 1.04; p=0.065). In Norway, individuals aged between 18 and 64 years were more likely to be infected with a resistant virus than those younger than 18 years (OR: 1.84, 95% CI: 1.09 to 3.11; p=0.022).

Infection with a resistant virus was not significantly associated with an increased risk of pneumonia, hospitalisation or clinical complication in any of the five countries. In Luxembourg, the mean duration of influenza illness was longer in cases infected with oseltamivir-resistant virus than in oseltamivir-susceptible infections (10 and seven days, respectively; p-value=0.025 by T test for the hypothesis of no difference between the two groups). There was no difference between the two groups with regards to the maximum temperature of fever (39.3 versus 39.3 °C). In Norway, resistant cases were at higher risk of developing pneumonia (RR 3.15, 95% CI: 0.72 to 13.89); however, this association was not statistically significant. The results of the Norwegian study have recently been published as a separate article [11]. In the UK, the epidemiological information was only collected from the 36 cases with oseltamivir-resistant infection, and bronchitis and pneumonia were the most commonly reported complications affecting six (17%) and eight (22%) cases, respectively.

Results of the pooled data analysis

Following merging of the five national databases, information was available on 1,169 individuals with an influenza A(H1N1) infection, of which 373 (32%) were oseltamivir-resistant. Information was incomplete for key variables such as presence of a chronic medical condition (58% missing values) and hospitalisations (45% missing values). The distribution of missing values was not substantially different between data coming from sentinel networks and data from non-sentinel sources. The proportion of missing information can be calculated by summing up the denominators of each variable reported in Tables 2 and 3 and comparing this with the total number of subjects reported in the Tables.

The analysis of risk factors for oseltamivir resistance was first undertaken separately by reporting source (sentinel and non-sentinel) and subsequently, since there were no relevant differences between the two sources, data from sentinel and non-sentinel sources were analysed together. By univariable analysis (Table 2), individuals aged between 18 and 64 years were almost twice as likely to have an infection with a resistant virus than those younger than 18 years (OR:1.93, 95% CI: 1.49 to 2.51). Only 10 individuals over the age of 64 years were reported and an association of resistance with older age could therefore not be ascertained. Those suffering from a chronic medical condition were 2.4 times more likely to be infected with a resistant virus than healthy individuals (OR:2.42, 95% CI: 1.32 to 4.41). Individuals identified through the sentinel network were less likely to be infected with a resistant virus than those identified through non-sentinel sources (OR:0.32, 95% CI: 0.25 to 0.42).

Following multivariable analysis, none of these factors remained statistically significant. After adjusting for reporting country and source of the sample, the age-group of 18-64 year-olds was associated with a higher risk of being infected with an oseltamivir-resistant virus than the younger age group (OR:1.39, 95% CI: 1.01 to 1.91), however the p value from the likelihood ratio test comparing the models with and without the variable age was <0.08 (Table 2).

The cohort analysis to investigate the effect of oseltamivir resistance on disease severity and complications was restricted to subjects reported by the sentinel networks. There were no significant differences in symptoms at the time of sampling between exposed (oseltamivir-resistant) and non-exposed (oseltamivir-susceptible) patients (Table 3). The risk of influenza disease complications (hospitalisation, pneumonia, otitis media or death) was low for all subjects and did not significantly differ between exposed and non-exposed cases (Table 3).

The sensitivity analysis conducted on both univariable and multivariable models did not reveal substantial differences between countries. Where differences were detected, these only concerned the magnitude but not the direction of the effect. Tables with data of the full sensitivity analyses can be provided by the corresponding author upon request.

Four influenza-related deaths were reported among oseltamivir-resistant cases detected through non-sentinel sources, of which three occurred in the UK and one in the Netherlands and none among oseltamivir-susceptible cases. These were two children (one newborn and one two year-old), one young adult and one person older than 65 years. With the exception of the newborn, all had a chronic medical condition that put them at higher risk of severe influenza and none had received influenza vaccination. None of these cases received oseltamivir treatment.

Discussion

This article provides a comprehensive analysis of the epidemiological information that was collected in Europe during the influenza season 2007-8 on individuals infected with an oseltamivir-susceptible or -resistant influenza A(H1N1) virus. Through the analysis of surveillance data and by combining the results of five national observational studies, we have provided evidence that infection with an oseltamivir-resistant A(H1N1) influenza virus was not related to any of the risk factors analysed. In particular, we did not identify any association between having a chronic medical condition and infection with an oseltamivir-resistant virus. This finding is in contrast with previous observations where higher levels of oseltamivir resistance were mainly reported in vulnerable groups such as children and immunosuppressed individuals and in association with oseltamivir treatment [12-14], and is consistent with the results of a similar investigation conducted in the United States (US) [15] and Norway [11] during the same influenza season. A possible explanation for this finding could be that the oseltamivir-resistant influenza A(H1N1) viruses analysed in this study had become resistant by a process other than the selective pressure of oseltamivir treatment.

We observed a slightly higher risk of being infected with an oseltamivir-resistant virus among adults (18-64 years-old) compared with those younger than 18 years. We think that the most likely explanation for this finding is the confounding effect of different attitudes in different countries on when to consult a GP, and the fact that countries had a very different prevalence of oseltamivir-resistant viruses. This hypothesis was supported by the reduction of the odds ratio towards unity that we observed when adjusting the effect of age for country reporting. Residual confounding that we were not able to adjust for may explain the borderline effect of age observed in the multivariable analysis.

Prior to the 2007-8 influenza season, studies conducted in animal models found that amino acid mutations in the neuraminidase protein causing oseltamivir drug resistance reduced the pathogenicity of the virus because of their effects on the neuraminidase enzyme function [16-20]. Our study found that individuals infected with an oseltamivir-resistant A(H1N1) virus experienced similar symptoms and risk of clinical complications as individuals infected with the same virus subtype susceptible to oseltamivir. Hence there was no clinical evidence that the resistant viruses differed from the susceptible viruses in terms of pathogenicity in humans. The four deaths reported in the UK and the Netherlands seem consistent with the incidence of influenza-associated mortality in risk groups and it is unlikely that oseltamivir resistance played a role. However, it should be noted that the relatively small sample size might have prevented detection of significant differences in rare outcomes such as deaths.

All the viruses that were analysed genetically showed the same drug resistance mutation, the substitution of histidine by tyrosine at residue 275 (H275Y) in the neuraminidase gene, which is known to confer high levels of resistance to oseltamivir *in vitro* [3], but has a reduced transmissibility [17]. However, the rare isolation of viruses carrying the H275Y mutation from ill patients without known exposure to neuraminidase inhibitors [21] may indicate that some compensatory mutations within the neuraminidase, the haemagglutinin or other genes may be influencing virus

transmissibility. Such compensatory mutations are likely to have determined the widespread circulation of fully transmissible and pathogenic oseltamivir-resistant influenza A(H1N1) viruses in Europe, although this still has to be ascertained. Limited variations in the susceptibility to neuraminidase inhibitors that occurred naturally over time (from 1997 to 2005) have been described for influenza A(H5N1) viruses, but do not seem to have clinical relevance so far [22].

The strength of our study is the consistency of results between countries and various sources of data (sentinel and non-sentinel), which validates the results of the pooled analysis. However, there are also important limitations that should be considered when interpreting the findings of this study. The main limitation is the high proportion of missing data for key variables. This was mainly due to the difficulties in collecting information on patients who had ILI months before the data collection started. In addition, data on follow-up outcomes may have been be inaccurate as they were collected from clinicians who were not necessarily aware of complications that may have occurred after they saw the patients. The study may also lack representativeness. In most of the countries, patients who underwent virological testing were selected neither randomly nor systematically, and clinicians may have preferentially tested patients with specific clinical characteristics or pre-existing conditions. In addition, since reporting for the sentinel cases was based on the standard case definition used for surveillance purposes, milder cases or those presenting with unusual clinical features may have been excluded from the study population. An information bias could have occurred if data for cases with oseltamivir-resistant virus infection were collected in more accurately than for cases with susceptible virus infection. We could not demonstrate this from the data available, but some of the participating countries that considered this issue found that clinicians were unaware of the oseltamivir resistance status of their patients at the time of the interview.

Even considering these limitations, this study has relevant public health implications. Subsequent results of global antiviral surveillance found that influenza A(H1N1) viruses resistant to oseltamivir have become predominant over susceptible strains, similarly to the evolution of circulating A(H3N2) viruses, most of which have become resistant to M2 inhibitors [23-26]. In Europe, preliminary results from the 2008-9 season show that while the A(H3N2) subtype predominated, almost all the influenza A(H1N1) viruses tested were oseltamivir-resistant [25]. Therefore, it is important that results from antiviral susceptibility surveillance are used to guide therapeutic decisions at an individual level. The US Centers for Disease Control and Prevention (CDC) issued recommendations for the use of antiviral medications in 2008-9. These took into account the strain-specific prevalence of oseltamivir resistance among circulating influenza A viruses in the US, where resistant influenza A(H1N1) viruses predominated in the 2008-9 influenza season, and advised to use zanamivir or a combination of oseltamivir and rimantadine rather than oseltamivir alone when influenza A(H1N1) virus infection or exposure is suspected [27]. These guidelines do not apply to Europe, where influenza A(H3N2) fully susceptible to neuraminidase inhibitors dominated during the season 2008-9 [28]. The findings of the present study suggest that influenza viruses naturally resistant to the currently available antivirals can rapidly emerge and circulate in the community. It is therefore important that new antiviral drugs against influenza are developed. Although the main tool for the prevention of influenza remains annual vaccination, there are circumstances when the use of antiviral drugs could play a pivotal role in preventing and reducing influenza morbidity. These would include the situation of a mismatch between the circulating and vaccine influenza strains, the control of outbreaks in special settings (e.g. nursing homes), or an influenza pandemic where vaccine is unlikely to be available until some months after the start of the pandemic.

The emergence of the 2009 H1N1 influenza pandemic raised concerns over the possible emergence of oseltamivir resistance. Despite the wide use of neuraminidase inhibitors both for prophylaxis and treatment during the pandemic, oseltamivir resistance has so far only been detected sporadically and resistant viruses did not efficiently transmit in the community [29,30]. Diversification of national antiviral stockpiles to include different types of antivirals has been advised in some European countries [1,31]. The pandemic influenza A(H1N1)v virus is currently fully resistant to adamantanes but susceptible to both available neuraminidase inhibitors, zanamivir and oseltamivir [32].

In general, the unexpected emergence of high levels of oseltamivir resistance in Europe during the season 2007-8 highlights the evolving nature of the influenza virus and the requirement for a flexible approach to disease control including regular review and updating of treatment guidelines and pandemic plans [33].

What are the implications from this experience for the rapid, early assessment that is essential following the appearance of a pandemic [34]? Important lessons learnt are: 1) Reliance on referred specimens, especially from hospitalised or otherwise severe cases is likely to give a biased view of the pattern of infection in the community. 2) Multi-national approaches are more difficult once countries have started independent analytic approaches. It would be preferable for countries to develop and agree in advance on proposals (i.e. mock-up study protocols) to obtain the epidemiological information that is needed at the beginning of a pandemic to guide control measures. This is the approach being taken by the ECDC in collaboration with WHO and such plans should take into account the limitations identified in this study.

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Introduction of human papillomavirus (HPV) vaccination in Belgium, 2007-2008

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This paper documents the progress of human papillomavirus (HPV) vaccine introduction in Belgium. Information on vaccine use is based on sales statistics and reimbursement claims. From November 2007 to November 2008, the National Institute for Health and Disability Insurance reimbursed the HPV vaccine for girls aged between 12-15 years. In December 2008, the age limit was extended to include girls up to the age of 18. In November 2008, the total number of HPV vaccines sold exceeded 530,000 doses. The number of vaccines reimbursed in Belgium, for the period November 2007-November 2008, corresponds to the amount required to fully vaccinate 44% of all girls aged between 12-15 years. However, the trend was decreasing over the last 10 months. By the current reimbursement policy, we can expect that maximum half of the target population can be reached. In Flanders (one of the three Communities in Belgium), the intention is to start, from September 2010, with a free school-based HPV immunisation for girls in the first year of secondary school (12 years of age), complemented with vaccination by a physician of choice. This strategy ensures a higher HPV vaccine coverage which is expected to be as high as the current coverage in the hepatitis B vaccination programme (approximately 80%) offered to boys and girls in the same age group and under the same circumstances.

Introduction

In 2004, 651 cases of cervical cancer (European-age standardised rate (E-ASR) 8.5/100,000 women-years) were reported in Belgium, and approximately 264 women (E-ASR 3.8/100,000 women-years) died from the disease [1,2]. Currently, screening for cervical cancer is mainly opportunistic in Belgium [3,4]. The screening coverage for cervical cancer, in the target age group (25-64 years), with a three-year interval, was 59% in 2000. However, the modal screening interval is 12 months, whereas the recommended interval is 36 months. Moreover, screening is often offered to women younger than 25 years of age. Therefore, the number of smears taken annually could theoretically cover the whole target population [5]. Nevertheless, organised screening according to European guidelines and in collaboration with the three Communities (Flemish, French, and Germanophonic), is planned within the new Cancer Plan [6,7]. It is estimated that 72% of all cervical cancers in Europe and North America are caused by the oncogenic human papillomavirus (HPV) types 16 and 18 [8]. The current paper updates a previous report on HPV vaccine introduction in Belgium, Luxembourg and the Netherlands [9], and provides more detailed information on the Belgian situation.

Recommendations and decision making in Belgium

On 2 May 2007, the Belgian Superior Health Council (SHC) made its first recommendations regarding vaccination against infections caused by HPV. The only vaccine available at that moment was the quadrivalent HPV-vaccine, containing virus-like particles of HPV types 6, 11, 16 and 18 (Gardasil, licensed in Belgium on 20 September 2006). Summarising the recommendations of the SHC to the health authorities:

- Organised HPV vaccination should be offered to a one-year birth cohort of girls between 10 and 13 years of age [10].
- Girls should preferably be vaccinated through the school health system within a scholar calendar year, free of charge, as currently done for hepatitis B vaccination [11]. In Belgium, 70-80% of the vaccines for school-age children are given through the school health system. Practicing physicians (general practitioners (GPs), paediatricians and gynaecologists) have a complementary role in this. The SHC therefore recommended that for HPV too, parents should have the option of having their child vaccinated by such practicing physicians.
- The additional protective effect of organised catch-up vaccination up to the age of 15 years was recognised but only recommended if health-economic evaluation would confirm that it is cost-effective.
- Vaccination at older ages (14-26 years) can be considered when delivering personal healthcare, for instance during a consultation related to contraception, taking into account prior sexual experience and stressing the importance of safe sex. Systematic preliminary HPV testing before vaccination was not recommended.
- It is considered necessary to set up an organised screening programme according to European guidelines [7,9], to register administration of the HPV vaccine and to monitor their effects.

The recommendation was updated on 5 December 2007 to include the bivalent vaccine (HPV types 16 and 18) (Cervarix, licensed in Belgium on 24 September 2007).

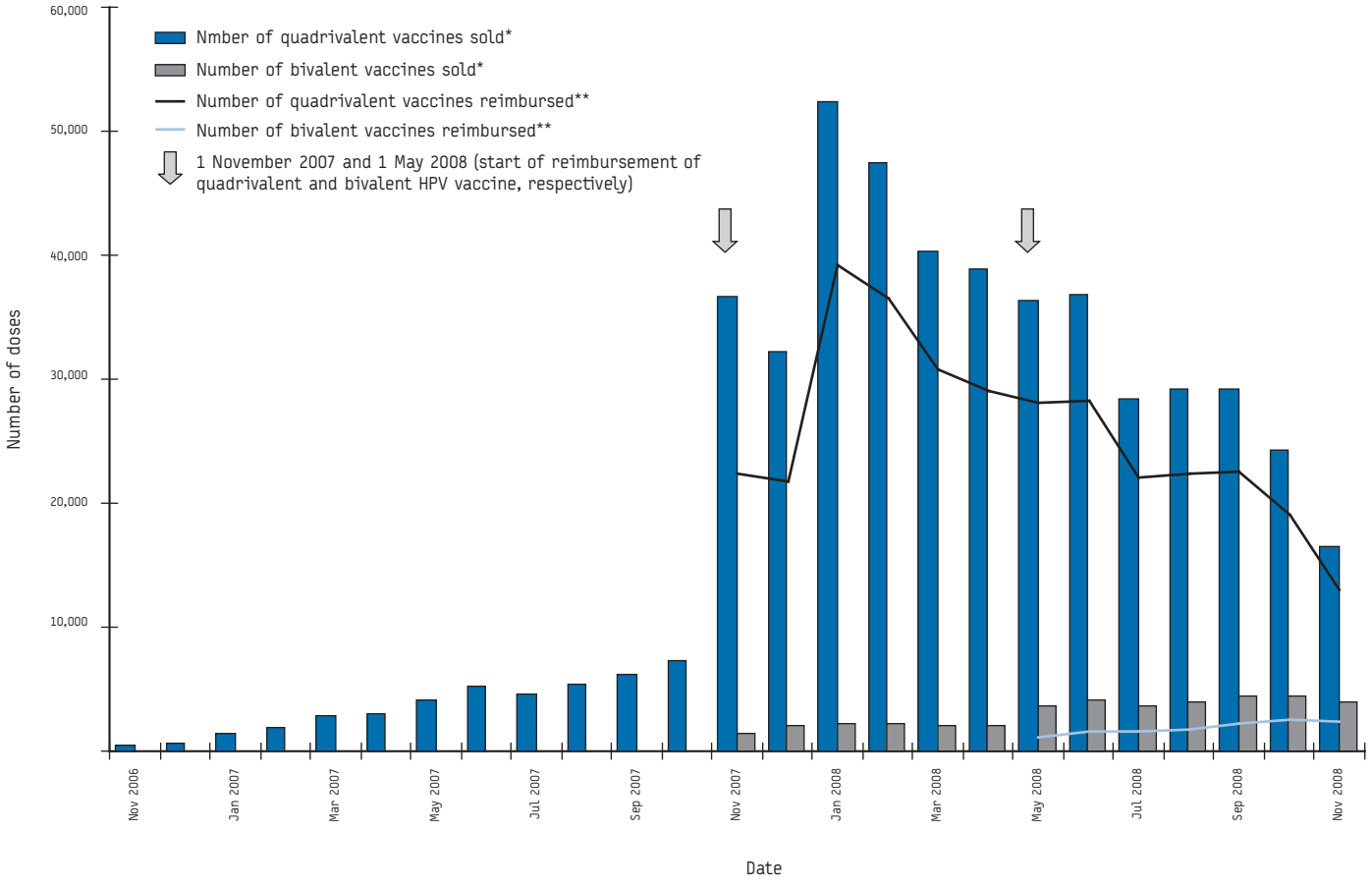
The SHC is the link between government policy and the scientific world in the field of public health. The council provides independent advice and recommendations to the Minister, on his/her specific request for information or on its own initiative. The Communities are free to implement these recommendations, even independent of each other.

The National Institute for Health and Disability Insurance (NIHDI) is a federal institution that organises, manages and supervises the correct application of the 'compulsory insurance' in Belgium [12]. It covers the whole population officially residing in Belgium. The NIHDI has decided, independently of the recommendation of the SHC, to reimburse opportunistic HPV vaccination for girls between the age of 12 and 15 years (for the quadrivalent vaccine since 1 November 2007 [13] and for the bivalent vaccine since 1 May 2008 [14]). In the framework of the National Cancer Plan, the age range for reimbursement was extended to include the age of 18 years as of 1 December 2008 [6]. This reimbursement of the HPV vaccines was communicated widely both in the scientific and the popular press.

The organisation of preventive healthcare in Belgium, including the management of the routine vaccination programme, is a responsibility of the three Communities. However, since 2004, in recognition of the high prices of some new vaccines, the NIHDI has been co-funding two thirds of the costs for vaccine purchase (only for vaccines purchased via tender, such as for the hepatitis B adolescent vaccination programme, the infant hexavalent vaccination programme, etc.). This mechanism of shared funding requires consensus on vaccination policies between all three Communities and federal authorities (the federal Ministry of Health together with the NIHDI). In 2008, the Ministry of the Flemish Community responsible for public health endorsed the recommendations of the SHC and the Flemish Vaccination Platform regarding HPV vaccination: i.e. offering HPV vaccination to a one-year birth cohort of girls between 10-13 years of age [15]. However, the Ministry of Health of the French Community did not follow the SHC advice [15]. Girls aged 12-18 years from the French

FIGURE

Number of vaccines sold and number of vaccines reimbursed per month for girls between 12 and 15 years of age, Belgium, Nov 2006-Nov 2008



* Source: Intercontinental Marketing Services (IMS) Health
** Source: The Belgian National Institute for Health and Disability Insurance
HPV: human papillomavirus

Community will be offered HPV vaccination by their GP or another physician, with the cost of the HPV vaccine partially reimbursed by the NIHDI and the remaining cost carried by the patient. Until now, the Germanophonic Community has not made a decision regarding a generalised immunisation programme for school girls against HPV.

Recently, legislation has changed and the consensus on vaccination policies between communities is no longer required, allowing for asymmetric immunisation policies over the different Communities [16]. The intention is to start free school-based HPV vaccination, at least in Flanders, in the school year 2010-2011, in a one-year cohort of girls in the first year of secondary school (12 years of age).

Vaccine sales and reimbursement data

Information on the total number of HPV vaccines sold in Belgium (complete wholesale data, not accounting for administration of the vaccine), was obtained from Intercontinental Marketing Services (IMS) Health (Figure: bars). IMS statistics show a cumulative amount of approximately 43,000 doses of the quadrivalent vaccine sold up to October 2007 (after the start in November 2006, sales figures gradually increased from ca. 400 to ca. 7,200 monthly doses). After the start of reimbursement in November 2007, a rapid increase in the monthly number of HPV vaccine doses sold was seen, up to 52,000 in January 2008. From then on, sales decreased progressively to 20,000 doses in November 2008. In total, about 532,000 HPV vaccine doses were sold in Belgium, up to November 2008.

The NIHDI HPV vaccine reimbursement data are also shown in the Figure (line curve), for the period November 2007-November 2008 (source NIHDI). At the start of reimbursement (in November and December 2007), the monthly number of reimbursed doses of the quadrivalent vaccine was around 22,000. In January 2008, the number increased to ca. 39,000 doses, but decreased afterwards to ca. 15,000 doses in November 2008. Over 1,000 doses of the bivalent vaccine were reimbursed in May 2008, which was the first month of reimbursement for this type of vaccine. This number increased up to 2,350 per month in November 2008. In total, over the 13-month period, 348,000 HPV vaccine doses were reimbursed. These reimbursed vaccines were administered by the GPs, paediatricians or gynaecologists of the 12-15 year-old girls.

The proportion of total vaccines sold that were reimbursed over the period where both IMS and reimbursement data were available, increased from 59% in November 2007 to about 75% in November 2008. The proportion of sold vaccines that were bivalent increased progressively from less than 4% before reimbursement to 19% in November 2008. The difference between sales and reimbursement figures (see Figure) presumably corresponds to vaccination beyond the target population, probably women older than 15 years buying it privately.

In Belgium, ca. 348,000 doses of HPV vaccine (both quadrivalent and bivalent) were reimbursed over a period of 13 months, which corresponds to an annual average of about 320,000 (ca. 27,000 per month); with this amount of vaccines one could theoretically reach a full three-dose coverage of 44% of all girls aged 12-15 years residing in Belgium. Around 61,000 monthly doses would be needed to reach complete coverage. Over the last six documented months ca. 31,500 doses were reimbursed per month and this quantity was following a negative trend. If this trend continues, we can expect that maximum half of the target population could be reached by the current reimbursement policy in Belgium.

Discussion and conclusion

The current policy of administration of the HPV vaccine in Belgium is estimated to cover maximum half of the targeted population. School-based free vaccination, complemented with vaccination by a physician of choice, is expected to guarantee a higher level of HPV vaccine coverage, effectiveness, cost-effectiveness and equity in healthcare access. Data from the recent immunisation coverage study in Flanders (2008) show that hepatitis B vaccine coverage offered at the age of 12 years achieved a coverage of approximately 90% [17]. In Flanders (one of the three Communities in Belgium), the intention is to start, from September 2010, a free school-based HPV immunisation, which is the preferred strategy option for HPV vaccine delivery in European countries proposed by the European Centre for Disease Prevention and Control [18]. In Flanders, this will be complemented by vaccination by a physician of choice (as is the situation for the national adolescent hepatitis B vaccination programme).

Current HPV vaccines are expensive, the duration of elicited immunity is still unknown and not all oncogenic HPV types are included. Therefore, careful surveillance is needed. In Belgium, the National Cancer Plan foresees registration of all organised vaccination efforts. Moreover, linkage of HPV vaccination status with the Belgian Cancer Registry is foreseen. However, international consultation is desirable, in order to orient the design of local surveillance plans allowing for international comparison.

Data on HPV vaccine sales and reimbursement will be collected continuously from the IMS and the NIHDI, both sources described in this paper. In the near future, the Scientific Institute of Public Health in collaboration with the Intermutualistic Agency, will analyse individual patient data from all reimbursed HPV vaccinations which will allow to estimate HPV vaccination coverage by number of doses, age and geographic unit.

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Competing interest

C Simoens and M Arbyn received travel funding from GSK and SPMSD, respectively (before 2008). P Van Damme has been principal investigator of bivalent and quadrivalent HPV vaccine trials, for which the University of Antwerp obtains contractual funding. All other authors declare no conflict of interest.

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EMCDDA Annual report 2009: cocaine and heroin maintain firm hold on Europe's drug scene

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Cocaine and heroin remain the drugs most strongly associated with drug problems, such as infectious diseases and drug-related death, and the available data do not suggest a decline in the prevalence of their use in Europe. The use of multiple drugs simultaneously or consecutively - polydrug use - is also of concern as it increases risks and complicates drug treatments. These results are presented in the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA) Annual report 2009 [1].

The report notes that the use of cocaine is steadily increasing with recent data from general population surveys in different countries pointing to either a stable or rising trend in use in the 15-34 age group. The countries with the highest prevalence of cocaine use (any use in the past year) in this group are Denmark, Spain, Ireland, Italy and the UK.

Indirect indicators also point to heroin use no longer declining or being on the increase. In the period 1990 - 2006 between 6,400 and 8,500 deaths caused by drugs were reported every year, most of which were related to the injection of opioids, and after declining for many years they showed an increase more recently [1,2]. Between 2006 and 2007, eight countries reported that heroin users entering treatment increased both in number and as a percentage of all treated drug users.

The incidence of reported newly diagnosed HIV infection among injecting drug users has remained low across the European Union, and compares relatively positive in a global context [3], especially if compared to the situation in Eastern Europe [4]. This may, at least partly, follow from the increased availability of prevention, treatment and harm reduction measures, including substitution treatment and needle and syringe programmes. Other factors, such as the decline in injecting drug use that has been reported in some countries [5], may also have played an important role.

Around 22.5 million Europeans (6.8 % of those aged 15-64) used cannabis in the past year. This makes cannabis the most commonly consumed illicit drug in Europe. But after having increased at a steady pace during the 1990s and early 2000s, general population and school surveys confirm that the popularity of the drug is declining, particularly among young people.

Despite the different trends reported by substance, polydrug use patterns are widespread, and the combined use of different substances is responsible for, or complicates, most of the problems related to drug use. For example, among young adults aged 15-34 in nine countries, those who use alcohol heavily or frequently were between two and six times more likely to have used cannabis during the past year and between two and nine times more likely to have used cocaine, compared to the general population.

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