Influenza activity in Europe during the winter 2005-2006 started late January - early February 2006 and first occurred in the Netherlands, France, Greece and England. Subsequently, countries were affected in a random pattern across Europe and the period of influenza activity lasted till the end of April. In contrast to the winter seasons in the period 2001-2005, no west-east pattern was detected. In 12 out of 23 countries, the consultation rates for influenza-like illness or acute respiratory infection in the winter 2005-2006 were similar or higher than in the winter 2004-2005, despite a dominance of influenza B viruses that normally cause milder disease than influenza A viruses. In the remaining 11 countries the consultation rates were lower to much lower than in the winter 2004-2005. The highest consultation rates were usually observed among children aged 0-14. The circulating influenza virus types and subtypes were distributed heterogeneously across Europe. Although the figures for total virus detections in Europe indicated a predominance of influenza B virus (58% of all virus detections), in many countries influenza B virus was predominant only early in the winter, whilst later there was a marked increase in influenza A virus detections. Among the countries where influenza A viruses were co-dominant with B viruses (9/29) or were predominant (4/29), the dominant influenza A subtype was H3 in seven countries and H1 in four countries. The vast majority of characterised influenza B viruses (90%) were similar to the B/Victoria/2/87 lineage of influenza B viruses that re-emerged in Europe in the winter 2004-2005 but were not included in the vaccine for the influenza season 2005-2006. This might help to explain the dominance of influenza B viruses in many countries in Europe during the winter 2005-2006. The influenza A(H3) and A(H1) viruses were similar to the reference strains included in the 2005-2006 vaccine, A/California/7/2004 (H3N2) and A/New Caledonia/20/99 (H1N1), respectively. In conclusion, the 2005-2006 influenza epidemic in Europe was characterised by moderate clinical activity, a heterogeneous spread pattern across Europe, and a variable virus dominance by country, although an overall dominance of influenza B viruses that did not match the virus strain included in
the vaccine was observed.

Introduction

Influenza has a considerable public health impact in Europe each winter. Although it is moderately contagious, it spreads rapidly by coughs and sneezes from people who are infected [1]. Influenza affects approximately 5-15% of the world’s population with upper respiratory tract infections during seasonal epidemics every year [2]. Seasonal epidemics are associated with substantial demands on healthcare resources and considerable costs due to increases in general practice consultation rates, clinical complications, hospitalisations, drug treatment and absence from work [3,4]. Although difficult to assess, it is estimated that between 250,000 and 500,000 people die from severe illness as a result of influenza virus infection every year [2].

The European Influenza Surveillance Scheme (EISS, http://www.eiss.org) is a collaborative network of primary care physicians, epidemiologists and virologists that aims to contribute to a reduction in morbidity and mortality in Europe by active clinical and virological surveillance of influenza [5,6]. The participating national reference laboratories have functioned within EISS as the Community Network of Reference Laboratories for Human Influenza in Europe (CNRL) since 2003. They report virus detection and identification data to EISS and work on improving the virological surveillance [7,8]. EISS aims to cover all member states of the European Union (EU), as required by EU Decision 2119/98/EC on the establishment of dedicated surveillance networks for communicable diseases [9]. During the winter 2005-2006, the EISS network included all 25 EU countries, as well as Norway, Romania and Switzerland. A total of 38 national influenza reference laboratories participated in EISS.

The identification of circulating viruses and the recognition of virological changes are major tasks for EISS in order to fulfil its early warning function [7]. There is a particular need to detect and monitor the emergence or re-emergence of viruses with pandemic potential and viruses that show a ‘mismatch’ with the vaccine strain components, and to monitor their clinical impact. During the winter period (from week 40 to week 20 of the following year) a Weekly Electronic Bulletin is published each Friday on the EISS website (http://www.EISS.org) and in the ECDC weekly Influenza News (http://www.ecdc.europa.eu/Health_topics/influenza/news_archive.html). This allows the network members, public health authorities and the general public to view influenza activity in all participating countries.

This paper presents an analysis and interpretation of influenza surveillance data collected by European countries that were members of EISS during the winter 2005-2006. In addition, the article presents an analysis of the relative and temporal distribution of influenza A and B viruses in the winter season on the basis of data from the past 10 years, as the high percentage and early appearance of influenza B viruses during the winter 2005-2006 were considered unusual.

Methods

Population

All 28 countries that were members of EISS during the winter 2005-2006 actively monitored
influenza activity from about week 40 of 2005 to about week 20 of 2006 (Table 1 below). In this paper, England, Northern Ireland, Scotland and Wales are referred to as separate countries because they have their own surveillance systems. EISS is therefore considered to include 31 countries. The characteristics of the sentinel networks are summarised in Table 1 of the article supplement (see: http://www.eiss.org/documents/eurosurveillance/eurosurveillance_supplement_2005_2006_winter.pdf). The median weekly population under clinical surveillance by the sentinel networks during the winter 2005-2006 varied from 0.4% to 100% of the total population of a country, representing a median number of 24.8 million inhabitants of Europe. In total, about 21,000 general practitioners (GPs), paediatricians and other physicians participated in the sentinel surveillance during the winter 2005-2006. However, the weekly number of physicians that actually reported was often lower. In general, the age distribution of the population under surveillance was representative for the age distribution of the total population in a country. However, in some countries the population under surveillance was skewed towards the lower age groups (partly due to a high proportion of paediatricians) and/or higher age groups. Further information on the representativeness of the population under surveillance in EISS can be found for most countries in Aguilera et al. [10].
Clinical surveillance

In each of the countries, except Finland, one or several networks of sentinel physicians reported consultation rates due to influenza-like illness (ILI) and/or acute respiratory infection (ARI) on a weekly basis (for case definitions see: http://www.eiss.org/html/case_definitions.html). Twenty-six countries reported ILI consultations per 100,000 population; Malta and Cyprus reported ILI per 100 consultations and France and Germany reported ARI consultations per 100,000 population. In some countries the doctors have patients’ lists, which can provide an exact population denominator. In other countries people have a free choice of doctors, which means that the population
denominator has to be estimated.

Virological surveillance

A proportion of the sentinel physicians, in most cases representative of the surveillance network in a country, also collects nose and/or throat swabs for virological surveillance using a swabbing protocol that guarantees representative swabbing during the winter period (see Table 1 in the article supplement) [10]. Combining clinical and virological data in the same population allows the evaluation of clinical reports made by the sentinel physicians and provides virological data for a clearly defined population - the general population that lives in the area served by the participating physician [11]. In addition to specimens obtained from physicians in the sentinel surveillance systems, the laboratories also collect and report results on samples obtained from other sources (e.g. from hospitals and non-sentinel physicians). These data are called ‘non-sentinel’ and are collected in order to have a second measurement of influenza activity (which contributes to early warning as the entire population is not covered by the sentinel system) and in order to assess the representativeness of the virological data obtained from the sentinel physicians [11]. Based on the collection of virological data, the total population under surveillance by EISS, during the winter 2005-2006, was almost equal to 495 million inhabitants living in the area covered by EISS [12].

The virological data includes mostly results from cell cultures followed by virus type and subtype identification and from rapid diagnostic enzyme-immunological or immunofluorescence tests identifying the virus type only. Many laboratories also use reverse transcription polymerase chain reaction (RT-PCR) routinely for detection, typing and subtyping. Almost 50% (15/31) of the countries reported antigenic characterisation data and almost 30% (9/31) of the countries reported genetic characterisation data of the virus isolates during the winter 2005-2006.

In addition to the circulation of the seasonal human influenza viruses, EISS laboratories monitored the possible transmission of the highly pathogenic avian influenza virus A(H5N1) to humans in the countries covered by EISS.

The timing of the circulation of influenza A and B viruses and their relative distribution in the winter seasons was analysed using 10-year EISS data (1996-2006).

Indicators

During the winter period, the weekly clinical and virological data were collected and analysed by the national centres and then processed into the EISS database the following week via the internet [13]. The clinical consultation rates, the indicators of influenza activity (the intensity of clinical activity and the geographical spread of influenza), as well as the dominant virus type/subtype circulating in the population were established on a weekly basis by the national co-ordinators based on agreed definitions (see Box below) that were published previously [8,14]. The dominant type/subtype for the whole winter season was estimated per country (Table 1 above) using the algorithm published previously [14].
Spatial analysis
A spatial analysis of the timing of peak influenza activity across Europe was carried out using regression analysis of plots of the longitude and latitude of the centre of each country against the week of peak influenza activity of each country, as described previously [14].

Statistics
SPSS version 14.0 for Windows was used for statistical analyses. A P-value <0.05 was considered significant.

Results
The seasonal influenza epidemic started late in Europe, with consultation rates for ILI or ARI above levels seen outside the winter period first reported in the Netherlands (week 1/2006), France (week 4/2006), and England and Greece (week 5/2006) (Graphs 1 and 2 in article supplement). Only two countries reported a high intensity of clinical activity, Estonia in weeks 11-12/2006 and Lithuania in week 8/2006 (Table 1 above). Most countries (19 out of 30) reported at maximum a medium intensity. However, 11 countries reported low or very low levels of intensity and/or consultation rates for ILI or ARI: Austria, Germany, Hungary, Italy, Poland, Portugal, Romania, Scotland, Slovenia, Sweden and Wales. Overall, in 12 out of 23 countries, the consultation rates for ILI or ARI in the 2005-2006 winter were similar or higher when compared with the 2004-2005 winter, whereas in the remaining 11 countries the rates were lower to much lower (Graph 2 in article supplement).
The ILI and ARI consultation rates in Europe reached their peak as early as week 1/2006 in Scotland and as late as week 13/2006 in the Czech Republic, Malta, Romania and Slovakia, indicating that the influenza epidemic took at least 13 weeks to spread across Europe.

In individual countries, the week of peak ILI/ARI consultation rates coincided roughly with the week of peak sentinel influenza virus detections. In the 25 countries with paired data that could be evaluated the median week of peak ILI/ARI consultation rates was 10 (range week 1 – 13) and the median week of peak virus detections was 9 (range week 5 – 15) (Table 1 above). In eight (32%) of the 25 countries, the week of peak consultation rates coincided exactly with the week of peak virus detections. Including the countries with a difference of one week between the two peaks, the peak rates coincided in 15 (60%) of the 25 countries.

In countries reporting age specific data (N=21), the highest consultation rates during the influenza peak were observed among children in the 0-4 and 5-14 age groups, although consultation rates in Norway and Wales were also high in the 15-64 age group compared to those in the other age groups (Table 1 above).

In contrast to the previous four winters (2001-2005), the spatial analysis revealed no west-east pattern in the timing of peak influenza activity across Europe during the 2005-2006 winter (R² = 0.032; P=0.491 for west-east and R² = 0.002; P=0.872 for south-north).

For Europe as a whole, the largest number of influenza virus positive specimens was detected in week 8/2006 (Figure 1). About 80% of all influenza A(H1) virus detections were from Belgium, England, France, Italy, Portugal and Spain. In addition, the only influenza A virus H subtype detected in Luxembourg was H1. Twelve countries reported laboratory results for detection of the A(H5N1) virus but none of the 112 specimens from suspected and (possibly) exposed humans analysed were positive for the A(H5N1) virus. For a detailed breakdown of the virological data for Europe as a whole and by country, by week and source (sentinel or non-sentinel) see Figure 2 below, as well as Graph 2 and Tables 2 and 3 in the article supplement.
Figure 1
Number of sentinel and non-sentinel specimens positive for influenza viruses, cumulative data for all European countries by week, winter 2005-2006

Europe (N = 11,349)
as of 4 August 2006

- Total A + B
- B
- Total A
- A (unsubtyped)
- A[H3]
- A[H1]
The distribution of virus types and subtypes by country and source (sentinel or non-sentinel) was analysed to evaluate the hypothesis that influenza B and A(H1N1) viruses are more often detected in sentinel specimens than in non-sentinel specimens (Tables 4 and 5 in the article supplement). By country (N=21), the proportion of type B viruses among viruses from sentinel specimens compared to viruses from non-sentinel specimens was significantly higher (P<0.05; Pearson Chi-Square) in ten countries, significantly lower (P<0.05) in two countries and not significantly different in the remaining nine countries. In contrast, by country (N=14), the proportion of A(H1) viruses among the type A viruses from sentinel specimens compared
to non-sentinel specimens was significantly (P<0.05) lower in five countries, significantly higher in Spain only (89% vs 78%; P=0.032), whilst it was not significantly different in the remaining eight countries.

By dominant type and subtype, the circulating influenza viruses were distributed heterogeneously across Europe (Table 1 above). Although the figures for Europe as a whole indicated a predominance for influenza B virus (58% of all virus detections) (Figure 2), in many countries early in the winter influenza B virus was predominant whilst later in the winter there was a marked increase in influenza A virus detections (Graph 2 in the article supplement). Influenza B virus was the dominant virus in 16 countries. In the countries where influenza A viruses were co-dominant with B viruses (9/29) or were predominant (4/29), the dominant influenza A virus subtype was H3 in seven countries and H1 in four countries (Table 1 above).

The circulation of influenza B virus in the winter 2005-2006 was exceptional compared with data from the last decade (Figure 3). The winter 2005-2006 was the only one in Europe in ten years in which influenza B viruses were dominant. Influenza B virus circulation was suppressed (<6% of all viruses) in the winters where there was a full-blown circulation of a new drift variant of the A(H3N2) virus, i.e. in the 1997-1998, 1999-2000 and 2003-2004 winters. In the other six winters the proportion of B viruses among all viruses did not exceed 36% (mean 27%; range 17-36%). In addition, the winter 2005-2006 was the only one in which, for Europe as a whole, influenza B viruses started to circulate and peaked earlier (3 weeks) than influenza A viruses. Of the previous nine winters, in four, the influenza B viruses started to circulate and peaked later than influenza A viruses (mean 5 weeks; range 3-7 weeks), in three, influenza A and B viruses started to circulate and peaked at the same time and in two, the timing could not be estimated as influenza B viruses were almost completely absent.
Of all 11,303 influenza virus detections, 3,128 have been antigenically and/or genetically characterised: 683 (28%) were A/New Caledonia/20/99 (H1N1)-like, 370 (12%) were A/California/7/2004 (H3N2)-like, 56 (2%) were A/Wisconsin/67/2005 (H3N2)-like (a drift variant of A/California/7/2004 included in the vaccine for the 2006-2007 winter), 1,816 (58%) were B/Malaysia/2506/2004-like (B/Victoria/2/87-lineage) and 203 (6%) were B/Jiangsu/10/2003-like (B/Jiangsu/10/2003 is a B/Shanghai/361/2002-like virus from the B/Yamagata/16/88-lineage that was included in the vaccine for the 2005-2006 influenza season).

**Discussion**

In the winter 2005-2006, influenza activity in Europe started late in January 2006, whereas in the previous winter it began in late December 2004 [14]. The 2005-2006 winter was the first one since 1996 in which, for Europe as a whole, the number of influenza B virus detections was higher than the number of influenza A virus detections (Figure 2). However, on a country level, virus type and even H-subtype dominance were very heterogeneous across Europe (Table 1 above). Most of the circulating influenza B viruses (90%) were similar to the B/Victoria/2/87 lineage of influenza B viruses that re-emerged in Europe in the winter 2004-2005 [14], but were not included in the vaccine for the influenza season 2005-2006. Remarkably, in a number of countries, a high number of influenza A(H1) viruses were detected compared to A(H3) viruses. Despite the predominant circulation of the B and A(H1) viruses, generally known to cause milder illness than A(H3) viruses [15], the peak of clinical influenza activity was similar or even higher in about half (12/23) of the countries, compared to the previous winter when A(H3) viruses were dominant [14] (Graph 2 in the article.
Previously, we reported that a pattern could be seen in the timing of peak influenza activity in countries across Europe, mainly being a west-east movement, sometimes accompanied by a south-north movement later on in the winter [14]. However, the winter 2005-2006 did not fit into this pattern, as influenza activity started to peak in countries located in different parts of Europe and, subsequently, spread randomly across the whole region (Graph 1 in the article supplement). Viboud et al. showed that in the USA severe influenza epidemics, dominated by A(H3N2), are more synchronous (i.e. spread more quickly from state to state) than the milder epidemics, generally caused by A(H1N1) and B viruses [16]. In addition, they showed that population size and strong long-range human movement connections between states seem to be important for synchrony and spatio-temporal spread of influenza. As the 2005-2006 winter in Europe was heterogeneous with regard to circulating virus types and subtypes by country and with regard to the location of countries were influenza activity initially started to increase, the observations of Viboud et al. might explain the absence of a pattern in the timing of peak influenza activity for countries across Europe in the 2005-2006 winter.

In 10 out of 21 countries, the proportion of influenza B viruses was significantly higher among viruses detected in sentinel specimens compared to non-sentinel specimens. It can be explained by the fact that influenza B virus infections are mostly mild [15] and patients usually do not need hospital care. Although this assumption of the link between mild infection and low hospitalisation rate could be applied also in case of A(H1N1) infections, in only one out of 14 countries the proportion of A(H1) viruses was higher among type A viruses from sentinel specimens compared to non-sentinel specimens, whereas in 5 out of 14 countries, the proportion of A(H1) viruses was significantly lower among influenza A viruses detected in sentinel specimens compared to non-sentinel specimens. Hence, the severity of disease caused by the influenza B and A(H1N1) viruses is probably not the only factor that explains the differences between viruses detected in sentinel and non-sentinel specimens. Possibly, differences in the age distribution between and within the population under surveillance in the sentinel systems (Table 1 above in the article supplement) and patients consulting a physician in the non-sentinel systems, differences in the age distribution of the patients from whom a swab is taken between and within the sentinel and non-sentinel systems, in combination with the patients’ vaccination and infection histories, might provide further explanations. More systematic analysis of available data and of the various surveillance systems is needed to draw more definitive conclusions.

The currently circulating influenza B viruses are antigenically and genetically divided into two distinct lineages represented by B/Yamagata/16/88 and B/Victoria/2/87 viruses, which have evolved to an extent that antibodies raised to viruses of one lineage offer reduced cross-reactive protection against viruses of the other lineage [17,18]. The trivalent influenza vaccine contains, however, only one B virus component. Because most B viruses isolated in the world by February 2005 were of the B/Yamagata/16/88 lineage type, the WHO recommended the inclusion of the B/Shanghai/361/2002-like virus (B/Yamagata/16/88 lineage) in the vaccine for the Northern Hemisphere 2005-2006 influenza season, similarly to the vaccine for the previous season 2004-2005 [17]. In Europe, however, already in the winter 2004-2005 the proportion of influenza B virus detections was higher than in the winter 2003-2004 - 17% compared to <1% respectively. Of these viruses, 43% belonged to the B/Victoria/2/87 lineage in the winter 2004-2005 as compared to 35% in the winter 2003-2004 [14,19]. This increasing trend continued in the winter 2005-2006 when about 90% of the detected influenza B viruses belonged to the B/Victoria/2/87 lineage viruses. The emergence of B/Victoria/2/87 lineage
viruses, which showed limited circulation in previous seasons, combined with the reduced cross immunity induced by B/Yamagata/16/88 lineage viruses and the mismatch with the vaccine may explain the dominance of influenza B viruses in the winter 2005-2006.

The World Health Organization announced the composition of the influenza vaccine for the Northern Hemisphere 2006-2007 influenza season in February 2006 [20]. Based on the analysis of influenza viruses from all over the world up until February 2006, the WHO modified the composition of the 2006-2007 influenza vaccine compared to the 2005-2006 vaccine by including a representative strain of the B/Victoria/2/87 lineage of influenza B viruses (B/Malaysia/2506/2004-like) and a more recent A(H3N2) strain [A/Wisconsin/67/2005 (H3N2)-like]. In Europe, the vaccine composition recommended by the European Agency for the Evaluation of Medicinal Products, which is based on the WHO recommendations, was adopted for the vaccination campaigns in winter 2006-2007 [21].

The patterns observed when comparing the proportion of circulating influenza B viruses and the timing of onset of circulation and peaking of influenza B viruses with influenza A viruses for Europe as a whole (Figure 3) are not necessarily the same for individual countries. This is because the data for Europe as a whole is cumulated per week and not compensated for the time it takes the epidemic to spread across Europe (at least 13 weeks for the winter 2005-2006). The analysis of the timing pattern of circulation of influenza A and B viruses on a country level (not shown in this paper) demonstrates that in each winter there are exceptions to the pattern observed for Europe as a whole, as has also been observed for the 2005-2006 winter (compare Figure 1 for Europe as a whole with Graph 2 in the article supplement for individual countries). The patterns observed for Europe as a whole should therefore not be overinterpreted, and for a thorough analysis of distribution patterns of virus types and subtypes across Europe a finer analysis (e.g. on the country level) is currently being carried out.

During the winter 2005-2006, the A(H5N1) influenza virus which in Asia had caused epizootics and cases of transmission to humans with fatalities [22] appeared in Europe causing outbreaks in poultry and wild birds [23]. EISS received laboratory reports of A(H5N1) testing of human specimens, especially from EISS countries experiencing outbreaks among poultry and wild birds; all were negative. In Europe, human cases were only detected in Turkey [24]. However, this "near miss" situation in the area covered by EISS stressed the importance of pandemic preparedness activities, including laboratory capacity. Therefore, the EISS network made available to all participating laboratories up-to-date RT-PCR detection protocols, recent sequence information and A(H5) controls for RT-PCR detection [7, 8]. Most laboratories participating in EISS now have the possibility to rapidly detect the A(H5) virus by molecular techniques. A recent EISS external quality assessment (EQA), carried out in collaboration with Quality Control for Molecular Diagnostics (http://www.qcmd.org), aimed at evaluating the detection, typing and subtyping of influenza viruses including the H5 virus, showed that about 65% (21/32) of the responding EISS laboratories were indeed capable of detecting the H5 virus. However, the study indicated also need for improvement, especially with regard to the sensitivity of the tests being used. Real-time RT-PCR tests outperformed block RT-PCR tests and the commercially available RT-PCR kits of which some failed to detect the A(H5) virus completely.

In conclusion, the 2005-2006 influenza epidemic in Europe was characterised by a late onset of influenza activity and a heterogeneous spread pattern across Europe. In addition, an uncommon overall dominance of influenza B viruses of the B/Victoria/2/87 lineage was
observed, as well as an earlier onset of circulation and peaking of influenza B virus compared to influenza A virus, and a relatively high proportion of influenza A(H1) viruses in a number of countries.

Contributors

The members of EISS contributed by weekly submission of influenza surveillance data to EISS during the winter 2005-2006. TJ Meerhoff, A Meijer, LE Meuwissen and WJ Paget carried out weekly analysis of the data and published the Weekly Electronic Bulletins during the winter 2005-2006. TJ Meerhoff extracted the clinical and virological data from the EISS databases for the paper and drafted the graphs for the supplement. A Meijer carried out the overall analysis of the data and prepared the body of the manuscript. J van der Velden, as chair person of EISS, contributed by supporting the daily operation of EISS during the winter 2005-2006.

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Article supplement

Available at:

The article supplement contains:

i) Lists of persons and institutes participating in EISS during the 2005-2006 winter period,

ii) Characteristics of the influenza surveillance networks in EISS,

iii) Animations of the timing of the change of the clinical intensity and geographic spread indicators by country in Europe,

iv) Graphs of the weekly consultation rates and virus detections by country, and

v) Tables with a detailed breakdown by country of the virological data from sentinel and non-sentinel sources.

References


