

# EPIDEMIOLOGICAL AND VIROLOGICAL ASSESSMENT OF INFLUENZA ACTIVITY IN EUROPE DURING THE 2003-2004 SEASON

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The 2003-2004 influenza season in Europe was dominated by the spread of the new drift variant A/Fujian/411/2002 (H3N2)-like virus which was not perfectly matched with the A(H3N2) component of the influenza vaccine. Sporadic cases of this virus were detected in Europe at the end of the 2002-2003 season and influenza activity associated with this virus began relatively early during the 2003-2004 season. Generally, influenza activity first occurred in the west of Europe (Ireland, the United Kingdom and the Iberian Peninsula) in October/November and gradually moved east across Europe, affecting Latvia, Lithuania and Poland during the months of January and February 2004. In general, the intensity of clinical activity was higher than during the 2002-2003 season (in 13 out of 20 networks) and, in countries reporting age specific data, the highest consultation incidences were observed among children aged 0-14. However, despite the emergence of the A(H3N2) drift variant, clinical incidences were not especially high compared with historical data. The composition of the 2004-2005 influenza vaccine has been modified compared with the 2003-2004 season and includes an A/Fujian/411/2002 (H3N2)-like virus strain and a new B virus strain (a B/Shanghai/361/2002-like virus).

Euro Surveill 2005; 10(4): 107-11

Published online Apr 2005

**Key words:** influenza, surveillance, epidemiology, virology, Europe

## Introduction

Influenza has an important public health impact each winter in Europe. It is associated with higher general practice consultation rates [1], increased hospital admissions [2] and excess deaths [2,3]. In England and Wales, the average number of excess deaths during influenza epidemic periods (1989-1998) was estimated to be 12 554 per season (range 0-27 587) [2]. Extrapolating these figures to the European Union (25 countries), the average number of excess deaths during influenza epidemic periods between 1989 and 1998 was about 107 000 per winter, with the total number in each country ranging from roughly 100 in Luxembourg and Malta to 19 500 in Germany. In recent winters, influenza activity in Europe has generally not been as intense as during the 1989-1998 period [4,5] and the average number of excess deaths has probably therefore been lower.

The European Influenza Surveillance Scheme (EISS) is a collaborative project [6-8] that aims to contribute to a reduction in morbidity and mortality due to influenza in Europe. During the 2003-2004 season, 25 surveillance networks from 22 European countries were active members of EISS. The scheme aims to include all member states of the European Union [9] and networks must meet the following criteria for full membership: 1) the surveillance network (consisting of sentinel physicians providing clinical data and national reference laboratories providing virological data) is nationally or regionally representative; 2) the authority of the network is recognised by the national or regional health authority

in the country or region; 3) the clinical surveillance and virological surveillance are integrated in the same population (community); 4) the network has functioned successfully for at least two years; and 5) the network can deliver data on a weekly basis.

Sixteen networks were full members of EISS during the 2003-2004 season and nine were associate members (Latvia, Luxembourg, Lithuania, Malta, Northern Ireland, Poland, Romania, the Slovak Republic and Sweden). Poland, Romania, the Slovak Republic and Sweden were associate members, as they did not combine clinical and virological data in the same population. Luxembourg, Malta, Northern Ireland, Latvia and Lithuania had this status as they did not fulfil the EISS criteria of two years of successful functioning prior to the 2003-2004 season, or were recent members of EISS. Including all members, the EISS project comprised 30 national influenza reference laboratories, at least 11 000 sentinel physicians, and presented surveillance data for a total population of 445 million inhabitants.

## Methods

EISS members actively monitored influenza activity from week 40/2003 (29/9/2003 – 5/10/2003) to week 20/2004 (10/5/2004 – 16/5/2004) during the 2003-2004 season. In each of the countries, one or several networks of sentinel physicians collected weekly (consultation) incidences of cases of influenza-like illness (ILI) and/or acute respiratory infection (ARI). Sentinel physicians also obtained nasal, pharyngeal, or nasopharyngeal specimens from a subset of patients and these were sent to the national reference laborator(y)(ies) for virological analysis. Combining clinical and virological data in the same population allows the validation of clinical reports made by the sentinel physicians and provides virological data in a clearly defined population (the general population that visits their physician with an ILI or ARI) [10]. In addition to specimens obtained from physicians in the sentinel surveillance systems, the laboratories also collected and reported results on specimens obtained from other sources (e.g. from hospitals or non-sentinel physicians). These data are called 'non-sentinel' in this paper and are collected to validate the virological data obtained from the sentinel physicians and to have a second measure of influenza activity.

The virological data included results mainly from typing and subtyping of viruses isolated using cell culture and additionally from rapid diagnostic enzyme-immunological or immunofluorescence tests identifying the virus type only. Many laboratories also used reverse transcription polymerase chain reaction (RT-PCR) routinely for detection and (sub)typing [11]. About 55% of the laboratories also reported antigenic characterisation data and about 30% of the laboratories reported genetic characterisation data of the virus isolates [12].

During the influenza season, the weekly clinical and virological data are processed and analysed by the national centres and then entered into the EISS database the following week via the internet ([www.eiss.org](http://www.eiss.org)) [13]. The indicators of influenza activity are established on a weekly basis by the national coordinators: the intensity of

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clinical activity (compared with historical data), the geographical spread of influenza (a World Health Organization indicator) and the dominant type/subtype circulating in the population. This allows members to view data in neighbouring countries and is the basis for the publication of a Weekly Electronic Bulletin that appears on the EISS website each Friday.

This paper presents epidemiological and virological data collected between week 40/2003 (29/9/2003 – 5/10/2003) and week 16/2004 (12/4/2004 – 18/4/2004). Week 16/2004 was chosen as some networks stopped collecting clinical data at the end of the season and data was therefore incomplete for weeks 17-20/2004.

**Results**

The influenza activity started in the west of Europe (Ireland, the United Kingdom (UK) and the Iberian Peninsula) in October/November and gradually moved east, affecting Lithuania, Slovenia, Latvia, Poland, Italy and Germany during the months of January/February 2004 [Table]. The peak weekly level of intensity and

geographical spread of influenza activity varied between the member countries during the 2003-2004 season [Table]. The peak intensity of clinical influenza activity (compared with historical data) ranged from low in Germany, Luxembourg and Wales, to high in nine networks. Most networks reported widespread influenza activity during the 2003-2004 season (16 out of 25). The peak levels of weekly ILI/ARI incidences in Europe were reached between week 46/2003 and 6/2004 [Table], with the majority of networks reporting peak levels before the end of the year (16 out of 24). A more detailed breakdown of the epidemiological data by country is available on the EISS website ([http://www.eiss.org/documents/eurosurveillance\\_supplement\\_2003-2004\\_season.pdf](http://www.eiss.org/documents/eurosurveillance_supplement_2003-2004_season.pdf)). In countries reporting age specific data, the highest consultation incidences were observed among children aged 0-14 (data not shown).

**TABLE**  
**Overview of influenza activity in the EISS networks during the 2003-2004 season**

Country Network	Week of peak clinical incidence	Intensity (peak weekly level) <sup>1</sup>	Week of peak virus detections <sup>2</sup>	Dominant virus type/subtype <sup>3</sup>	Geographical spread (peak weekly level) <sup>4</sup>
<b>Influenza-like illness</b>					
England	46	Medium	47	A(H3N2)	Widespread
Ireland	46	Medium	45-47	A(H3N2)	Widespread
Northern Ireland	46	Medium	46	A(H3)	Local
Scotland	46	Medium	48	A	Widespread
Portugal	47	High	47	A(H3N2)	Widespread
Spain	47	Medium	47	A(H3N2)	Widespread
Wales	48	Low	46	n.a.	Local
Malta	49	High	n.a.	n.a.	Widespread
Norway	50	High	49	A(H3N2) & A(H1N2)	Widespread
Belgium	51	Medium	49	A(H3N2)	Widespread
Denmark	51	High	51	A(H3N2)	Widespread
Luxembourg	51	Low	51	A	Local
Netherlands	51	Medium	51	A(H3)	Widespread
Switzerland	1	High	51	A(H3)	Widespread
Slovak Republic	4	Medium	6	A(H3)	Widespread
Lithuania	5	Medium	2	n.a.	Local
Slovenia	5	High	3-4	A(H3N2)	Widespread
Latvia	5	High	4	A(H3N2)	Regional
Poland	6	High	9	A	Regional
Italy	6	Medium	6	A(H3N2)	Widespread
Sweden	n.a.	Medium	n.a.	n.a.	Regional
<b>Acute respiratory infections</b>					
France	49	Medium	51	A(H3N2)	Widespread
Romania	51	High	51	A(H3N2)	Widespread
Czech Republic	51	Medium	51	A(H3)	Regional
Germany	6	Low	11	A(H3N2)	Regional

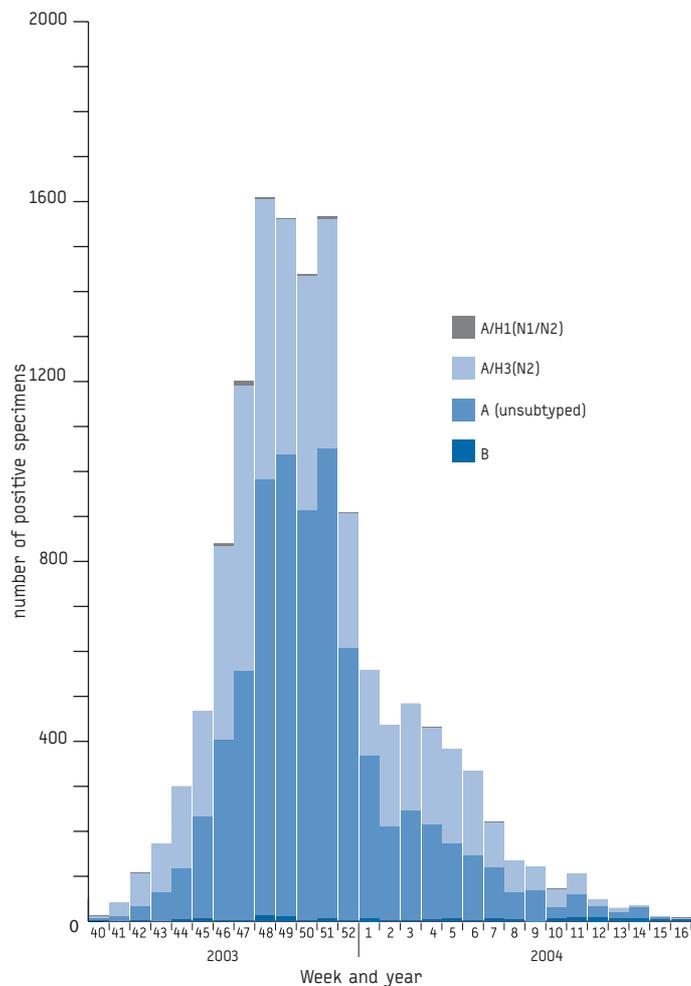
n.a.: not applicable as no data is available or insufficient data is available.

- The intensity of clinical activity compares the weekly clinical morbidity rate with historical data: Low = no influenza activity or influenza activity at baseline level; Medium = usual levels of influenza activity; High = higher than usual levels of influenza activity; Very high = particularly severe levels of influenza activity (less than once every 10 years).
- Assessment based on sentinel and non-sentinel data.
- Assessment based on: 1) sentinel and non-sentinel data (primary assessment sentinel data); 2) minimum number of sentinel/non-sentinel positive isolates: 10 for the season and these must represent at least 10% of total positive isolates reported during the season; 3) possibility to have two dominant virus types/subtypes (limits: 45%:55% and 55%:45%).
- The geographical spread is a WHO indicator that has the following levels: No activity = no evidence of influenza virus activity (clinical activity remains at baseline levels); Sporadic = isolated cases of laboratory confirmed influenza infection; Local outbreak = increased influenza activity in local areas (e.g. a city) within a region, or outbreaks in two or more institutions (e.g. schools) within a region. Laboratory confirmed; Regional activity = influenza activity above baseline levels in one or more regions with a population comprising less than 50% of the country's total population. Laboratory confirmed; Widespread = influenza activity above baseline levels in one or more regions with a population comprising 50% or more of the country's population. Laboratory confirmed.

The figure presents the total number of specimens positive for influenza viruses by week during the 2003-2004 season. The largest number of positive specimens was detected before the new year, between week 48/2003 and 51/2003. Detections continued during the first three months of 2004, but at a lower level. The peak weekly level of influenza virus detections varied among the member countries, and coincided roughly with the week of peak clinical morbidity [TABLE].

**FIGURE**

**Total number of sentinel and non-sentinel specimens positive for influenza viruses by week during the 2003-2004 season, EISS, Europe**



A total of 13 652 sentinel and non-sentinel specimens were positive for influenza virus during the 2003-2004 influenza season. The largest number of positive specimens were reported by France (3607), England (1704), Belgium (1260), Scotland (1139) and Norway (1000). Less than one per cent of the specimens (0.86%) were positive for the influenza B virus. The predominant viruses by country are shown in the table. A more detailed breakdown of the virological data by country is available as a Supplement on the EISS website. Influenza A virus was predominant in all countries that reported virological data (> 91% of all influenza virus isolates per country; total N=13 535). In most countries, the haemagglutinin of the influenza A isolates was subtyped (range: 0% – 100% of total influenza A isolates, average 50%, median 44% per country; total N=5841), and the predominant subtype was H3 (excluding the one country that reported no subtyping, > 90% of H-subtyped isolates per country; total N=5781). Among the 5841 subtyped influenza A virus isolates, only 60 (1.0%) were A(H1) and of the 36 neuraminidase subtyped A(H1) isolates, 22 had the N1 and 14 had the N2 subtype. EISS received no reports of influenza A(H5N1), A(H7N2) or A(H7N3)

viruses that caused outbreaks among poultry in Asia, Canada and the United States (US), and also infected humans [14-17].

Of a total of 3457 virus isolates, the haemagglutinin was antigenically characterised. The largest number of characterisations was reported by Latvia (796), Germany (491), France (392), the Netherlands (390), and England (348). Over 97% of the characterised isolates had an A/Fujian/411/02 A(H3N2)-like H3 haemagglutinin. There were 46 isolates with an H3 haemagglutinin similar to the vaccine strain A/Moscow/10/99 (H3N2), 34 with an H1 haemagglutinin similar to the vaccine strain A/New Caledonia/20/99 (H1N1) and seven with a haemagglutinin similar to the vaccine strain B/Hong Kong/330/2001. There were 11 non-vaccine strain reports of influenza B isolates: seven with a haemagglutinin similar to the B/Sichuan/379/99-like virus (in the Netherlands (3), Switzerland (2), France and Germany) and four with a haemagglutinin similar to the B/Shanghai/361/2002-like virus (in England (2), Italy and Norway). Of the antigenically characterised isolates, 166 were also genetically characterised and all haemagglutinins were antigenically and genetically similar to the same vaccine strain. In addition, 138 isolates were characterised genetically only, which added 132 more viruses with an A/Fujian/411/2002 (H3N2)-like haemagglutinin, four more with an A/New Caledonia/20/99 (H1N1)-like haemagglutinin and two more with a B/Shanghai/361/2002-like haemagglutinin (from Norway). The B/Shanghai/361/2002-like viruses were detected at the end of the 2003-2004 season.

**Discussion**

The 2003-2004 influenza season in Europe was dominated by the emergence and spread of the new drift variant A/Fujian/411/2002 (H3N2)-like virus. Sporadic cases of this virus were detected at the end of the 2002-2003 season in Switzerland and Norway [6] and activity related to this virus started relatively early during the 2003-2004 winter compared with previous seasons. The intensity of clinical activity was higher than during the 2002-2003 season in 13 out of 20 networks [6], but did not reach particularly high levels compared with historical data [4,5,18].

The general west-east spread of influenza activity across Europe during the 2003-2004 season has also been observed during previous winter seasons. Plotting the peak weeks of clinical sentinel activity against the longitude and latitude of each network in EISS during five winter seasons (1999-2000 to 2003-2004) indicated that there was a west-east spread of influenza activity in three of five seasons (2003-2004, 2002-2003 and 2001-2002) and that in one of the seasons (2001-2002), there was also a south-north spread [19]. Another finding of this analysis was that influenza activity during the 2003-2004 season, for Europe as a whole, was longer (18 to 22 weeks) than in recent winters (e.g. 14 to 18 weeks during the 2001-2002 season) [19].

The identification of circulating viruses within the population and the recognition of virological changes are important tasks for EISS. There is a particular need to detect and monitor the emergence or re-emergence of viruses with pandemic potential and viruses that have a 'mismatch' with the vaccine strain components. The virological database was therefore upgraded at the beginning of the 2003-2004 season so that more detailed information could be collected (e.g. separate recording of H and N subtyping and antigenic and genetic strain characterisation results) and the database could be quickly and easily modified to collect information on emerging influenza viruses (e.g. a new avian influenza virus). These developments proved particularly relevant in the light of the emergence of avian influenza outbreaks and transmission to humans in South East Asia (H5N1), Canada (H7N3) and the US (H7N2) in 2004 [14-17].

Objective determination of the predominant virus by type and H- and N-subtype in a country was difficult as in many countries only a minority of influenza A virus isolates was haemagglutinin subtyped and the neuraminidase even to a lesser extent. More importantly, determining the H- and N-subtype of influenza A viruses is necessary to detect the emergence of new (avian) subtypes or reassortant viruses, illustrated by the emergence of the A(H1N2) reassortant virus in 2001 [20]. EISS is aiming at H- and N-subtyping of at least a representative sample of isolates throughout the season in each country in order to fulfil its early warning function [12].

The predominant virus circulating in Europe during the 2003-2004 season was the new drift variant A/Fujian/411/2002 (H3N2)-like virus. The A(H3N2) Fujian-like virus is antigenically different from the influenza A/Moscow/10/99 (H3N2) virus strain included in the 2003-2004 vaccine and there were concerns about the effectiveness of the vaccine in preventing influenza illness [6]. Studies have shown that estimates of influenza vaccine effectiveness ranged from 25% to 49% in children and 38% to 52% in adults in preventing illness during the 2003-2004 influenza season in the US [21]. Although estimated protection rates are higher when the match between the vaccine and circulating virus is good (70-90% in adults <65 years) [21], our epidemiological data for the 2003-2004 season indicate that the season was not particularly intense compared with historical data [18]. At the beginning of the 2003-2004 season, there were reports of deaths in children in the UK [22] which received considerable media attention and initially seemed to confirm the concerns about the escape of the A(H3N2) Fujian-like virus from pre-existing or vaccine induced anti-A(H3N2) immunity. Although we observed the highest clinical incidences among children aged 0-14 in countries reporting age specific data, these were not especially high compared with historical data (data not shown). From these observations, we may conclude that, despite the A(H3N2) Fujian-like virus being antigenically different from the previously circulating A(H3N2) virus and the A(H3N2) virus used in the vaccine, illness was not particularly severe.

The composition of the influenza vaccine for the 2004-2005 season (northern hemisphere winter) was announced by the World Health Organization in March 2004 [23]. Based on the analysis of influenza viruses from all over the world till February 2004, the A/Moscow/10/99 (H3N2)-like and B/Hong Kong/330/2001-like vaccine strains in the influenza vaccine of 2003-2004 have been exchanged for more current viruses. The European influenza vaccine [24] for the 2004-2005 season contains:

- A/NewCaledonia/20/99(H1N1)-like virus (the currently used vaccine virus is reassortant virus IVR-116 which is derived from A/NewCaledonia/20/99).
- A/Fujian/411/2002 (H3N2)-like virus (the currently used vaccine virus is reassortant virus X-147 which is derived from A/Wyoming/3/2003).
- B/Shanghai/361/2002-like virus (the currently used vaccine virus is B/Jiangsu/10/2003).

The spread of virus strains in Europe during the 2004-2005 season will be carefully monitored by the virological, epidemiological and clinical experts within EISS. Assessments of the influenza activity will be made in collaboration with the WHO Collaborating Centre in London and will be reported on the EISS website on a weekly basis.

#### Members of EISS

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#### Acknowledgements

EISS would not exist without the regular participation of sentinel physicians across Europe. We would like to thank them for making this surveillance scheme possible.

#### Participants

**Belgium** – Scientific Institute of Public Health, Brussels

**Czech Republic** – National Institute of Public Health, Prague

**Denmark** – Statens Serum Institut, Copenhagen

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## ORIGINAL ARTICLES

### Outbreak report

# HEPATITIS A OUTBREAK AMONG MSM LINKED TO CASUAL SEX AND GAY SAUNAS IN COPENHAGEN, DENMARK

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During an outbreak of hepatitis A predominantly among men who have sex with men (MSM) in Copenhagen, Denmark, in 2004, we did a case-control study to determine risk factors for infection. A case was an MSM > 17 years, living in Copenhagen, with IgM positive hepatitis A infection diagnosed between June and August 2004, and without a household contact with a hepatitis A case before onset of illness. Controls were selected at the Copenhagen Pride Festival. The study included 18 cases and 64 controls. Sixteen of 18 cases and 36/63 controls had sex with casual partners (OR<sub>MH</sub> 5.6, 95% CI 1.2-26.9). Eleven of 18 cases and 14/62 controls had sex in gay saunas (OR<sub>MH</sub> 4.2, 95% CI 1.5-11.5). Sex at private homes appeared to be protective (OR<sub>MH</sub> 0.2, 95% CI 0.1-0.7). Casual sex including sex in gay saunas was an important risk factor for the spread of HAV among MSM in Copenhagen. The results are in accordance with findings in other European outbreaks. As the general immunity to hepatitis A decreases and the outbreak potential increases, we recommend health education and hepatitis A vaccination to all MSM not living in monogamous relationships, especially if they visit gay saunas or other places with frequent partner change. To stop spread of hepatitis A among MSM in Europe, a European consensus on prevention and control measures may be required.

*Euro Surveill* 2005; 10(5): 111-4

Published online May 2005

**Key words:** Case-control study, hepatitis A, homosexuality, male; sexual behaviour

## Introduction

In Denmark, anti-HAV IgM positive hepatitis A virus (HAV) infection is notifiable by clinicians. HAV is not regarded as endemic in Denmark and susceptibility in the population is high. The majority of infections are imported by children of foreign origin returning from visits to friends and relatives in endemic countries [1]. Subsequent secondary spread in childcare institutions is a common cause of small outbreaks. Outbreaks of hepatitis A among men who have sex with men (MSM) have been reported from several cities in Europe and worldwide. In Copenhagen, outbreaks among MSM occurred in 1977 [2] and in 1991 [3]; with 21 and 17 reported cases of hepatitis A respectively. Studies have shown that hepatitis A is a sexually transmitted infection (STI) in MSM. The main risk factors identified are oral-anal sex (rimming) or digital-anal sex [4,5], visiting certain bars or saunas [6,7,8], having sex with anonymous partners or group sex [4,5]. Social contact of a non-sexual nature and contaminated food [7] also contribute to infection.

From January 2004 an outbreak of hepatitis A affecting predominantly MSM occurred in Copenhagen [9]. In April, active case finding in collaboration with laboratories was set up. Awareness of hepatitis A diagnosis and the need for reporting was raised among clinicians. Apart from ordinary precautions in a hepatitis A outbreak, such as increased hygiene and immunoglobulin for close contacts, vaccination was recommended for MSM not living in monogamous relationships. Further information for MSM was provided by a national STI campaign carried out by the Danish gay organisation STOP AIDS and the Danish National Association for Gays and Lesbians. The outbreak continued, and in August 2004, the Statens Serum Institut (SSI) and STOP AIDS carried out a case-control study to determine risk factors for hepatitis A infection in this outbreak in order to inform targeted preventive measures.

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