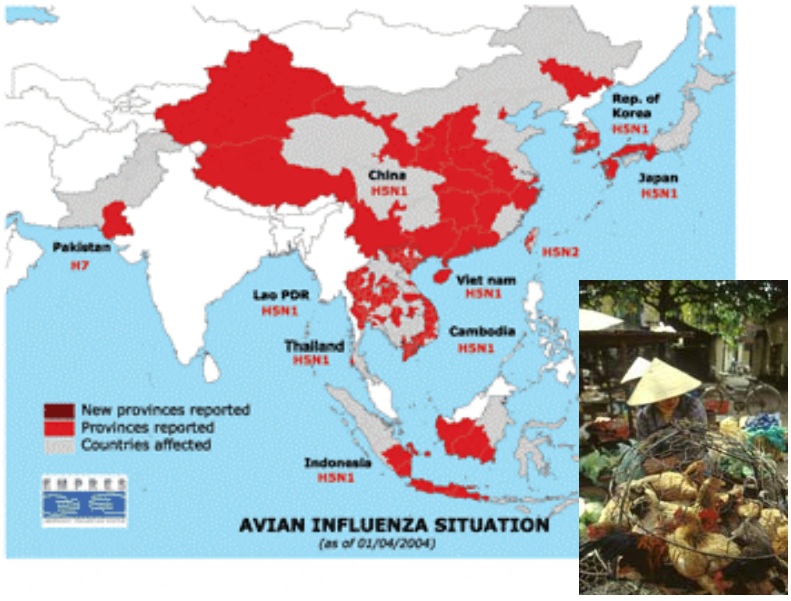
FEDERAL OFFICE OF PUBLIC HEALTH
BERNE - SWITZERLAND

HUG
Hôpitaux Universitaires de Genève

INFLUENZA SURVEILLANCE IN SWITZERLAND

SENTINELLA STUDY

WINTER SEASON 2003/2004



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1. Acknowledgements

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2. Résumé / Zusammenfasssung / Abstract

2.1. Résumé

La saison grippale 2003/04 a été précoce. L'épidémie a débuté dès le mois de Septembre 2003 pour culminer au cours de la première semaine de l'année 2004. Elle s'est enfin terminé dès le début du mois de février. La saison a été plutôt intense en comparaison avec les précédentes années. L'épidémie s'est déclaré dans le nord ouest du continent européen, puis s'est propagé en une vague allant d'ouest en est. Cette année, 99 % des souches grippales détectées étaient des souches influenza A (H3N2). Seuls 2 spécimens de virus influenza B et 1 influenza A (H1N1) ont été détectés dans le réseau de surveillance Sentinelle. La circulation de virus influenza A (H3N2) est généralement associée à des épidémies plutôt sévères. En Suisse, une proportion importante et inhabituelle de sujets ayant présenté une infection par le virus influenza et ayant moins de 20 ans a été observée. Cette particularité a également été vérifiée dans d'autre pays d'Europe et d'Amérique. Cependant, la proportion de patients âgés de plus de 60 ans n'étaient pas négligeable. Une surmortalité de 8 personnes sur 66 au total a été évaluée 15 jours après le pic épidémique dans ces classes d'age dans le canton de Genève.

Les souches influenza prédominantes cette année étaient antigéniquement proches de la souche influenza A/Fujian/411/02 (H3N2). Cette souche a déjà circulé au cours de la fin de la saison 2002/03 en Suisse comme dans d'autres pays Européens. Cette souche présente une antigénicité un peu différente de celle de la souche influenza A/Moscow/10/99 (H3N2) incluse dans le vaccin 2003/04. Cependant, la protection de ce vaccin contre la souche influenza A/Fujian/411/2002 a été jugée suffisante.

De nouvelles épidémies grippales aviaires d'une amplitude sans précédent ont été observées dans des élevages de volailles dans plusieurs pays d'Asie dès le mois de Décembre 2003 et pendant plusieurs mois. Au Vietnam et en Thaïlande, 34 cas d'infections humaines ont également été rapportés, dont 23 personnes sont décédées. Ces épidémies ont été causées par une souche aviaire hautement pathogène influenza A (H5N1). 100 millions de poulets d'élevage ont été abattus par mesure préventive.

2.2. Zusammenfasssung

Die Grippe Epidemie hat in der Saison 2003/04 frühzeitig begonnen. Schon im September konnten die ersten Viren der Saison nachgewiesen werden wobei das Maximum in der ersten Januarwoche beobachtet wurde. Die Epidemie war anfangs Februar beendet. Im Vergleich zu den vorangegangenen Epidemien war die diesjährige eher intensiv. In Europa begann die Epidemie im Nordwesten des Kontinents und wanderte dann gegen Osten. 99% der nachgewiesenen Viren waren dieses Jahr vom Typ Influenza A (H3N2). Nur in zwei Sentinella Proben wurden Influenza B gefunden und in einer zusätzlichen Probe ein Influenza A (H1N1). Im allgemeinen sind beim Vorherrschen der Influenza A (H3N2) die Epidemien intensiver. In der Schweiz war Unerwartetherweise ein grosser Anteil der betroffenen Patienten unter 20 Jahren. Die Eigenheit dieser Saison wurde auch im übrigen Europa und in Amerika registriert. Auch die über 60 Jährigen waren von der Grippewelle betroffen. Eine erhöhte Mortalität wegen Grippe von 8/66 Personen wurde im Kanton Genf 2 Wochen nach dem Maximum der Epidemie beobachtet.

Die Mehrheit der Influenzastämme war mit der Variante Influenza A/Fujian/411/02 (H3N2) verwandt. Dieser Stamme zirkulierte in der Schweiz gegen das Ende der letzten Saison wie auch im übrigen Europa. Der Stamm weicht etwas von dem im Impfstoff 2003/04 enthaltenen Influenza A/Moskau/10/99 (H3N2) ab. Hingegen erzeugte der Impfstoff trotzdem einen Impfschutz welcher als genügend eingestuft wurde.

Eine neue, in einem noch nie gekannten Ausmasse, Epidemie von Vogelgrippe wurde im Dezember in mehreren asiatischen Ländern beobachtet. Diese Ausbrüche dauerten mehrere Monate bis diese unter Kontrolle gebracht werden konnten. In Vietnam und in Thailand wurden 34 Patienten infiziert wovon 23 verstarben. Diese Ausbrüche wurden durch einen hoch pathogenen aviären Influenza A (H5N1) verursacht. 100 Millionen Hühner wurden geschlachtet um eine weitere Ausbreitung zu verhindern.

2.3. Abstract

The influenza season of 2003/04 started early. The epidemic began in September 2003 to culminate during the first week of 2004. It finally finished at the beginning of February. The season was rather intense in comparison to the preceding years. The epidemic was declared in the northwest of the Europe, then spread to the east. This year, 99 % of influenza viruses detected were influenza A (H3N2) viruses. Only 2 specimens contained influenza B and 1 influenza A (H1N1). The samples came from the Sentinella network. The circulation of influenza A (H3N2) viruses is generally associated with severe epidemics. In Switzerland, an important and unusual high proportion of subjects of less than 20 years presented an infection by an influenza virus. This characteristic was also observed in other countries of Europe and America. However, the proportion of infection in the more than 60 years old can not be neglected. An excess of mortality of 8 out of 66 deaths was observed in this age group in the canton of Geneva 15 days after the peak of the epidemic.

Influenza strains that predominated this year were antigenically related to influenza A/Fujian/411/02 (H3N2) virus. This strain already circulated at the end of the 2002/03 season in Switzerland like in other European countries. The antigenicity of this new variant is slightly different from the strain influenza A/Moscow/10/99 (H3N2) included in the 2003/04 vaccine. However, the protection induced in people by the 2003/04 vaccine against the influenza A/Fujian/411/2002 variant was considered to be sufficient.

New avian outbreaks with a high intensity were observed in breeding farms for poultry in several Asian countries since December 2003 and in the epidemic lasted for several months. In Vietnam and in Thailand, 34 cases of human infections were also reported, of which 23 people died. The epidemics were caused by a highly pathogenic avian influenza virus (influenza A (H5N1)). 100 millions of chickens were culled for preventive measure.

3. Introduction

The 2003/04 influenza season in Switzerland started relatively early following the wave coming mainly from France and spread slowly from west to east. The season was quite high when considering peak and duration in comparison to previous seasons as shown in figure 1 which illustrates the rate of influenza illnesses observed in Switzerland during the last 12 years.

The Sentinella surveillance network consists of around 220 general practitioners and paediatricians spread across the country who monitor the rate of influenza-like illnesses observed in their practice each week based on a clinical definition. A subgroup of 54 of these cases is sampled for influenza detection and subsequent typing. This surveillance system focuses only on the detection of influenza virus circulation and not other types of respiratory viruses.

The 2003/04 season was characterised by the circulation of mainly one predominant strain, A/Fujian/411/02 (H3N2). Only one influenza A (H1N1) and two influenza B viruses were identified by the Sentinella network. This is a major difference compared to the previous season which was characterised by the co-circulation of multiple influenza types and subtypes.

After four years of rapid test surveillance in addition to cell culture, this additional tool for surveillance was no longer used. Although it represented a valuable tool used directly in the medical office by network practitioners, it could not be conducted this year for technical reasons.

This season was also marked by the shadow of avian influenza which emphasises the need for the national reference centre to be fully prepared for the detection of new virus types. It shows clearly that each centre should have the ability to use RT-PCR assays for the detection of new viruses. For security reasons, cell culture needs to be avoided. Collaboration with other national influenza centres was of prime importance for the exchange of adequate controls.

For the first time in 11 years we had the opportunity to detect an influenza A during the peak of the heatwave and drought in August in a young child. Family members also presented

influenza-like symptoms but no samples were taken for confirmation by a laboratory test. Moreover, no travel history or contacts could be identified. This was however the only confirmed case and it remained unexplained.

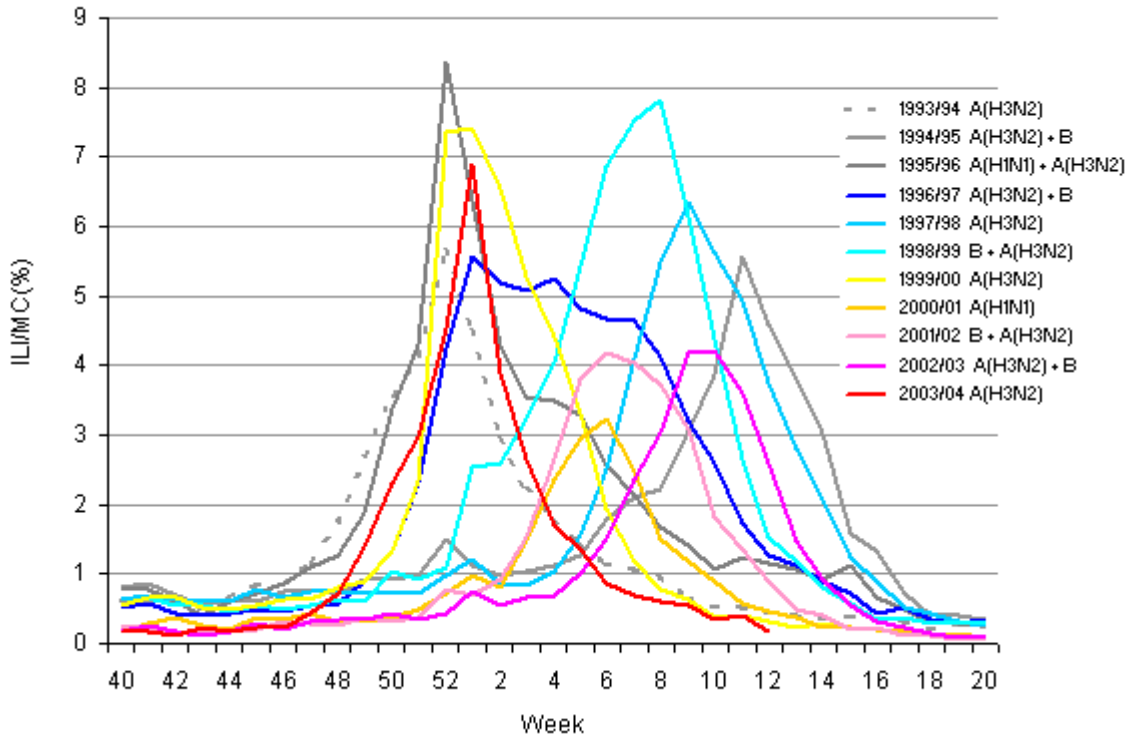


Figure 1 : Influenza epidemics monitored during 11 influenza seasons, 1993/94 to 2003/04.
ILIMC : medical contacts for influenza-like illness
(figure kindly provided by Reto Hagmann, Swiss Federal Office of Public Health)

4. Methods for the detection of respiratory viruses

4.1. Influenza surveillance by the Sentinella system

Fifty four general practitioners, of which 8 paediatricians, and 5 laboratories from hospitals participated in the surveillance this year. The number of participants was the same as the one from the last year. The distribution of the participants over the country is shown in Figure 2. From a subgroup of subjects (limited to 2 cases per week and per practitioner) with influenza-like illness, respiratory samples were sent to the reference laboratory.

Due to the fact that influenza infections occur in a period when other respiratory illness are observed, specific criteria are used for a specific selection of subjects with an influenza disease. The following case definition is used : high fever (more than 38°C), high sickness sensation, myalgia or general pain. Additional symptoms such as cough, rhinorea, and

arthralgia can be present but are facultative. Mainly positive samples were sent to the National Centre for Influenza by the hospitals. The purpose was a confirmation of the result and characterisation of the strains.

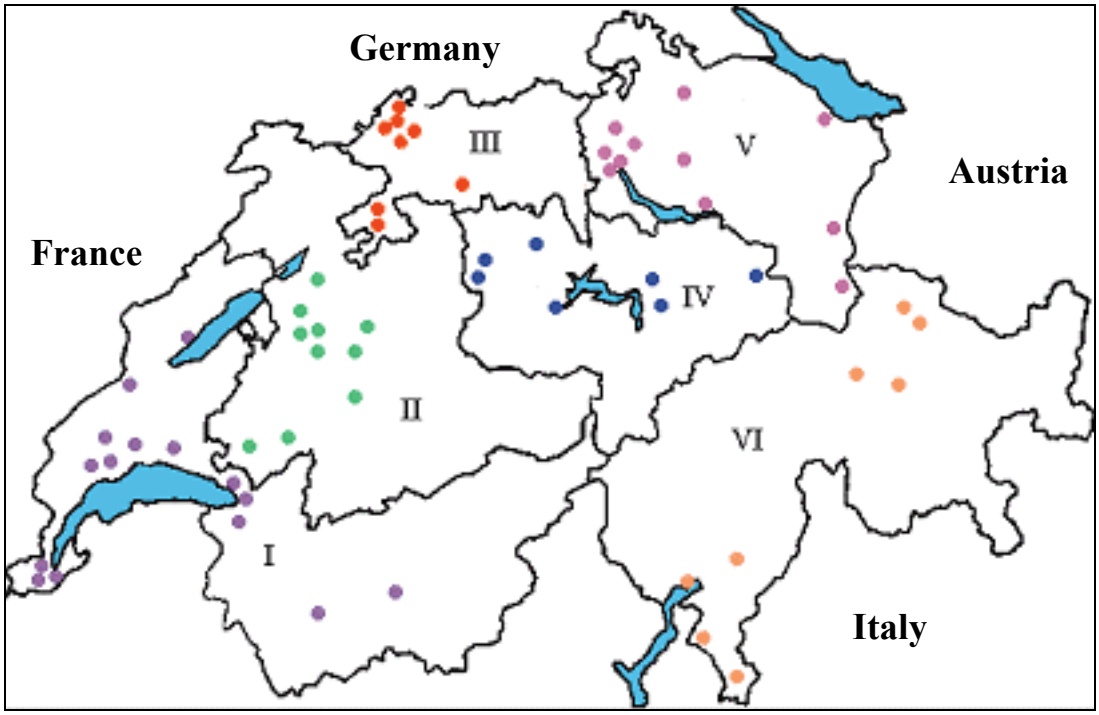


Figure 2 : Geographical distribution of the participants in the Sentinella network. Each participant is represented by a dot coloured according to the region where he is located. Our country is divided in 6 regions made on a different number of cantons. The composition of the different regions is described in the Legend. ***Region I****: Genève (GE), Vaud (VD), Valais (VS) and Neuchâtel (NE),* ***Region II****: Bern (BE), Fribourg (FR) and Jura (JU),* ***Region III****: Basel-Stadt (BS), Basel-Land (BL), Aargau (AG) and Solothurn (SO),* ***Region IV****: Luzern (LU), Zug (ZG), Nidwalden (NW), Obwalden (OW), Uri (UR),Schwyz (SZ) and Glarus (GL),* ***Region V****: Zürich (ZH), Schaffhausen (SH), Thurgau (TG), St. Gallen (SG), Appenzell-Innerhoden (AI) and Appenzell-Ausserhoden (AR),* ***Region VI****:Graubünden (GR), Ticino (TI).*

4.2. Detection of respiratory viruses

Respiratory viruses were detected and characterised following the procedure described in Figure 3. Virus isolation was performed by cell culture inoculated on three different cell lines (MDCK, LLC-MK2 and A549) at two different temperature (37°C and 33°C). Screening of cultures and identification of respiratory viruses were done by immunofluorescence using monoclonal antibodies. Through this seven different respiratory viruses can be detected and identified (influenza A and B, parainfluenza 1, 2, and 3, adenovirus and respiratory syncytial virus.

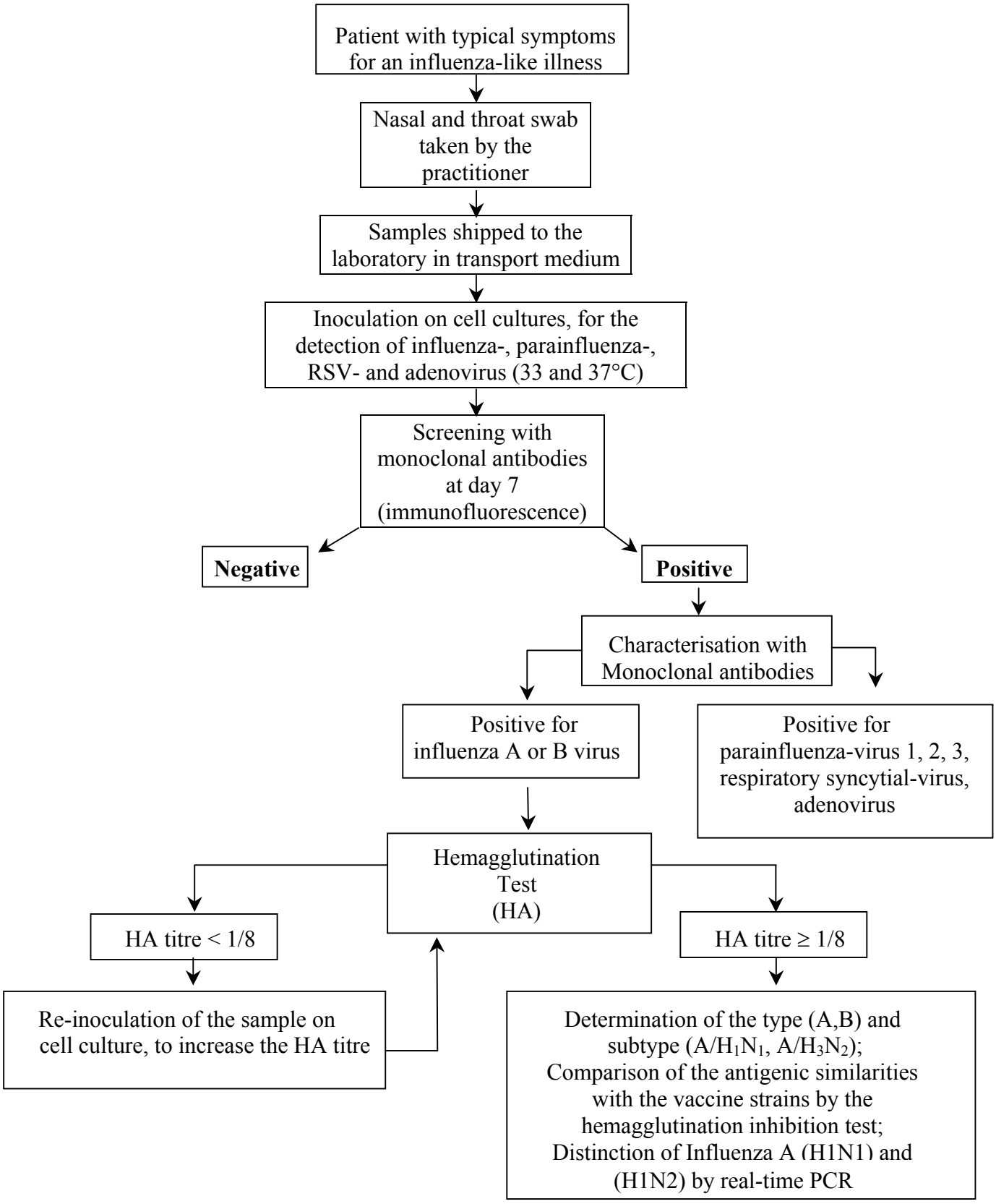


Figure 3: Procedure applied for the detection of respiratory viruses by cell culture

4.3. Characterisation of influenza viruses

Once an influenza virus was identified further characterisation was done by an hemagglutination inhibition assay with type specific animal sera produced in ferrets. Below are the antigenic tables that are used for the typisation of influenza strains isolated from clinical samples (Table 1). These tables show antibody titres obtained after incubation of standard antisera with standard influenza strains. Comparison of these titres with the one obtained for the clinical sample allow to define the nature of the strain isolated. Criteria for comparison are described in Table 1.

Table 1 : Inhibition of the hemagglutination (IHA) titre of standard influenza strains incubated with each of the standard antisera. The homologue IHA titre (HT) obtained after incubation of standard strain with the antiserum specific of this strain is mentioned in bold. The titre obtained with a strain isolated from a sentinella sample (ST) is compared with the homologous titre : if the ratio ST/HT is lower or equal to 4, the strain is considered as antigenically related to the standard strain. If the ratio is higher than 4, the strain is considered as significantly different from the standard strain.

Influenza A/H3N2	**Antisera**		
Strains	A/Panama/2007/99	A/New-York/55/01	A/Wyoming/3/03
A/Panama/2007/99	**1024**	256	128
A/New-York/55/01	1024	**512**	128
A/Wyoming/3/03	64	16	**1024**

Influenza B	**Antisera**				
Strains	B/Hong Kong/335/01	B/Shandong/7/97	B/Brisbane/32/02	B/Sichuan/379/99	B/Beijing/184/93
B/Hong Kong/335/01	**32**	512	128	< 8	< 8
B/Shandong/7/97	64	**512**	128	< 8	< 8
B/Brisbane/32/02	64	256	**256**	< 8	< 8
B/Sichuan/379/99	< 8	< 8	< 8	**128**	32
B/Beijing/184/93	< 8	< 8	< 8	32	**64**

Influenza A/H1N1	**Antisera**			
Strains	A/N.Caledonia/20/99	A/Egypt/96/02	A/Beijing/262/95	A/Bayern/7/95
A/N.Caledonia/20/99	**128**	128	64	< 8
A/Egypt/96/02	256	**512**	64	< 8
A/Beijing/262/95	128	64	**512**	32
A/Bayern/7/95	< 8	< 8	32	**2048**

A drawback of this approach is that only predefined HA of the virus are targeted. Variations in other proteins, such as the neuraminidase (e.g., H1N1 and H1N2 virus) cannot be distinguished with the IHA method. In the case of an influenza virus which could not be characterised by the present assay, Taqman real-time RT-PCR and sequence analysis were used. The different methods used together with their goal are listed below. Primers and probes are indicated in table 3.

The detection of genome sequences by real-time RT-PCR were used for :

- Discrimination between influenza A and B viruses using primers specific for the influenza A matrix and for the influenza B hemagglutinin protein respectively

- Discrimination between the N1 and N2 glycoprotein of influenza A viruses (influenza A (H3N2), A (H1N1) or A (H1N2) viruses)

- Detection of the avian hemagglutinin H5 and H7 containing viruses. For influenza A (H5N1) viruses, a standard antiserum can also be used for the IHA reactions on the virus (Table 2).

Table 2 : Antigenic table of influenza A (H5N1) inactivated virus with standard influenza antisera

	Standard Antisera (WHO)					
	A/Hong Kong 156/97 (H5N1)	**A/Moscow 10/99 (H3N2)**	**A/Panama 2007/99 (H3N2)**	**A/Hong-Kong 1550/02 (H3N2)**	**A/N-Caledonia 20/99 (H1N1)**	**A/Egypt 96/02 (H1N2)**
Inactivated A (H5N1) strain (WHO 1997)	**8192**	< 8	< 8	< 8	< 8	< 8

Table 3 : Primers and probes used in real-time PCR for the detection and characterisation of influenza viruses.

Target virus	Primers/ Probes	Sequence	Target gene
Influenza A	Forward primer	5'- GGA CTG CAG CGT AGA CGC TT -3'	**Matrix**
	Reverse primer	5'- CAT CCT GTT GTA TAT GAG GCC CAT -3'	
	Probe	5'- CTC AGT TAT TCT GCT GGT GCA CTT GCC A -3'	
Influenza B	Forward primer	5'- AAA TAC GGT GGA TTA AAT AAA AGC AA -3'	**Hemagglutinin**
	Reverse primer	5'- CCA GCA ATA GCT CCG AAG AAA -3'	
	Probe	5'- CAC CCA TAT TGG GCA ATT TCC TAT GGC -3'	
Neuraminidase 1 (N1)	Forward primer	5'- ATG GTA ATG GTG TTT GGA TAG GAA G -3'	**Neuraminidase**
	Reverse primer	5'- AAT GCT GCT CCC ACT AGT CCA G -3'	
	Probe	5'- TGA TTT GGG ATC CTA ATG GAT GGA CAG -3'	
Neuraminidase 2 (N2)	Forward primer	5'- AAG CAT GGC TGC ATG TTT GTG -3'	**Neuraminidase**
	Reverse primer	5'- ACC AGG ATA TCG AGG ATA ACA GGA -3'	
	Probe	5'- TGC TGA GCA CTT CCT GAC AAT GGG CT -3'	
Influenza A/H5	Forward primer	5'- CCCAAATATGTGAAATCAAACAGATT-3'	**Hemagglutinin**
	Reverse primer	5'- CAAATAGTCCTCTCTTTTTTCTTCTTCTC-3'	
	Probe	5'- TGCGACTGGACTCAGAAATACCCCTCA-3'	
Influenza A/H7	Forward primer	5'- GGC AAC AGG AAT GAA GAA TGT TCC-3'	**Hemagglutinin**
	Reverse primer	5'- AAT CAG ACC TTC CCA TCC ATT TTC-3'	
	Probe	5' AGG CCT ATT TGG TGC TAT AGC GGG TTT CAT -3'	

5. Results

5.1. Epidemiology of the season 2003/04

5.1.1. Detection of the different respiratory viruses

The winter surveillance of influenza by the Sentinella network started on 20 September 2003 and lasted for 28 weeks until 2 April 2004. The first influenza viruses were already detected early in September and subsequently through all the season until April. Six hundred and thirty nasopharyngal swabs were received during the surveillance. The analysis of results are shown in figure 4. Two hundred and sixty-nine respiratory viruses were found (figure 4a). Of these, 234 (87%) were influenza viruses and 35 were other respiratory viruses (13%, figure 4b). The majority were influenza A viruses: 232 were influenza A, and 2 were influenza B (Figure 4c). Influenza A viruses could be subtyped as following: 226 influenza A (H3N2) viruses and 1 influenza A (H1N1) virus only. Five influenza A viruses could not be subtyped due to low

titre obtained after cell culture. The characteristics of influenza viruses will be discussed in more detail in chapter 5.3.1.

5.1.2. Detection of respiratory viruses during the winter season

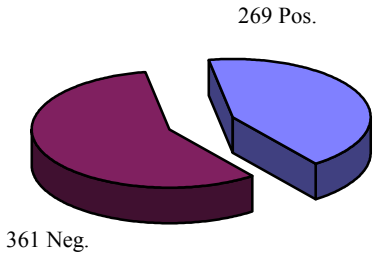
Sporadic detection of influenza viruses started as early as week 43 (table 4). From then on, the number of viruses detected per week continued to increase and reached a maximum of 66 viruses detected during week 50. The number of positive samples started to decrease and became sporadic after week 7. This kinetics rate per week resembled the one observed with the values of MC-ILI (figure 5). A low increase of the rate of consultations for influenza-like illness was detected during week 43 together with the first influenza virus detection. The MC-ILI then continued to increase, bypassed the threshold during week 50, and reached a maximum value of 68.8 ‰ during week 1. A decrease was then observed below the threshold during week 5 (13.7 ‰). In other words, the epidemic persisted during 7 weeks (table 4).

A significant decrease of the number of influenza viruses was observed during weeks 52 and 1 and then started to increase again (figure 5). This corresponded to the school holiday period where schools were closed and working activities reduced. In addition, practitioners were also on holiday which explains the lower number of samples received.

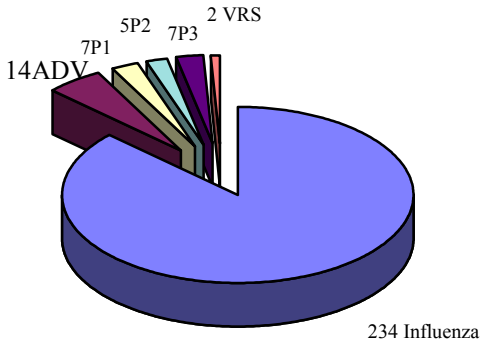
The majority of influenza viruses detected were related to influenza A (H3N2) viruses. Only two influenza B viruses (weeks 48 and 11) and one influenza A (H1N1) (week 11) were detected during this season. Information on the subtype of influenza viruses will be discussed in the chapter 5.3.1. Detection of other respiratory viruses were observed sporadically during the epidemic.

Similar to other seasons, the number of samples sent by the Sentinella practitioners increased greatly during the epidemic phase and were low in the weeks before and after the epidemic phase. The average number of samples received during the week before and after the epidemic phase were 16 and 11, respectively. As a result, the percentage of positive samples per week fluctuated strongly in the pre- and post-epidemic phase. During the epidemic phase, the average was at 48 per week with a high percentage of positive samples.

a)



b)



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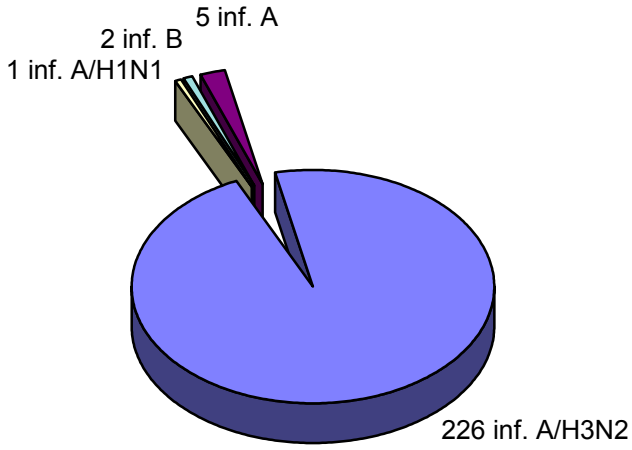
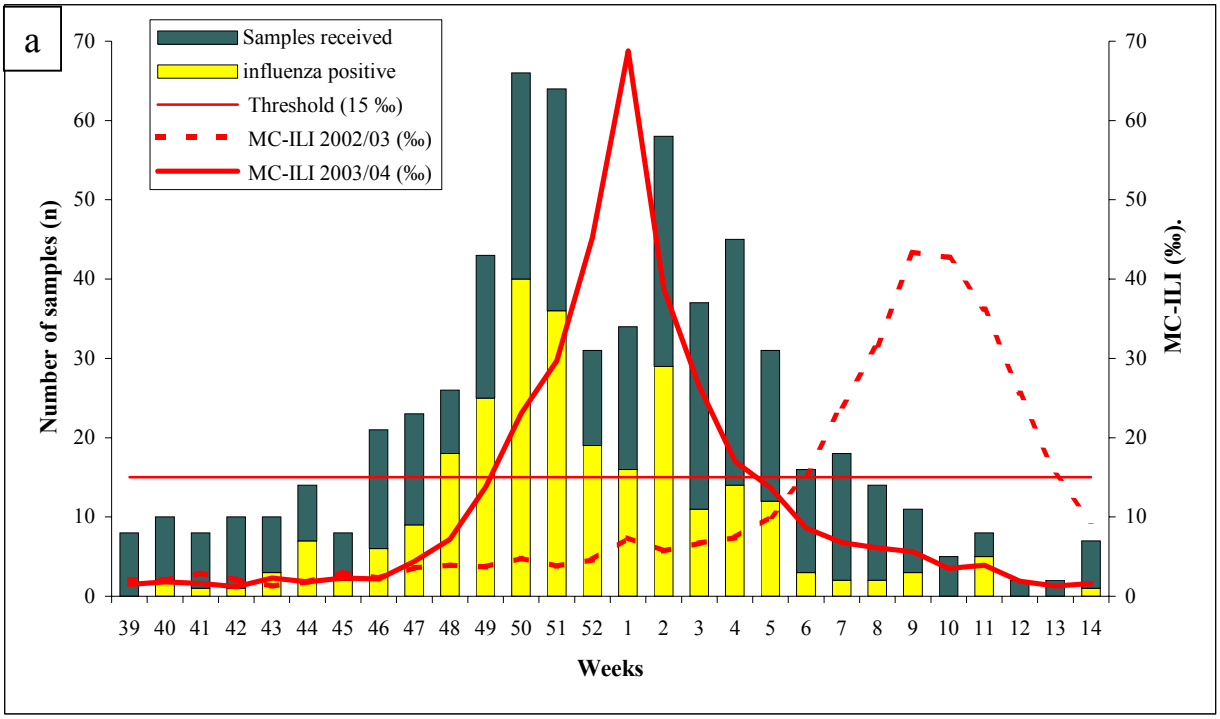


Figure 4: Proportion of nasopharyngal samples positive for influenza or other respiratory viruses during the 2003/04 season (n = 630). **a)** Number of positive and negative samples received during the season. **b)** Number of different respiratory viruses detected. **c**) Type of influenza viruses detected (Inf. = influenza viruses)

Table 4: Detection of respiratory viruses during the 2003/04 season.
MC-ILI: proportion of medical consultations for influenza-like illness; influ A: influenza A; not typed: influenza A which could not be sub-typed. Influ. B: influenza B; other resp. viruses: other respiratory viruses.

Week 03/04	Dates		MC-ILI (‰)	Samp. rec.	Influ. A			Influ.B	Other resp. viruses	Total virus (n)	Total virus (%)
					undet.	H3N2	H1N1				
39	**20-sept-03**	**26-sept-03**	1.5	8						**0**	0
40	**27-sept-03**	**03-oct-03**	1.8	10					2P1	**2**	20
41	**04-oct-03**	**10-oct-03**	1.6	8					1ADV	**1**	13
42	**11-oct-03**	**17-oct-03**	1.2	10					1ADV	**1**	10
43	**18-oct-03**	**24-oct-03**	2.3	10		2			1P1	**3**	30
44	**25-oct-03**	**31-oct-03**	1.8	14					2P2 3P3 2P1	**7**	50
45	**01-nov-03**	**07-nov-03**	2.3	8		2				**2**	25
46	**08-nov-03**	**14-nov-03**	2.2	21		5			1P3	**6**	29
47	**15-nov-03**	**21-nov-03**	4.4	23		9				**9**	39
48	**22-nov-03**	**28-nov-03**	7.2	26		16		1	1P3	**18**	69
49	**29-nov-03**	**05-dec-03**	13.8	43		21			2P2 1VRS 1ADV	**25**	58
50	**06-dec-03**	**12-dec-03**	23.1	66	1	36			1P1 1P2 1ADV	**40**	61
51	**13-dec-03**	**19-dec-03**	29.7	64		34			1P1 1P3	**36**	56
52	**20-dec-03**	**26-dec-03**	45.2	31	2	17				**19**	61
1	**27-dec-03**	**02-janv-04**	68.8	34		15			1ADV	**16**	47
2	**03-jan-03**	**09-jan-03**	38.8	58	1	26			1ADV 1P3	**29**	50
3	**10-jan-04**	**16-jan-04**	26.5	37		9			2ADV	**11**	30
4	**17-jan-04**	**23-jan-04**	17	45		14				**14**	31
5	**24-jan-04**	**30-jan-04**	13.7	31		9			3ADV	**12**	39
6	**31-jan-04**	**06-feb-04**	8.6	16		2			1ADV	**3**	19
7	**07-feb-04**	**13-feb-04**	6.8	18		2				**2**	11
8	**14-feb-04**	**20-feb-04**	6.1	14	1				1ADV	**2**	14
9	**21-feb-04**	**27-feb-04**	5.6	11		3				**3**	27
10	**28-feb-04**	**05-mar-04**	3.5	5						**0**	0
11	**06-mar-04**	**12-mar-04**	3.9	8		3	1	1		**5**	63
12	**13-mar-04**	**19-mar-04**	1.9	2						**0**	0
13	**20-mar-04**	**26-mar-04**	1.3	2						**0**	0
14	**27-mar-04**	**02-apr-04**	1.6	7		1			1ADV 1VRS	**3**	43
			Total	**630**	**5**	**226**	**1**				
					232			**2**			
					234				**35**	**269**	**43 %**



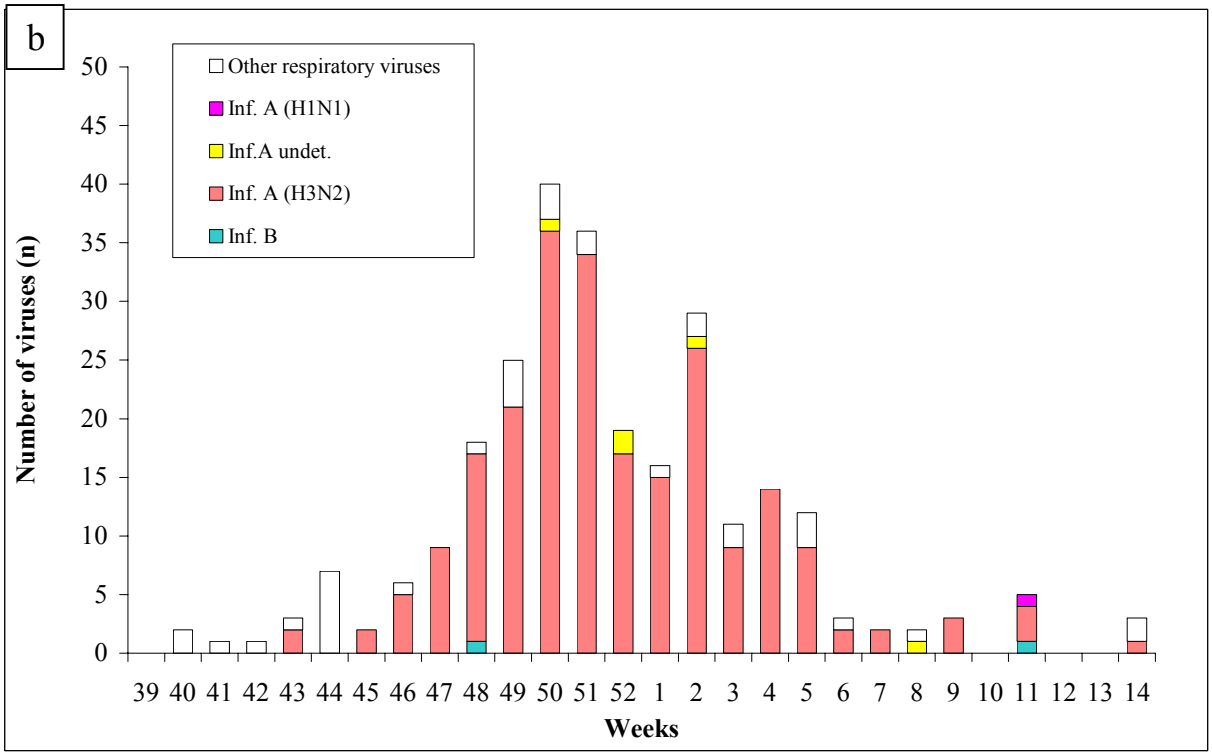


Figure 5: a) Number of samples received and influenza viruses detected per week.
MC-ILI: medical contacts for influenza-like illness; threshold: percentage of medical contacts for influenza-like illness indicating the presence of an epidemic (15 ‰).
b) Type of viruses detected per week. Inf. A undet. : influenza A viruses which were not subtyped; inf. A (H1N1): influenza A (H1N1) virus; inf. A (H3N2): influenza A (H3N2) virus; inf. B: influenza B virus.

5.1.3. Evaluation of the epidemic intensity

The intensity of the 2003/04 season has been analysed by the determination of the epidemic index (**EI**). This value is calculated with the values of MC-ILI, based on the following formula mentioned below (Chappuis et al., 1996). The epidemic index is a good indicator of an influenza epidemic. This value is proportional to the duration and to the intensity of an epidemic. A major advantage of this indicator is that the intensities of different seasons can be directly compared.

$$\mathbf{EI = [\Sigma Ca - (1.4 \times n)] / n}$$

Ca: values of % MC-ILI ≥ 1.5 (threshold for the epidemic)
n : number of weeks with Ca ≥ 1.5

Table 5: Calculation of the epidemic index for the 2003/04 season

	Values
ΣCa	24.91
n	7 (week 50 to 4)
EI = (Σ Ca-1.4n)	2.16

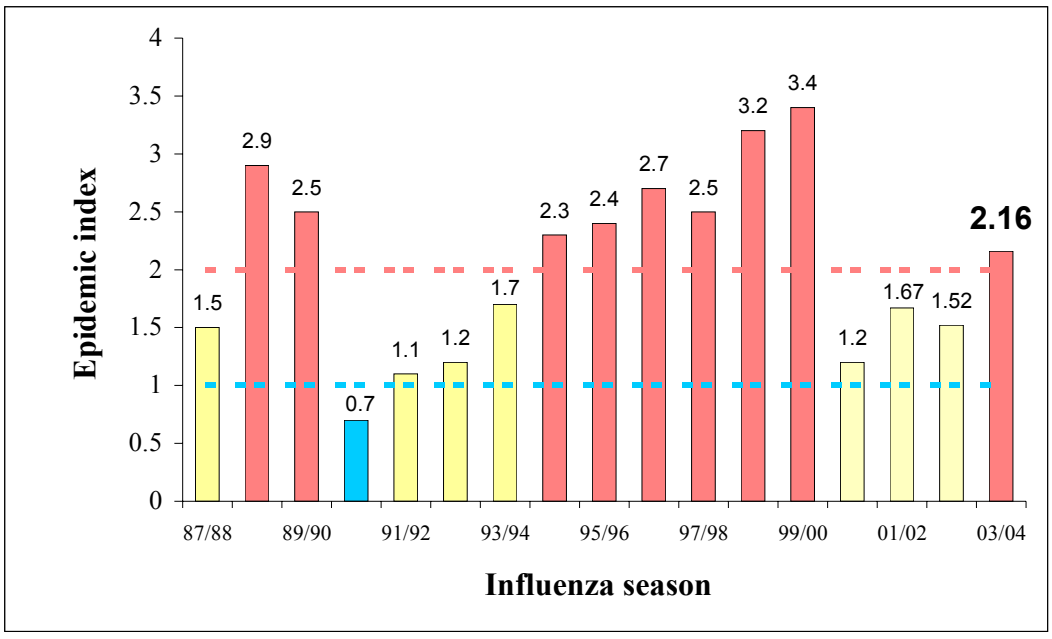


Figure 6: Epidemic index (EI) of the seasons between 1987/1988 and 2003/04.
EI ≤ 1: blue; 1 < EI ≤ 2: yellow; 2 < EI: red

The epidemic index value of 2.16 obtained for the season 2003/04 is higher when compared with those calculated for the last three previous seasons (figure 6). However, it is in the range of the values observed for 1994/95 and 1999/2000 which were between 2.3 and 3.4. In all these seasons, influenza A (H3N2) viruses circulated at a high frequency (6/6 seasons), and were predominant in 4/6 seasons. This observation is not surprising since several reports showed that influenza A (H3N2) viruses are associated with more severe influenza epidemics (Kaji et al., 2003).

As a point of comparison, several parameters of previous seasons are reported in table 6 such as the duration, the maximum value of MC-ILI and the week when the peak was observed. The 2003/04 season was one of the fourth most early seasons observed together with the seasons 1995/96, 1996/97 and 1999/2000 with the peak of the MC-ILI values reached during week 1. The maximum value of MC-ILI registered during this season is the 4th highest value of the last 10 seasons and was at 68.8 ‰. In contrast, the epidemic lasted for 7 weeks only and was the second shortest season after 2000/01.

Table 6: Overview of the intensity of the last 10 seasons.
Duration: number of weeks where the MC-ILI were above or equal to the threshold (15 ‰);
Maximum value of MC-ILI: maximum value observed during the whole season.

Season	Duration (n = weeks)	Maximum value of MC-ILI (‰)	Peak (week of the year)
1994/95	10	55	11
1995/96	12	82	52
1996/97	13	57	1
1997/98	11	62.2	9
1998/99	11	77.7	7
1999/00	8	75.3	1
2000/01	5	32.9	6
2001/02	8	41.6	6
2002/03	8	43.4	9
2003/04	7	68.8	1

Other characteristics of previous seasons are shown in table 7 such as the nature of influenza strains circulating, number of samples received and the number of participants. During the 2003/04 season, mainly one type of influenza A virus circulated: influenza A (H3N2) virus. It was also the case during the 1994/95, 1997/98 and 1999/2000 seasons. MC-ILI values of that seasons were the highest observed of the 10 previous editions, with the exception of the 1995/96 season. During that season, influenza A (H1N1) virus was predominant but a high percentage of influenza A (H3N2) was also detected and which explained the high value of MC-ILI observed.

Table 7: Overview of previous seasons
dominant subtypes of a particular season are in bold type

Season	STRAINS			
	A (H1N1)	A (H1N2)	A (H3N2)	B
1987/1988	10			**56**
1988/1989	**25**		6	1
1989/1990	**60**			10
1990/1991	1		3	**56**
1991/1992	19		**147**	
1992/1993			9	**55**
1993/1994			**16**	1
1994/1995	1		**153**	39
1995/1996	**146**		109	30
1996/1997	2		**234**	109
1997/1998	5		**321**	
1998/1999			83	**143**
1999/2000			**115**	
2000/2001	**110**		1	13
2001/2002		1	103	**130**
2002/2003	1	5	**125**	52
2003/2004	1		**225**	2

5.1.4. Influenza activity observed in different regions

5.1.4.1. Participation of the practitioners

Samples received by the Sentinella participants have been classified according to their location. Results are given in detail in table 8. Fifty-nine participants sent 630 samples. Of these, 234 influenza viruses were detected. On average, 11 samples have been sent per participant during the season. This participation is comparable to that observed in the three previous seasons (Thomas et al. 2003 and 2002). A slightly higher participation was observed in region 3 where 13 samples per practitioner were sent in and which represents the best participation of the 6 regions. Regions 1 and 6 also showed a good participation with 13 and 11 samples per practitioner, respectively. However, a high heterogeneity can be observed among participants. For example, 3/9 participants of region 6 sent 80/101 samples (Table 8). In regions 2 and 5, several practitioners sent also less than 10 samples in the season : 6/10 and 8/10 respectively. These results show that a more homologous participation of the practitioners would be desirable for the Sentinella network in order to be more representative.

Table 8 : Number of samples sent in per Sentinella participant

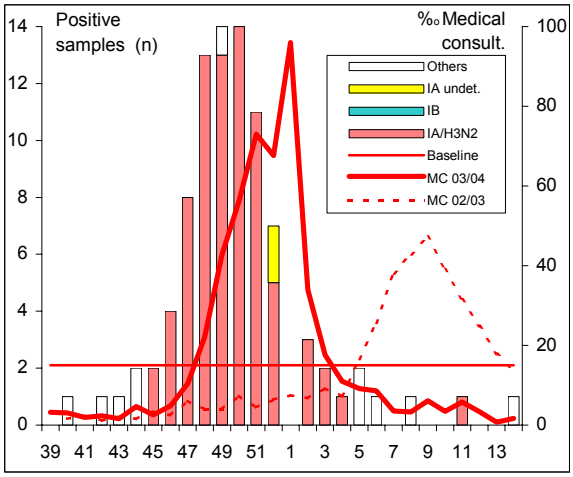
N° Region	Influenza viruses detected (n)	Total number of samples	Positive (%)
Region 1 GE,VD,VS,NE	15	192	41
Region 2 BE,FR,JU	10	75	44
Region 3 BS,BL,AG,SO	8	104	43
Region 4 LU,ZG,NW,OW,UR,SZ,GL	7	72	32
Region 5 ZH,SH,TG,SG,AI,AR	10	86	38
Region 6 GR,TI	9	101	24

5.1.4.2. Kinetics of the epidemic in the 6 regions

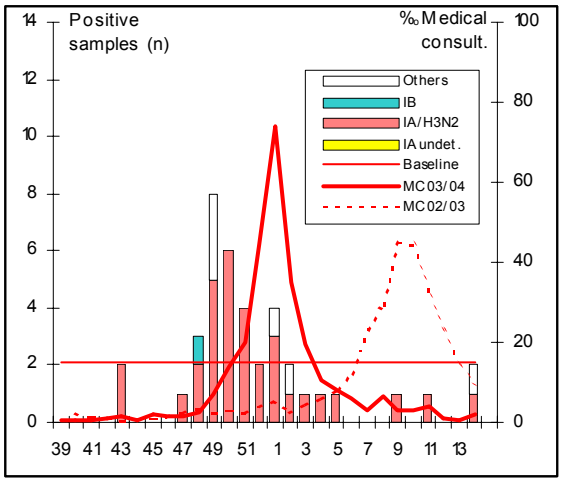
The same type of virus circulated in the six regions of Switzerland. Kinetics observed in the six regions were comparable (figure 7). However, in region 1, viruses started to be detected earlier than in other regions, namely week 45. In this region, MC-ILI was higher than the threshold during week 48. In other regions in comparison, viruses started to be detected two weeks (region 2) to five weeks later (region 3 and 6). MC-ILI values in those regions were higher than threshold two weeks (regions 3 and 6) to four weeks later (region 4) than in region 1. MC-ILI values in all six regions reached maximal value during the same week.

MC-ILI values were higher in regions 1, 2 and 3 than in the 3 other regions. In addition, the number of influenza viruses detected were also higher in these regions. For example, in region 2, 33 viruses were detected by 10 participants while in region 6, 24 viruses were detected by participants only. In region 3, 45 viruses were detected by eight participants while in region 4, 23 viruses were detected by seven participants only. Influenza viruses circulated at a higher level in the western part of Switzerland (regions 1, 2 and 3).

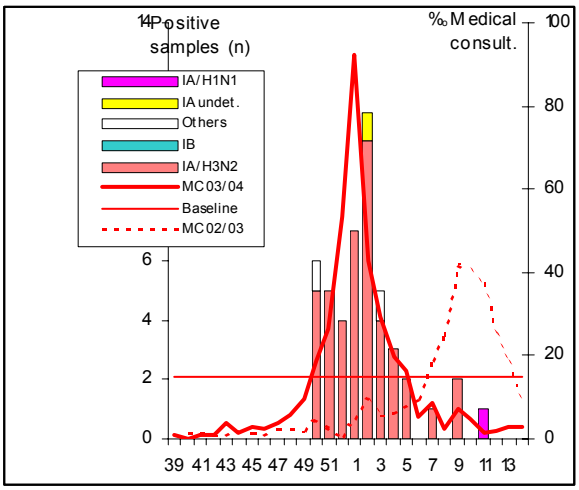
Region 1 : GE, VD, VS, NE



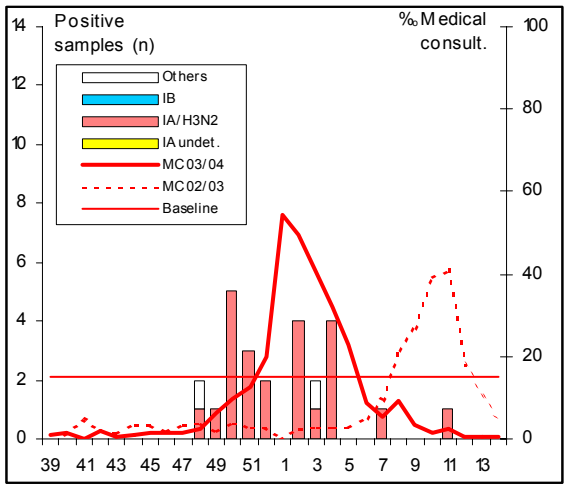
Region 2 : BE, FR, JU



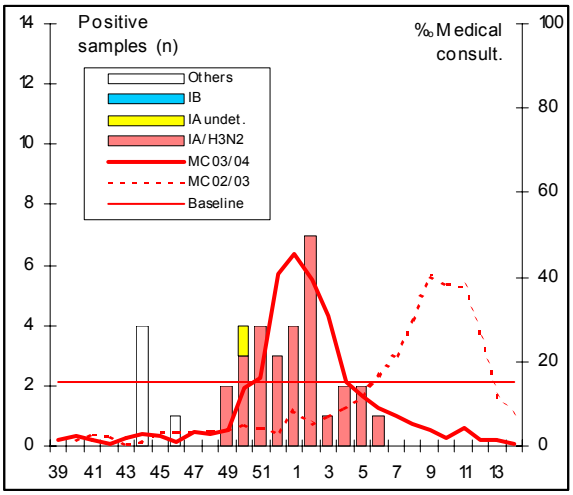
Region 3 : BS, BL, AG, SO



Region 4 : LU, ZG, NW, OW, UR, SZ, GL



Region 5 : ZH, SH, TG, SG, AI, AR



Region 6 : GR, TI

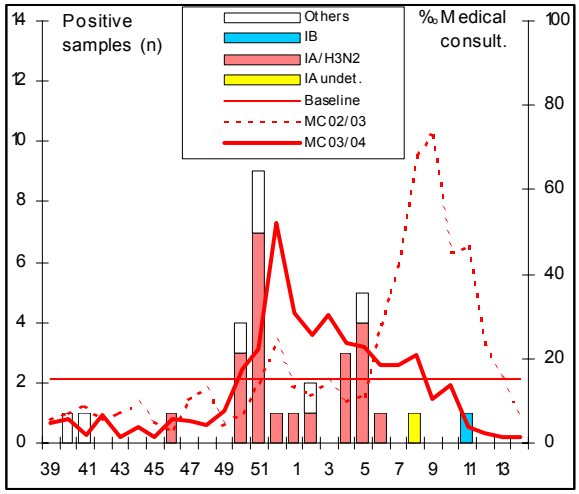


Figure 7: Number of respiratory viruses detected per week and per region. Others: adenovirus, respiratory syncytial virus, parainfluenza viruses; IA: influenza A virus; A/H3N2 : influenza A (H3N2) viruses; undet: subtype undetermined; IB: influenza B viruses. ‰ MC: medical consultation for ILI

5.2. Persons infected with influenza viruses

5.2.1. Clinical data

Persons recruited by the Sentinella surveillance network present typical symptoms that are specific to influenza-like illness. Each Sentinella sample is sent in with a request form containing a description of the symptoms present in a particular patient. An analysis of this data was performed at the end of this season and results are summarised in table 9.

As observed previously (Thomas et al., 2003 and 2002), the most frequent symptoms were fever and cough (97% and 89%, respectively) followed by myalgia, rhinitis and headache. Other symptoms were present in a lower frequency.

Table 9 : Classification of symptoms associated with persons infected with influenza virus according to frequency. 234 persons infected with influenza were analysed.

Symptoms	Frequency (%)
Fever	**97**
Cough	**89**
Myalgia	73
Rhinitis	71
Headache	70
Sweat	53
Chills	48
Sputum	31
Pharyngitis	26
Adenopathy	16

5.2.2. Frequency of the detected viruses in the age groups

The number of samples received and influenza viruses detected during the season have been classified according to age groups. Ten different age groups have been defined, as shown in figure 8. The highest number of samples received and viruses detected were observed in the three age groups between 10 and 39 years old. This observation was also made during the previous seasons and will be discussed in chapter 6 in more detail.

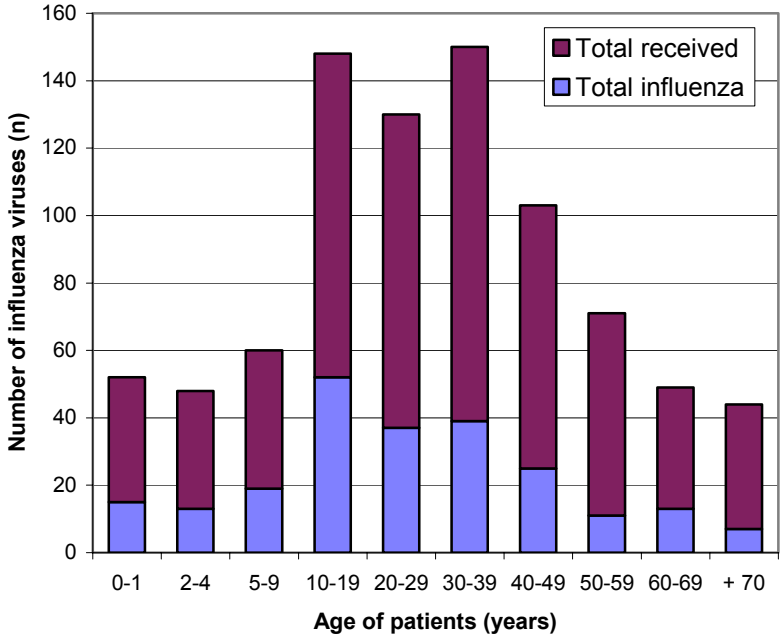


Figure 8: Distribution of samples received and number of influenza viruses detected per age group

A particularity of this season was that the highest number of influenza viruses was detected in younger age groups with 42 % of influenza viruses detected in samples of persons younger than 20 years old (table 10). In comparison, 41/200 (20%) influenza viruses were detected in this age group during the 2002/03 season. At the beginning of the 2003/04 season, the percentage of influenza viruses detected in this age group was even higher. On 21 November 2003, 61% of viruses were detected in Sentinella patients younger than 20 years old and on 12 December 2003, this percentage was 59%.

Table 10: No. of viruses detected and samples received during the season

	Virus detected (n)		%
Weeks	All age groups	< 20 years old	
21.11.2003	13	8	**61**
28.11.2003	30	15	**50**
06.12.2003	53	30	**57**
12.12.2003	75	44	**59**
19.12.2003	121	67	**55**
02.04.2003	234	99	**42**

5.2.3. Influence of the influenza epidemic on the mortality in the canton of Geneva

After infection with influenza, the risk of complication is high in patients with chronic disease and in the elderly (over 60 years old). They constitute a high risk group for influenza infection. Impact of the epidemic on this age group depends on different factors, such as the origin of the circulating strain, the intensity of the epidemic and others. An influence of the influenza epidemic on the mortality rate of the population of more than 60 years old could be observed in previous seasons in the canton of Geneva during the seasons 1996/97, 1997/98 and 1999/2000 (Thomas et al., 1997, 1998 and 2000). To evaluate the impact of the 2003/04 influenza season on elderly people, we collected data on the mortality rate in the canton of Geneva during the surveillance period of influenza epidemic.

The weekly mortality rates were collected from the Register Office of the canton of Geneva. The more than 60 years old age group was considered for this analysis. In Figure 9, the mean of the weekly death rate registered between week 38 of 2003 and week 15 of 2004 is represented (green curve). For comparison, the means of the weekly death rate observed between 1991 and 2003 are also represented (pink curve). The epidemic period was defined by the medical contacts for influenza-like illness (red curve) and detection rate of influenza viruses detected in the canton of Geneva.

An increase of the weekly death rate over the mean +2s can be observed during weeks 2 and 3 (green curve). As in previous seasons, the increase of the death rate related to the influenza epidemic occurs usually one or two weeks after the peak of MC-ILI. In the canton of Geneva, MC-ILI culminated during week 1 (red curve). For the season 2003/04, the increase of the death rate over the mean of this age group (weeks two and three) follows exactly with a delay of 1 to 2 weeks after the peak of MC-ILI (week 1). In comparison with the means of the weekly death rates observed during the last 12 years (pink curve) the death rate observed this season during the weeks 2 and 3 is higher. To determine whether these values are statistically different, the mean of the weekly death rate observed during the seasons 1991/92 to 2003/04 has been calculated and two standard deviations were added. This value is equal to 66 and is represented as a pink dot line in figure 9. The death rates registered during weeks 2 and 3 (69 and 71) were higher than this threshold. This means that an excess of eight deceased persons was observed in the population of more than 60 years old 1 to 2 weeks after the peak of MC-ILI.

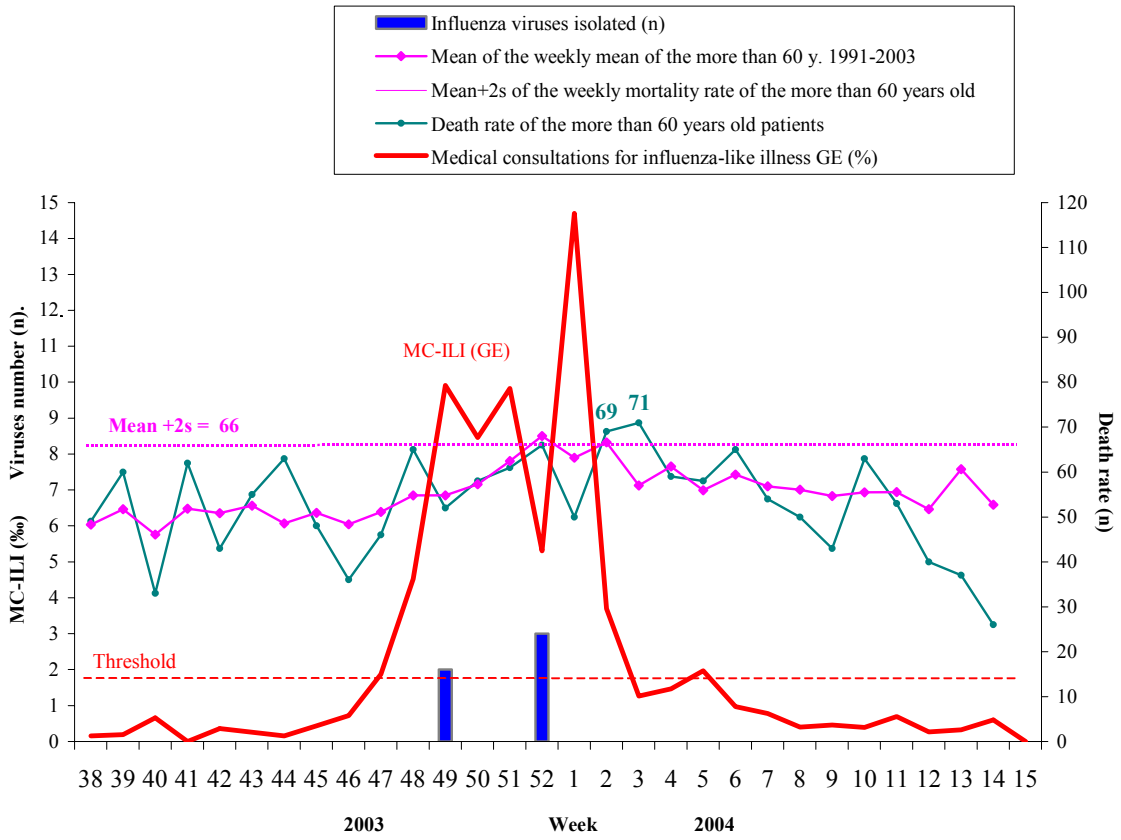


Figure 9 : Influence of the influenza epidemic on the mortality rate in people older than 60-years-old in the canton of Geneva during the 2003/04 season.
The numbers of deaths were obtained from the records of the Register Office of the Canton of Geneva published by the Public Health Authorities of Geneva; Mean +2s: mean number of deceased people older than 60.years-old + 2 standard deviation; MC-ILI GE (%): medical contacts for influenza-like symptoms in the state of Geneva.

5.3. Characteristics of influenza viruses detected during the 2003/04 season

5.3.1 Switzerland

Of 630 samples, 232 influenza A and 2 influenza B viruses were detected. Further characterisation of the viruses was done by inhibition of the hemagglutination and the RT-PCR reactions. Results of these analyses are shown in the annexes 1, 2 and 3. Two hundred and two influenza A (H3N2) were antigenically related to the strain influenza A/Wyoming/3/03 (H3N2) which is a derivative of influenza A/Fujian/411/02 (H3N2) (Annex 1). This strain was predominant in all European countries in 2003/04. In 2003, it started to circulate in Switzerland, as in other European countries, during the second half of the season. The hemagglutinin showed an attenuated titre in inhibition of the hemagglutination reaction using antiserum specific for the 2003/04 vaccine strain influenza A/Panama/10/99 (H3N2)

virus. Based on the predominance in the northern hemisphere, this strain will be included in the 2004/05 vaccine composition.

One strain (annex 1, ID n° 4904, p48) was analysed as antigenically related to influenza A/New-York/55/01 (H3N2). This strain is related to the vaccine strains influenza A/Panama/2007/99 and A/Moscow/10/99 (H3N2). The person was a 20-year-old man resident in the canton of Fribourg and was the only case.

Nineteen influenza A (H3N2) strains detected during the season reacted poorly with antisera directed against influenza A (H3N2) (annex 1, squared in red, p48 and 49). The attenuated titres obtained with antisera showed that these viruses were better recognised by A/Wyoming/3/03 (H3N2) antiserum than by others but with a lower affinity. A majority of these specimens were sent to MRC London for further analysis as inhibition of the hemagglutination with more recent antisera and sequencing analysis. Inhibition of the hemagglutination test showed a higher reactivity of these strains with A/Fujian/411/02 antiserum and the more recent A/Kumamoto/102/02 than with the A/Wyoming/3/03. This variability in inhibition of the hemagglutination test was also observed for recent isolates from other European countries and is considered to be normal (Lin Yipu, personal communication). Sequence analysis showed no strict correlation between the titre obtained with inhibition of the hemagglutination test and changes in the hemagglutinin sequence.

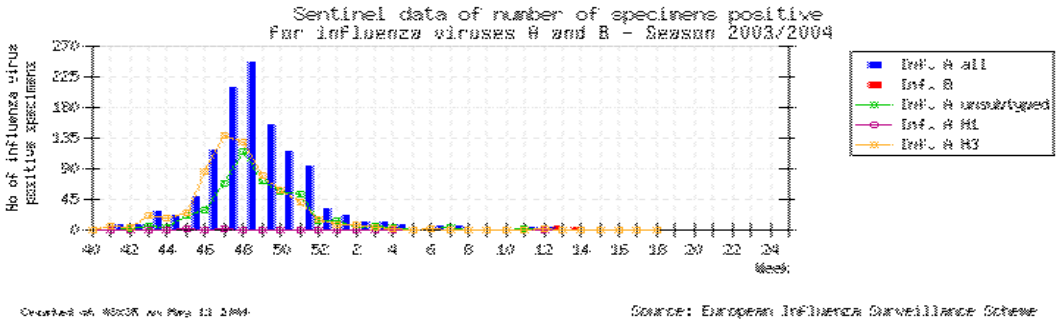
One influenza A (H1N1) virus was also detected during this season (annex 2). The nature of the two peripheral proteins, hemagglutinin and neuraminidase, were analysed by inhibition of the hemagglutination reaction and RT-PCR respectively, as described in chapter 2. Results of these analysis confirmed that the strain was related to influenza A/New Caledonia/20/99 (H1N1) virus. This strain was included in the 2003/04 vaccine. The sporadic case was found in a 9-year-old subject living in the canton of Solothurn. This was the only case found so far.

Two influenza B viruses were also detected and were antigenically related to influenza B/Sichuan/379/99. This strain was not included in the 2003/04 vaccine. However, the population was immunised in previous seasons against this virus. In fact, the strain was included in the 2001/02 vaccine and circulated between 2000 and 2002. This may explain a very limited circulation and impact of this virus in the population during this season.

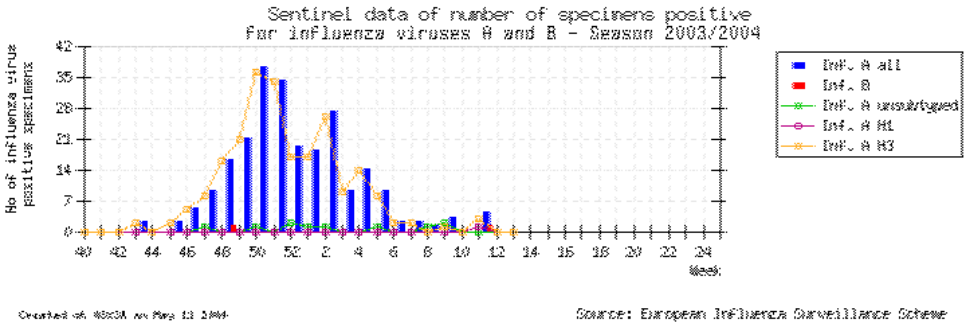
5.3.2. Influenza epidemics in the northern hemisphere

In Europe, the influenza epidemic 2003/04 started early in comparison to previous seasons. The first outbreak caused by influenza viruses was described in Ireland as early as in September 2003 (Fitzgerald M. et al., 2003). Then, other European countries of the western part were also affected, namely Portugal, Spain, Great Britain and France. Switzerland was affected a few weeks after the influenza epidemic started in France. Figure 10 shows the, kinetic curves of the MC-ILI in different European countries. In France, influenza viruses started to be detected during week 43. The number of viruses detected culminated between weeks 48 to 51 and started then to decrease. In Switzerland, influenza viruses started to circulate during week 45 and the number culminated between the weeks 50 and 51. In comparison to France, the influenza epidemic was observed with a delay of 2 weeks. It started later in Italy and Germany. Influenza virus started to circulate during week 47 in both countries. The detection rate started to increase slowly to reach its peak during week 5 in Germany and week 6 in Italy. The epidemic in Europe moved from the western and northern part to the eastern and southern part.

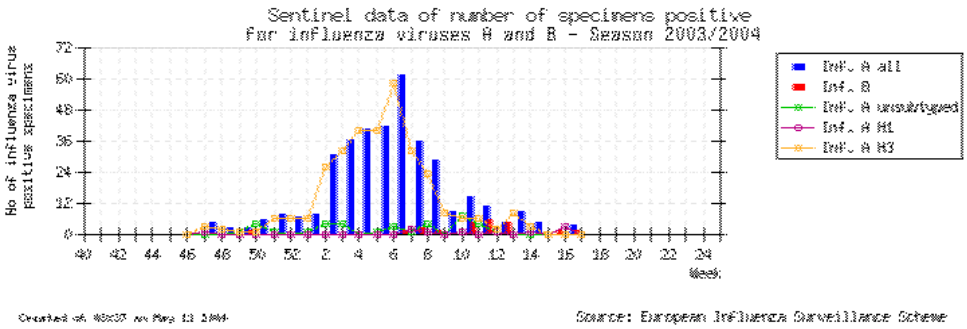
France



Switzerland



Italy



Germany

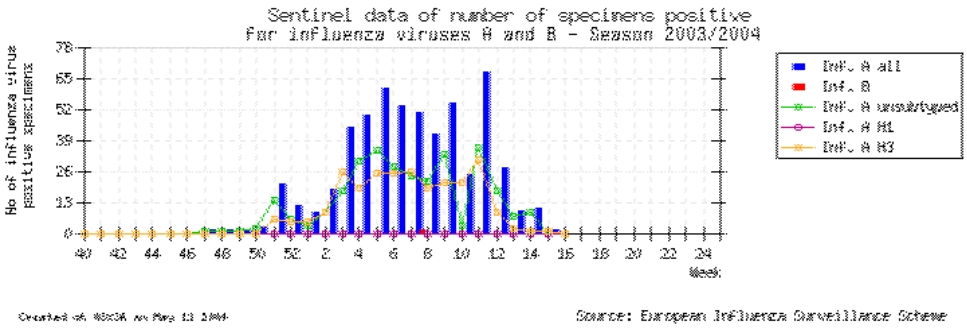


Figure 10: 2003/04 influenza epidemics in France, Switzerland, Italy and Germany. Data were taken from the European Influenza Surveillance Scheme database. For more information, see *http://www.eiss.org*. Inf. A and Inf. B are abbreviations for influenza A and influenza B viruses.

5.4. Influenza viruses circulating in animals

5.4.1. Avian influenza in Asia

In late January 2004, WHO reported human cases of severe disease caused by an influenza A (H5N1) strain of avian origin. Cases were detected in Vietnam and Thailand. Additional human cases were reported through mid-March. In total, 34 human cases were officially declared by WHO of which 23 were fatal. These human infections were directly linked to outbreaks of a highly pathogenic avian influenza A (H5N1) in poultry of these two countries. Since mid-December 2003 through February 2004, outbreaks of H5N1 infection in poultry were detected in these two countries and in six additional Asian countries : Cambodia, China, Indonesia, Japan, Laos, and the Republic of Korea (figure 11). WHO activated its influenza pandemic preparedness plan in response to confirmation of human cases in Vietnam and Thailand. As preventive measure, more than 100 millions of birds were culled in those countries.

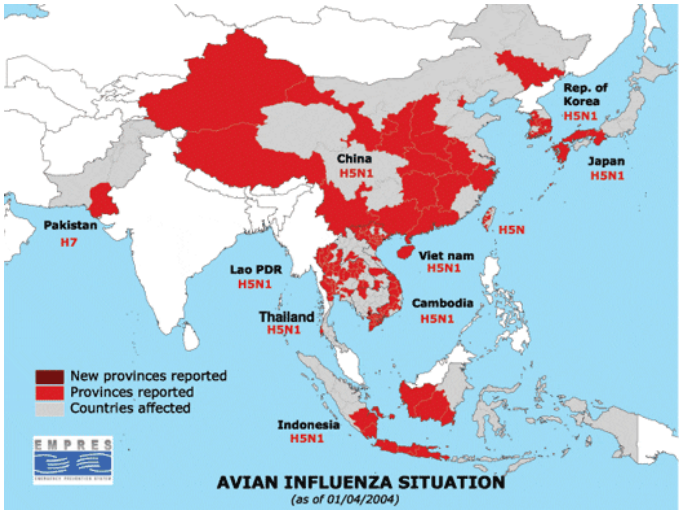


Figure 11: Map on the situation of avian influenza A (H5N1) virus outbreak. Update of 01.04.2004. Map is reproduced from EMPRES *(http://www.fao.org/ag/againfo/subjects/en/health/diseases-cards/avian_update.html)*

Influenza A viruses of avian origin have already demonstrated the capacity to infect human and cause severe diseases. In the past, several clinical cases were related (Table 11). Last year, major outbreaks in breeding farms were due to avian influenza A (H7N7) in The Netherlands. Additional outbreaks were then observed in Germany and Belgium with the

same influenza virus. 89 human cases and 1 fatal case was caused by this virus in The Netherlands. Influenza A (H5N1) virus was also detected in a boy and his father in early 2003. The father died. In 1997, a major outbreak occurred in poultry in Hong Kong. Again, an avian influenza A (H5N1) was the origin of the outbreak. Thousands of chickens died rapidly after infection. 18 human victims were observed of which 6 were fatal (Table 11). However, even if the subtype A/H5N1 of the virus was the same, both viruses were antigenically and genetically different. A major difference was that the 2004 avian influenza virus was highly pathogenic for water fowl. In contrast, and as usually observed, the avian influenza A (H5N1) virus from 1997 was not pathogenic for wild birds. Studies are still under process to explain this difference.

These outbreaks by an avian influenza strain are a great concern for public health. This virus demonstrated its capacity to infect humans and cause severe infections, with a high fatality rate on different occasions since 1997. At the moment, there is no vaccine for preventive protection (WHO, 2004).

Table 11 : avian influenza outbreak (Karcher F., 2004, Lubroth et al., 2004)

Date	Locality	Virus	Elimination of Poultry	Human cases	Fatal human cases
1997	Hong Kong	H5N1	1.5 Million Chickens	18	6
1999	Hong Kong	H9N2	No	2	0
2003	The Netherlands Germany Belgium	H7N7	30 Million Chicken	89	1
2003	Hong Kong China	H5N1	22000 chickens	2	1
2003	Hong Kong	H9N2	No	1	0
2004	Vietnam Thailand	A (H5N1)	> 100 Millions	34	23
2004	Canada	A (H7N3)	Unknown	2	0

5.4.2. Avian influenza in Canada

Since 21 February 2004, hundred of thousand of chickens died after an avian influenza A (H7N3) infection in British Columbia. At the beginning of April, 12 poultry workers involved in culling developed flu-like symptoms, despite protective clothing. Two of them have been confirmed as infected with influenza A (H7N3). The Canadian government decided to slaughter birds infected in order to contain an outbreak of bird flu (Abbott A., 2004). At this moment, 42 commercial and 11 backyard premises have been infected (CFIA, 2004).

5.4.3. A diagnostic test for the detection of influenza A (H5N1) viruses

A diagnostic test was already developed last year for the detection of influenza A (H5N1) viruses from swabs of human patients (Thomas et al, 2003). The method was a Real-Time RT-PCR that can detect specifically the hemagglutinin H5 of influenza A (H5N1) viruses. This method was tested on the new influenza A (H5N1) virus that circulated in humans in Asia earlier this year. A positive control was obtained from the WHO international collaborating Centre at London (MRC), a cDNA of an influenza A/Vietnam/1203/04 (H5N1) virus obtained from a human infected in Vietnam by this virus.

The hemagglutinin of influenza A (H5N1) viruses detected in humans during previous years seems to be different (Horimoto et al., 2004). However, RT-PCR can still detect influenza A (H5N1) strains from 2004. A positive reaction is presented in figure 12 using the new influenza A (H5N1) virus and our previously developed primers. The sensitivity and specificity of the reaction was comparable with the one of last year (data not shown).

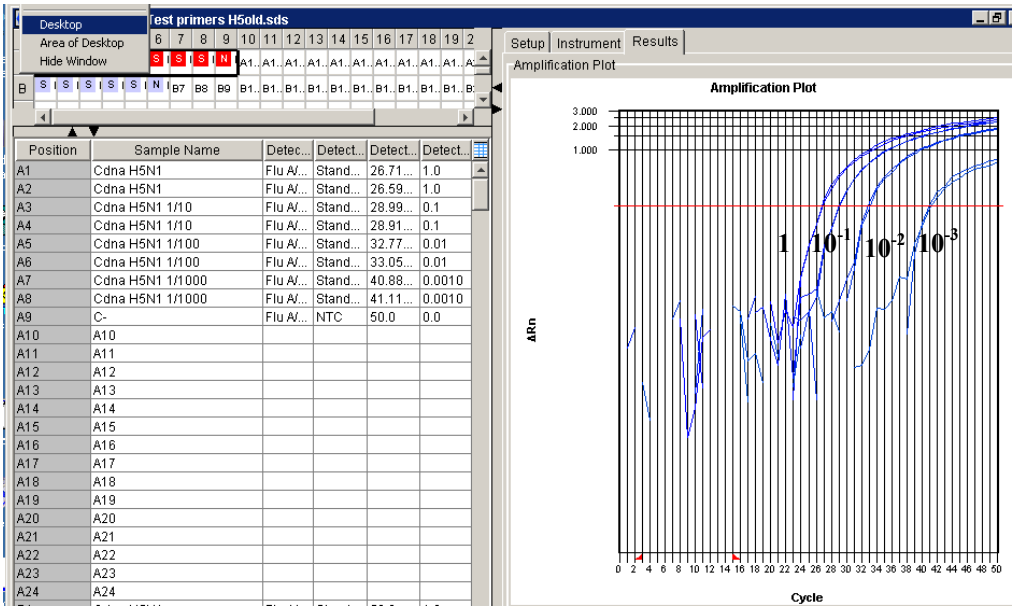


Figure 12: Amplification curve obtained with A/Vietnam/1203/04 (H5N1) cDNA detected with a Real-Time PCR on a Abi Prism DNA amplification sequence 7900. cDNA pure and a ten-fold serial dilution was tested (10^{-1} to 10^{-3}). Each curve with corresponding dilution are represented on the graph.

5.5. Recommended composition of the 2004/05 influenza vaccine

WHO recommended that vaccines to be used in the 2004/05 northern hemisphere influenza season contain the following :

- **an A/New Caledonia/20/99(H1N1)-like virus**
- **an A/Fujian/411/2002(H3N2)-like virus[a]**
- **a B/Shanghai/361/2002-like virus[b]**

a. *The currently used vaccine virus is A/Wyoming/3/2003.*
A /Kumamoto/102/2002 is also available as a vaccine virus.

b. *Candidate vaccine viruses include B/Shanghai/361/2002..*
and B/Jilin/20/2003 which is a B/Shanghai/361/2002-like virus.

6. Discussion

In Switzerland, the first influenza virus of the new season was an influenza A/Fujian/411/2002 (H3N2)-like virus detected in the middle of August. The patient was a three-year-old girl living in the canton of Neuchatel and the two parents as well as her younger brother presented similar symptoms some days earlier. Surprisingly, no travel history was documented in the family.

The Swiss 2003/04 season was one of the earliest epidemics of the last 12 years and started in mid-December following a wave coming from Ireland and France where influenza A/Fujian/411/2002 (H3N2) virus circulated as early as September. The strains detected during summer in Switzerland and in early autumn in Ireland were antigenically identical to the one that caused the major epidemic observed in Europe during the following weeks.

The intensity of the influenza epidemic this year was quite high in comparison with the previous seasons. The peak of influenza-like illnesses observed in the community in 2003/04 reached the top four of the last eleven years (Figure 1). During the first weeks of 2004, we can estimate that approximately 70‰ of the medical consultations of our network practitioners were motivated by an influenza-like illness. In comparison, the peak of the three other most intense seasons ranged from 73 ‰ in 1999/2000 to 82 ‰ in 1995/96.

The mortality rate observed during the influenza season in elderly persons (60 years or older) in the canton of Geneva was analysed. During the two weeks following the MC-ILI peak, the weekly death rate was higher than the mean death rates. A similar observation was made during the 1999/2000, 1997/98 and 1996/97 epidemics (Thomas et al., 2000 and 1998, Chappuis et al., 1997). Of note, the predominant virus in these 3 three epidemics was also an influenza A (H3N2) virus. Although these observations suggest a relation between this increased mortality rate and influenza, this should be interpreted with caution given the relatively small numbers and the multiple possible biases.

The predominant strain in Switzerland during the 2003/04 season was the same as in the majority of countries of the northern hemisphere, as well as countries of the southern hemisphere, i.e., an influenza A/Fujian/411/2002 (H3N2). It represented 84% of all respiratory viruses detected by the Sentinella network, and 96% of influenza viruses. This

new strain resulted from an antigenic drift of the A/Moscow/10/99 influenza A (H3N2) circulating in the previous years. Although related to the vaccine strain, A/Moscow/10/99 (H3N2), A/Fujian/411/2002 is antigenically slightly different. This variant appeared in 2002 in Asia, and started to circulate in Europe, specifically in Switzerland at the end of the 2002/03 season. The proportion of this strain on the total of influenza viruses isolated during the 2002/03 season in Switzerland increased gradually to become the dominant subtype at the end of the season.

This subtype was not included into the 2003/04 influenza vaccine since it represented a very small percentage of influenza viruses detected in the middle of February when the vaccine composition was decided. Second, there was no isolate related to this strain that gave high viral titre on eggs**.** This characteristic could result in problems of vaccine production. This event has already been observed in 2000 with the production of an influenza A/Moscow/10/99 (H3N2)-like strain that was poorly growing on eggs. Production and distribution of the vaccine was delayed from October to November/December 2000. This could have had severe potential consequences if the season had been as early as the one of this year.

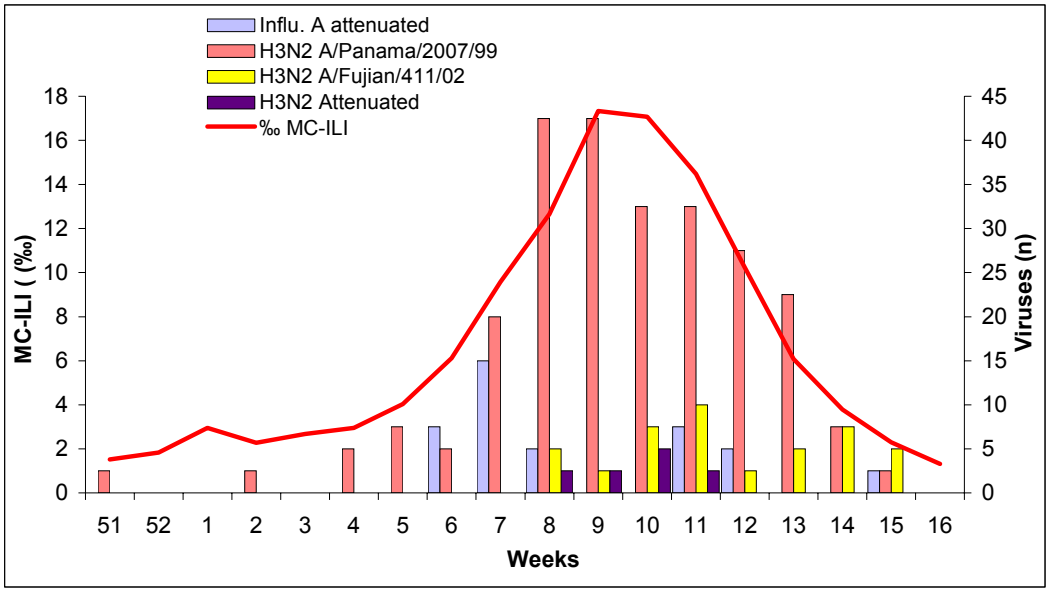


Figure 13: Different subtypes of influenza A viruses detected during the 2002/03 season. Influ: influenza, H3N2 attenuated : influenza A viruses detected per immunofluorescence and that showed an attenuated titre in IHA reaction with standard antisera

The difference of surface antigens between the vaccine strain A/Moscow/10/99 and the new variant A/Fujian/411/2002 suggests a possible reduction of protective titre after vaccination with the 2003/04 vaccine. However, serological assays showed that approximately 76% of adults and 72% of elderly vaccinated with the 2003/04 vaccines developed antibodies at a protective titre against A/Fujian/411/2002-like viruses. This demonstrates that the 2003/04 vaccine gave sufficient protection against influenza A/Fujian/411/2002-like strains (WHO, 2003).

In Switzerland, the highest number of samples came from the age groups between 10 and 39-years-old similar to all previous seasons. However, this year the proportion of positive cases was significantly higher among the younger portion of the studied population and was particularly high in those less than 20-years-old. The proportion of viruses of this age class represented 42% of the total number of influenza viruses detected. During the early phase of the epidemic, until mid-December, this percentage was even higher (59%). This confirmed the observation made in other countries. For example, in USA, the CDC observed a higher incidence of influenza in children. Thirty-one American states reported an unusually high number of deaths among <18 years old patients after an influenza infection. Since 1 October 2003 to 9 of January 2004, 93 patients with a median age of 4 years died (Shui I. Et al., 2004). In Ireland, Portugal and the United Kingdom, the age group of children less than 15-years-old were also more affected (Meier A., EISS Coordinator Centre, personal communication). These age groups were less affected by different influenza A (H3N2) viruses circulating during previous seasons. In addition, the rate of vaccination of young people is lower than in the adult population. As a consequence, young people have certainly a lower protection rate than older people. Douglas Fleming (Royal College of General Practitioners, United Kingdom) stated that this highest incidence in children did not differ from some previous seasons observed during the last 10 years (communication to EISS members). It only differed from the three last seasons which have been weak influenza epidemics with a low percentage of children affected.

A major outbreak of avian influenza was observed in Asia this year. Millions of animals were slaughtered and human cases have also been detected. Later on, another outbreak of avian influenza was reported in Canada and in Texas. These events stressed the need for the Swiss national centre of influenza to develop a collaboration between international partners and the importance to share rapidly information and reagents.

7. Bibliography

Abbot A., "Canadian bird flu prompts mass cull", Nature Science update, *http://www.nature.com/nsu/nsu_pf/040405/040405-3.html*

Canadian Food Inspection Agency (CFIA), "Avian influenza – Information for the general public" 2004 *http://www.inspection.gc.ca/english/anima/heasan/disemala/avflu/avflue.shtml*.

Chappuis S., M.F. Paccaud, W. Wunderli. « Surveillance of influenza in Switzerland between 1987 and 1995 ». Schweiz Med Wochenschr 1996, 29; 126 (26) : p1135-42

Fitzgerald M., C. Danis, M. Conlon, J. Connell. Outbreak of influenzas A (H3N2) in another Dublin school predates previously reported outbreak in Ireland. Eurosurveillance 2003, 43, Vol. 7, *http://www.eurosurveillance.org/ew/2003/031023.asp*

Horimoto T, Fukuda N, Iwatsuki-Horimoto K, Guan Y, Lim W, Peiris M, Sugii S, Odagiri T, Tashiro M, Kawaoka Y., Antigenic differences between H5N1 human influenza viruses isolated in 1997 and 2003. J Vet Med Sci. 2004 Mar; 66(3):303-5.

Kaji M, Watanabe A, Aizawa H., « Differences in clinical features between influenza A H1N1, A H3N2, and B in adult patients". Respirology 2003 Jun, 8 (2), p231-3.

Karcher, Franz, P. Gugliemetti, M. Ciotti, "Avian influenza in Asia : update from the health threats unit at DG SANCO", European Commission. *Eurosurveillance 2004, 8 (5*) : p1–6.

Lubroth J., V. Martin, H. Wagner, H. Niggemann, "Update on the avian influenza (as of 27/05/2004)", FAO Task force on avian influenza*, Technical* ***bulletin 15***, p1-9. *http://www.fao.org/docs/eims/upload/158745/AVIbull015.pdf*

Thomas Y., L. Kaiser, W. Wunderli. Influenza Surveillance in Switzerland, Sentinella study. Winter 2002/03. 2003.

Thomas Y., L. Kaiser, W. Wunderli. "Influenza Surveillance in Switzerland, Sentinella study. Winter 1999/2000", 2000.

Thomas Y., L. Kaiser, W. Wunderli. Influenza Surveillance in Switzerland, Sentinella study. Winter 1997/98, 1998.

Thomas Y., L. Kaiser, W. Wunderli. "Influenza Surveillance in Switzerland, Sentinella study. Winter 1996/97".

WHO : "Avian influenza A(H7) human infections in Canada", WHO update, 05/04/2004, p 1. *http://www.who.int/csr/don/2004_04_05/en/*

WHO. Recommended composition of influenza virus vaccine for use in the 2003/04 influenza season – Northern hemisphere. Weekly Epidemiological Record. 22 February 2003. 9 : 78. 57-64 (*http://www.who.int/docstore/wer/pdf/2003/wer7809.pdf*)

Annexe 1 : Antigenic analysis of influenza A (H3N2)-like strains

	Antisera		
A (H3N2) strains	A/Panama	A/New York	A/Wyoming
A/Panama/2007/99	**1024**	256	128
A/NY/55/01	1024	**512**	128
A/Wyoming/3/03	64	16	**1024**

Date	ID	Typisation result	HAI titres			
28.nov.03	6190	Inf A H3N2 Wyoming/3/03	128	128	2048	
10.déc.03	6810	Inf A H3N2 Wyoming/3/03	128	128	2048	
11.déc.03	6898	Inf A H3N2 Wyoming/3/03	128	128	2048	
07.avr.04	4315	Inf A H3N2 Wyoming/3/03	128		2048	
10.déc.03	6811	Inf A H3N2 Wyoming/3/03	64	64	2048	
29.déc.03	7500	Inf A H3N2 Wyoming/3/03	128	128	1024	Londres
05.janv.04	7622	Inf A H3N2 Wyoming/3/03	128	128	1024	
06.janv.04	7696	Inf A H3N2 Wyoming/3/03	128	128	1024	
25.févr.04	9770	Inf A H3N2 Wyoming/3/03	128		1024	
15.déc.03	7022	Inf A H3N2 Wyoming/3/03	64	256	1024	Londres
28.nov.03	6185	Inf A H3N2 Wyoming/3/03	64	128	1024	
22.déc.03	7392	Inf A H3N2 Wyoming/3/03	64	128	1024	Londres
23.déc.03	7446	Inf A H3N2 Wyoming/3/03	64	128	1024	Londres
21.janv.04	8430	Inf A H3N2 Wyoming/3/03	64	128	1024	
19.nov.03	5787	Inf A H3N2 Wyoming/3/03	64	32	1024	
10.déc.03	6814	Inf A H3N2 Wyoming/3/03	64	32	1024	
10.déc.03	6819	Inf A H3N2 Wyoming/3/03	64	32	1024	
30.déc.03	7524	Inf A H3N2 Wyoming/3/03	64	32	1024	
05.janv.04	7615	Inf A H3N2 Wyoming/3/03	64	32	1024	
06.nov.03	5331	Inf A H3N2 Wyoming/3/03	64	16	1024	
17.déc.03	7213	Inf A H3N2 Wyoming/3/03	64		1024	
12.févr.04	9330	Inf A H3N2 Wyoming/3/03	64		1024	
01.mars.04	9902	Inf A H3N2 Wyoming/3/03	64		1024	
12.mars.04	3350	Inf A H3N2 Wyoming/3/03	64		1024	

Date	ID	Typisation result	HAI titres			
25.nov.03	6048	Inf A H3N2 Wyoming/3/03	128	128	512	
25.nov.03	6050	Inf A H3N2 Wyoming/3/03	128	128	512	
22.déc.03	7389	Inf A H3N2 Wyoming/3/03	64	256	512	Londres
18.nov.03	5748	Inf A H3N2 Wyoming/3/03	64	128	512	
19.nov.03	5788	Inf A H3N2 Wyoming/3/03	64	128	512	
25.nov.03	6057	Inf A H3N2 Wyoming/3/03	64	128	512	
26.nov.03	6088	Inf A H3N2 Wyoming/3/03	64	128	512	
27.nov.03	6164	Inf A H3N2 Wyoming/3/03	64	128	512	
03.déc.03	6413	Inf A H3N2 Wyoming/3/03	64	128	512	
03.déc.03	6417	Inf A H3N2 Wyoming/3/03	64	128	512	
04.déc.03	6531	Inf A H3N2 Wyoming/3/03	64	128	512	
05.déc.03	6573	Inf A H3N2 Wyoming/3/03	64	128	512	
08.déc.03	6675	Inf A H3N2 Wyoming/3/03	64	128	512	
10.déc.03	6813	Inf A H3N2 Wyoming/3/03	64	128	512	
11.déc.03	6903	Inf A H3N2 Wyoming/3/03	64	128	512	
12.déc.03	6936	Inf A H3N2 Wyoming/3/03	64	128	512	
15.déc.03	7028	Inf A H3N2 Wyoming/3/03	64	128	512	
16.déc.03	7105	Inf A H3N2 Wyoming/3/03	64	128	512	
16.déc.03	7106	Inf A H3N2 Wyoming/3/03	64	128	512	
16.déc.03	7113	Inf A H3N2 Wyoming/3/03	64	128	512	
16.déc.03	7139	Inf A H3N2 Wyoming/3/03	64	128	512	
18.déc.03	7279	Inf A H3N2 Wyoming/3/03	64	128	512	
23.déc.03	7443	Inf A H3N2 Wyoming/3/03	64	128	512	
30.déc.03	7537	Inf A H3N2 Wyoming/3/03	64	128	512	
25.nov.03	6051	Inf A H3N2 Wyoming/3/03	64	64	512	
02.déc.03	6374	Inf A H3N2 Wyoming/3/03	64	64	512	
02.déc.03	6375	Inf A H3N2 Wyoming/3/03	64	64	512	
03.déc.03	6414	Inf A H3N2 Wyoming/3/03	64	64	512	
04.déc.03	6537	Inf A H3N2 Wyoming/3/03	64	64	512	
10.déc.03	6812	Inf A H3N2 Wyoming/3/03	64	64	512	
10.déc.03	6817	Inf A H3N2 Wyoming/3/03	64	64	512	
15.déc.03	7031	Inf A H3N2 Wyoming/3/03	64	64	512	
23.déc.03	7450	Inf A H3N2 Wyoming/3/03	64	64	512	
29.déc.03	7499	Inf A H3N2 Wyoming/3/03	64	64	512	

Date	ID	Typisation result	HAI titres		
29.déc.03	7501	Inf A H3N2 Wyoming/3/03	64	64	512
29.déc.03	7504	Inf A H3N2 Wyoming/3/03	64	64	512
30.déc.03	7525	Inf A H3N2 Wyoming/3/03	64	64	512
30.déc.03	7534	Inf A H3N2 Wyoming/3/03	64	64	512
30.déc.03	7536	Inf A H3N2 Wyoming/3/03	64	64	512
06.janv.04	7702	Inf A H3N2 Wyoming/3/03	64	64	512
08.janv.04	7843	Inf A H3N2 Wyoming/3/03	64	64	512
13.janv.04	8074	Inf A H3N2 Wyoming/3/03	64	64	512
14.janv.04	8122	Inf A H3N2 Wyoming/3/03	64	64	512
17.nov.03	5687	Inf A H3N2 Wyoming/3/03	64	32	512
18.nov.03	5744	Inf A H3N2 Wyoming/3/03	64	32	512
10.déc.03	6816	Inf A H3N2 Wyoming/3/03	64	32	512
12.déc.03	6930	Inf A H3N2 Wyoming/3/03	64	32	512
12.déc.03	6935	Inf A H3N2 Wyoming/3/03	64	32	512
16.déc.03	7116	Inf A H3N2 Wyoming/3/03	64	32	512
06.janv.04	7698	Inf A H3N2 Wyoming/3/03	64	32	512
13.janv.04	8075	Inf A H3N2 Wyoming/3/03	64	32	512
14.janv.04	8120	Inf A H3N2 Wyoming/3/03	64	32	512
19.janv.04	8322	Inf A H3N2 Wyoming/3/03	64	32	512
02.déc.03	6370	Inf A H3N2 Wyoming/3/03	64	16	512
13.janv.04	8071	Inf A H3N2 Wyoming/3/03	64	8	512
28.janv.04	8732	Inf A H3N2 Wyoming/3/03	64		512
28.janv.04	8734	Inf A H3N2 Wyoming/3/03	64		512
29.janv.04	8789	Inf A H3N2 Wyoming/3/03	64		512
06.févr.04	9115	Inf A H3N2 Wyoming/3/03	64		512
09.févr.04	9175	Inf A H3N2 Wyoming/3/03	64		512
18.nov.03	5743	Inf A H3N2 Wyoming/3/03	32	<16	512
08.janv.04	7858	Inf A H3N2 Wyoming/3/03	32	128	512
25.nov.03	6049	Inf A H3N2 Wyoming/3/03	32	64	512
25.nov.03	6055	Inf A H3N2 Wyoming/3/03	32	64	512
16.déc.03	7110	Inf A H3N2 Wyoming/3/03	32	64	512
09.janv.04	7890	Inf A H3N2 Wyoming/3/03	32	64	512
14.janv.04	8115	Inf A H3N2 Wyoming/3/03	32	64	512
02.déc.03	6367	Inf A H3N2 Wyoming/3/03	32	32	512

Date	ID	Typisation result	HAI titres			
15.déc.03	7024	Inf A H3N2 Wyoming/3/03	32	32	512	
16.déc.03	7111	Inf A H3N2 Wyoming/3/03	32	32	512	
16.déc.03	7125	Inf A H3N2 Wyoming/3/03	32	32	512	
19.déc.03	7310	Inf A H3N2 Wyoming/3/03	32	32	512	
08.janv.04	7842	Inf A H3N2 Wyoming/3/03	32	32	512	
12.janv.04	7971	Inf A H3N2 Wyoming/3/03	32	32	512	
18.nov.03	5742	Inf A H3N2 Wyoming/3/03	32	16	512	
19.déc.03	7325	Inf A H3N2 Wyoming/3/03	32	16	512	
19.déc.03	7327	Inf A H3N2 Wyoming/3/03	32	16	512	
22.déc.03	7385	Inf A H3N2 Wyoming/3/03	32	16	512	
22.déc.03	7390	Inf A H3N2 Wyoming/3/03	32	16	512	
12.janv.04	7977	Inf A H3N2 Wyoming/3/03	32	16	512	
19.déc.03	7319	Inf A H3N2 Wyoming/3/03	32	8	512	
05.janv.04	7614	Inf A H3N2 Wyoming/3/03	32		512	
29.janv.04	8788	Inf A H3N2 Wyoming/3/03	32		512	
10.févr.04	9233	Inf A H3N2 Wyoming/3/03	32		512	
12.mars.04	3344	Inf A H3N2 Wyoming/3/03	32		512	
12.mars.04	3351	Inf A H3N2 Wyoming/3/03	32		512	
22.janv.04	8508	Inf A H3N2 Wyoming/3/03	<8	16	256	
19.nov.03	5786	Inf A H3N2 Wyoming/3/03	64	128	256	
25.nov.03	6053	Inf A H3N2 Wyoming/3/03	64	128	256	Londres
18.déc.03	7275	Inf A H3N2 Wyoming/3/03	64	64	256	
22.janv.04	8501	Inf A H3N2 Wyoming/3/03	64	64	256	
16.janv.04	8251	Inf A H3N2 Wyoming/3/03	64	32	256	
26.nov.03	6087	Inf A H3N2 Wyoming/3/03	64	16	256	
26.déc.03	7482	Inf A H3N2 Wyoming/3/03	32	128	256	
05.janv.04	7611	Inf A H3N2 Wyoming/3/03	32	128	256	
08.janv.04	7850	Inf A H3N2 Wyoming/3/03	32	128	256	
07.nov.03	5361	Inf A H3N2 Wyoming/3/03	32	64	256	
18.nov.03	5741	Inf A H3N2 Wyoming/3/03	32	64	256	
28.nov.03	6191	Inf A H3N2 Wyoming/3/03	32	64	256	
01.déc.03	6287	Inf A H3N2 Wyoming/3/03	32	64	256	
02.déc.03	6368	Inf A H3N2 Wyoming/3/03	32	64	256	
02.déc.03	6372	Inf A H3N2 Wyoming/3/03	32	64	256	

Date	ID	Typisation result	HAI titres		
04.déc.03	6533	Inf A H3N2 Wyoming/3/03	32	64	256
16.déc.03	7115	Inf A H3N2 Wyoming/3/03	32	64	256
17.déc.03	7204	Inf A H3N2 Wyoming/3/03	32	64	256
19.déc.03	7309	Inf A H3N2 Wyoming/3/03	32	64	256
19.déc.03	7331	Inf A H3N2 Wyoming/3/03	32	64	256
23.déc.03	7448	Inf A H3N2 Wyoming/3/03	32	64	256
29.déc.03	7502	Inf A H3N2 Wyoming/3/03	32	64	256
05.janv.04	7605	Inf A H3N2 Wyoming/3/03	32	64	256
07.janv.04	7758	Inf A H3N2 Wyoming/3/03	32	64	256
08.janv.04	7840	Inf A H3N2 Wyoming/3/03	32	64	256
09.janv.04	7893	Inf A H3N2 Wyoming/3/03	32	64	256
20.janv.04	8379	Inf A H3N2 Wyoming/3/03	32	64	256
26.nov.03	6093	Inf A H3N2 Wyoming/3/03	32	32	256
04.déc.03	6532	Inf A H3N2 Wyoming/3/03	32	32	256
05.déc.03	6575	Inf A H3N2 Wyoming/3/03	32	32	256
11.déc.03	6902	Inf A H3N2 Wyoming/3/03	32	32	256
11.déc.03	6906	Inf A H3N2 Wyoming/3/03	32	32	256
11.déc.03	6908	Inf A H3N2 Wyoming/3/03	32	32	256
11.déc.03	6909	Inf A H3N2 Wyoming/3/03	32	32	256
11.déc.03	6912	Inf A H3N2 Wyoming/3/03	32	32	256
16.déc.03	7109	Inf A H3N2 Wyoming/3/03	32	32	256
16.déc.03	7117	Inf A H3N2 Wyoming/3/03	32	32	256
17.déc.03	7185	Inf A H3N2 Wyoming/3/03	32	32	256
19.déc.03	7324	Inf A H3N2 Wyoming/3/03	32	32	256
19.déc.03	7326	Inf A H3N2 Wyoming/3/03	32	32	256
22.déc.03	7384	Inf A H3N2 Wyoming/3/03	32	32	256
30.déc.03	7526	Inf A H3N2 Wyoming/3/03	32	32	256
30.déc.03	7532	Inf A H3N2 Wyoming/3/03	32	32	256
05.janv.04	7610	Inf A H3N2 Wyoming/3/03	32	32	256
16.janv.04	8252	Inf A H3N2 Wyoming/3/03	32	32	256
23.janv.04	8533	Inf A H3N2 Wyoming/3/03	32	32	256
01.déc.03	6286	Inf A H3N2 Wyoming/3/03	32	16	256
03.déc.03	6421	Inf A H3N2 Wyoming/3/03	32	16	256

Date	ID	Typisation result	HAI titres		
04.déc.03	6535	Inf A H3N2 Wyoming/3/03	32	16	256
17.déc.03	7202	Inf A H3N2 Wyoming/3/03	32	16	256
18.déc.03	7272	Inf A H3N2 Wyoming/3/03	32	16	256
18.déc.03	7276	Inf A H3N2 Wyoming/3/03	32	16	256
19.déc.03	7307	Inf A H3N2 Wyoming/3/03	32	16	256
22.déc.03	7388	Inf A H3N2 Wyoming/3/03	32	16	256
23.déc.03	7440	Inf A H3N2 Wyoming/3/03	32	16	256
05.janv.04	7623	Inf A H3N2 Wyoming/3/03	32	16	256
06.janv.04	7699	Inf A H3N2 Wyoming/3/03	32	16	256
06.janv.04	7703	Inf A H3N2 Wyoming/3/03	32	16	256
06.janv.04	7705	Inf A H3N2 Wyoming/3/03	32	16	256
07.janv.04	7753	Inf A H3N2 Wyoming/3/03	32	16	256
08.janv.04	7862	Inf A H3N2 Wyoming/3/03	32	16	256
23.janv.04	8529	Inf A H3N2 Wyoming/3/03	32	16	256
17.déc.03	7205	Inf A H3N2 Wyoming/3/03	32	8	256
18.déc.03	7266	Inf A H3N2 Wyoming/3/03	32	8	256
05.janv.04	7625	Inf A H3N2 Wyoming/3/03	32	8	256
09.janv.04	7891	Inf A H3N2 Wyoming/3/03	32	8	256
22.janv.04	8507	Inf A H3N2 Wyoming/3/03	32	8	256
12.janv.04	7983	Inf A H3N2 Wyoming/3/03	32		256
20.janv.04	8382	Inf A H3N2 Wyoming/3/03	32		256
26.janv.04	8599	Inf A H3N2 Wyoming/3/03	32		256
26.janv.04	8600	Inf A H3N2 Wyoming/3/03	32		256
26.janv.04	8601	Inf A H3N2 Wyoming/3/03	32		256
26.janv.04	8603	Inf A H3N2 Wyoming/3/03	32		256
28.janv.04	8729	Inf A H3N2 Wyoming/3/03	32		256
29.janv.04	8791	Inf A H3N2 Wyoming/3/03	32		256
29.janv.04	8792	Inf A H3N2 Wyoming/3/03	32		256
02.févr.04	8881	Inf A H3N2 Wyoming/3/03	32		256
01.mars.04	9901	Inf A H3N2 Wyoming/3/03	32		256
09.déc.03	6754	Inf A H3N2 Wyoming/3/03	16	32	256
09.déc.03	6757	Inf A H3N2 Wyoming/3/03	16	32	256
11.déc.03	6904	Inf A H3N2 Wyoming/3/03	16	32	256
17.déc.03	7211	Inf A H3N2 Wyoming/3/03	16	32	256

Date	ID	Typisation result	HAI titres			
05.janv.04	7616	Inf A H3N2 Wyoming/3/03	16	32	256	
15.janv.04	8201	Inf A H3N2 Wyoming/3/03	16	32	256	
26.nov.03	6089	Inf A H3N2 Wyoming/3/03	16	16	256	
11.déc.03	6889	Inf A H3N2 Wyoming/3/03	16	16	256	
17.déc.03	7197	Inf A H3N2 Wyoming/3/03	16	8	256	
08.janv.04	7846	Inf A H3N2 Wyoming/3/03	16	8	256	
19.janv.04	8324	Inf A H3N2 Wyoming/3/03	16	8	256	
20.janv.04	8374	Inf A H3N2 Wyoming/3/03	16	8	256	
22.déc.03	7391	Inf A H3N2 Wyoming/3/03	16		256	
28.janv.04	8736	Inf A H3N2 Wyoming/3/03	16		256	
24.oct.03	4904	Inf A H3N2 New York/55/01	64	512	128	
16.déc.03	7114	Influenza A H3N2 :	32	32	128	Londres
16.déc.03	7124	Influenza A H3N2 :	32	32	128	Londres
16.déc.03	7136	Influenza A H3N2 :	32	32	128	Londres
16.déc.03	7138	Influenza A H3N2 :	32	32	128	
17.déc.03	7212	Influenza A H3N2 :	32	32	128	Londres
17.déc.03	7214	Influenza A H3N2 :	32	16	128	Londres
11.déc.03	6907	Influenza A H3N2 :	16	32	128	Londres
26.déc.03	7488	Influenza A H3N2 :	16	32	128	Londres
26.déc.03	7489	Influenza A H3N2 :	16	16	128	Londres
05.déc.03	6577	Influenza A H3N2 :	16	8	128	Londres
15.déc.03	7023	Influenza A H3N2 :	16	8	128	Londres
17.déc.03	7193	Influenza A H3N2 :	16	8	128	Londres
09.janv.04	7896	Influenza A H3N2 :	16	8	128	
21.janv.04	8433	Influenza A H3N2 :	16	8	128	
21.janv.04	8437	Influenza A H3N2 :	16		128	
06.janv.04	7710	Influenza A H3N2 :	8	8	128	
07.janv.04	7752	Influenza A H3N2 :	8	8	128	
16.janv.04	8254	Influenza A H3N2 :	16		64	
19.nov.03	5785	Influenza A H3N2 :				Londres

Date	ID	Typisation result	IHA titres	
26.déc.03	7483	Influenza A	Undetermined	Londres
26.déc.03	7487	Influenza A	Undetermined	Londres
12.janv.04	7984	Influenza A	Undetermined	Londres

Annexe 2 : Antigenic analysis of influenza A (H1N1)-like strains

	Antisera			
A (H1N1) strains	A/New Caledo.	A/Egypt	A/Beijing	A/Bayern
A/New Caledonia/20/99	**128**	128	64	< 8
A/Egypt/20/99 (H1N2)	256	**512**	64	< 8
A/Beijing/262/95	128	64	**512**	32
A/Bayern/7/95	< 8	< 8	32	**2048**

Date	ID	Typisation result	IHA titres				
19.03.03	6190	Inf A H1N1 New Cal/20/99	256	256	64	< 8	Londres

Annexe 3 : Antigenic analysis of influenza B-like strains

	Antisera				
B strains	B/Hong Kong	B/Shandong	B/Brisbane	B/Sichuan	B/Beijing
B/Hong Kong/335/01	**32**	512	128	< 8	< 8
B/Shandong/7/97	64	**512**	128	< 8	< 8
B/Brisbane/32/02	64	256	**256**	< 8	< 8
B/Sichuan/379/99	< 8	< 8	< 8	**128**	32
B/Beijing/184/93	< 8	< 8	< 8	32	**64**

Date	ID	Typisation result	IHA titres					
21.11.03	6159	Inf B/Sichuan/379/99	< 8	< 8	< 8	128	64	Londres
18.03.04	3578	Inf B/Sichuan/379/99	< 8	< 8	< 8	128	64	Londres