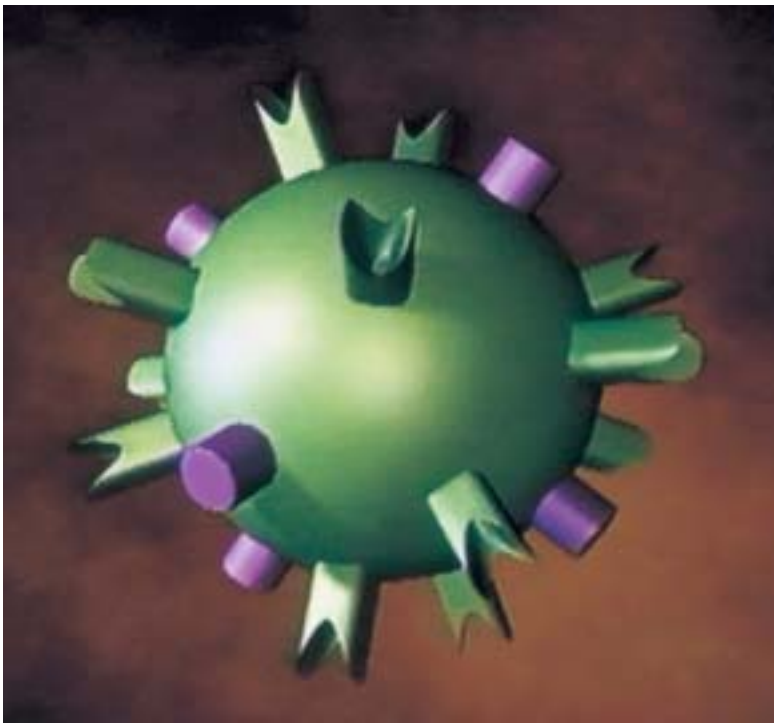
FEDERAL OFFICE OF PUBLIC HEALTH
BERNE - SWITZERLAND

HUG
Hôpitaux Universitaires de Genève

SWISS INFLUENZA SURVEILLANCE SENTINELLA STUDY

WINTER SEASON 2001/2002



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Cover : scheme of an influenza virus (hemagglutinin protein is represented in green, neuraminidase protein is represented in pink). Kindly communicated by GlaxoWellcome.

TABLE OF CONTENTS

1. SUMMARIES (French, German and English)

Résumé

La surveillance hivernale de la grippe a débuté le 22 Septembre 2001 et s'est terminée le 12 Avril 2002. L'épidémie a été modérée cette année, à un niveau comparable à celle de l'année dernière. Aucune influence sur la mortalité des plus de 60 ans n'a été détecté.

Deux types de virus grippaux ont circulé dans des proportions voisines au cours de la saison, les virus influenza A (H3N2) et influenza B. Un premier virus influenza B a été détecté au cours de la semaine 46. Puis les virus influenza A (H3N2) ont commencé à circuler dès la semaine 50. Ces 2 types de virus ont été détectés sporadiquement jusqu'à la semaine 3. Les contacts médicaux pour symptômes de grippe ont alors franchi le seuil épidémique au cours de cette même semaine.

Le pic épidémique a ensuite été atteint au cours des semaine 5 et 6. Les contacts médicaux sont restés au-dessus du seuil pendant 8 semaines.

Au cours de la saison, 607 prélèvements ont été reçus pour analyse. Sur les 237 virus influenza, 107 (45%) étaient du type influenza A et 130 (55 %) étaient du type influenza B. Parmi les virus influenza A, 103 étaient antigéniquement proches des souches vaccinales influenza A/Moscow/10/99 (H3N2) ou A/Panama/2007/99 (H3N2), 3 n'ont pas pu être typés et 1 était proche de la souche influenza A (H1N2) nouvellement apparue. La grande majorité des souches influenza B étaient antigéniquement proches de la souche vaccinale influenza B/Sichuan/379/99. En revanche, une souche proche de la souche influenza B/Hong Kong/330/01 a été détectée au cours de la semaine 5 dans la région 5. Cette souche détectée pour la première fois en Europe cette année sera incluse dans le vaccin 2002-03.

Enfin, une souche influenza A (H1N1) d'origine porcine a été détectée dans la 6ème semaine chez un éleveur de porcs de 57 ans originaire du canton de Saint Gall. Enfin cette année, aucun excès du taux de mortalité des personnes âgées de plus de 60 ans n'a été mis en évidence

Summary

The surveillance of this years' influenza season started on the 22nd of September and lasted until the 15th of April. It was a moderate season and the intensity can be compared with the one from the year before. No influence of the influenza epidemic could be observed on the death rate of the 60 years or older.

Two types of influenza virus circulated in approximately equal frequency. They belonged to influenza A (H3N2) subtype and to influenza B. The first case, an influenza B virus, was detected in the 46th week. Influenza A could be detected for the first time during the 50th week. These two types of virus circulated sporadically until the 3rd week the time point where the medical consultation rate passed over the threshold.

The peak of the medical consultation for influenza-like illness was reached during week 5 whereas the highest number of influenza virus could be detected during week 6. The medical consultation rate stayed on an epidemic level until the 8th week.

During the season 607 samples have been treated by our laboratory. 237 influenza virus could be detected of which 107 (45%) were of the influenza A type and 130 (55%) were of the influenza B type. Among the influenza A 103 were related to influenza A/Moscow/10/99 (H3N2) or A/Panama/2007/99 (H3N2). Three influenza A could not be further characterised and one was of the influenza A (H1N2) type. The majority of the influenza B viruses detected were related to influenza B/Sichuan/379/99. However one influenza B/HongKong/330/01 could be detected in region 5 during the 5th week. This strain was detected the first time in Europe this winter and will be included in the vaccine for the next season.

During the week 6, a sporadic case of influenza A (H1N1) from swine was detected in a 50 years old farmer in the state of St. Gallen.

Zusammenfassung

Die Überwachung der Grippe in der Wintersaison 2001/2002 begann am 22 September und dauerte bis zum 12. April 2002. Die diesjährige Epidemie war von geringer Intensität und ist mit der vorherigen Saison vergleichbar. Da die Grippeepidemie nicht sehr intensive war konnte auch kein Einfluss auf die Todesfallrate bei Leuten welche über 60 jährig sind beobachtet werden.

Zwei Typen von Influenzaviren zirkulierten parallel etwa mit gleicher Häufigkeit während dem ganzen Winter Es waren dies Influenza A (H3N2) und Influenza B. Der erste Nachweis eines Influenza B Virus gelang in der 46. Woche. Influenza A H3N2 Viren konnten ab der 50. Woche nachgewiesen werden. Bis zur 3. Woche 2002 traten aber nur sporadische Fälle auf. Erst ab diesem Zeitpunkt erreichten die Deklarationen für grippeartige Erkrankungen der Sentinellaärzte den epidemischen Schwellenwert. Das epidemische Maximum wurde zwischen der 5. und der 6. Woche erreicht während die höchste Zahl an Influenzaviren in der 6. Woche beobachte wurde. Die Arztkontakte blieben bis zur 8. Woche über den epidemischen Grenzwert.

Während der ganzen Saison wurden vom NZI 607 Proben untersucht. Dabei wurden 237 Influenzaviren nachgewiesen von denen 107 (45%) Influenza A und 130 (55%) vom Typ Influenza B waren. 103 Influenza A Viren waren nahe verwandt mit Influenza A/Moskau/10/99 (H3N2) oder A/Panama/2007/99 (H3N2). Drei der nachgewiesenen Influenzaviren konnten nicht genauer charakterisiert werden und ein Virus war mit H1N2 verwandt, ein Stamm der erst kürzlich in Europa aufgetreten ist.

Der grösste Teil der Influenza B Viren waren verwandt mit dem im Impfstoff enthaltenen Influenza B/Sichuan/379/99. Hingegen konnte ein Influenza B Virus nachgewiesen werden welcher mit Influenza B Hong Kong/330/01 nahe verwandt ist. Dieser Stamm konnte in der 5. Woche in der Region 5 nachgewiesen werden. Dieser Typ konnte in Europa zum ersten Mal in dieser Saison gefunden werden und wird im Impfstoff für die nächste Saison enthalten sein.

In der 6. Woche konnte im Kanton St. Gallen ein Influenza A (H1N1) nachgewiesen werden. Wie ausgedehnte Untersuchungen zeigten, war dieses Virus nahe verwandt mit einem Stamm welcher in Schweinen in Europa zirkuliert.

2. ACKNOWLEDGEMENTS

We thank all the members of the Sentinella network as well as the practitioners who participated in the rapid surveillance project.

We highly appreciated the support of ROCHE-PHARMA for this rapid surveillance.

We also thank the Swiss Federal Office of Public Health, and particularly Mrs Daniela Müller for their collaboration. We also appreciated the collaboration with for Dr A. Hay, Mr A. Douglas and Mrs Vicki Gregory from the WHO Reference Centre in London, MRC (United Kingdom).

Special thanks go to Dr Michel F. Paccaud who performed a high amount of work for the analysis of the mortality data from Geneva. His high expertise is always appreciated.

We also would like to thank all the European Influenza Centres, for the regular communication of the results about the influenza activity. Together with them, EISS, and WHO are also thanked for their efficient and always present collaboration during the epidemic.

And last, but not least, thanks to Mrs Sabine Grünenwald for her excellent technical assistance, and the other staff of our laboratory for their support during the season.

3. INTRODUCTION

Since 1987, the surveillance of the activity of influenza viruses has been included into the Sentinel program. With this system it was possible to maintain the number of participants on a more or less constant level. However in the less densely populated areas a sufficiently high participation was always difficult to achieve.

The winter surveillance of this year was done between the 22nd of September 2001 and the 12th April 2002. Like in the previous season, the epidemic was moderate. Moreover, the epidemic was characterised by the parallel circulation of two different type of influenza strains : influenza A (H3N2) and influenza B. An influenza B strain not previously detected in Europe and an influenza A (H1N2) early appeared were also sporadically detected in Switzerland during the season.

In addition for the third consecutive season it was possible to use a rapid test for the surveillance of the influenza epidemics. This approach has to be considered as a complement to the classical surveillance scheme and allows to detect the development of the epidemic more rapidly.

4. RESULTS OF THE 2001/2002 SURVEILLANCE SEASON

4.1. Methods for the detection of respiratory viruses

4.1.1. Surveillance in the classical Sentinella study

In the Sentinella network, practitioners took throat and nasal swab from patients with an influenza illness, with the restriction of 2 swabs per week. Respiratory viruses are identified by cell culture performed on 3 different cell lines (MDCK, LL-CMK2 and A549). Screening and identification of respiratory viruses were done by using monoclonal antibodies (Table 1). Trough this, seven different respiratory viruses can be detected : namely influenza A, influenza B, parainfluenza 1, 2, and 3, adenovirus and respiratory syncytial virus (RSV). Subtyping of influenza viruses was done subsequently by an hemagglutination inhibition assay.

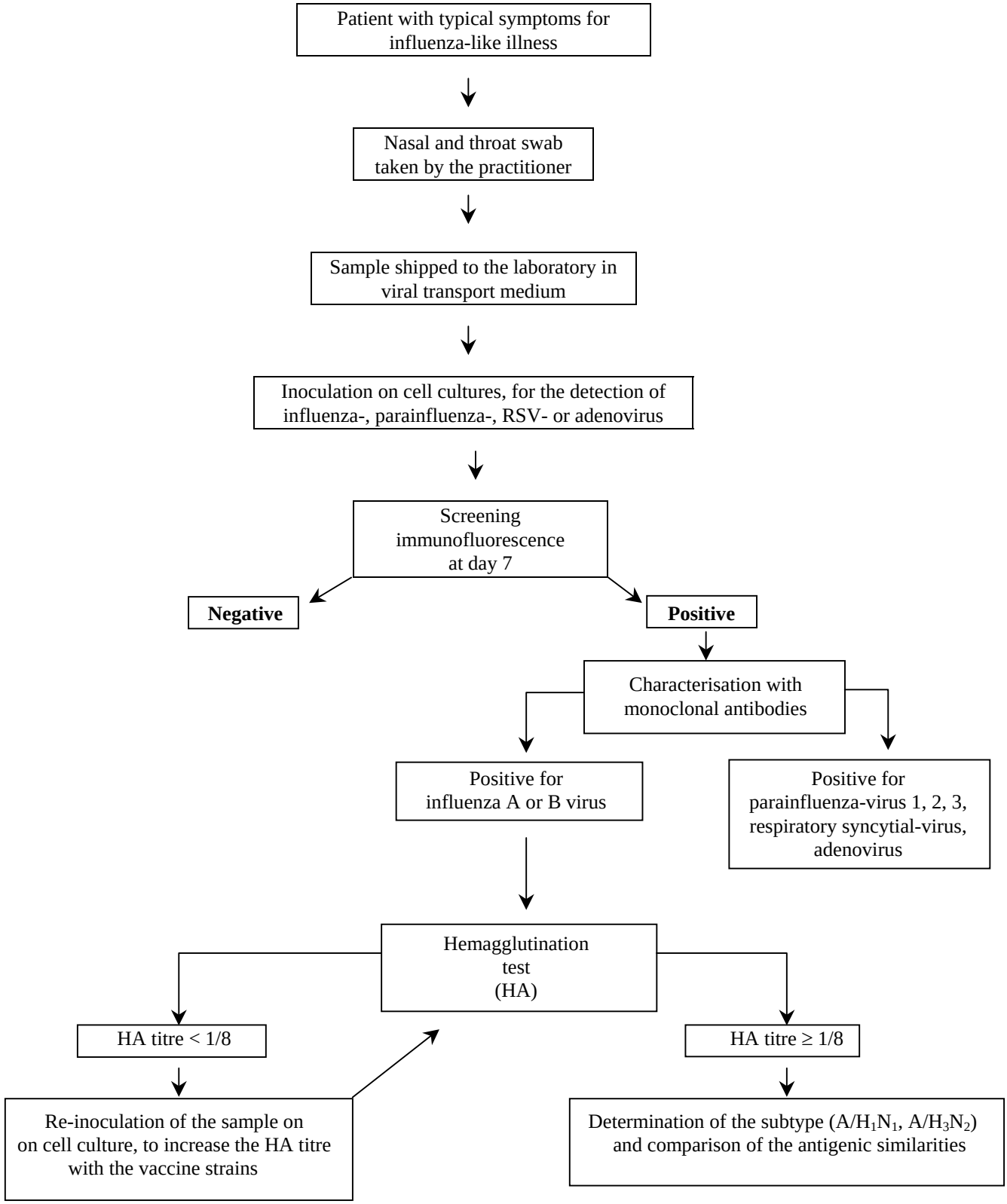
4.1.2. Surveillance with a rapid antigen detection test

For the third year, an additional surveillance of influenza epidemic was done by the use of a rapid antigen test. The goals of this surveillance was provide rapid results on the spread of the epidemic. The rapid availability of data about the epidemic provides a useful information for the practitioner during the whole influenza season. This project was a collaboration between the Federal Office of Public Health in Bern (Sentinella network), the National Centre of Influenza and ROCHE-PHARMA (Switzerland).

138 Sentinella practitioners performed the influenza A/B Rapid Test. This test can be executed on the bedside and allows the detection of influenza virus in about 15-20 minutes. The test consists of an immunochromatographic strip for the capturing of the antigens and monoclonal antibodies specific for influenza A and influenza B capturing of the antigens and monoclonal antibodies specific for influenza A and influenza B antigens for the detection of the antigens (Figure 1a). This strip must be soaked in a throat swab treated with an extraction buffer and incubated with the monoclonal antibodies. After chromatography, the presence of influenza viruses was revealed by a colorimetric reaction. The first line on the top corresponds to an internal control and must be present in each run (see Figure 1b). The second line is visible when influenza virus antigen is present in the sample. Patients were selected

with typical influenza-like symptoms. At the end of the working day, results were sent by fax to our laboratory. These results were used for the update of the internet site (twice per week).

Table 1 : Method for the detection of respiratory viruses by cell culture.



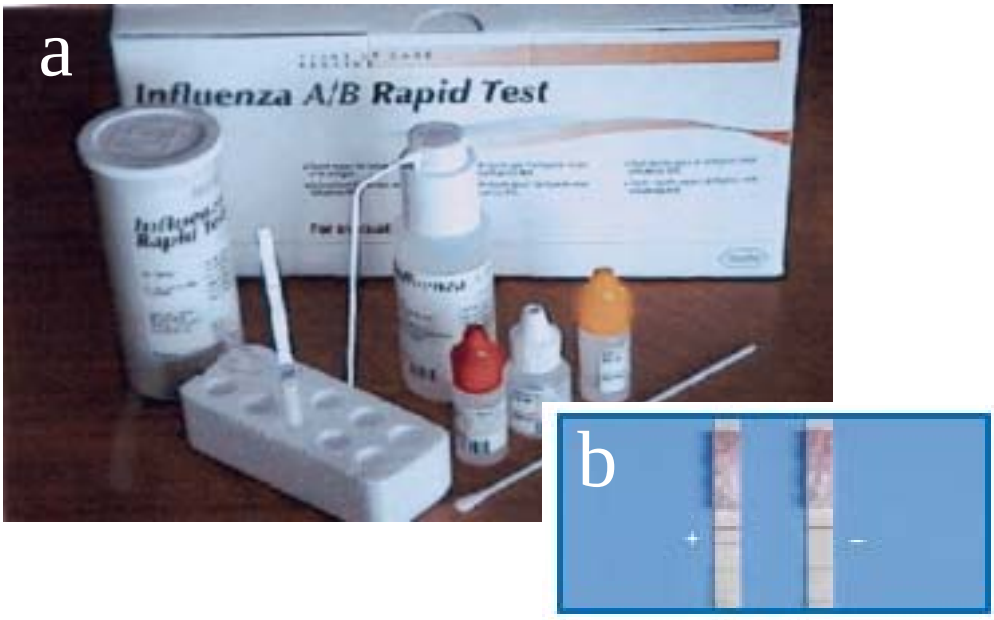


Figure 1 : **a.** Influenza A/B Rapid test used for the surveillance. **b.** Detail of the immunoassay strip for the detection of influenza A and influenza B viral antigen : positive test is on the left-hand side indicated with the + sign, the negative test is on the right hand side indicated with the - sign.

4.2. Epidemiological results

4.2.1. Geographical distribution of Sentinella practitioners

For the surveillance, our country is divided into 6 different regions containing a variable number of cantons (2 to 7 ; Table 2). Forty-nine Sentinella practitioners and 5 hospitals participated in the surveillance of influenza during the 2001-02 season. The distribution of participants is presented on the Figure 2 with coloured points according to their location.

Table 2 : distribution of the different cantons in the six regions.

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)

An effort has been made to have a network of participants as homogenous as possible. Children are good indicators for the onset of the influenza epidemic. They are usually the first persons infected with influenza virus. 7 paediatricians are enrolled in the network.

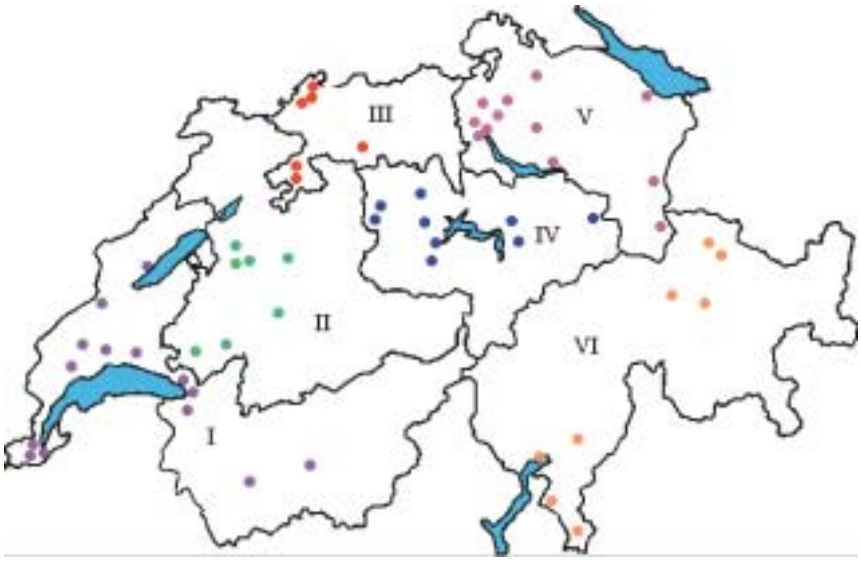


Figure 2 : Geographical distribution of the participants in the Sentinella network. Each participant is represented by a point. The regions are distinguished by different colour codes.

4.2.2. Frequency of the detection of the different respiratory viruses

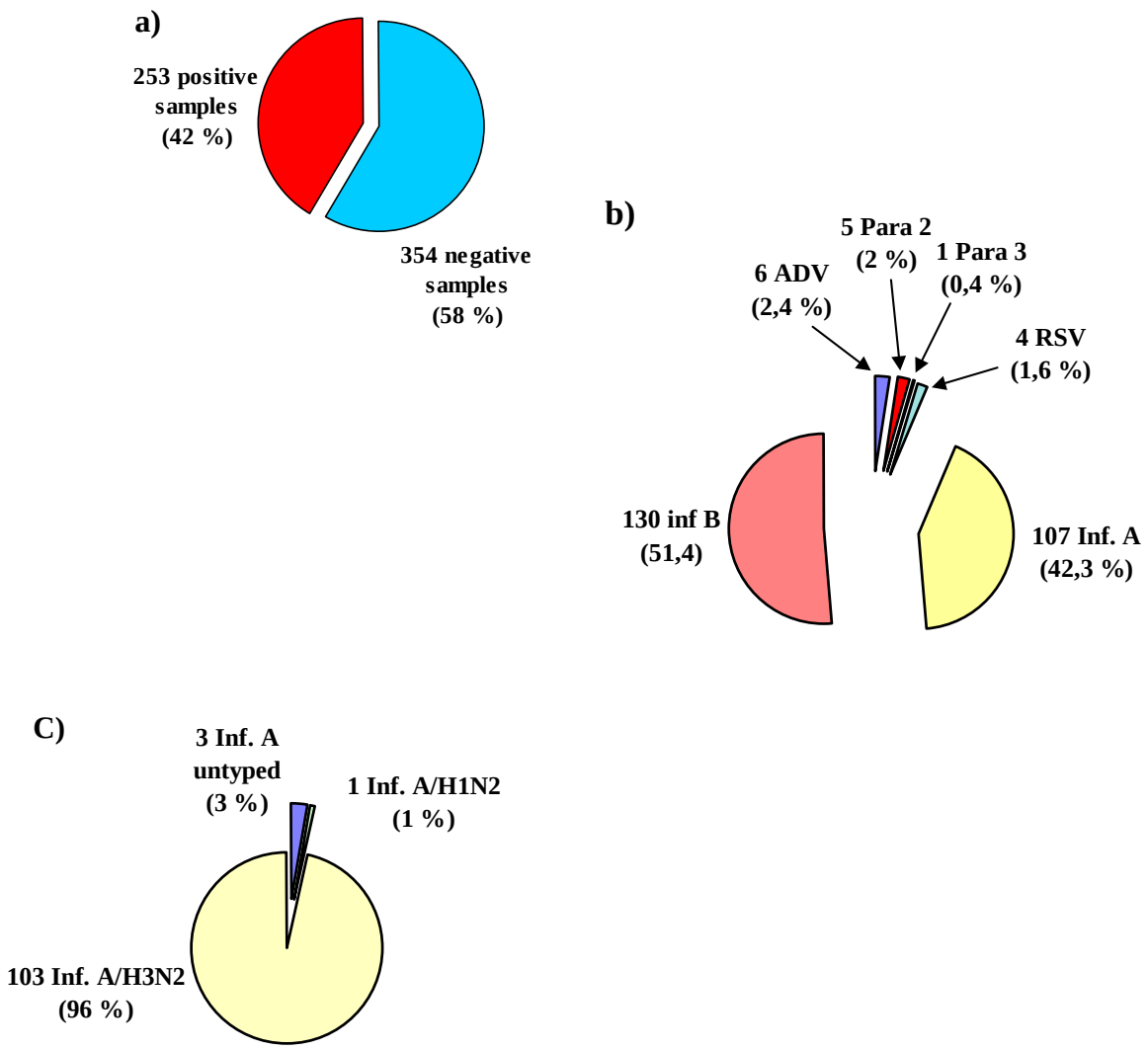


Figure 3 : Results obtained from the 628 samples during the 2001/2002 season. **a** : number of positive and negative samples received during the season. **b** : number of the different respiratory viruses detected. Inf.A : influenza A; Inf.B : influenza B; ADV : adenovirus; Para : parainfluenza 1; 2 or 3. **c** : type of influenza A viruses detected.

The winter surveillance of influenza activity lasted for 29 weeks : it started on the 22nd of September 2001 and terminated on the 12th of April 2002 and. 607 nasal and throat swabs were received during this period for the detection of influenza. As observed on the Figure 3a, 253 of these samples were positive for one of the 7 respiratory viruses (42 %). 237 influenza viruses were detected, representing 94 % of the total number of viruses found. Only 16 respiratory viruses (6 %) other than influenza virus were detected during this season (Figure 2b). 107 were characterised as influenza A (42 %) and 130 as influenza B (51 %). The majority of influenza A viruses were antigenically related to influenza A (H3N2) (96 %, Figure 3c). Only one influenza A subtype could be distinguished by sequence analysis. It was related to the recently detected human influenza A (H1N2) variant. 3 influenza A viruses could not be subtyped du to a low titter after several passages on cell culture. The characteristics of the different influenza subtypes detected during the season will be discussed in more details in chapter 4.4.

4.2.3. Detection of respiratory viruses during the winter season

As can be seen from the results presented in table 3 and Figure 4, influenza 2001/2002 season was moderate but in comparison to 2000/2001, the activity was slightly higher (1). The epidemiological indicator to follow the epidemic is the percentage of medical consultation for influenza-like illness (% MC-ILI). This value indicates the percentage of patients showing typical influenza symptoms in comparison to the total of medical consultations (typical symptoms are sudden onset of high fever (> 38°C), respiratory tract infections, myalgia, generalised pain, high degree of malaise and/or weakness with or without rhinitis, cough, arthralgia). These numbers were obtained on a weekly basis from the public health authorities in Bern (OFSP). The results of the season are presented table 3 and Figure 4. The epidemic threshold is reached when the national MC-ILI is above 1.5 %. This year, this was the case during the 2nd and 3rd week of 2002. Eight influenza viruses were detected in the 3rd week and positive isolation increased during the following weeks. The highest number of viruses was observed at the week 5 reaching 41 positive samples. MC-ILI reached the maximum one week later. After this peak, influenza activity was decreasing. MC-ILI stayed above the threshold until week 11. In the following weeks, sporadic cases were identified.

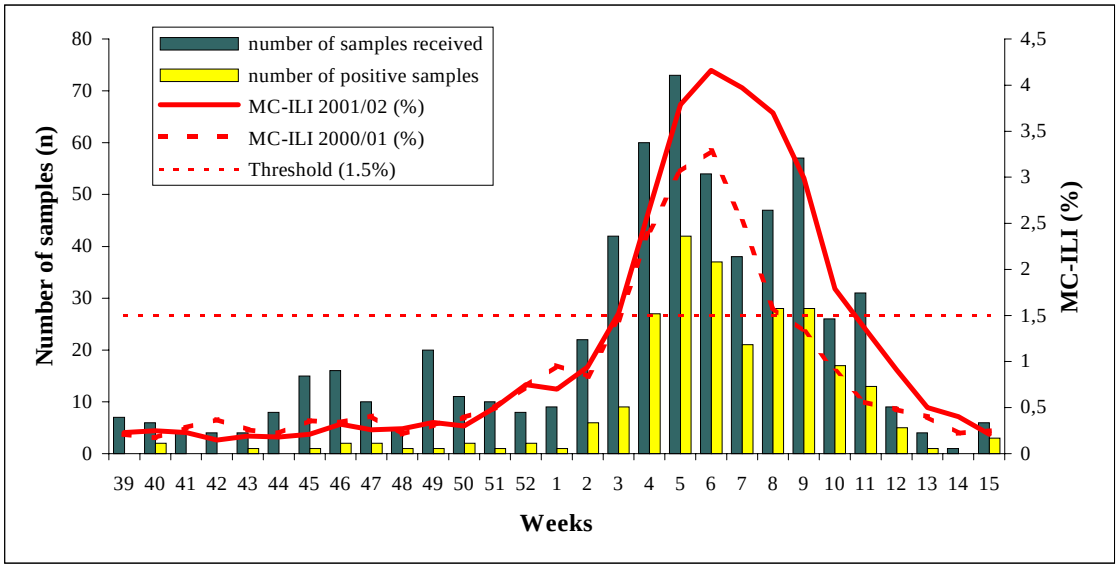
The kinetics of the detected influenza viruses correlated well to the MC-ILI curve. However, a difference of about one week was observed between the two indicators (1 and 2). This difference was already observed in previous seasons (5).

Both types of influenza A and influenza B viruses circulated on parallel during the whole season. Influenza B viruses could be detected at a slightly higher frequency. The influenza B virus was detected during the week 46, which is quite early and unusual. Both type of viruses were detected sporadically in the following weeks until the 3rd week. From then, the number of influenza A and influenza B viruses were similar during the remaining weeks of the epidemic. We received in average 21 samples per week, with a maximum of 73 samples in week 5. During the pre-epidemic period, before the 3rd week, the percentage of positive samples for influenza fluctuated between 0 and 27 %, with an average of 6 %. During the epidemic period, between the weeks 3 and 10, this percentage increased and ranged between 19 and 67 %, with an average of 51 %. Finally, between week 11 and 15, the values of the percentage of positive samples started to gradually decrease with an average of 34 %. The high percentage of positive samples observed during the peak of the season is not unusual. The situation can be compared to the one observed during the 1995/96 season where three different type of influenza viruses circulated (A (H1N1), A (H3N2) and B viruses; Table 7).

Table 3 : Detection of respiratory viruses during the 2001/2002 influenza season.
MC-ILI : proportion of medical consultations for influenza-like illness; influ. A : influenza A; Not typed : influenza A which has not been sub-typed. Influ. B : influenza B. Other resp. viruses : other respiratory viruses.

Weeks 01/02	Dates	MC-ILI (%)	Samp. Rec.	Influ. A undet.	Influ. A H1N2	Influ. A H3N2	Influ. B	Total influ. viruses	Pos. Rate Influ. (%)	Other resp. viruses
39	22 sep - 28 sep	0,23	7							
40	29 sep - 5 oct	0,25	6							*1 ADV, 1 Para2*
41	6 oct - 12 oct	0,23	4							
42	13 oct - 19 oct	0,15	4							
43	20 oct - 26 oct	0,19	4							*1 Para 3*
44	27 oct - 2 nov	0,18	8							
45	3 nov - 9 nov	0,21	15							*1 ADV*
46	10 nov - 16 nov	0,32	16				1	1	6	*1 ADV*
47	17 nov - 23 nov	0,26	10							*1 ADV, 1 Para 2*
48	24 nov - 30 nov	0,27	5							*1 VRS*
49	1 dec - 7 dec	0,34	20							*1 VRS*
50	8 dec - 14 dec	0,3	11			1	1	2	18	
51	15 dec - 21 dec	0,5	10							*1 Para 2*
52	22 dec - 28 dec	0,75	8			1	1	2	25	
1	29 dec - 4 jan	0,7	9			1		1	11	
2	5 jan - 11 jan	0,94	22			2	4	6	27	
3	12 jan - 18 jan	1,52	42			4	4	8	19	*1 VRS*
4	19 jan - 25 jan	2,66	60			11	14	25	42	*2 ADV*
5	26 jan – 1st feb	3,79	73			20	21	41	56	*1 VRS*
6	2 feb - 8 feb	4,16	54	1		12	23	36	67	*1 Para2*
7	9 feb - 15 feb	3,97	38			9	12	21	55	
8	16 feb - 22 feb	3,7	47			13	14	27	57	*1 Para2*
9	23 feb – 1st mar	2,99	57		1	12	15	28	49	
10	2 mar - 8 mar	1,79	26			8	9	17	65	
11	9 mar - 15 mar	1,35	31	1		4	8	13	42	
12	16 mar - 22 mar	0,91	9			4	1	5	56	
13	23 mar - 29 mar	0,5	4				1	1	25	
14	30 mar - 5 Apr	0,4	1							
15	6 Apr - 12 Apr	0,21	6	1		1	1	3	50	
		Total	**607**	**3**	**1**	**103**	**130**	**237**	**39**	***16***
				107						

a.



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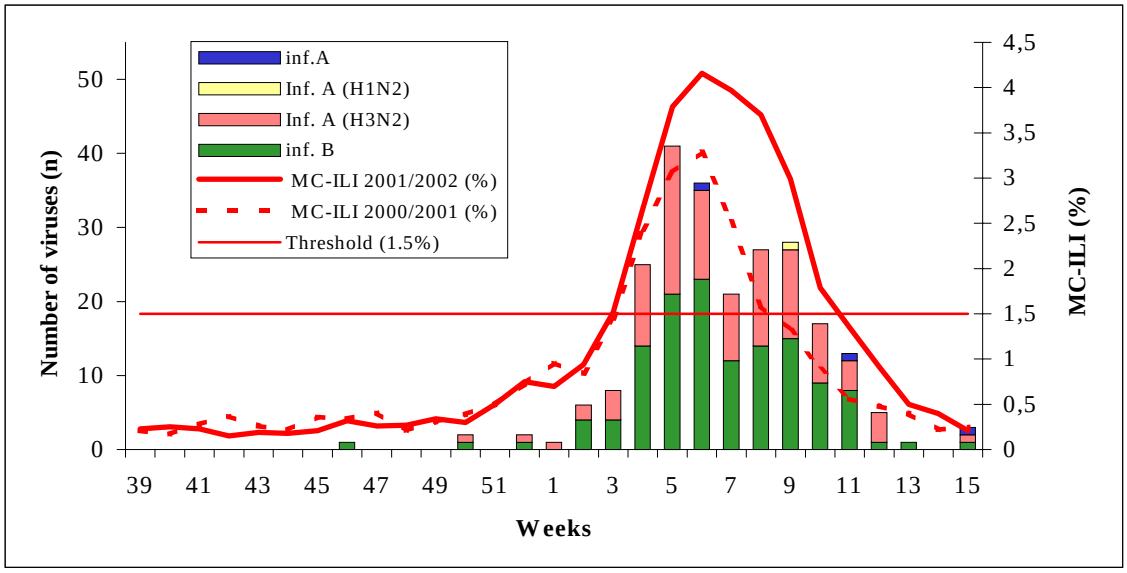


Figure 4 : a) Number of samples received and number of positive results obtained per week Samp. received : total number of samples received per week ; positive : positive for the presence of any respiratory virus ; MC-ILI : medical contacts for influenza-like illness; Threshold : percentage of medical contacts for influenza-like illness indicating the epidemic threshold (1.5 %). b) Type of viruses detected per week. Inf. A : 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.

4.2.4. Epidemic index (EI)

The intensity of influenza epidemic can be characterized by the epidemic index (**EI**). This value is calculated with the % of MC-ILI, based on the following formula (5) :

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

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

n : number of weeks with Ca ≥ 1.5

Table 4 : Calculation of the epidemic index for the 2001/2002 season

Weeks 2001/2002	MC-ILI (%)		
39	0.23		
40	0.25		
41	0.23		
42	0.15		
43	0.19		
44	0.18		
45	0.21		
46	0.32		
47	0.26		
48	0.27		
49	0.34		
50	0.3		
51	0.5		
52	0.75		
1	0.7		
2	0.94		
3	**1.52**		
4	**2.66**	**ΣCa**	**24.58**
5	**3.79**	**n (number of weeks)**	**8**
6	**4.16**		
7	**3.97**	**EI = [Σ (Ca) - (1.4 x n)] / n**	**EI = 1.67**
8	**3.7**		
9	**2.99**		
10	**1.79**		
11	1.35		
12	0.91		
13	0.5		
14	0.4		
15	0.21		

During 8 weeks, MC-ILI values were higher than 1.5 % (between week 3 and 10). The sum of MC-ILI registered during these weeks is 24.58. With this, the epidemic index of the 2001/2002 season is **1.67** (Table 4).

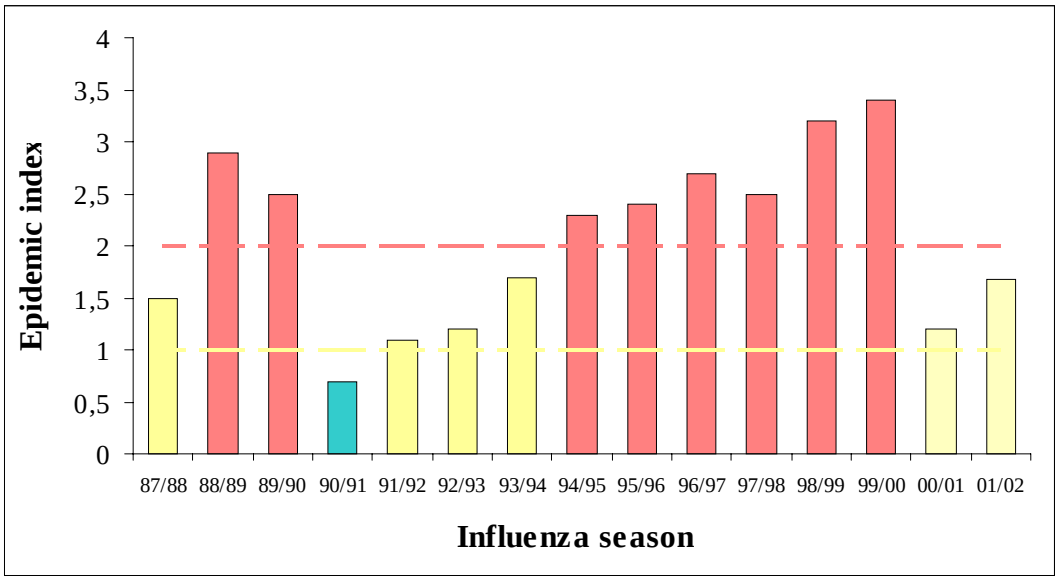


Figure 5 : Epidemic index (EI) of the influenza seasons between 1987/1988 and 2000/2001. EI ≤ 1 : blue; 1 < EI ≤ 2 : yellow; 2 < EI : red.

The values of the epidemic index observed since 1987 have schematically been represented in Figure 5. The value of the 2001/2002 season can be compared to the one observed in the seasons 1987/88 and between 91 and 94. All these seasons showed a weak to moderate activity.

Table 5 : Summary of the MC-ILI of the last 8 seasons. Duration : number of weeks where the MC-ILI were above or equal to the threshold (1.5 %); maximum value of MC-ILI : maximum value observed during the whole season; week : week where the peak of MC-ILI was observed.

Season	Duration (n weeks)	Maximum value of MC-ILI (%)	Week n° of the peak
1994/1995	10	5.5	11
1995/1996	12	8.2	52
1996/1997	13	5.7	1
1997/1998	11	6.2	9
1998/1999	11	7.8	7
1999/2000	8	7.5	1
2000/2001	5	3.3	6
2001/2002	8	4.2	6

4.2.5. Influenza activity observed in the different regions

The 607 samples received during the 2001/2002 season were classified according to the participants (Table 6). In total, 49 practitioners and 5 Hospitals participated this year. On average, 11 samples were taken and sent in per practitioner. This average is comparable to the one observed during the previous season (1). In regions 1 and 6, the number of samples sent per the participant was higher than the average (15 respectively 18 swabs/participant). In contrast to that, the average number of samples sent per the participant in regions 2 and 5 was

lower (6 respectively 7 swabs/participant). Finally, in regions 3 and 4, the average was of 11 swabs/participant.

The participation was moderate and can be compared with the one observed during the 2000/01 season (Table 7, 1). The moderate participation is probably linked to the weak activity of influenza virus during the last two seasons.

If we look at the at the epidemic in the different regions we can make the following conclusions. The kinetic of the epidemics was quite comparable in all the 6 different regions (Figure 6). However, several significant differences could be noticed. So, the maximum value of MC-ILI registered in the region 1 was approximately 7% and therefore higher than in any other region (between 3.4 and 5.7 %). On parallel also, the number of influenza viruses detected in this region was higher than in the others ones (Table 6). The number of viruses detected in region 1 in the peak (week 5) was 16. Whereas in the other regions between 5 and 9 viruses were detected. On the other hand, the maximum value of MC-ILI was observed two to three weeks earlier in region 1 and 3 than in the rest of the country (region 1 and 3 : week 5; region 2, 4 and 5 : week 7; region 6 : week 8).

Other regional differences could be observed. Influenza A and influenza B viruses circulated in all the six regions. However, the number of influenza types detected in the regions were not the same. In region 1, 46 influenza A vs 29 influenza B and in region 3, 17 influenza A vs 11 influenza B were found (Figure 6). In contrast to that influenza B was the most abundant virus in the regions 2, 4, 5 and 6. In our neighbouring countries similar situations could be observed. In France, a majority of influenza A (H3N2) viruses was detected as soon as the week 47 and with a maximum rate of detection observed during the week 3 (Figure 7). This kinetic is comparable to the ones observed in our regions 1 and 3. In these regions, the maximum of influenza viruses was detected one week (region 3) or two weeks later (region 1) (Figure 6). In Italy however, the majority of influenza viruses detected was of the type B. The first cases were detected in the week 48 and reached its maximum during the 5^{th} week. In Switzerland, in the regions with more influenza B viruses, the maximum rate of virus detection was observed 1 week (region 2 and 5) and 4 weeks later in

region 6. In region 4, the maximum of influenza B virus found was during the 5th week with a second uprise during the week 10, with as many influenza A as influenza B virus detected (Figure 7).

These observations suggests two things. First, two epidemics hit Switzerland this year. The influenza A came from France and hit first region 1, spreading then to the rest of the country. Second, other region of Switzerland have been more affected with an influenza B coming from Italy (region 4, 5 and 6). The epidemic was hardly influenced by the one from Germany because this one started late with a peak of the activity only during the 12th week (Figure 7).

Table 6 : Distribution of the samples per Sentinella participant.

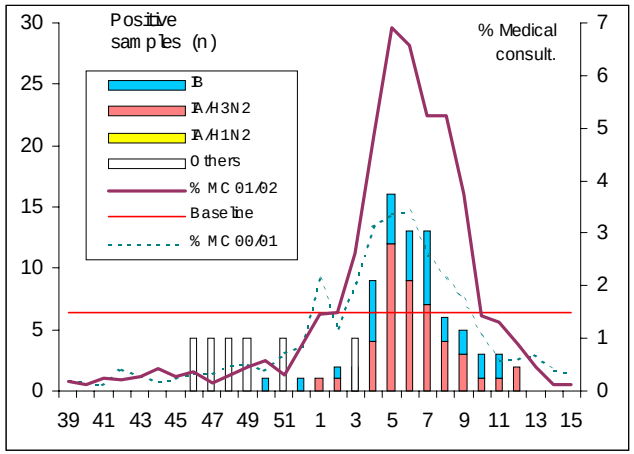
	Participant code	Canto	Samples (n°)	Influenza viruses detected (n)	Total number of samples (n)	Total number of Positive samples (n)
Region 1	107	GE	7	0		
	119	VD	14	6		
	141	GE	14	3		
	147	VS	30	10		
	155	VD	12	6	**204**	**76**
	178	VS	6	4		
	186	NE	36	13		*37%*
	188	VD	17	8		
	189	VS	9	3		
	702	VD	9	1		
	709	VD	15	8		
	901	GE	8	5		
	905	VD	22	8		
	906	GE	5	0		
Region 2	222	FR	2	0		
	235	FR	18	9		
	243	BE	17	8	**44**	**22**
	256	BE	4	3		
	276	BE	1	0		*50%*
	772	BE	1	1		
	903	BE	1	1		
Region 3	313	AG	10	5		
	331	SO	19	6	**66**	**29**
	371	BL	5	2		
	727	BL	22	11		*44%*
	787	AG	1	0		
	788	AG	9	5		
Region 4	294	LU	25	11		
	347	NW	17	6		
	375	LU	10	6		
	408	GL	17	4	**102**	**42**
	418	GL	3	0		
	466	SZ	5	2		*41%*
	467	LU	6	2		
	853	OW	15	9		
	883	LU	4	2		
Region 5	511	ZH	4	3		
	514	SG	2	2		
	515	ZH	18	9		
	521	TG	14	5		
	533	ZH	3	2	**82**	**35**
	536	SG	6	1		
	561	ZH	2	2		*43%*
	571	ZH	12	6		
	579	SG	5	4		
	747	SG	2	1		
	751	SH	8	0		
	902	ZH	6	0		
Region 6	284	TI	34	17		
	378	GR	3	3	**109**	**34**
	451	GR	26	11		
	636	TI	38	3		*31%*
	637	TI	7	0		
	816	TI	1	0		
				TOTAL	**607**	**238**

Table 7 : Summary of previous seasons.

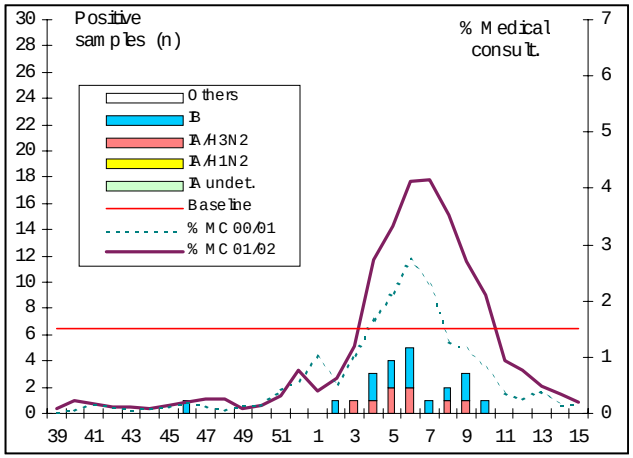
Dominant subtypes of a particular season are in bold

Season	Strains		Total number of samples received	Number of participants	Swab/Participant
	subtype	Number (n)			
1987/1988	***B*** *A/H1N1*	**56** 10			
1988/1989	***A/H_1N_1*** *A/H_3N_2* *B*	**25** 6 1			
1989/1990	***A/H_3N_2*** *B*	**60** 18			
1990/1991	***B*** *A/H_3N_2* *A/H1N1*	**56** 3 1			
1991/1992	***A/H3N2*** *A/H1N1*	**147** 19			
1992/1993	***B*** *A/H3N2*	**55** 9			
1993/1994	***A/H_3N_2*** *B*	***16*** *1*			
1994/1995	***A/H3N2*** *B* *A/H1N1*	**153** 39 1	767	45	17
1995/1996	***A/H_1N_1*** ***A/H_3N_2*** *B*	**146** **109** 30	847	37	23
1996/1997	***A/H_3N_2*** ***B*** *A/H1N1*	**234** **109** 2	1140	54	21
1997/1998	***A/H_3N_2*** *A/H_1N_1*	**321** 5	1164	49	24
1998/1999	***B*** ***A/H3N2***	**143** **83**	1010	54	19
1999/2000	***A/H_3N_2***	**115**	672	47	14
2000/2001	***A/H_1N_1*** *B* *A/H3N2*	**110** 13 1	628	60	11
2001/2002	***B*** ***A/H3N2*** *A/H1N2*	**130** **103** 1	607	54	11

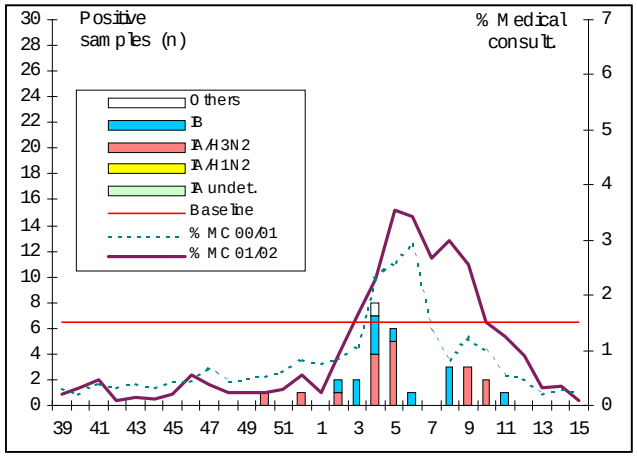
Region 1 : GE, VD, VS, NE



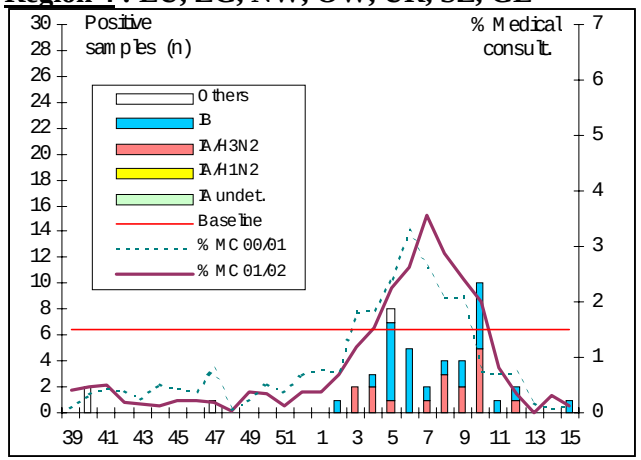
Region 2 : BE, FR, JU



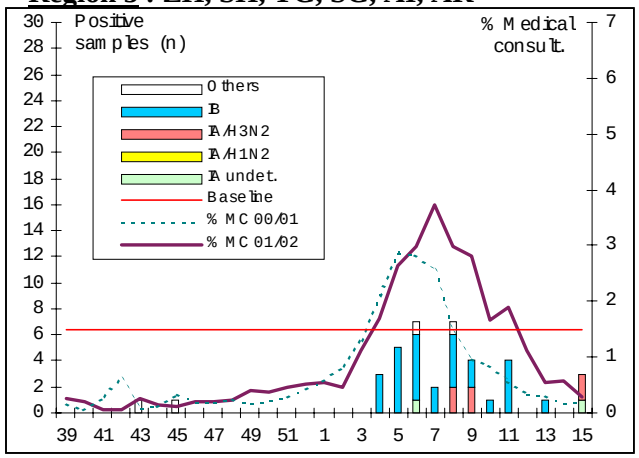
Region 3 : BS, BL, AG, SO



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



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



Region 6 : GR, TI

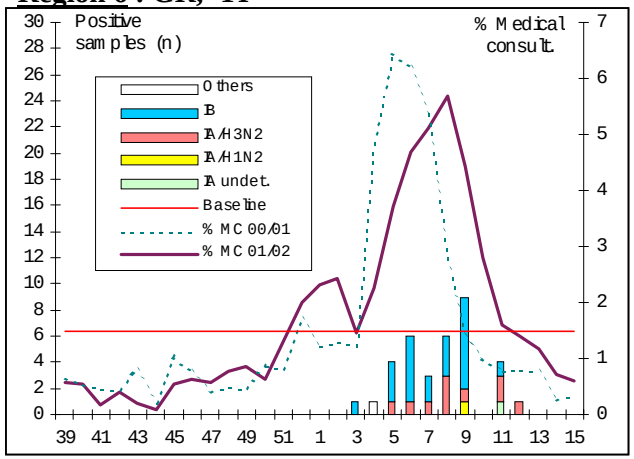
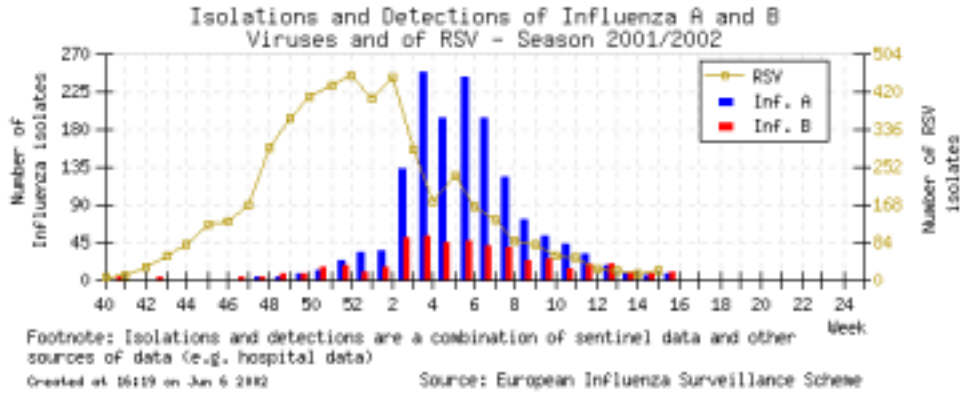
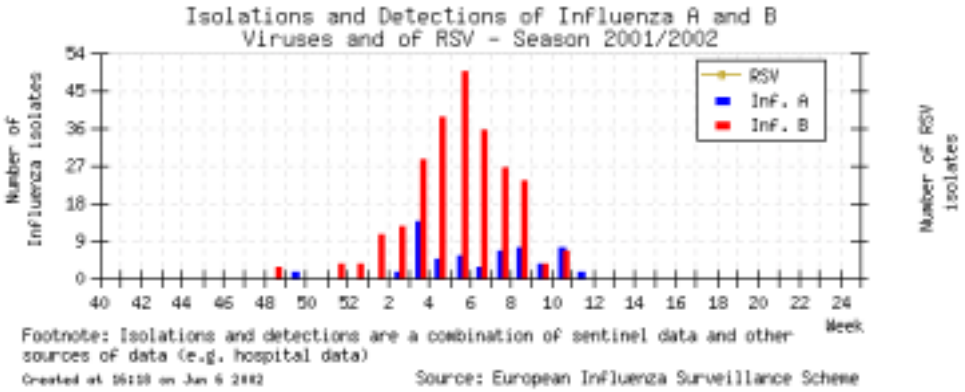


Figure 6 : Number of respiratory viruses detected per week and per region. Others : Adenovirus, Respiratory Syncitial virus, Parainfluenza viruses ; IA : influenza A viruses ; IB : influenza B viruses ; % MC : percentage of med. cons. for influenza-like illness.

France



Italy



Germany

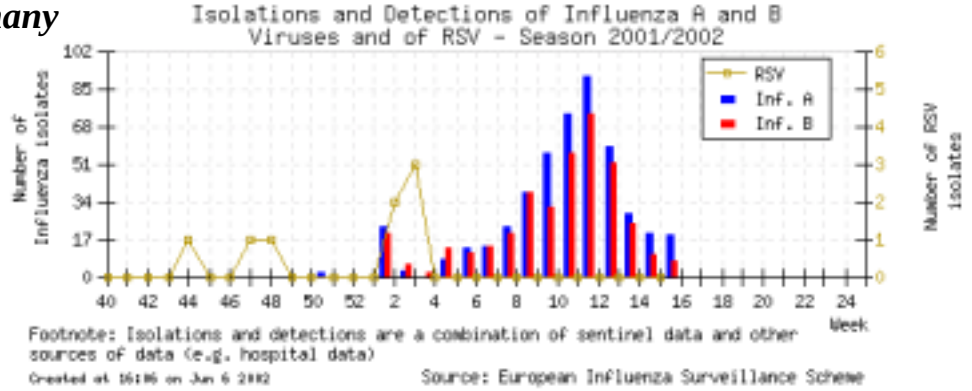


Figure 7 : 2001/2002 influenza epidemic in France, Italy and Germany. The data were taken from the European Influenza Surveillance Scheme database. For more informations, see *http://www.eiss.org*. Inf. A and Inf. B represent influenza A and influenza B viruses.

4.3. Characteristics of patients infected with influenza viruses

4.3.1. Clinical data

Infection with influenza is associated with typical symptoms. With the material for sending in samples, a questionnaire was included. The questionnaires were returned and used to analyse the symptoms associated with the circulating strains. The frequency of each symptom observed in the patients was calculated and separated according to the type of influenza strain that was detected (Table 8).

Table 8 : Symptoms and clinical signs of the patients infected with influenza A and B viruses. 100 patients infected with influenza A viruses and 115 with influenza B viruses were included in this study. The values indicate the frequency of the symptoms (%) observed.

	Adenopathy	**Pharyngitis**	**Headache**	**Expectorations**	**Fever**	**Chills**	**Myalgy**	**Rhinitis**	**Sweat**	**Cough**
Influenza A (%)	16	27	67	29	**94**	46	68	64	44	**84**
Influenza B (%)	17	37	70	30	**95**	34	71	66	49	**89**

No significant difference have been observed or found between the percentages of symptoms in patients infected with an influenza A or influenza B. The most frequently observed symptoms were fever and cough (94-95 % respectively 84-89 %). These two symptoms were also the most frequently observed ones in the past seasons. Myalgy (68 and 71 %), Headache (67 and 70 %) and rhinitis (64 and 66 %) were observed less frequently. Other symptoms were observed at a lower frequency than the previously cited one.

4.3.2. Age groups

The number of swabs and viruses detected during the surveillance period have been classified according to the age group (Figure 8 and 9). The highest number of swabs came from the three age groups comprised between 20-49 years old. 54 % of all the swabs were obtained from these age groups. 14 % of the swabs were obtained from the 10-19 years old (Figure 8). The same tendency was observed in previous seasons (2, 3 and 4). An explanation for this might be that patients between 20 and 49 years belong to professionally most active population. After an influenza infection, they cannot return to their job very quickly. For this reason, they need to consult their practitioner to obtain a medical certificate.

The largest number of influenza viruses have been detected in the age groups comprised between 10-29 years old with 90 viruses detected. In the age groups 30-39 and 40-49 years old 34 respectively 31 viruses were detected respectively. The highest rate of positive samples was not observed in the age groups with highest number of swabs received. So, the percentage of positive samples received from the 10-19 years old was higher than the one from the 30-39 years old (55 % vs 33 %). In addition, the percentage of positive samples of all the age classes below 29 years old was higher than the one of the age classes higher than 30 years old patients (47 respectively 33 %).

The distribution of influenza A and influenza B viruses according to age classes is presented in Figure 9. As can be concluded, influenza B viruses were more frequent in the age classes between 2 and 59 years old. In contrast to that, influenza A viruses were more frequent than influenza B in the 60 years and older. This was already the case in preceding seasons (3 and 4).

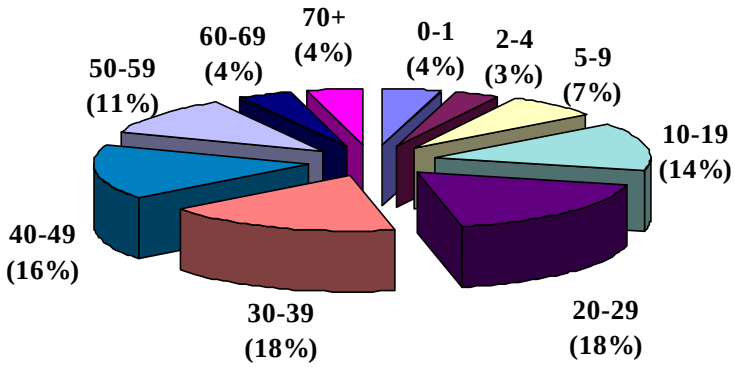


Figure 8 : Distribution of the samples received according to the age of the patients

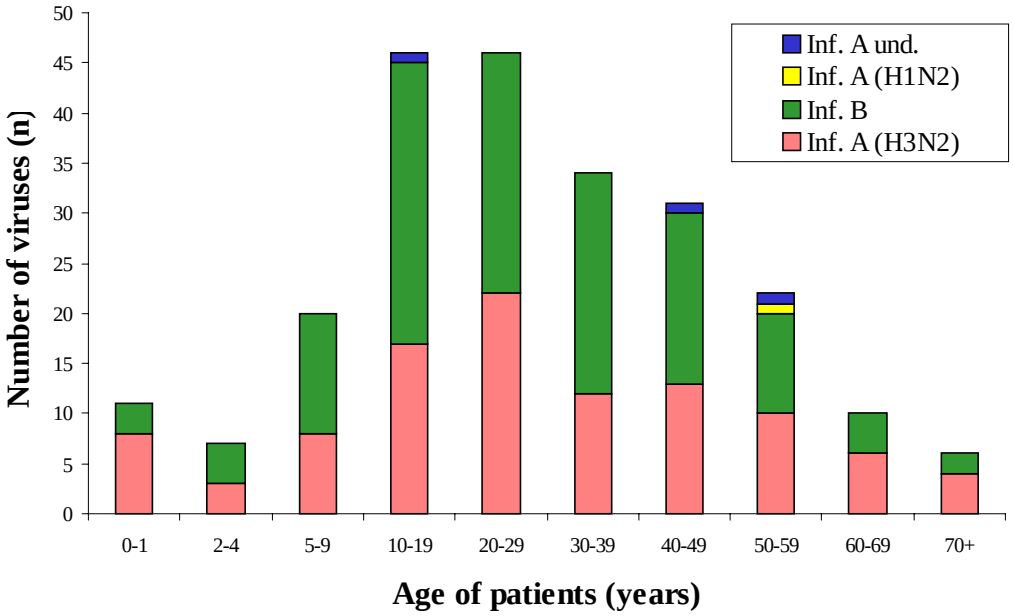


Figure 9 : distribution of viruses detected according to the age of the patients.

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

Infections with influenza virus in elderly people can be the cause of complications and therefore might have an impact on mortality rate. The impact depend on different on different factors linked to the severity of the epidemic (6). An excess of the mortality of the more than 60 years old people could be observed in previous seasons in the canton of Geneva (1996/97, 1997/98 and 1999/2000, 2 and 4). Normally when an effect was observed, it occurred one to two weeks after the peak of the medical consultations for influenza-like illness. The same method as in previous seasons was used for the analysis to evaluate the impact of the 2001/2002 epidemic.

The weekly mortality records issued by the Register Office of the canton of Geneva were used for analysis. The major group of high risk people (the more than 60 years old) was analysed and the weekly death rate of this group of patients is represented in Figure 9 (green curve). To evaluate the rate, the means of the weekly mortality rate of the more than 60 years old patients observed during the 9 last seasons have been calculated and are presented in Figure 9 (blue curve). The upper limit has been defined as the mean of all the weekly means registered between 1991-2002 (with the exception of 1992-93 season) incremented with 2 standard deviations (2s). This value is represented as a blue line (M+2s). The weekly values of the medical contacts for influenza-like illness and the number of viruses detected in the canton of Geneva are also indicated (red line respectively purple bars, Figure 10).

As shown by the graph, no significant difference between the values of the weekly number of deaths during the 2001-02 season (green curve) and the global mean values registered during the 9 seasons (blue curve) can be detected. This season, The highest activity of the epidemic in Geneva could be detected during the 5th week. Indeed, the highest numbers of MC-ILI and of viruses isolated were registered during that period of the season. On parallel, also the highest consultation rate (MC-ILI) was registered during the same period. Moreover, the peak of MC-ILI value observed in the canton of Geneva is the highest one registered in the whole country (7.96 %). During this week and in the following ones, no significant increase of the death rate could be observed. The values of death rates of the more than 60 years old people remained below the upper limit of M+2s (80.54, Figure 10). From this we can conclude that no excess mortality could be detected in the canton of Geneva during the 2001-02 season. This compares with what was observed during the previous season.

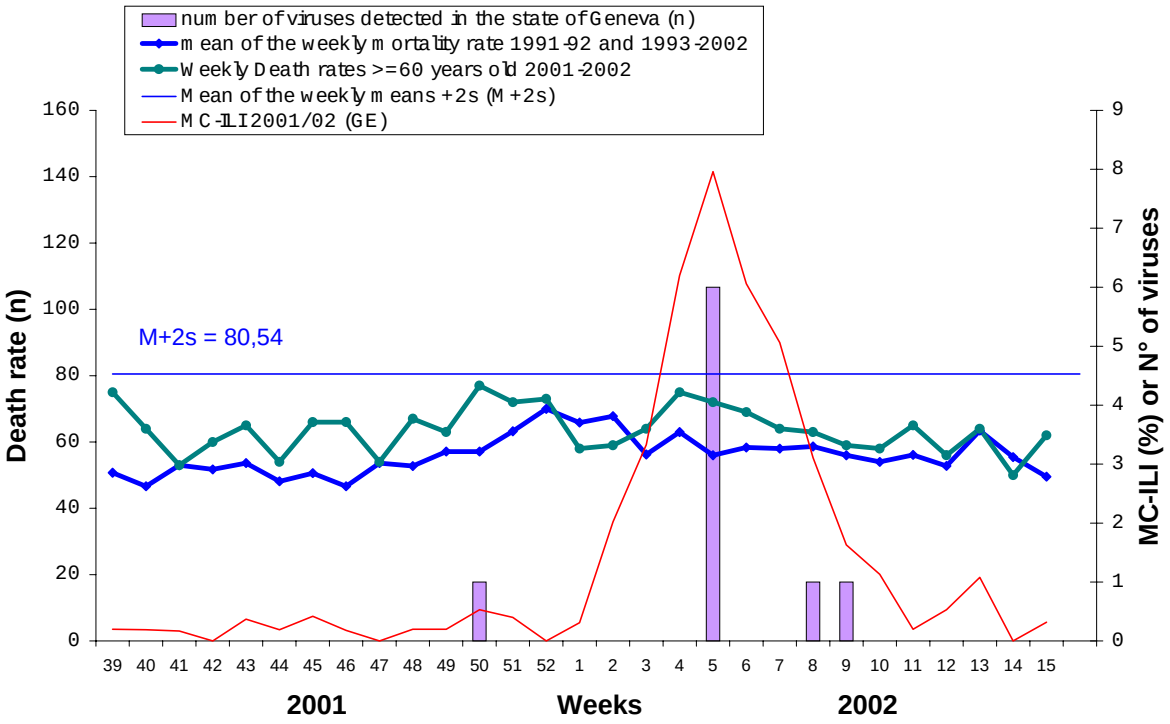


Figure 10 : Influence of influenza infection on the mortality of people older than 60 years in the canton of Geneva during the season 2001/2002. +2s : mean number of deceased people older than 60 years + 2 standard deviation derived from the records of the Register Office of the Canton of Geneva; numbers of deaths were published by the public health authorities of Geneva; MC-ILI GE (%) : medical contacts for influenza-like symptoms in the state of Geneva, MC-ILI CH (%) : medical contacts for influenza-like symptoms in Switzerland.

4.4. Characterisation of influenza viruses detected during the 2001/2002 season

4.4.1 Switzerland and Northern hemisphere

Among the 607 samples obtained from the Sentinel doctors (Table 3) 238 cases (39.2%) contained an influenza virus. The cultures were screened by immunofluorescence with a pool of monoclonal antibodies. Further characterisation of the detected virus strains was done by the hemagglutination inhibition test. The following variants could be observed during the winter season :

90/107 influenza A were of the type of influenza A/Moscow/10/99 (H3N2) or of the closely related influenza A/Panama/2007/99 (annex 1). 1/107 influenza A was of the subtype influenza A (H1N2). The characterisation of the type of the neuraminidase was done by the reference centre in London. This type of virus was isolated from outbreaks or sporadic cases

in Egypt, Israel, the UK and the USA (7). It is a product of a genetic reassortment between Influenza A/New-Caledonia/20/99 (H1N1) and Influenza A/Moscow/10/99 (H3N2). Another influenza A (H1N1) was detected but apparently was not of human origin (not included in Table 3). The particular characteristics of this virus will be discussed below. 130 influenza B viruses could be detected of which 129 were related to the influenza B/Sichuan/379/99 subtype. One strain was related to the subtype influenza B/Hong-Kong/330/01.

4.4.2. Relation of virus isolates to the vaccine strains

In annex 1, the hemagglutination inhibition titres are indicated of the different influenza virus isolates which could be detected during the season. The first three lines of the annex 1A, B and C indicate the homologous titres obtained with known standard strains including the vaccine strain. 32 isolates were compared (annex 1A) to influenza A/Moscow/10/99 (H3N2) and 45 were compared (annex 1B) to influenza A/Panama/2007/99 (H3N2). If we compare the fraction **(homologous titre divided by the titre of the corresponding sample**) we can make the following conclusion. Only 5/32 show a fraction of one or two, this means that they were closely related to the vaccine strain. 27 strains however showed a fraction of 4 or 8 and therefore were less closely related to the A/Moscow/10/99 strain.

In annex 1B, 25 samples showed a fraction of one or two against influenza A/Panama/2007/99 (H3N2). In other words a larger number of samples were more closely related to the influenza A/Panama/2007/99 (H3N2). 20 virus strains showed a fraction of 4 or higher.

113 influenza B were closely related to the influenza B/Sichuan/379/99 strain which was included in the 2001/2002 vaccine (annex 1C). Even if a large number of isolates obtained not a fraction of one or two they were anyhow confirmed by the reference centre to be related to the B vaccine strain (not shown). However from the sample number 8329 an influenza B with a fraction of 128 was obtained. Because we could not characterise the strain any further the sample was shipped to the reference centre. The results from the centre are shown in the table 9. The virus was very poorly related to the vaccine strain and therefore vaccinated people infected with this virus were probably hardly protected by the 2001/2002 vaccine against this virus. This new strain will be included in the vaccine for the 2002/2003 season (8).

Table 9 : Inhibition of the Hemagglutination test Result of the samples 8329 from Geneva

Antisera ***Virus***	**Antibody (rabbit) against influenza B Shandong/7/97**	**Antibody (ferret) against influenza B Hong Kong/330/01**	**Antibodies (ferret) against influenza B Sichuan/379/99**
B/Shandong/7/97	**320**	2560	<
B/Hong-Kong/330/01	160	**5120**	<
B/Sichuan/379/99	<	<	**640**
No 8329 (Geneva)	80	1280	<

4.4.3. Influenza Virus of non-human origin

In a sample obtained from a 50 years old man an influenza A virus was detected. The man was living in the eastern part of Switzerland and he consulted his doctor on the 6th of February because of flu-like symptoms. Because the virus gave no reaction against any human influenza strain antisera, the strain was shipped to the reference centre in London. Genetic and antigenic analysis showed, that this strain was related to influenza A (H1N1) Sw/IV/1455/99. This virus is closely related to influenza viruses which circulate actually in swine in Europe. Further investigations by the general practitioner revealed that the man is a farmer and is breeding swine. His animals were sick showing respiratory symptoms a few weeks ago so that he had to call the veterinarian.

Apparently the farmer picked up his flu from the swine. This way of transmission, called zoonosis, is known from other cases. However it represents a dangerous way how the human influenza virus can acquire new genetic information in particular if porcine strains and human adapted influenza virus have the opportunity to circulate on parallel in the population.

4.4.4. Influenza epidemics in the Northern Hemisphere

Influenza A (H3N2) virus strains were clearly dominant over influenza A (H1N1). Isolates of the H3N2 subtype were related to the vaccine strain influenza A/Moscow/10/99 or to influenza A/Panama/2007/99. This situation was observed in Northern America as well as in other European countries.

A new recombinant between influenza A/New-Caledonia/20/99 (H1N1) and influenza A/Moscow/10/99 (H3N2) started to show up (7). The recombinant virus influenza A (H1N2) caused outbreaks in Canada, the United States as well as in the United Kingdom. In other countries like Israel, Egypt, France and the Netherlands, this strain remained sporadic. Influenza A (H1N1) was clearly a minor cause of epidemics in the northern hemisphere and could be found in Iceland, Italy, Portugal Romania and Spain (9 and 10).

Influenza B circulated in many countries on parallel with influenza A (H3N2). In Europe mainly the subtype influenza B/Sichuan/379/99 was observed. Influenza B/Hong-Kong/330/01 stayed sporadic. In contrast to that influenza B strains detected in Canada were mainly of this latter subtype. It needs to be mentioned that vaccinated people were not well protected (compare 4.4.2.) against the infection with this virus because the protective titer against this variant was considerably reduced. For this reason the vaccine for the next season will contain this new strain.

4.5. Rapid Surveillance

For the third season, surveillance of influenza epidemics was done by the additional use of a rapid antigen test. It was executed by the Sentinella practitioners. One of the objectives of this surveillance is to provide information on the influenza epidemic in a rapid way.

In the classical surveillance system, two indicators of an influenza epidemic are provided on a weekly basis. Sentinella practitioners declare the percentage of consultations for influenza-like illness : MC-ILI. A smaller group of practitioners take swabs from patients presenting typical influenza-like symptoms. The presence of influenza viruses in the samples is done by the use of cell culture and immunofluorescence. The delay to obtain these two indicators has been evaluated during 3 different seasons. MC-ILI is available after a delay of 5 days (± 1). The presence of influenza viruses detected with cell culture is provided after 10 days (± 3). Through the application of rapid test, information about an epidemic can be obtained between 1 and 5 days after execution of the test. The result of the surveillance of this year will be presented in this chapter.

The surveillance with the rapid test was conducted between October 13th 2001 and March 29th 2002. The details of the surveillance were summarised in the table 10 and in Figure 10. 138 practitioners received the rapid antigen test one to two weeks before the beginning of the surveillance. Formation of the participants was organised at the very beginning of the surveillance by mailing three coded samples to all the participants (2 positives and one negative sample). Results were reported to the participants and are summarised in the annex 2. 111 practitioners executed 1597 (Table 10). 303 influenza viruses have been detected with rapid test. The percentages of positive samples detected between the week 42 of 2001 and 15 of 2002 was 19 % for the rapid test and 40 % for cell culture in the same period. The difference in the positive rate suggests that the rapid test has a lower sensitivity than the cell culture.

The higher number of participants in the surveillance with rapid test allows a more detailed information on the influenza epidemic. The data could be presented for the regions, (Figure 10). The number of positive samples detected by the rapid test were indicated per week (green bars), and MC-ILI are indicated as a red curve. The kinetics of the weekly values

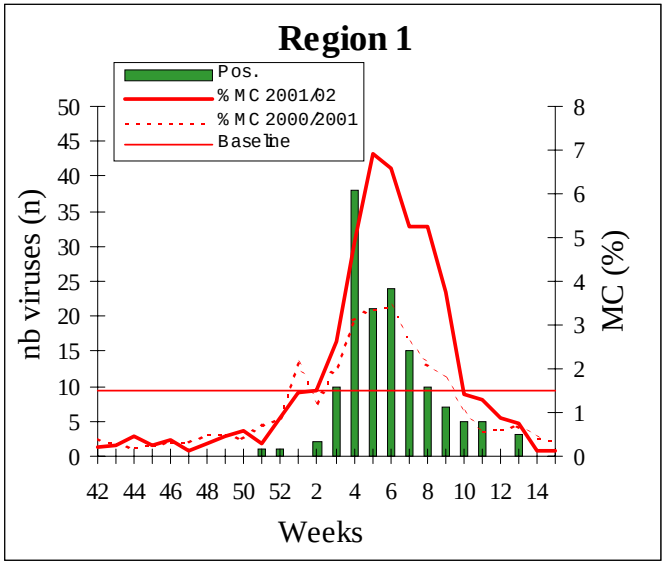
of MC-ILI and the one of influenza viruses detected are comparable. Influenza viruses could be detected approximately in the same week as the MC-ILI started to increase and reached the threshold (region 1, 2, 3, 4 and 5). The maximum number of viruses and the maximum of MC-ILI that were detected approximately in the same week (region 1, 2, 4 and 5, Figure 10). The same is true for the decrease phase (1, 2, 3 and 5). It must be added that in region 4 and 6, the rate of virus detection was low. Therefore, the kinetic was difficult to be estimated. In these two regions, the number of practitioners participating in the rapid test surveillance was rather low, (12 respectively 9 participants). In the other regions, the number of practitioners was between 15 and 25.

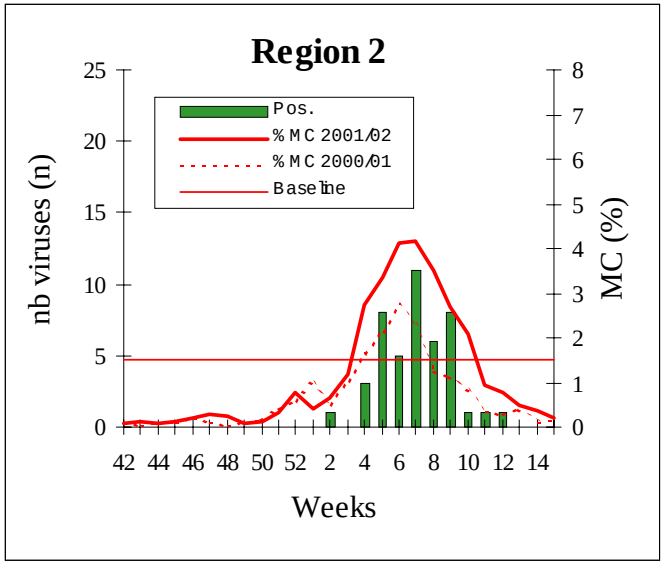
As already mentioned in chapter 4.2.5, five regions were affected at approximately the same level. However, region 1 was different. As could be shown by the surveillance with cell culture and the MC-ILI, this region has been affected to a higher level than the others. This was also reflected by the results of the rapid test. 142 influenza viruses were detected in this. In comparison to that in region 5 only 64 viruses were found (Figure 10 and Figure. 6).

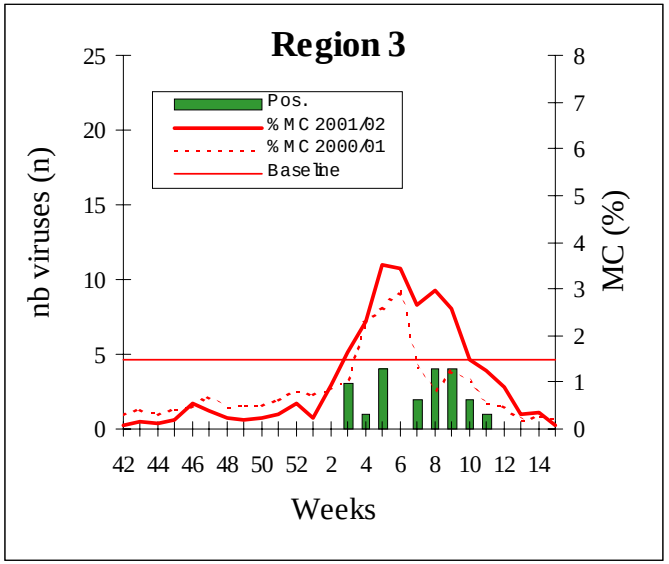
In conclusion, the rapid test surveillance during the 2001-02 season confirmed what was observed in the 2 previous seasons. The rapid test surveillance is able to give information on influenza epidemic with accuracy. The added value of this surveillance is that the information is more rapidly available than with the classical system.

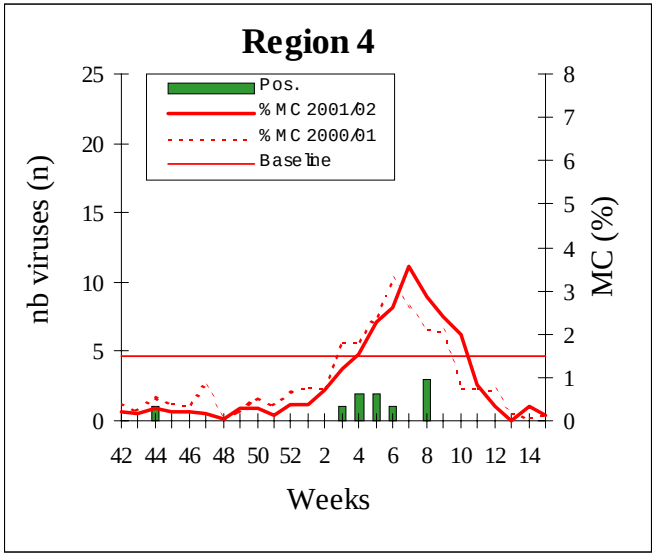
Table 10 : comparison of the weekly results obtained by the rapid surveillance and the Sentinella surveillance

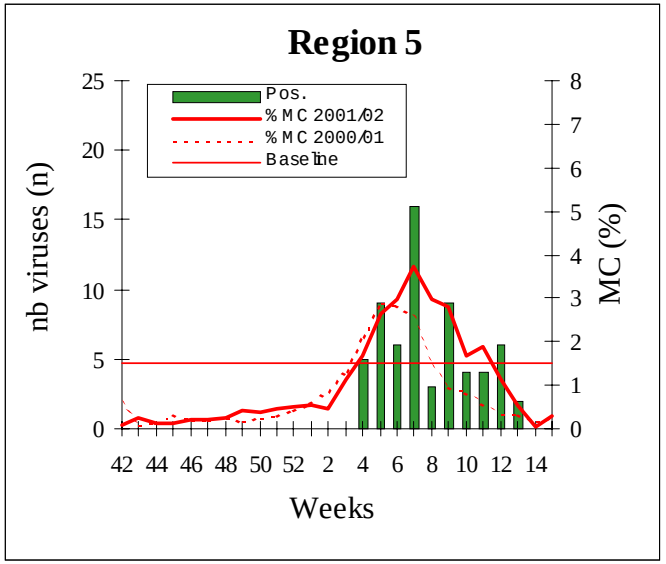
		Sentinelle			***Rapid test***		
Week	MC-ILI (%)	Samples received	Number of positives	Positive rate (%)	Number tested	Number of positives	Positive rate (%)
42	0,15	4	0	0	1	0	0
43	0,19	4	0	0	8	1	13
44	0,18	8	0	0	7	1	14
45	0,21	15	0	0	19	0	0
46	0,32	16	1	6	20	0	0
47	0,26	10	0	0	15	0	0
48	0,27	5	0	0	21	0	0
49	0,34	20	0	0	17	0	0
50	0,3	11	2	18	6	0	0
51	0,5	10	0	0	18	1	6
52	0,75	8	2	25	19	1	5
1	0,7	9	1	11	11	0	0
2	0,94	22	6	27	51	3	6
3	1,52	42	8	19	128	17	13
4	2,66	60	25	42	244	50	20
5	3,79	73	42	58	251	45	18
6	4,16	54	36	67	209	38	18
7	3,97	38	21	55	169	45	27
8	3,7	47	27	57	115	28	24
9	2,99	57	28	49	117	31	26
10	1,79	26	17	65	59	14	24
11	1,35	31	13	42	47	14	30
12	0,91	9	5	56	24	7	29
13	0,5	4	1	25	21	7	33
		583	**235**	***40***	**1597**	**303**	***19***











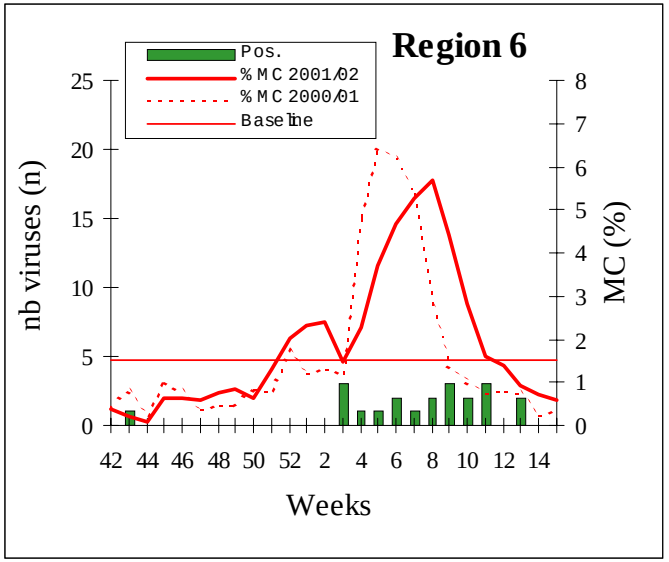


Figure 11 : Number of positive samples detected per week and per region with the rapid antigen test. Pos : influenza virus detected with the rapid test; MC (%) : percentage of medical contacts for influenza-like illness. In the region 1, the graduation of the vertical axis is different than for the other regions.

4.6. Recommended composition of the 2001/2002 influenza vaccine

WHO recommended the following strains to be included in the influenza vaccines for the 2001-2002 season (8) :

A/Moscow/10/99 (H3N2)-like virus
A/New Caledonia/20/99 (H1N1)-like virus
B/Hong-Kong/330/01-like virus

5. DISCUSSION

The 2001/2002 season was a moderate one. The weak activity of the season is reflected in a small epidemic index (Figure 5) and its short duration of 8 weeks. Most of the influenza viruses were detected in the age classes between 10 and 59 years old. In the age groups considered at high risk (below 4 years and over 60 years) only few influenza viruses could be found. This explains why no influence on the mortality of the more than 60 years old could be observed in the state of Geneva.

Another particularity of the season was that the influenza A H3N2 was probably introduced from France (Rhone Alps) into Geneva and the influenza B strains through Italy into the state of Tessin. As a consequence the two types of influenza viruses circulated over the whole period at about the same frequency in all the regions of the country.

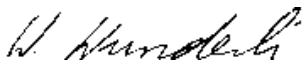
The characterisation of the different viruses detected showed that the influenza A (H3N2) as well as the influenza B were closely related to the viruses comprised in the vaccine (Annex 1A-1C). Vaccinated people were therefore efficiently protected against influenza viruses. However one strain (influenza B/Hong Kong/330/01) showed a greater difference (Table 9). As the results from the reference centre showed vaccinated persons would have been poorly protected against this strain. Fortunately this virus was detected only sporadically

in Europe. However in Canada this influenza B was already causing localised outbreaks.

A reassortant between influenza A/Moscow/10/99 (H3N2) and influenza A/New Caldeonia/20/99 (H1N1) could be detected. This influenza A (H1N2) virus is carrying the neuraminidase from the Moscow strain and the hemagglutinin from the New Caledonia strain. For this reason vaccinated people were protected against this variant.

An influenza A (H1N1) from swine was detected in a farmer (chapter 4.4.3.). Vaccination would not have protected against this virus. Fortunately no further spread of the virus was observed in the surroundings of the patient.

Geneva, 28th June 2002



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Annex 1A : IHA titers of influenza A/Moscow/10/99 (H3N2) isolates

The values mentioned in this table are the inhibition of the hemagglutination titer obtained with the 3 different human influenza antisera used.

A/Mos/10/99 : influenza A/Moscow/10/99 (H3N2)
A/Pan/2007/99 : influenza A/Panama/2007/99 (H3N2)
A/Ire/10586/99 : influenza A/Ireland/10586/99 (H3N2)

N° sample	Date swab	Typisation	**A/Mos/10/99**	**A/Pan/2007/99**	**A/Ire/10586/99**
A/Mos/10/99			***1024***	*1024*	*1024*
A/Pan/2007/99			*512*	***1024***	*1024*
A/Ire/10586/99			*256*	*1024*	***2048***
9778	27-févr-02	InfA H3N2 Moscow/10/99	1024	1024	1024
8403	31-janv-02	InfA H3N2 Moscow/10/99	512	512	1024
9483	21-févr-02	InfA H3N2 Moscow/10/99	512	512	1024
3157	06-mars-02	InfA H3N2 Moscow/10/99	512	256	512
6493	14-déc-01	InfA H3N2 Moscow/10/99	512	128	256
7134	08-janv-02	InfA H3N2 Moscow/10/99	256	256	512
7936	23-janv-02	InfA H3N2 Moscow/10/99	256	256	512
7948	23-janv-02	InfA H3N2 Moscow/10/99	256	256	512
8441	01-févr-02	InfA H3N2 Moscow/10/99	256	256	512
8456	01-févr-02	InfA H3N2 Moscow/10/99	256	256	512
8806	07-févr-02	InfA H3N2 Moscow/10/99	256	256	512
8818	07-févr-02	InfA H3N2 Moscow/10/99	256	256	512
8925	11-févr-02	InfA H3N2 Moscow/10/99	256	256	512
9401	20-févr-02	InfA H3N2 Moscow/10/99	256	256	512
9494	21-févr-02	InfA H3N2 Moscow/10/99	256	256	512
9622	25-févr-02	InfA H3N2 Moscow/10/99	256	256	512
8330	30-janv-02	InfA H3N2 Moscow/10/99	256	128	512
8811	07-févr-02	InfA H3N2 Moscow/10/99	256	128	512
9784	27-févr-02	InfA H3N2 Moscow/10/99	256	128	512
9499	21-févr-02	InfA H3N2 Moscow/10/99	256	128	256
9047	13-févr-02	InfA H3N2 Moscow/10/99	128	128	512
7773	21-janv-02	InfA H3N2 Moscow/10/99	128	128	256
8132	28-janv-02	InfA H3N2 Moscow/10/99	128	128	256
8303	30-janv-02	InfA H3N2 Moscow/10/99	128	128	256
8446	01-févr-02	InfA H3N2 Moscow/10/99	128	128	256
8548	04-févr-02	InfA H3N2 Moscow/10/99	128	128	256
8707	06-févr-02	InfA H3N2 Moscow/10/99	128	128	256
8817	07-févr-02	InfA H3N2 Moscow/10/99	128	128	256
8051	25-janv-02	InfA H3N2 Moscow/10/99	128	128	128
8308	30-janv-02	InfA H3N2 Moscow/10/99	128	128	128
8320	30-janv-02	InfA H3N2 Moscow/10/99	128	128	128
7656	17-janv-02	InfA H3N2 Moscow/10/99	128	64	256

Annex 1B : IHA titers of influenza A/Panama/2007/99 (H3N2) isolates

The values mentioned in this table are the inhibition of the hemagglutination titer obtained with the 3 different human influenza antisera used.

A/Pan/2007/99 : influenza A/Panama/2007/99 (H3N2)
A/Mos/10/99 : influenza A/Moscow/10/99 (H3N2)
A/Ire/10586/99 : influenza A/Ireland/10586/99 (H3N2)

N° sample	Date swab	Typisation	**A/Pan/2007/99**	**A/Mos/10/99**	**A/Ire/10586/99**
A/Pan/2007/99			***1024***	*512*	*1024*
A/Mos/10/99			*1024*	***1024***	*1024*
A/Ire/10586/99			*1024*	*256*	***2048***
8287	30-janv-02	InfA H3N2 Panama/2007/99	1024	512	1024
9707	26-févr-02	InfA H3N2 Panama/2007/99	1024	512	1024
8288	30-janv-02	InfA H3N2 Panama/2007/99	1024	256	1024
9007	12-févr-02	InfA H3N2 Panama/2007/99	512	512	1024
9143	14-févr-02	InfA H3N2 Panama/2007/99	512	512	1024
9343	19-févr-02	InfA H3N2 Panama/2007/99	512	512	1024
9560	22-févr-02	InfA H3N2 Panama/2007/99	512	512	1024
9878	28-févr-02	InfA H3N2 Panama/2007/99	512	512	1024
9918	1-mars-02	InfA H3N2 Panama/2007/99	512	512	1024
3094	5-mars-02	InfA H3N2 Panama/2007/99	512	512	1024
9001	12-févr-02	InfA H3N2 Panama/2007/99	512	512	512
9487	21-févr-02	InfA H3N2 Panama/2007/99	512	512	512
8406	31-janv-02	InfA H3N2 Panama/2007/99	512	256	1024
8542	4-févr-02	InfA H3N2 Panama/2007/99	512	256	1024
9000	12-févr-02	InfA H3N2 Panama/2007/99	512	256	1024
7938	23-janv-02	InfA H3N2 Panama/2007/99	512	256	512
8321	30-janv-02	InfA H3N2 Panama/2007/99	512	256	512
8803	7-févr-02	InfA H3N2 Panama/2007/99	512	256	512
9003	12-févr-02	InfA H3N2 Panama/2007/99	512	256	512
9153	14-févr-02	InfA H3N2 Panama/2007/99	512	256	512
9876	28-févr-02	InfA H3N2 Panama/2007/99	512	256	512
9921	1-mars-02	InfA H3N2 Panama/2007/99	512	256	512
9149	14-févr-02	InfA H3N2 Panama/2007/99	512	256	256
8285	30-janv-02	InfA H3N2 Panama/2007/99	512	128	1024
9501	21-févr-02	InfA H3N2 Panama/2007/99	512	64	512
9239	18-févr-02	InfA H3N2 Panama/2007/99	256	256	512
9702	26-févr-02	InfA H3N2 Panama/2007/99	256	256	512
9974	4-mars-02	InfA H3N2 Panama/2007/99	256	256	512
8550	4-févr-02	InfA H3N2 Panama/2007/99	256	256	256
8449	1-févr-02	InfA H3N2 Panama/2007/99	256	128	512
9144	14-févr-02	InfA H3N2 Panama/2007/99	256	128	512
7411	14-janv-02	InfA H3N2 Panama/2007/99	256	128	256
7555	16-janv-02	InfA H3N2 Panama/2007/99	256	128	256
8319	30-janv-02	InfA H3N2 Panama/2007/99	256	128	256
9154	14-févr-02	InfA H3N2 Panama/2007/99	256	128	256
9354	19-févr-02	InfA H3N2 Panama/2007/99	256	128	256
9777	27-févr-02	InfA H3N2 Panama/2007/99	256	128	256
9920	1-mars-02	InfA H3N2 Panama/2007/99	256	128	256
7192	9-janv-02	InfA H3N2 Panama/2007/99	256	64	256
8642	5-févr-02	InfA H3N2 Panama/2007/99	128	128	256
3102	5-mars-02	InfA H3N2 Panama/2007/99	128	128	256
8857	8-févr-02	InfA H3N2 Panama/2007/99	128	64	256
9500	21-févr-02	InfA H3N2 Panama/2007/99	128	64	256
3106	5-mars-02	InfA H3N2 Panama/2007/99	128	64	256
9562	22-févr-02	InfA H3N2 Panama/2007/99	128	64	128

Annexe 1C : IHA titers of influenza B isolates

The values mentioned in this table are the inhibition of the hemagglutination titer the 3 different human influenza antisera used.

B/Sich/379/99 : influenza B/Sichuan/379/99; B/Yama/166/98 : influenza B/Yamagata/166/98; B/Beij/184/93 : influenza B/Beijing/184/93; B/Shan/7/97 : influenza B/Shandong/7/97

N° sample	Date swab	Typisation	**B/Sich/379/99**	**B/Yama/166/98**	**B/Beij/184/93**	**B/Shan/7/97**
B/Sich/379/99			***1024***	*64*	*128*	*<16*
B/Yama/166/98			*256*	***512***	*64*	*<16*
B/Beij/184/93			*256*	*2048*	***2048***	*<16*
B/Shan/7/97			*<16*	*<16*	*<16*	***2048***
3104	05-mars-02	InfB Sichuan/379/99	256	64	128	-
8810	07-févr-02	InfB Sichuan/379/99	256	64	64	<16
9235	18-févr-02	InfB Sichuan/379/99	256	64	32	<16
9246	18-févr-02	InfB Sichuan/379/99	256	64	64	<16
9623	25-févr-02	InfB Sichuan/379/99	256	64	32	<8
9701	26-févr-02	InfB Sichuan/379/99	256	64	64	-
9872	28-févr-02	InfB Sichuan/379/99	256	64	512	-
9236	18-févr-02	InfB Sichuan/379/99	256	32	32	<16
9237	18-févr-02	InfB Sichuan/379/99	256	32	32	<16
9238	18-févr-02	InfB Sichuan/379/99	256	32	32	<16
9257	18-févr-02	InfB Sichuan/379/99	256	32	32	<16
9506	21-févr-02	InfB Sichuan/379/99	256	32	32	-
3093	05-mars-02	InfB Sichuan/379/99	128	128	256	-
9493	21-févr-02	InfB Sichuan/379/99	128	128	64	-
9780	27-févr-02	InfB Sichuan/379/99	128	128	64	-
9781	27-févr-02	InfB Sichuan/379/99	128	128	32	-
9978	04-mars-02	InfB Sichuan/379/99	128	128	256	-
3155	06-mars-02	InfB Sichuan/379/99	128	64	64	-
3156	06-mars-02	InfB Sichuan/379/99	128	64	64	-
3268	08-mars-02	InfB Sichuan/379/99	128	64	64	-
3442	12-mars-02	InfB Sichuan/379/99	128	64	128	-
3446	12-mars-02	InfB Sichuan/379/99	128	64	128	-
8050	25-janv-02	InfB Sichuan/379/99	128	64	32	16
8101	28-janv-02	InfB Sichuan/379/99	128	64	32	<8
8243	29-janv-02	InfB Sichuan/379/99	128	64	16	<8
8286	30-janv-02	InfB Sichuan/379/99	128	64	32	<8
8392	31-janv-02	InfB Sichuan/379/99	128	64	64	<8
8443	01-févr-02	InfB Sichuan/379/99	128	64	32	<8
8544	04-févr-02	InfB Sichuan/379/99	128	64	32	<8
8646	05-févr-02	InfB Sichuan/379/99	128	64	64	<8
8702	06-févr-02	InfB Sichuan/379/99	128	64	32	<8
8703	06-févr-02	InfB Sichuan/379/99	128	64	32	<8
8709	06-févr-02	InfB Sichuan/379/99	128	64	32	8
8716	06-févr-02	InfB Sichuan/379/99	128	64	32	16
8804	07-févr-02	InfB Sichuan/379/99	128	64	32	8
8853	08-févr-02	InfB Sichuan/379/99	128	64	32	<8
8918	11-févr-02	InfB Sichuan/379/99	128	64	32	8
8921	11-févr-02	InfB Sichuan/379/99	128	64	32	<8
9004	12-févr-02	InfB Sichuan/379/99	128	64	16	8
9051	13-févr-02	InfB Sichuan/379/99	128	64	32	8
9341	19-févr-02	InfB Sichuan/379/99	128	64	32	<8
9347	19-févr-02	InfB Sichuan/379/99	128	64	32	<8
9351	19-févr-02	InfB Sichuan/379/99	128	64	32	<8
9404	20-févr-02	InfB Sichuan/379/99	128	64	32	<8
9504	21-févr-02	InfB Sichuan/379/99	128	64	32	-
9509	21-févr-02	InfB Sichuan/379/99	128	64	64	-
9706	26-févr-02	InfB Sichuan/379/99	128	64	16	-
9709	26-févr-02	InfB Sichuan/379/99	128	64	64	-
9782	27-févr-02	InfB Sichuan/379/99	128	64	64	-
9868	28-févr-02	InfB Sichuan/379/99	128	64	256	-

N° sample	Date swab	Typisation	B/Sich/379/99	B/Yama/166/98	B/Beij/184/93	B/Shan/7/97
B/Sich/379/99 **B/Yama/166/98** **B/Beij/184/93** **B/Shan/7/97**			***1024*** *256* *256* *<16*	*64* ***512*** *2048* *<16*	*128* *64* ***2048*** *<16*	*<16* *<16* *<16* ***2048***
9875	28-févr-02	InfB Sichuan/379/99	128	64	128	-
9881	28-févr-02	InfB Sichuan/379/99	128	64	128	-
9912	01-mars-02	InfB Sichuan/379/99	128	64	64	-
3220	07-mars-02	InfB Sichuan/379/99	128	32	64	-
3260	08-mars-02	InfB Sichuan/379/99	128	32	128	-
7862	22-janv-02	InfB Sichuan/379/99	128	32	32	-
7864	22-janv-02	InfB Sichuan/379/99	128	32	16	-
7906	23-janv-02	InfB Sichuan/379/99	128	32	32	-
7920	23-janv-02	InfB Sichuan/379/99	128	32	32	-
7941	23-janv-02	InfB Sichuan/379/99	128	32	32	<8
7952	23-janv-02	InfB Sichuan/379/99	128	32	16	16
8400	31-janv-02	InfB Sichuan/379/99	128	32	32	32
8809	07-févr-02	InfB Sichuan/379/99	128	32	16	<8
8919	11-févr-02	InfB Sichuan/379/99	128	32	32	<8
8929	11-févr-02	InfB Sichuan/379/99	128	32	16	8
9151	14-févr-02	InfB Sichuan/379/99	128	32	32	<8
9152	14-févr-02	InfB Sichuan/379/99	128	32	16	<8
9352	19-févr-02	InfB Sichuan/379/99	128	32	32	<8
3158	06-mars-02	InfB Sichuan/379/99	64	64	64	-
7188	07-janv-02	InfB Yamana/166/98	64	64	64	16
7497	15-janv-02	InfB Sichuan/379/99	64	64	64	<8
8099	28-janv-02	InfB Sichuan/379/99	64	64	32	16
8239	29-janv-02	InfB Sichuan/379/99	64	64	32	8
8543	04-févr-02	InfB Sichuan/379/99	64	64	32	<8
8700	06-févr-02	InfB Sichuan/379/99	64	64	32	<8
9917	01-mars-02	InfB Sichuan/379/99	64	64	64	-
3103	05-mars-02	InfB Sichuan/379/99	64	32	64	-
3262	08-mars-02	InfB Sichuan/379/99	64	32	64	-
3373	11-mars-02	InfB Sichuan/379/99	64	32	64	-
7413	14-janv-02	InfB Sichuan/379/99	64	32	16	-
7705	18-janv-02	InfB Sichuan/379/99	64	32	32	8
7706	18-janv-02	InfB Sichuan/379/99	64	32	16	8
7871	22-janv-02	InfB Sichuan/379/99	64	32	16	-
7950	23-janv-02	InfB Sichuan/379/99	64	32	32	<8
8004	24-janv-02	InfB Sichuan/379/99	64	32	16	<8
8016	24-janv-02	InfB Sichuan/379/99	64	32	16	<8
8059	25-janv-02	InfB Sichuan/379/99	64	32	16	8
8241	29-janv-02	InfB Sichuan/379/99	64	32	16	<8
8242	29-janv-02	InfB Sichuan/379/99	64	32	32	<8
8245	29-janv-02	InfB Sichuan/379/99	64	32	16	<8
8325	30-janv-02	InfB Sichuan/379/99	64	32	32	<8
8326	30-janv-02	InfB Sichuan/379/99	64	32	16	<8
8327	30-janv-02	InfB Sichuan/379/99	64	32	16	<8
8394	31-janv-02	InfB Sichuan/379/99	64	32	16	<8
8445	01-févr-02	InfB Sichuan/379/99	64	32	32	8
8551	04-févr-02	InfB Sichuan/379/99	64	32	<8	<8
8637	05-févr-02	InfB Sichuan/379/99	64	32	16	<8
8706	06-févr-02	InfB Sichuan/379/99	64	32	32	<8
8814	07-févr-02	InfB Sichuan/379/99	64	32	16	<8
8860	08-févr-02	InfB Sichuan/379/99	64	32	16	<8
8915	11-févr-02	InfB Sichuan/379/99	64	32	16	<8
8916	11-févr-02	InfB Sichuan/379/99	64	32	16	<8
9337	19-févr-02	InfB Sichuan/379/99	64	32	16	<8
9350	19-févr-02	InfB Sichuan/379/99	64	32	16	<8
9703	26-févr-02	InfB Sichuan/379/99	64	32	16	<8
9708	26-févr-02	InfB Sichuan/379/99	64	32	32	-
6943	03-janv-02	InfB Sichuan/379/99	64	16	32	<8
9497	20-févr-02	InfB Sichuan/379/99	64	16	16	4
8624	05-févr-02	InfB Sichuan/379/99	32	64	32	<8
6615	18-déc-01	InfB Sichuan/379/99	32	32	32	32
7563	16-janv-02	InfB Sichuan/379/99	32	32	32	8
5384	22-nov-01	InfB Sichuan/379/99	32	16	64	-
8003	24-janv-02	InfB Sichuan/379/99	32	16	8	<8

Annex 1C

Annex 2 A

Zusammenfassung der Resultate des Ringversuches für die Grippesaison 2001/2002 : Grippeüberwachung mittels Antigen-Schnelltest

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Einleitung

Seit 1999 wird im Sentinella-System neben der herkömmlichen Überwachung der Grippe mit Erfassung der Grippeverdachtsfälle und des Nachweises der Viren in Zirkulation mittels Zellkultur ein Antigen-Schnelltest eingesetzt. Der Schnelltest ist ein zusätzliches Mittel zur Erfassung von Grippeverdachtsfällen und dient der Verbesserung der Aussagekraft der Grippe-Surveillance im Rahmen des Sentinella-Systems. Der Test wird bei Patientinnen und Patienten mit grippeähnlichen Symptomen (ILI) angewendet und kann von der Ärztin/ vom Arzt direkt in der Praxis durchgeführt werden. Er bietet die Möglichkeit, einen Influenzaverdacht zu erhärten. Sensitivität und Spezifität des Tests sind allerdings ungenügend, um einen allfälligen Behandlungsentscheid vom Testresultat abhängig zu machen. Die Testergebnisse stehen im Vergleich zum klassischen Virusnachweis durch Zellkultivation innerhalb kurzer Zeit zur Verfügung und liefern wertvolle Informationen zur jeweils aktuellen Grippesituation. Auswertungen der Testergebnisse können schnell publiziert und der Öffentlichkeit zugänglich gemacht werden.
Um eine hohe Qualität der Resultate und Zuverlässigkeit des Tests zu gewährleisten, macht eine Ausbildung bezüglich der Handhabung des Testes Sinn. Vor Beginn der Überwachungssaison 2001/2002 wurde aus diesem Grunde ein Ringversuch durchgeführt. Den Teilnehmern sollte die Möglichkeit geboten werden, sich selbst zu prüfen und nach einer Beratung allfällige Probleme in der Durchführung des Tests zu beheben. In der Folge werden die Ergebnisse des Ringversuches zusammengefasst.

Methoden und Material

Für den Nachweis von Influenza Virus Antigen aus Rachenabstrichen wurde der FLU A/B-RAPID ASSAY® der Firma Roche verwendet. Die Testkits mit Reagentien und Testmaterial für insgesamt 50 Rachenabstriche wurden von der Firma gratis zur Verfügung gestellt und den Teilnehmern Anfang Oktober 2001 zugestellt. Die Tests wurden gemäss der Anleitung des Herstellers durchgeführt.
Jeder Teilnehmer erhielt im Rahmen des Ringversuches ein Set von drei Proben, wovon eine Probe negativ, eine schwach positiv und eine deutlich positiv war. Alle Probensets waren von identischer Zusammensetzung, wurden jedoch verschieden kodiert. Die positiven Proben enthielten M Protein von Influenza A, waren somit nicht infektiös und daher unbedenklich für die Handhabung in einem Praxislabor. Jede der drei Proben enthielt 100 µl Probelösung. Die Teilnehmer erhielten eine Kurzanweisung, wie diese Proben zu handhaben seien und ein Fax-Formular zur Übermittlung der Testergebnisse innerhalb einer Frist von 14 Tagen an das NZI. Nach Ablauf der Einsendefrist wurde den Teilnehmern das Formular mit den zu erwartenden Resultaten zurückgesandt.
Zur Beratung der Teilnehmer, welche nicht alle Proben korrekt identifiziert hatten, wurde folgendes Vorgehen gewählt. Jenen Teilnehmern, welche die stark positive Probe richtig nachgewiesen hatten, wurde für eine weitere Kontrolle ein zweites Set von Proben zusammen mit einem Resultatbogen zugestellt. Diejenigen Teilnehmer, welche keine der positiven Proben nachweisen konnten, wurden durch die Arbeitsgruppe (NZI, Roche, BAG) telefonisch kontaktiert, um mögliche Probleme bei der Handhabung der Proben oder der Schnelltests herauszufinden. Erst nachdem eine plausible Fehlerquelle eruiert werden konnte, erhielten die Praxen ein weiteres Set von Proben. Konnten auch bei der zweiten Selbstkontrolle die positiven Proben nicht identifiziert werden, so

erfolgte eine zweite telefonische Kontaktaufnahme durch die Arbeitsgruppe.

Resultate

Für die Grippesaison 2001/2002 schrieben sich 127 Sentinella-Ärztinnen und Ärzte zur Teilnahme an der Schnelltestudie und am Ringversuch ein. Insgesamt 114 (89,9%) der registrierten Teilnehmer sandten Testergebnisse per Fax an das NZI zurück. Nach Einsendeschluss (5. November 2001) wurden die erhaltenen Resultate analysiert. Es zeigte sich folgendes Bild: 51 Teilnehmer (40%) erkannten alle drei Proben korrekt, 42 (33%) erkannten nur die stark positive Probe und 21 Teilnehmer (17%) konnten keine der zwei positiven Proben identifizieren (vgl. Tab.1.).

Tabelle 1: Übersicht der Resultate von 114 Teilnehmern

Alle Proben richtig nachgewiesen	**Nur die stark positive Probe nachgewiesen**	**Keine der zwei positiven Proben nachgewiesen**
51	42	21
40%	33%	17%

In einer zweiten Runde des Ringversuches zeigten sich folgende Resultate: In der Gruppe der Teilnehmer, die in der ersten Runde die stark positive Probe korrekt nachgewiesen hatten und die nicht telefonisch kontaktiert wurden, identifizierten bis auf drei (7,1%) Praxen beim zweiten Durchgang alle Teilnehmer (39; 92,9%) alle drei Proben korrekt. Praxen, welche telefonisch kontaktiert wurden, um Hilfestellung zu leisten, und um mögliche Fehlerquellen zu erurieren, identifizierten die Proben im zweiten Durchlauf zu 81% korrekt. In vier Fällen (19%) erfolgte eine zweite Kontaktaufnahme per Telefon.
Wie im persönlichen Gespräch deutlich wurde, umfassen die Ursachen für inkorrekte Testergebnisse verschiedene Punkte. In einigen Fällen kam es zu Fehlern bei der Durchführung der Tests, weil der Prozessablauf nicht genau gemäss Protokoll erfolgte. Es bereitete teilweise Mühe, dass der Schnelltest mit einer vorbereiteten Probelösung anstatt eines Rachenabstriches angewendet werden musste. Im Weitern stellte die Handhabung der Probelösungen von je 100µl eine Schwierigkeit dar und führte in einigen Fällen zu Verlust der Lösung. Ferner zeigte sich eine gewisse Unsicherheit bei der Interpretation der Testergebnisse. Enzymatisch schwach positive Resultate wurden oft fälschlicherweise als negativ eingestuft.

Erläuterungen
Reagentien in Form von Kits sind üblicherweise so konzipiert, dass die Durchführung der Tests ohne zusätzliche Hilfsmittel und ohne spezielle Laborinfrastruktur möglich ist. Gewisse Produkte sind in der Handhabung soweit vereinfacht, dass die Durchführung auch nicht speziell ausgebildetem Laborpersonal ermöglicht wird. Der in dieser Studie eingesetzte Influenza-Schnelltest gehört zu dieser Kategorie von Reagentien und erfüllt diesbezüglich somit die Anforderung, um in einer Arztpraxis im Rahmen des Sentinella-Systems eingesetzt zu

werden.
Es gehört heute zur guten Praxis im Labor (GLP), dass alle Analysen mehr oder weniger regelmässig einer externen Qualitätskontrolle unterzogen werden. Das heisst mittels bekannten aber anonymisierten Proben soll überprüft werden, ob das Labor die zu erwartenden Resultate produzieren kann. Damit soll nicht nur geprüft werden, ob der Test richtig durchgeführt wird, sondern ob der ganze Ablauf, begonnen mit der Probenannahme, Testdurchführung und Resultatübermittlung, fehlerfrei abläuft.
Der von uns organisierte Ringversuch ist nicht als eigentliche Qualitätskontrolle zu verstehen, sondern sollte vorallem dazu dienen, die Teilnehmer mit der Methodik vertraut zu machen und das Erkennen und Ausräumen allfälliger Probleme zu ermöglichen. Die Resultate zeigen eindeutig, dass eine solche Kontrolle sinnvoll ist. Insgesamt 40% der Teilnehmer erhielten im ersten Durchgang drei richtige Resultate. Die restlichen Teilnehmer benötigten eine zusätzliche Ausbildung. Auch wenn ein Schnelltest einfach ist in der Anwendung, kann die Erstanwendung Probleme bieten.
Die häufigste Fehlerquelle war, dass die schwache Bande, welche mit der schwach positiven Probe erhalten wurde, als negativ beurteilt wurde. Ein zweiter häufiger Punkt war das kleine Probenvolumen, welches von uns zur Verfügung gestellt wurde. Durch den Transport wurde die Probelösung im ganzen Röhrchen und im Deckel verteilt, sodass bei der Testdurchführung einiges der Originalprobe verloren ging und dadurch die verfügbare Virusmenge vermindert wurde.
Diese Resultate zeigen eindeutig, das auch bei all den Vorbereitungen und mit schriftlichen Gebrauchsanweisungen, eine praktische Ausbildung, die die individuelle Mediation berücksichtigt, nötig ist, um den Anwender mit dem Test vertraut zu machen. Der Lerneffekt durch die Mitteilung der Resultate und der Möglichkeit, eine zweite Testserie durchführen zu können, war hingegen sehr befriedigend. Vor allem die Praxen, welche die schwach positve Probe falsch interpretiert hatten, profitierten von dieser Gelegenheit. Eine geringe Zahl von Teilnehmern (19%) benötigten detaillliertere Informationen und eine zweite direkte Kontaktnahme, um gegebene Probleme beheben zu können.
Zusammenfassend kann gesagt werden, das auch bei der Anwendung von sogennanten Schnelltests eine individuelle Ausbildung der Benützer notwendig ist. Dies vor allem, um sich mit dem System vertraut zu machen und um bei der Interpretation von Resultaten die nötige Sicherheit und Erfahrung zu gewinnen.

Bei dieser Gelegenheit möchten wir allen beteiligten Praxen für die Teilnahme am Ringversuch sowie für die konstruktive Zusammenarbeit bestens danken. Es ist Ihr Verdienst, dass das Schnellsystem zur Grippeüberwachung so gut funktioniert.

Annex 2B

Résumé des résultats des essais collectifs lors la grippe 2001/2002: Surveillance de la grippe à l'aide du test antigénique rapide

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Introduction

Depuis 1999, un test antigénique rapide de la grippe est utilisé par le réseau Sentinella, en plus de la surveillance habituelle avec enregistrement des cas suspects de grippe et mise en évidence des virus en circulation au moyen de cultures de cellules.
Ce test rapide est un moyen supplémentaire pour détecter les cas suspects de grippe. De plus, il améliore et renforce la fiabilité du système de surveillance Sentinella. Le test est employé pour les patients et les patientes qui présentent des symptômes grippaux (ILI) et il peut être utilisé directement au cabinet médical. Il permet de confirmer une suspicion d'influenza. La sensibilité et la spécificité du test ne sont cependant pas suffisantes pour fonder la décision de traiter sur ce seul résultat. Comparés à la confirmation classique de virus par culture de cellules, les résultats du test sont plus rapidement disponibles et fournissent de précieuses informations sur la situation momentanée de la grippe. La publication des résultats peut se faire rapidement et être accessible au grand public.
Pour garantir la qualité des résultats et la fiabilité du test, une formation sur l'utilisation pratique du test s'avère utile. En conséquence, un essai collectif a été effectué avant le début de la période de surveillance 2001/2002.
Les participants ont eu la possibilité de s'exercer eux-mêmes et après avoir pris conseil, ils ont pu résoudre les problèmes éventuellement soulevés lors du test. Les résultats de l'essai collectif sont résumés ci-après.

Matériel et méthodes

Pour la mise en évidence des antigènes du virus influenza dans les prélèvements, on a utilisé le FLU A/B-RAPID ASSAY® de la société Roche. Les kits de test avec réactifs et matériel d'essai pour 50 prélèvements ont été offerts par la maison Roche et remis aux participants début octobre 2001. Les tests ont été pratiqués conformément aux instructions du fabricant.
Chaque participant à l'essai collectif avait reçu un ensemble de trois échantillons, dont un négatif, un faiblement positif et un nettement positif. Tous les kits d'échantillons avaient la même composition mais des codes différents. Les échantillons positifs contenaient la protéine M des virus d'influenza A, qui, n'étant pas infectieuse, ne représentait pas de risque lors des manipulations en laboratoire de cabinet. Chacun des trois échantillons contenait 100 µl de solution d'essai. Les participants ont tous reçu une notice expliquant comment manipuler ces échantillons et un formulaire de fax pour transmettre dans les 14 jours les résultats des tests au CNI. Une fois écoulé le délai d'expédition, le formulaire a été retourné aux participants avec les résultats attendus.
Pour conseiller les participants qui n'ont pas identifié correctement tous les échantillons, la procédure suivante fut choisie: tous les participants ayant reconnu l'échantillon très positif ont reçu un second kit d'échantillons pour un nouveau contrôle, avec une feuille de résultats. Les participants n'ayant reconnu aucun des échantillons positifs ont été contactés par téléphone par le groupe de travail (CNI, Roche, OFSP), afin de découvrir les problèmes rencontrés dans le maniement des échantillons ou des tests rapides. Une fois les sources d'erreur plausibles décelées, les praticiens ont reçu un nouveau kit d'échantillons. Si, après le second auto-contrôle, les échantillons positifs n'étaient pas identifiés, le groupe de travail rappellait

le praticien.

Résultats

Pour la saison de grippe 2001/2002, 127 médecins Sentinella se sont inscrits pour l'étude portant sur les tests rapides et l'essai collectif. 114 (89,9 %) d'entre eux ont renvoyé les résultats des tests par fax au CNI. Après l'échéance du 5 novembre 2001, les résultats reçus ont été analysés et reportés dans le tableau ci-dessous. 51 participants (40 %) ont identifié les trois échantillons correctement, 42 (33 %) n'ont identifié que l'échantillon nettement positif et 21 participants (17 %) n'ont identifié aucun des échantillons positifs (cf. Tableau 1).

Tableau 1: Résultats des 114 participants

Tous les échantillons sont identifiés	Seul l'échantillon nettement positif est identifié	Aucun échantillon n'est identifié
51	42	21
40 %	33 %	17 %

Une deuxième série d'essais a donné les résultats suivants : Dans le groupe des participants ayant identifié correctement les échantillons très positifs lors de la première série et qui n'ont pas été contactés par téléphone, tous les praticiens (39; 92,9 %) sauf trois (7,1%) ont identifié correctement les trois échantillons lors de la deuxième série. 81 % des praticiens ayant bénéficié de conseils par téléphone pour rechercher les sources d'erreur possibles ont identifié les échantillons lors de la deuxième série correctement. Dans quatre cas (19 %), un second entretien téléphonique a suivi.

Les entretiens personnels ont révélé plusieurs sources d'erreur d'identification. Dans certains cas, les erreurs s'étaient produites parce que le protocole d'utilisation n'avait pas été suivi exactement. Dans d'autres cas, des problèmes se sont posés parce que le test rapide utilisait une solution d'essai au lieu du frottis pharyngé. Par ailleurs, la manipulation des échantillons de 100µl présentait une difficulté et a causé, dans plusieurs cas, une déperdition de la solution. De plus, un certain flottement s'est produit lors de l'interprétation des résultats. Les tests enzymatiques faiblement positifs ont souvent été considérés à tort comme négatifs.

Commentaires

Les réactifs présentés sous forme de kits sont conçus de façon à ce que l'utilisation du test soit possible sans aide supplémentaire ni infrastructure spéciale du laboratoire. Pour certains produits, les manipulations sont simplifiées au point qu'elles puissent être confiées à un personnel de laboratoire sans formation spéciale. Le diagnostic rapide de grippe utilisé pour l'essai collectif appartient à cette catégorie de réactifs et, à cet égard, il satisfait aux conditions requises pour être utilisé dans un cabinet médical dans le cadre du système Sentinella.
Il appartient aujourd'hui à une bonne pratique de laboratoire (GPL) que toutes les analyses subissent plus ou moins régulièrement un

contrôle externe de qualité qui vérifie sur des échantillons connus mais anonymes si le laboratoire est en mesure de produire les résultats attendus. Il faut donc contrôler non seulement si le test est effectué correctement, mais également si l'ensemble de l'opération se déroule sans faute, à commencer par la réception de l'échantillon, le déroulement du test et la transmission des résultats.
L'essai collectif que nous avons organisé ne doit pas être considéré à proprement parler comme un contrôle de qualité. Il devait avant tout servir à familiariser les participants avec le test et permettre de cerner et d'éliminer d'éventuels problèmes. Les résultats montrent clairement l'utilité de ce genre de contrôle. 40 % des participants ont d'emblée obtenu les trois bons résultats. Les autres participants ont eu besoin d'un complément de formation. Même pour un test rapide facile à utiliser, la première manipulation peut poser des problèmes.
L'erreur la plus fréquente s'est produite avec l'échantillon faiblement positif, qui a été considéré comme négatif. La deuxième source d'erreur tient à la petitesse de l'échantillon que nous avions mis à disposition. Pendant le transport, la solution de l'échantillon s'est dispersée dans le tube ainsi que sur le couvercle, de sorte qu'une partie de l'échantillon d'origine s'est perdue lors de l'utilisation du test, ce qui a réduit d'autant la quantité de virus disponible.
Il ressort clairement de ces résultats que, malgré toutes les phases préparatoires et les modes d'emplois fournis, il est utile de prévoir une formation pratique prenant en compte la médiation personnelle pour familiariser l'utilisateur avec le test. En revanche, la communication des résultats et la possibilité de refaire une seconde série de tests a eu un effet pédagogique très satisfaisant. Ce sont surtout les praticiens qui ont mal interprété les échantillons faiblement positifs qui ont profité de cette opportunité. Un nombre restreint de participants (19 %) ont eu besoin d'informations plus détaillées et d'une nouvelle prise de contact pour résoudre les problèmes rencontrés.
On peut donc conclure également à l'utilité d'une formation individuelle de l'utilisateur lors de l'emploi dudit test rapide, surtout pour le familiariser avec le système et pour lui fournir l'assurance et l'expérience nécessaires pour interpréter les résultats.

Nous saisissons l'opportunité qui nous est donnée ici pour adresser nos vifs remerciements à tous les praticiens qui ont participé à cet essai pour leur collaboration constructive. C'est à eux que l'on doit le bon fonctionnement du système rapide de surveillance de la grippe.