Influenza surveillance

Pietro Crovari · Roberto Gasparini

Introduction

In the Middle Ages influenza epidemics were attributed to the negative influence from planets in conjunction, hence the name given to this disease.

The influenza virus was isolated only in 1933 (Smith, 1935), nevertheless the nosological picture of the disease had already been documented for a few centuries. Starting from the XVI century there are clear descriptions of epidemics in Great Britain (Thompson, 1852).

Historically, the pandemic outbreak referred to as "Spanish" is frequently mentioned. It occurred in 1918–1919 and affected 200 000 000 people, causing 20 000 000 deaths.

More recently there were two other serious pandemic outbreaks, though they were definitely less severe than the "Spanish" one. In 1957 we had the influenza known as the "Asian" outbreak and in the winter of 1968–1969 the "Hong Kong" outbreak.

The characteristics of the pathogenic agent are responsible for the recurrence of influenza epidemics. The influenza virus belongs to the *Orthomyxoviridae* family and has a particular set of genes. In fact, the genetic information is located on 8 RNA segments. This means that there is a high probability of gene rearrangement among the different strains of the virus.

What is particularly important is the presence on the surface of the virion of two glycoproteins. The first, known as haemagglutinin (H), recognises the receptor and is responsible for adhesion and fusion of the virus to the membrane of respiratory cells. The second, known as neuroaminidase (N), allows the release of newly formed viruses outside the infected cell. The peculiar epidemiological progress of the disease can be explained by variations in these two antigens.

The characteristics of the nucleoprotein enable to distinguish the 3 types of influenza viruses: A, B and C. The A viruses show greater shifts and/or minor drifts in the antigenic set. The B viruses show only minor drifts while the C viruses do not show any important variation and consequently have fairly small epidemiological relevance.

The shift in the H or N antigen represents a greater variation. When this happens the result can be widespread diffusion of the virus with very extensive epidemics.

The drifts, which are much more frequent, are instead associated with subsequent punctiform mutations in gene segments of H and N antigens, with more modest but not irrelevant consequences on the epidemiological progress of the disease.

The most authoritative hypothesis to explain the appearance of shifts is the hybridisation of human and animal viruses (birds, swine, etc.) (Scholtisseck, 1983).

At present, subtypes H3N2, H1N1 and H1N2 of the A virus circulate together, in addition to B viruses belonging to at least two genomic lineages (B/Victoria/2/87 and B/Yamagata/16/88).

W. Kirch (ed.), *Public Health in Europe*

The impact of the disease is particularly perceptible during pandemic outbreaks. During these circumstances, the morbidity and mortality due to influenza result in considerable social damage. Nevertheless, even during inter-pandemic periods the damage is considerable. For instance, Sullivan (1996) estimated that in the USA the disease causes an average of 17 to 50 million cases every year, from 165 to 233 million sick days, from 43 to 70 million days of limited activity or days in bed, from 4 to 24 million medical visits, 314.000 hospitalisations and 20 000 deaths. It seems that in England, every year, an average of 3000 to 5000 deaths occur, while more extensive epidemics, like the one that occurred in the winter of 1989/1990, caused 30 000 deaths. It seems that in Italy the number of influenza cases that probably occurred during the 2001/2002 winter, assessed with the method of sentinel physicians and paediatricians, was 2 610 611 during the 8 weeks of the epidemic (Crovari, Submitted for publication).

We should bear in mind that the spreading of the virus is accompanied with that of other respiratory micro-organisms, such as Respiratory Syncytial iruses, Parainfluenza viruses, Adenoviruses, Coronaviruses, Rhinoviruses, etc. Moreover, we cannot ignore other pathogens, such as *Streptococcus pneumoniae, Haemophilus Influentiae, Mycoplasma pneumoniae*, etc.

In the Northern hemisphere influenza activity occurs during winter, from October to April, whereas in the Southern hemisphere it occurs from April to October. In the tropical areas, influenza activity is always present, with recrudescence during the more cold-humid periods (Kilbourne, 1987).

Objectives and methods of influenza surveillance

The objectives of the surveillance of influenza disease are essentially two, i.e. to limit the impact of the disease (morbidity, mortality, costs, etc.) and to quickly identify the predominant viral variants.

These are the methods available. Morbidity studies through clinical/epidemiological surveillance (sentinel physicians and paediatricians), surveys on extra mortality from respiratory diseases and all other causes (Serfling, 1964; CDC, 1997), studies on extra hospitalisations (Gasparini, 1992), surveys on the use of drugs (antibiotics, antipyretics, cough remedies, etc.), surveys on absenteeism (from work, school, etc.), health economy analyses (cost-effectiveness, cost-benefits, etc.), studies on increased requests for medical house calls, etc.

Virological surveillance enables to monitor the variability of influenza viruses and answers the demand for continuous update of the composition of the vaccine.

In spite of the fact that the above-mentioned study methods provide important indications, they are individually inadequate in providing an adequate picture of the epidemiology of the disease (Nicholson, 1998).

Virological surveillance

The global virological surveillance network, created by the World Health Organisation (WHO) in 1947 (Hampson, 1996), has rapidly expanded since the Sixties and includes approximately 110 National Centres distributed in 83 countries, which collaborate very closely. They are linked to 4 WHO Centres, in Europe (London), in the USA (Atlanta), in Australia (Melbourne) and Japan (Tokyo). Their “mission” is to monitor the new variants of the influenza viruses, so as to be able to choose the most suitable ones for the production of vaccines for the following season. It is for this reason that every February experts from all over the world gather at the WHO in Geneva where the formulation for the Northern hemisphere is defined. The same thing occurs in September for the Southern hemisphere.

An attempt is currently underway to increment the exchange of information and reagents for the typing of viral strains among the different national centres, and to ensure that all the centres be equipped with IT (Lavanchy, 1999). The FluNet Web site has been set up to provide updated data.

Since 1995 the European Influenza Surveillance Scheme (EISS) has been set up at European level. The results of participating countries, gathered in a single database, can be looked up via Internet.

In Italy, there has been for some time a virological surveillance network that includes different regions (Liguria, Lombardy, Tuscany, Emilia Romagna, Lazio, Umbria, etc.) and is linked to the National Centre in Rome. More recently, from 1st November 1999, there is an active national surveillance network (InfluNet) (Gasparini, 2001) that, through sentinel physicians and paediatricians, ensures better monitoring of the new influenza virus variants in addition to the clinical/epidemiological surveillance discussed afterwards.

Starting from the assumption that the samples coming from the population better represent the progress of virosis in the entire population (Nicholson, 1998), the Italian virological surveillance is based on the activity of free-choice general practitioners and paediatricians. The activity of the latter is extremely precious because, as is well known, children represent the prime target of the virus. It is only to identify viruses that cause more serious infections that samples coming from hospitalised patients are examined (Watson, 1995). To improve the performance of virological tests it is a good idea to examine the definition of an influenza case as specified by the WHO. In fact, influenza, at least in subjects aged >3 years, is characterised by sudden onset, high fever (often >38–$39\,^{\circ}$C), at least one symptom of respiratory apparatus involvement (cold, pharyngitis, laryngitis, tracheitis, etc.) and at least one systemic symptom (asthenia, anorexia, muscle pains, etc.).

Laboratory diagnosis methods are different in terms of sensitivity and specificity. Today we have quick tests for diagnosis at the patient's bedside (often useful to correctly orient the treatment), isolation in embryonated chicken eggs or in cell cultures (MDCK) (Meguro, 1979), identification with the haemoagglutination inhibition test and through the polymerase amplification reaction (Polymerase Chain Reaction; PCR) (Atmar, 1996) and isolate genotyping. These last two methods allow us to focus on molecular epidemiology results, which are very useful for making forecasts. Recently, this method has enabled the Surveillance Centre at the University of Genoa to genotype a fair number of B viruses, after the identification of strains belonging to the B/Victoria/2/87 lineage, which had been absent from Europe for many years (see Fig. 1 and 2) (Ansaldi, in press).

For successful laboratory activity it is also important to take samples of the pathological material. Taking material from throat and nose seems to be the most practical way to isolate the virus (Fleming, 1995).

Clinical/epidemiological surveillance

Sentinel physicians and paediatricians carry out the clinical/epidemiological surveillance. Based on the above-mentioned definition of an influenza case, a group of healthcare professionals every day send the diagnoses of disease to a special data processing Centre. The weekly morbidity is then calculated and is reported on a special Web site, so that there is a return of information to physicians and paediatricians.

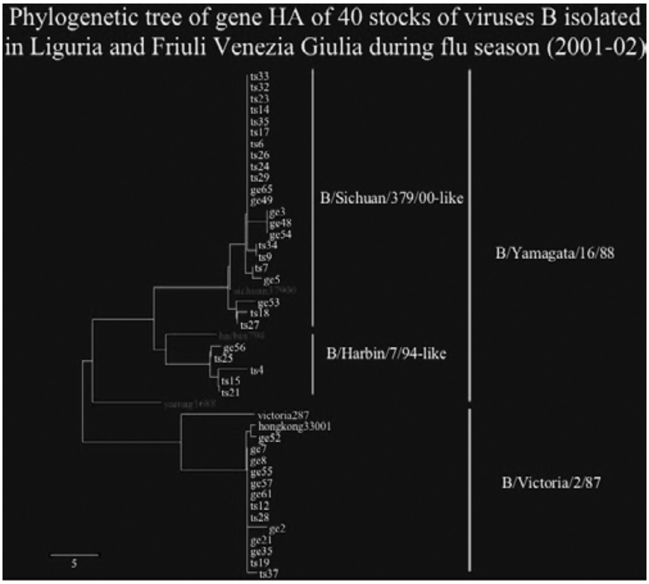

Fig. 1. Phylogenetic tree of gene HA of 40 stocks of viruses B isolated in Liguria and Friuli Venezia Giulia during flu season (2001–2002)

Aminoacidic sequence of antigenic sites A and B of 40 stocks of viruses B isolated in Liguria and Friuli Venezia Giulia during flu season (2001-02)

	Site A (145-150)	Site B (161-168)	(197-205)	
Sichuan/379/00	NATSKS	PRdDNNKT	NKTQMKNLY	
Ge49 (14 isolati)	______	________	_________	B/Sichuan/379/00-like
Ge3, Ge48, Ge54	___N__	________	_________	
Ge53	______	________	D________	
Ge56	_____R	_K_____N	_________	B/Harbin/7/94-like
Ts4	______	_K_____N	__Y______	
Ts15, Ts21, Ts25	______	_K_____N	_________	
Ge7 (10 isolati)	_V_NGN	_KNE____	_EA__AK__	B/Victoria/2/87
Ge52, Ts37	_V_NGN	_KNE____	TEA__AK__	
Ge2	_V_NGN	_KNE____	_EA__AK_F	

Fig. 2. Aminoacidic sequence of antigenic sites A and B of 40 stocks of viruses B isolated in Liguria and Friuli Venezia Giulia during flu season (2001–2002)

A network of General Practitioners belonging to the English Royal College of General Practitioners exists since 1967. Through this system it has been possible to make good estimates of the onset and severity of the epidemics that occurred in England and Wales in 1989, 1993 and 1995 (Fleming, 1996).

A similar system, created in Belgium in 1985 by the Institute of Hygiene and Epidemiology (Snacken, 1996), includes approximately 50 physicians and 50 paediatricians.

In Holland, during the 1982–1992 period, the sentinel stations of physicians at the National Institute for primary care (NIVEL) were able to reduce the annual average of morbidity from influenza to 425 cases every 10 000 inhabitants (Knottnerus, 1996). Even though the incidence of influenza in the community seems to be from 3 to 6 times higher

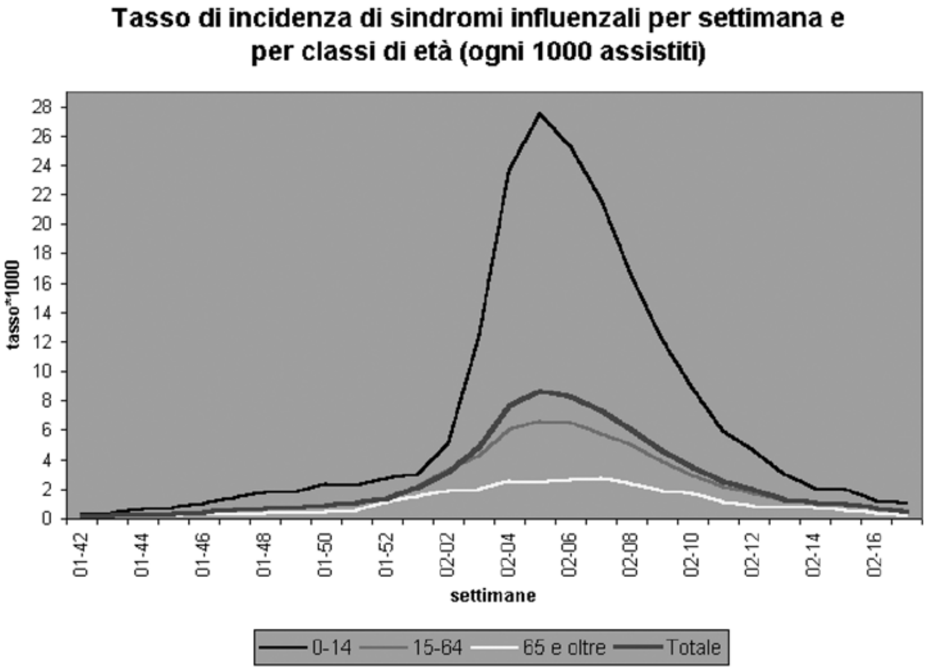

Fig. 3. Influenza morbidity (per 1000 inahabitants), in different classes of ages, in Italy during 2001/02 winter season

than that observed by physicians and paediatricians, because most of the cases do not come to the attention of physicians, the influenza activity is very well monitored by the method of sentinel healthcare professionals (Knottnerus, 1996). One of the problems to be solved has to do with the representative value of the patients monitored. They should be well distributed over the whole territory (in fact, there may be diversities in terms of age distribution, presence of conditions predisposing towards complications, vaccine coverage, etc.) and usually, given the circulation of the disease, it is estimated that at least 1% of the population should thus be monitored (Knottnerus, 1996).

The results supplied by this type of surveillance are particularly valuable in monitoring the activity trend, especially if connected with the virological data of the same population and with other clinical activity indicators (Nicholson, 1998). Another benefit is the exact identification of the start of the epidemic, through intensified virological controls and the use of specific drugs for treatment and prevention of more serious complications in subjects at risk.

At the Italian level, after local experiments implementing a detection system based on sentinel physicians, a national surveillance network is active since 1st November 1999. The gathered data are centrally processed by the Health Sciences Department at the University of Genoa and the Istituto Superiore di Sanità (Ministry of Health Institute). In addition, the results can be looked up, almost in real time, on the Web site: Cirinet.it.

The physicians who joined the Influnet system in the 2000/2001 season were 845 and the Italian population studied was an average of 1.96% of the total. The results for that season subdivided according to age groups, are shown in Figure 3. The comparison of the results of the winters 1999/00, 2000/01 and 2001/02 are shown in Figure 4.

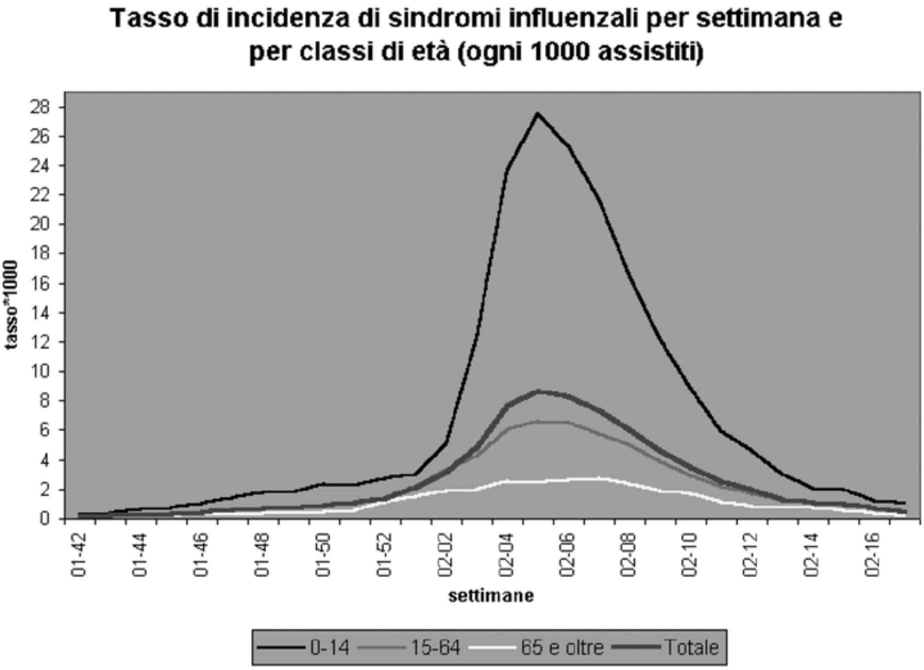

Fig. 4. Influenza morbidity (per 1000 inahabitants), in different classes of ages, in Italy during 2001/02 winter season

Other indicators of influenza activity

Surveillance of extra mortality and extra hospitalisations

At the time of maximum influenza virus circulation there is an increase in mortality, which is not recorded during non-epidemic periods, as can be observed from the statistical survey on all respiratory affections. This is not surprising if we consider that the influenza disease is particularly serious in elderly subjects, who pay a high toll in mortality during each epidemic occurrence.

The annual measurement of this finding (mortality due to respiratory diseases, excluding tuberculosis and tumours) is one of the most objective indices of the impact of influenza. In fact, the degree of increased mortality detected during the influenza season is a direct and reliable index of the severity of the epidemic episode that has occurred.

Farr already anticipated this surveillance system in the last century; the actual method was refined by Serfling in 1963 and has been used for 30 years by the WHO (Assaad, 1971).

The additional mortality is identified by comparing the rates of mortality from respiratory diseases with the rates one might expect (expected mortality) in the absence of influenza activity.

This methodology, not always used univocally, may be biased by, for instance, epidemics from other agents responsible for respiratory infections, etc.

Other interesting elements for the epidemiological study of influenza can be provided by the study of extra hospitalisations for influenza, pneumonias, as well as other respiratory and heart diseases. Barker in 1987 had already worked out a methodology similar to that for the study of extra mortality, which also enabled important assessments of the direct costs of the disease.

Surveillance of absenteeism from school and workplace

Very useful indications for influenza surveillance can result from surveys on absenteeism from the workplace. In Italy this is possible by examining the certificates of illness that general practitioners send to the National Institute of Social Insurance, reporting the diagnosis of the disease. Based on the cases labelled as influenza, it is possible to make reliable estimates (though probably overestimated) on its incidence. It is interesting to point out that the highest peak in absenteeism from the workplace occurs one week after that of maximum absenteeism from school. This confirms that children are the first target of the virus and represent an important link in the transmission chain.

Surveys on absenteeism from the workplace were carried out in Siena on 29 659 workers aged between 20 and 60 years (Gasparini, 2000). These surveys enabled us to extrapolate that more than 20 000 000 cases occurred among Italian workers in the 1989–1995 period.

Another parameter that enables us to assess the impact of influenza on society is school absenteeism. This indicator seems to be among the most sensitive to detect the start of an influenza epidemic. Studies on this topic (Gasparini, 1990) suggest that we are faced with an epidemic rekindling, when the daily percentage of school absenteeism is more than 10% of the pupils.

Increased demand for medical visits and use of drugs

The greatest request for medical visits for acute respiratory diseases coincides with the highest peak in influenza activity (Sullivan, 1996). Thus, this is one of the indicators that can be used for disease surveillance. This indicator has been used in two of the most important studies on the impact of influenza on the population of the USA. In the study carried out by Monto et al. (1971) in Tecumseh, the estimated number of medical calls was 26–29 visits for influenza per 1000 inhabitants per year. In the study carried out by Glezen et al. (1984) in Houston, it was 99 visits per 1000 inhabitants per year. On the basis of these results, Sullivan estimated that every year in the USA there is an average of 4 to 24 million visits for influenza.

As for the use of drugs, it is clear that the prescription of antipyretics, antibiotics and cough remedies during the periods of maximum diffusion of influenza viruses is considerably higher. It is therefore obvious that a study of increases in the use of drugs is not only useful in taking the pulse of the diffusion of the virus, but is helpful in having a better picture of the economic damage caused by this disease.

Conclusions

There are also other methods of surveillance for influenza activity, such as registration of all respiratory affections diagnosed as influenza in health clinics, emergency rooms, etc. Nevertheless, it is important to consider that some types of studies are particularly indicated to detect the initial moment of the disease (for instance the method of sentinel physicians) while others allow more accurate estimates of the actual severity of the influenza epidemic. However, it is necessary to combine several methods to have a sufficiently clear picture of the social impact of the virosis. On these bases it is then possible to carry out cost-benefit studies of vaccination or other preventive and therapeutic treatments (amantadine, zanamivir, oseltamivir, peramivir, etc.).

Based on a recently carried out survey (Crovari, submitted for publication), we were able to estimate that the cost of the influenza epidemic in the winter of 2001/2002 in Italy, during the 8 weeks of maximum diffusion, was 1 billion and 349 million Euros.

Another survey carried out in the winter of 2000/2001 (Gasparini, 2002), allowed us to estimate that the net benefit of vaccination was 110.20 Euros per elderly vaccinated subject.

It is, therefore, quite clear that surveillance of the disease is very important, also in light of the number of travels and migrations and the facility of travelling from one end of the earth to another in a few hours. This means that a viral strain that has appeared in a geographical area can be transported in every part of the world in much shorter times than in the past. This likelihood was particularly feared during the H5N1 influenza virus epidemic, which occurred in Hong Kong in 1997 (Shortridge, 1999). In that year there were serious epidemic episodes among poultry and 18 cases among the population, 6 of which deadly. It was a virus that was potentially very dangerous for man but, fortunately, the killing of 1.5 million chickens avoided the threat. This threat, however, is still present since among the many biological weapons that might be used, there is more than one utilizable influenza virus.

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