

Postprint Version	1.0
Journal website	http://dx.doi.org
Pubmed link	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12686088&query_hl=5
DOI	10.1016/S0264-410X(03)00066-5

* Corresponding author. Tel.: +44-121-426-1125; fax: 44-121-428-2084.
E-mail address: dfleming@rcgpbbhamresunit.nhs.uk (D.M. Fleming).

The evolution of influenza surveillance in Europe and prospects for the next 10 years

D.M. FLEMING^{A,*}, J. VAN DER VELDEN^B, W.J. PAGET^B

a Birmingham Research Unit of the Royal College of General Practitioners, Lordswood House, 54 Lordswood Road, Harborne, Birmingham B17 9DB, UK
b NIVEL, P.O. Box 1568, 3500 BN Utrecht, The Netherlands

ABSTRACT

This report traces the evolution of surveillance programmes for influenza in the United Kingdom and countries of western Europe since the World Health Organisation (WHO) resolution to establish an international influenza reference centre in 1947. The introduction of clinical surveillance schemes in the late 1960s and their gradual integration with laboratory-based surveillance is described, with particular emphasis on the need for integrated surveillance based on population-specific denominators. The function of the European Influenza Surveillance Scheme (EISS), its work programme in the last 5 years, and the likely direction of future developments is outlined. The report advocates the EISS model of influenza surveillance, which involves the integrated collection of clinical and laboratory data in the same population using sentinel practitioners.

Key messages

- **The ever changing nature of influenza viruses makes continuing surveillance essential.**
- **Integrated clinical and laboratory based surveillance in defined populations is needed.**
- **High quality surveillance has to be resourced appropriately.**
- **The impact of vaccination programmes also needs to be regularly monitored.**

1. SURVEILLANCE BEFORE 1990

The initial stimulus for undertaking influenza surveillance was provided in 1933 with the first isolation of an influenza virus [1]. For the previous 50 years, *Haemophilus influenzae* had been thought to be the agent responsible for the disease [2]. Before then, beliefs were much conditioned by the Italian word 'influenza', which means the influence of the stars and heavenly bodies on epidemics of cough and fever [3]. Even in distant times, the significance of cough and fever was clearly appreciated. Whilst the impact of epidemic respiratory disease on winter mortality had been recognised for centuries, the pandemic of 1918 alerted the western world to the potential of influenza. In 1946, a vaccine against influenza was developed and tested in military recruits in the USA. Early on, it was appreciated that annual updating of the vaccine would be necessary [4]. With these factors as background, the World Health Organisation (WHO) in 1947 resolved "to establish an international centre to collect and disseminate information on epidemics, strain type and vaccine composition to develop standard operating procedures; to provide an international training facility" [5,6].

In response to the WHO initiative, the first international influenza centre was established in Mill Hill in London. In 1957, virus isolates and serology reports from throughout the nation began to be collated centrally, though these were generally few in number and not always delivered promptly. In 1967, information began to be gathered from patients consulting in sentinel practices [7]. This development addressed the need for obtaining timely information and opened up opportunities for estimating the impact of influenza in primary care.

When sentinel practice-based surveillance was first introduced in the UK, an attempt was made to distinguish clinically between influenza-like illness (ILI) and what was referred to as epidemic influenza. Data on both were reported separately from other respiratory infections such as acute bronchitis. Reports of epidemic influenza were closely associated with proven virological influenza activity in the community. From the surveillance perspective, however, reports of an increased incidence of ILI provided an earlier indication of influenza epidemics.

Surveillance schemes similar to the one in the UK were established in the Netherlands [8], Scotland [9] and Portugal [10] in the early 1970s. Sentinel networks were established in France, Belgium and Spain during the 1980s [11–13]. These surveillance systems have been largely modelled on the scheme developed by the Royal College of General Practitioners. In the Netherlands, reporting has been based on precise case definitions; in Portugal, a symptom scorecard has been used for each reported case and only those scorecards meeting six of ten criteria are considered to indicate a diagnosis of influenza virus infection; in some networks guidelines rather than definitions are used. However, in spite of differences in case definitions and physician compliance with their use, these sentinel practice-based systems have all successfully delivered timely warnings of epidemic conditions. It has proved difficult, however, to use them to predict the magnitude of epidemics [14]. Observations in the sentinel networks in England and Wales (Weekly Returns Service; WRS) and the Netherlands (the Dutch Sentinel Network; DSN) demonstrated that epidemics in both countries lasted about 8–10 weeks, a finding since confirmed in other European networks. When considering the impact of influenza on mortality, most estimates have been based on all-cause mortality, a minority on pneumonia and influenza mortality and almost none on influenza-proven mortality [15]. These estimates parallel those for influenza-related morbidity. Influenza virus infection may cause a spectrum of clinical illness well beyond the usual ‘case definition’. Participants in the sentinel networks continue to raise the question of whether it is better to report ILI or total acute respiratory infections (ARI). Ideally, both should be separately recorded.

In some countries, laboratory reporting was extended in the 1970s to include respiratory syncytial virus (RSV) and mycoplasma infections and this has been maintained since. In England and Wales, RSV and influenza viruses usually circulate at the same time (Fig. 1), making it difficult to estimate the impact of infection due to each of these agents. In most years, the maximum number of RSV reports is 10 times that of the influenza virus reports. The difficulty of comparison is further compounded because 87% of RSV isolates are obtained from children less than 2 years in age, whereas the converse applies to influenza. This illustrates a basic reality of clinical practice: physicians investigate patients largely to confirm or negate their clinical diagnoses. They cannot find what they do not look for. In general, paediatricians have not looked for influenza as a cause of lower respiratory tract infection in children and general practitioners and adult physicians have not looked for RSV as a cause in adults. Surveillance involving the routine investigation of suitable specimens for both RSV and influenza viruses has produced an entirely different picture: both agents have been found to cause disease in all age groups [16]. Thus, accurate surveillance requires looking for what is not expected and it needs to be properly structured. It cannot be achieved simply as a by-product of the routine investigation of patients as part of disease management.

[FIGURE 1]

2. SURVEILLANCE 1990–2000

By 1990, influenza surveillance was well established in most European countries. Most of these surveillance programmes, however, were fragmented and only minimal attempts had been made to present surveillance data from clinical and laboratory reports derived from the same population.

Furthermore, the surveillance networks in each European country were operating autonomously without regard to similar activities in other countries. To address this problem, in 1989 the European Commission funded the Eurosentinel Project [17]. This project brought together sentinel networks from several different countries with the goal of harmonising their practice-based surveillance activities. A number of initiatives were undertaken, including one concerned specifically with influenza. Existing links between influenza virologists and epidemiologists were exploited to establish a new spirit of collaboration. As a result, integrated systems of clinical and laboratory surveillance were developed. In the ensuing years, the umbrella name under which these activities developed changed first to ENSCARE and then to EISS, reflecting in part the vicissitudes of funding arrangements [18–20].

EISS is an acronym for one of several European information systems concerned with influenza. Its unique contribution reflects its main objective, which is to encourage and support the collection of integrated clinical and virological information from definable populations wherever possible. Its operations depend on contributions from all parties (sentinel physicians, virologists and epidemiologists). Currently EISS is funded primarily by each national influenza surveillance organisation. These resources are complemented by EU funds that catalyse international collaboration between the national networks. Limited resources are provided by the pharmaceutical industry to support specific projects within EISS. During the 2001–2002 influenza season, the project included 18 countries, 25 national influenza reference laboratories and at least 10,500 sentinel physicians. It covered a total European population of 438 million [20].

The international collaboration fostered by EISS has revealed several general problems pertaining to international collaboration in surveillance. They are summarized below.

2.1. Clinical issues

- If persons are to be counted only when they consult their physicians, how are we to deal with differences in health care systems that influence the way people consult and differences imposed by sickness certification arrangements?
- Because the science of epidemiology depends upon population-specific denominators, how do we obtain these denominators when registries of individual persons enrolled in specific practices do not exist in several countries (e.g. France, Belgium and Germany)?
- How can individual datasets that provide unique proxies for influenza activity within a country be compared internationally?

2.2. Laboratory issues

- Does it matter that different laboratories use different investigation methods when the WHO envisaged standardised laboratory procedures?
- Is it worth expanding the range of viruses and other micro-organisms investigated?
- How many specimens are needed to deliver accurate virological surveillance in a cost-effective manner?

In addition to identifying several problems, international collaboration between the surveillance networks has resulted in several positive achievements. These include:

- Agreed age ranges for reporting clinical incidence and the age groups 0–4, 5–14, 15–64, 65years.
- The use of population denominators and, where they do not exist, the use of the proportion of physicians in the country or locality to provide an indication of the population under surveillance. Where data are reported from different types of primary care provider (e.g. general practitioner or paediatrician), incidence rates are calculated separately.
- The introduction of a structured investigation of the operation of sentinel practices.
- The use of a quality control programme in laboratories.
- Agreement to include RSV as a secondary organism to be reported routinely.
- Enhanced communication of integrated European surveillance information by the EISS Website (<http://www.eiss.org>).

The Hong Kong chicken flu incident [21] and heightened appreciation of the threat posed by bioterrorism following the attacks of September 11, 2001 have sharpened the international focus on

pandemic preparedness. European countries have since come together in their desire to develop a common European preparedness plan. Since preparedness is mainly dependent on what is currently in place, and not on what might be done if an unpredictable event should occur, we believe that EISS, with its international organisation, shared experience and multi-disciplinary networking, has enhanced pandemic preparedness in Western Europe. Although the funding of surveillance networks in several countries has not been adequately addressed, the organisation has greatly improved European collaboration in influenza-related matters. A number of issues still need to be resolved before the ultimate objective of obtaining internationally comparable data can be achieved, but much progress has already been made.

3. SURVEILLANCE IN 2000 AND BEYOND

Fifty years since the WHO resolution in 1947, the need for surveillance has expanded. Whereas surveillance in 1947 was dominated by the need for virus identification, strain type analysis and optimal vaccine strain choice, it is now equally important to obtain other kinds of information for optimal individual patient management and epidemic control. This expanded view has moved the focus of surveillance towards the point of delivery of care.

For individual patients, the increase in therapeutic options means that better information must be obtained from community-based surveillance if these are to be used effectively. For national approaches to influenza management, determining the optimal vaccination policy and the most appropriate allocation of health care resources depends on what is happening with the disease in the population rather than on simply identifying the causal organism. This point is illustrated in surveillance information on the incidence of ILI in England and Wales reported by the Weekly Returns Service for the influenza epidemics of 1969, 1989, 1993 and 1999 [22]. Fig. 2 shows the age-specific weekly incidence of ILI over the 4 weeks preceding the peak, the peak and the 4 succeeding weeks of each epidemic. The data illustrate clearly the importance of knowing the different patterns of ILI-related clinical activity for each epidemic. In the pandemic of 1969, the highest ILI incidence rates were reported in the working population (15–44 and 45–64 years in age). In these age groups, there were undoubtedly many additional people who did not consult physicians, thereby lessening the potential burden on health services. In 1989 (and in 1993), the impact was the greatest in children 0–4 and 5–14 years in age. This pattern of ILI largely affected primary care physicians who were called on to provide home visits and other emergency medical services for young children with high fever. Since children usually respond rapidly to an influenza virus infection and are seen promptly by physicians, they may benefit from antiviral treatment. In contrast, during the Millennium winter of 1999/2000, influenza primarily affected older age groups (45–64 and 65 years and over) and scarcely affected children. Whilst this epidemic had a relatively small impact on the general community, it almost crippled hospital-based health care facilities in England and Wales.

[FIGURE 2]

Advances in technology present new opportunities for extracting information from primary care. The electronic medical record has arrived, although physicians have yet not mastered the best ways of using it. In the Weekly Returns Service, data are now collected and transmitted in an automated manner twice a week. Sentinel physicians maintain their electronic patient records in a disciplined manner, recording for each consultation the working diagnosis and type of episode thereby distinguishing new episodes of illness from ongoing consultations. This discipline is not difficult to maintain once acquired. Given the appropriate infrastructure, it allows real time data capture on any illness. Whilst influenza remains at the top of the list of conditions for which such information is desirable, bio-terrorism poses new threats for which clinical incident information may be essential. In this context, surveillance has to be structured according to syndromes rather than micro-organisms. Only in a minority of situations can the organism be identified at the point of initial contact. However, syndrome-based surveillance poses other questions; for example, we may look for influenza but what about the other causes of acute febrile respiratory illness?

Expensive drugs are often wasted in treating minor self-limited conditions and antibiotics are often prescribed when they are not needed, contributing to the problem of increasing antibiotic resistance.

These practices emphasise the need for improving diagnostic precision. The introduction of rapid diagnostic tests that can be used in the consulting room brings a new dimension to surveillance [23,24]. These tests must not be allowed to eclipse formal virological culture which remains essential for the purposes specified in the 1947 WHO surveillance declaration. Moreover, the currently available tests are not yet sensitive enough to justify clinical decisions to withhold treatment. Neither are they likely to assume a major role in individual patient management because of their costs and the added resources needed in the consultation setting. However, they have potential value as a surveillance tool used in appropriately resourced sentinel practices, monitoring representative populations [24]. Surveillance is likely to shift to a primary emphasis on the point of delivery of care. It behoves investigators to put in place reliable systems to capture these data.

Vaccination is widely accepted as the cornerstone of influenza prevention and many new vaccines are being developed. A further need for surveillance therefore, concerns the effectiveness of vaccination policy, not just the effectiveness of vaccination. Since most countries have vaccination policies based on a mix of age and high-risk medical conditions, monitoring programmes will need to link vaccination status with specific high-risk conditions. This subject is currently under discussion within EISS.

4. CONCLUSIONS

The need for virological surveillance outlined in the WHO recommendations of 1947 continues, but the objectives of surveillance have expanded from disease identification to epidemic disease management. This change emphasises the need for nationally comparable data and, in particular, data on clinical impact that are relevant to both vaccination and treatment policies. Because influenza is an ever-changing target, the need for surveillance is constant. Although surveillance systems may be complemented by individual studies for specific purposes, continuous and efficient routine surveillance remains essential. Current biases in sample collection that focus on individual patient diagnosis for disease management seriously limit the usefulness of such data for surveillance purposes. However, structured investigation within the framework of integrated community and laboratory-based sentinel surveillance networks has been firmly established. These networked systems provide a solid foundation for future developments in influenza surveillance.

TABLES

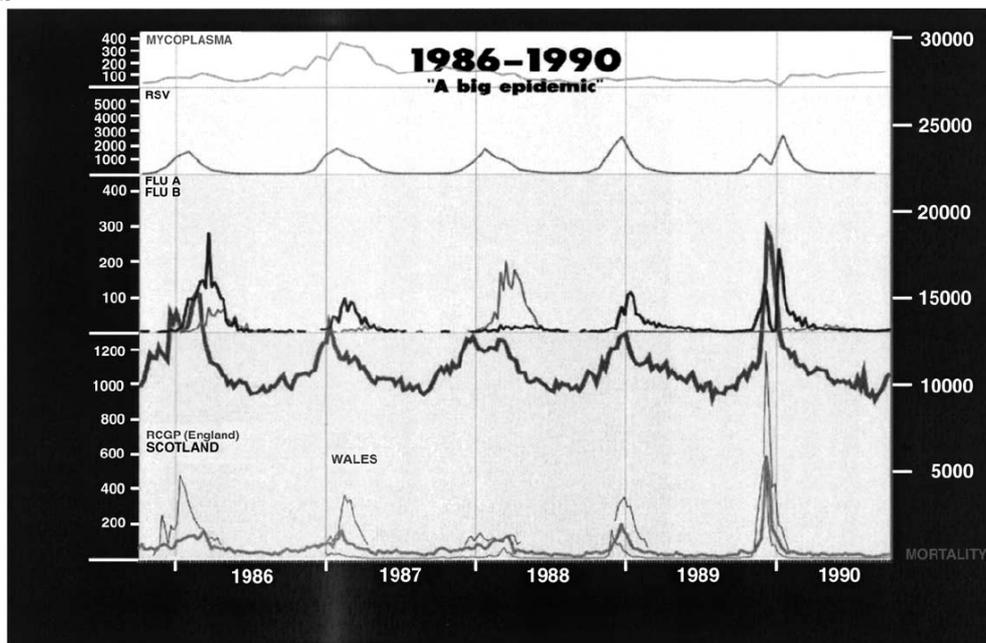


Fig. 1. Mycoplasma reports, RSV reports, influenza A and B reports, deaths (all causes), clinical incidence data for influenza-like illness (RCGP England, Scotland and Wales) by week 1986-1990 (figure supplied by PHLS London).

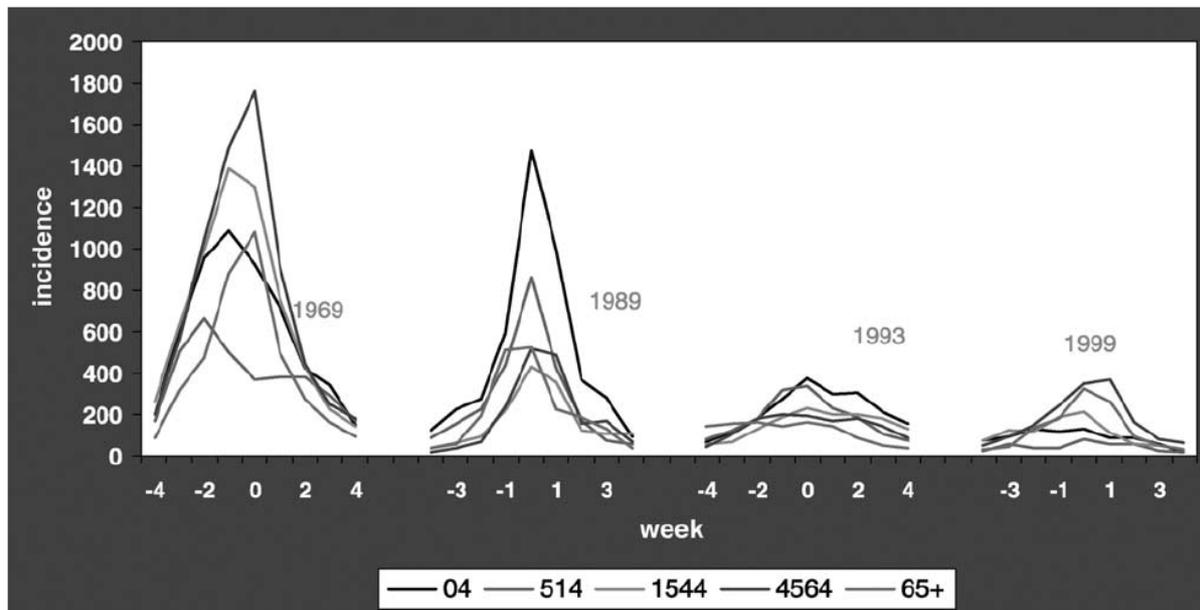


Fig. 2. Incidence of influenza-like illness in 9 weeks surrounding epidemic peak: 1969, 1989, 1993 and 1999.

REFERENCES

- [1] Smith W, Andrews CH, Laidlaw PP. A virus obtained from influenza patients. *Lancet* 1933;ii:66–8.
- [2] Pfeiffer L. Die aetiologie der influenza. *Z Hyg Infectiouskr* 1893;13:357–86.
- [3] di Camugliano GN. The chronicles of a Florentine family. London: Jonathan Case; 1933. p. 1200–470.
- [4] Francis T. Vaccination against influenza. *Bull World Health Org* 1953;8:725–41.
- [5] World Health Organization. Minutes of the third session of the interim commission held in Geneva, 31 March to 12 April 1947. Geneva: United Nations, WHO; 1947.
- [6] Kitler ME, Gavinio P, Lavanchy D. Influenza and the work of the World Health Organization. *Vaccine* 2002;20:S5–S14.
- [7] Influenza. The Birmingham Research Unit of the Royal College of General Practitioners. *J R Coll Gen Pract* 1977;27:544–51.
- [8] Bartelds AIM, Fracheboud J, van der Zee J, editors. The Dutch sentinel practice network relevance for public health policy. Studies from the continuous morbidity registration sentinel stations of the Netherlands. Utrecht: Netherlands Institute of Primary Health Care (NIVEL); 1989. p. 60.
- [9] Campbell DM, Paixao MT, Reid D. Influenza and the ‘spotter’ general practitioners. *J R Coll Gen Pract* 1988;38:418–21.
- [10] Andrade HR, Figueredo MV, Oliveira MG, Paixao MT, Falcao JM. Influenza during the years 1991–1992 and 1992–1993. Results of epidemiological surveillance. *Saude Numeros* 1993;8:17–21.
- [11] Hannoun C, Dab W, Cohen JM. A new influenza surveillance system in France: the Ile-de-France ‘GROG’. 1. Principles and methodology. *Eur J Epidemiol* 1989;5:282–93.
- [12] Snacken R, Lion J, Van Casteren V, et al. Five years of sentinel surveillance of acute respiratory infections (1985–1990): the benefits of an influenza early warning system. *Eur J Epidemiol* 1992;8(4):485–90.
- [13] Perez-Brena P P, de Miguel C, Ordobas M, et al. Sistema de vigilancia para el estudio de la circulacion gripal en Madrid Durant el quiqenio 1986–1991. *Med Clin (Barc)* 1994;102:401–6.
- [14] Fleming DM, Zambon M, Bartelds AIM, de Jong JC. The duration and magnitude of influenza epidemics: a study of surveillance data from sentinel general practices in England, Wales and The Netherlands. *Eur J Epidemiol* 1999;15:467–73.
- [15] Nguyen-Van-Tam JS. Epidemiology of influenza. In: Nicholson KG, Webster RG, Hay AJ, editors. *Textbook of influenza*. Oxford: Blackwell Science; 1998. p. 181–206.
- [16] Zambon MC, Stockton JD, Clewley JP, Fleming DM. Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. *Lancet* 2001;358: 1410–6.
- [17] Van Casteren V, Leurquin P. Eurosentinel: development of an international sentinel network of general practitioners. *Methods Inf Med* 1992;21:147–52.

- [18] Fleming DM, Cohen J-M. Experience of European collaboration in influenza surveillance in the winter of 1993–1994. *J Public Health Med* 1996;18(2):133–42.
- [19] Snacken R, Bensadon M, Strauss A. The CARE Telematics Network for the surveillance of influenza in Europe. *Methods Inf Med* 1995;34:518–22.
- [20] Paget WJ, Meerhoff TJ, Goddard NL. Mild to moderate influenza activity in Europe and the detection of novel A (H1N2) and B viruses during the winter of 2001–2002. *Eurosurveillance* 2002;7(11): 147–57.
- [21] Shortridge KF. Influenza—a continuing detective story. *Lancet* 1999;(Suppl IV):29.
- [22] Fleming DM. Influenza diagnosis and treatment: a view from clinical practice. *Philos Trans R Soc Lond B* 2001;356:1933–43.
- [23] Borriello SP. Science medicine and the future. Near patient microbiological tests. *BMJ* 1999;319:298–301.
- [24] Fleming DM. A perspective from general practice on selected influenza topics: near patient tests, influenza in pregnancy, influenza in children. In: Potter CW, editor. *Influenza*. Amsterdam: Elsevier; 2002. p. 123–44.