Influenza diagnosis and treatment: a view from clinical practice

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Influenza is a descriptive term for respiratory epidemic disease presenting with cough and fever. Influenza viruses are probably the most important of the pathogens that cause this condition. Clinical influenza occurs almost every winter in England and Wales and the outbreaks last 8–10 weeks. In recent years, influenza B virus outbreaks have occurred in January and February, whereas influenza H3N2 virus outbreaks have generally started long before Christmas. Influenza H3N2 virus outbreaks pressurize health service resources in winter more than influenza B viruses, that do not have the same impact in elderly people. Infections with influenza H1N1 viruses are also usually less severe in their impact than those with influenza H3N2 viruses, but, unlike influenza B viruses, influenza H1N1 viruses have a pandemic potential along with influenza H3N2 viruses. A diagnosis of respiratory infection in primary care is based on the presenting symptoms set within the context of the current pattern of consultations of patients with similar illness. Measurement of temperature, inspection of the throat and examination of the chest or ears add a little to the diagnostic process, but in general these procedures do not help in identifying the organism. However, if it is known that influenza viruses are circulating in the community, the probability of influenza as the cause is greatly increased, as was shown in clinical trials of neuraminidase antivirals. Maximum confusion occurs when respiratory syncytial virus (RSV) and influenza co-circulate. Although RSV infection can occur throughout the winter in young children, it assumes more of an epidemic character just before Christmas in children and possibly in adults just after. During seven of the last 20 winters, influenza has been prevalent around Christmas/New Year. In routine virological surveillance of influenza-like illness in the community during the winters of 1997, 1998 and 1999, *ca.* 30% of swab specimens yielded influenza viruses and 20% RSV. Given the limitations for routine surveillance, including variations in the interval between illness onset and specimen capture, the quality of swab, delays in transport, the growth properties of virus culture methods, etc., these figures probably underestimate the impact of both viruses in the community. The impact of influenza is considered against the background of total respiratory infections presenting to general practitioners over the last 10 years and some comparisons are made with the 1969 pandemic experience. Lessons relevant to pandemic planning are drawn. Current options for investigation and treatment are compared with those available in 1969. These include near-patient tests for assisting with diagnosis, widespread use of vaccination as a preventive in patients at increased risk, the availability of amantadine and the newer neuraminidase inhibitor antivirals and changes in the delivery of health care. Major advances in the understanding of influenza and improvements in investigation and treatment have taken place over the last 30 years. However, there are many obstacles before these can be translated into effective management of influenza sufferers and control of major epidemics.

Keywords: influenza; pandemic; neuraminidase; surveillance; vaccination

1. INTRODUCTION

‘From the country doctor’s point of view nothing alters the character of his work with the possible exception of a measles epidemic, in the same way as this disease, for an influenza epidemic may transform a busy but orderly existence into a nightmare’ (Pickles 1984, p. 30).

The onset of an influenza epidemic is not difficult to recognize in general practice. However, the correct diagnosis of virological influenza is not so easy. Throughout winter, many persons present in general practice with respiratory illness caused by pathogens (mostly viral) other than influenza. The problem is compounded by the

confusion surrounding the word ‘influenza’. It has a long history and has been clinically assigned to epidemics of cough and fever since at least the thirteenth century (Di Camugliano 1933), but the first influenza virus was only identified in 1933 (Smith *et al.* 1933). Many other viruses are now known to have caused a similar clinical syndrome.

Three issues are considered here from the perspective of a prescribing doctor: the impact of influenza as measured in the consulting population with particular reference to the 1969 pandemic, the diagnosis of influenza and the practical issues surrounding effective treatment. Pandemics are infrequent. However, influenza occurs

Figure 1. Average incidence of ARI (in children of 0–4 years per 100 000) over the winters of 1989–1999 with an adjustment excluding weeks when influenza viruses were circulating. Estimated excess incidence.

Figure 2. Average incidence of ARI (in children of 5–14 years per 100 000) over the winters of 1989–1999 with an adjustment excluding weeks when influenza viruses were circulating. Estimated excess incidence.

Figure 3. Average incidence of ARI (in adults of 15–44 years per 100 000) over the winters of 1989–1999 with an adjustment excluding weeks when influenza viruses were circulating. Estimated excess incidence.

every year and even mild epidemics seriously disrupt the normal running of our health services. In recent years, influenza has been associated with an average of 12 500 excess deaths each winter (Fleming 2000).

2. THE IMPACT OF INFLUENZA

(a) *Acute respiratory infections*

For the purpose of this report, winter extends from week 40 (beginning of October) to week 20 (mid-May), which covers the period of influenza surveillance programmes in European sentinel practice networks (Fleming & Cohen 1996). The term acute respiratory infection (ARI) embraces all new episodes of acute

Figure 4. Average incidence of ARI (in adults of 45–64 years per 100 000) over the winters of 1989–1999 with an adjustment excluding weeks when influenza viruses were circulating. Estimated excess incidence.

Figure 5. Average incidence of ARI (in adults of 65 years and over per 100 000) over the winters of 1989–1999 with an adjustment excluding weeks when influenza viruses were circulating. Estimated excess incidence.

respiratory illness that are believed to be caused by infection. Thirty per cent of ARIs in children are attributable to lower respiratory tract illness, whereas in older adults (aged 65 years and over) the proportion of lower respiratory tract infection (66%) is twice that attributable to upper respiratory tract infection (Fleming *et al.* 1993). In this age group, 50% of cases are diagnosed as acute bronchitis.

The average incidence of ARI in children of 0–4 years during winter weeks in the 10 year period 1989–1998 that was reported to the sentinel network of the Royal College of General Practitioners (the Weekly Returns Service) is compared with the average derived after excluding weeks when influenza viruses were known to be circulating (figure 1). (Details of the method have been published elsewhere in Fleming *et al.* (1999)). The data are presented as 3 week, moving averages in order to smooth anomalies associated with the Christmas/New Year holiday periods. Incidence data for ARI in children of 5–14 years and in adults of 15–44 years, 45–64 years and 65 years and over are similarly presented in figures 2–5, respectively. The average weekly numbers of deaths (all ages by date of registration) are also presented in figure 5.

These graphical presentations provide particular insights into the impacts of influenza, that are summarized here.

- (i) The burden of ARI in pre-schoolchildren is not substantially different regardless of whether influenza is circulating or not. It is particularly large in weeks

46–50 (December), which is a period of known high circulation of respiratory syncytial virus (RSV).

- (ii) The incidence of ARI in schoolchildren (5–14 years) peaks during every half term in winter (typically weeks 44–50, 1–7, 8–14) and falls at Christmas and Easter. These data imply that school closure substantially limits the spread of ARI. The average impact of influenza was particularly noticeable in the weekly periods of weeks 40–44 before Christmas and in weeks 4–8 in the New Year. These peaks reflect the average over the last decade in which influenza H3N2 virus epidemics have predominated before Christmas and influenza B virus epidemics have predominated in February.
- (iii) The impact of influenza in adults (15–44 years) averaged over the 10 years is discernible throughout the winter. It is equally strong from November through to February. Although this age group is clearly affected by both A and B viruses, there is no evidence for the half-term cycle seen in schoolchildren.
- (iv) The overall impact of influenza in adults of 45–64 years is similar in magnitude and seasonal impact to that in the 15–44 years age group.
- (v) The first notable feature in adults of 65 years and over is the similarity of the weekly trend for deaths. (The dip in deaths recorded in week 52 reflects the closure of registrar offices over the Christmas/New Year period.) This trend has been previously demonstrated for the years 1986–1990 and is now confirmed in these extended and more recent data. Respiratory illness and mortality peak in the first week of the year regardless of ambient temperature and regardless of whether or not influenza is circulating. The relative impact of influenza at that time of the year is comparatively small, but the background level of respiratory infections is twice that in November or April.

There are many important messages with regard to the management of the winter pressures on the health service (Hanratty & Robinson 1999). Respiratory illness in the elderly is a major cause of emergency admission. It calls for long bed occupancy and puts pressure on intensive care facilities. The background rate of respiratory infection at the turn of the year is so consistently high that, however intensive the influenza vaccination campaign or however low the level of influenza activity, there will always be pressure on both primary and secondary care resources. During the first 3 weeks of the year it is worth considering the deliberate restriction of planned surgical admissions for non-emergency procedures involving intensive care facilities. Concentration on minor and day surgery procedures at this time might represent the most sensible use of surgical resources. In planning for a pandemic it is necessary to structure the plan in relation to differing seasons of the year.

In an average winter, pre-school children presented 78 939 episodes per 100 000 population: 4069 of these episodes are attributable to influenza, accounting for 5.2% of all ARIs in this age group (table 1). The data for all ages combined discloses 25 493 episodes of ARI per 100 000 population, 2205 of which are attributable to influenza. The maximum attributable proportion was

found in the 5–14 years age group (10.8%). Applied to the population of England and Wales, these rates are equivalent to 13.37 million episodes of ARI presenting for care in an average winter, of which 1.16 million are attributable to influenza. Translating these rates to the experience of a typical general practitioner with a registered list of 2000 patients, one would expect *ca.* 550 episodes of ARI, 50 of which are attributable to influenza. The patient registered list includes 130 pre-school children and 320 persons over 65 years: these groups presented 100 and 68 episodes of ARI, respectively (five of which are attributable to influenza in each age group).

(b) *Influenza-like illness*

Influenza-like illness (ILI) is the most sensitive indicator of true influenza activity among the diagnoses that make up the ARI total. In recent years, the incidence of ILI that has been recorded in practice sentinel networks has been consistently associated with increased virus isolation from swab specimens collected in the community and has provided a reliable monitor of influenza activity (Fleming & Cohen 1996; Fleming *et al.* 1999). Outbreaks of ILI occur almost every winter, usually lasting 8–10 weeks, but are highly variable in timing and magnitude (Fleming & Cohen 1996).

The rates of ILI over the 34 years of surveillance of the Weekly Returns Service peaked before the New Year in only 6 years, whereas they peaked over the Christmas/New Year period in 11 years (weeks 49–2). Influenza A viruses (H3N2 or H3N1) were responsible for all outbreaks in which the peak incidence occurred before week 2 in the New Year. A particular virus predominated in most outbreaks, although it is not unusual to isolate more than one strain in the same winter. Influenza B followed influenza H3N2 in 1996–1997 and there was also an influenza H3N2 virus outbreak over the Christmas period in 1998–1999. The incidence by age in these two epidemics is contrasted in figure 6. The 5–14 years age group was relatively spared in both holiday periods, but many children consulted with ILI in early January in 1997–1998, whereas this was not the case in 1998–1999. Similar incidence patterns were observed in the Dutch sentinel practice network (Fleming *et al.* 1999). These findings suggest that the children missed the influenza H3N2 outbreak because they were not at school, but that, when they returned in January, they were caught up in the influenza B epidemic that followed. The experience in the outbreak of 1999–2000 was very similar to that of 1998–1999, where schoolchildren were also comparatively spared.

The impact of influenza in the elderly and the pressures on hospital resources deflect attention from the significance of influenza in children. The average weekly incidence of ARI and selected diagnoses in children over the 10 years 1989–1998 is superimposed graphically in figure 7 as 3 week moving averages per 100 000 children of 0–4 years. A similar presentation is made for children of 5–14 years in figure 8. Respiratory infections diagnosed as ILI are a comparatively small part of the total respiratory infections, but appreciable increases are evident in all diagnoses contributing to the ARI total. The relationship of otitis media to ILI and to all other respiratory infections is particularly significant. There are two pre-school

Figure 6. Incidence of ILI (per 100 000) by age group in 1996–1997 (left) and 1998–1999 (right).

Table 1. Persons presenting with ARI per 100 000 population of England and Wales: average percentage of ARI attributable to influenza during the winters of 1989–1999.

age group	cumulative incidence			persons in England and Wales	
	ARI	attributable to influenza	% attributable to influenza	ARI	influenza
0–4 years	78 939	4069	5.2	25.64	1.32
5–14 years	32 468	3492	10.8	22.06	2.37
15–44 years	20 714	1696	8.2	45.56	3.73
45–64 years	18 493	1603	8.7	22.38	1.94
65+ years	21 346	1622	7.6	17.69	1.34
all ages	25 493	2205	8.6	133.65	11.56

Figure 7. Incidence of respiratory illnesses by week averaged over 10 winters from 1989–1990 to 1998–1999 in children of 0–4 years (per 100 000).

Figure 8. Incidence of respiratory illnesses by week averaged over 10 winters from 1989 to 1998 in children of the 5–14 years age group (per 100 000).

Figure 9. The age-specific clinical incidence of ILI reported in the Weekly Returns Service in the influenza epidemic periods in 1969–1970, 1989 and 1999–2000.

children diagnosed with a common cold for every one with otitis media, regardless of the time of winter (Royal College of General Practitioners 1999).

As was shown earlier (table 1), the relative proportion of the ARI total that is attributable to influenza infection is less in pre-school children than in adults. A number of factors are relevant. First, adults are less likely to consult with minor respiratory infections. Second, young children develop a sharper febrile response to respiratory infections and this provides an increased pressure for consulting. Third, young children are susceptible to more respiratory pathogens than adults and this is particularly the case for RSV. Fourth, doctors may be rather more resistant to diagnosing influenza in young children, particularly at an age before they can articulate their own symptoms. Data from the Public Health Laboratory Service regarding virological investigation of ARIs in hospitalized patients over the years 1991–2000 show that, for every influenza virus isolated in children under 5 years of age, there were 30 RSV infections reported. Community-sampled specimens for the same age group have shown approximately twice as many RSV isolations as influenza viruses (Zambon *et al.* 2001). By implication therefore, either RSV is a much more serious disease than influenza in children or influenza is not investigated to the same extent in hospitalized patients. A number of reports have drawn attention to the importance of influenza as a cause of respiratory illness in young children (Glezen *et al.* 1997; Izurueta *et al.* 2000; Neuzil *et al.* 2000). In a clinical trial of oseltamivir in children, the influenza positivity in patients recruited on clinical grounds was found to be 65% (Whitley *et al.* 2001). All these factors point to the conclusion that doctors do not recognize or certainly do not diagnose influenza in children as they do in adults.

3. THE PANDEMIC INFLUENZA OF 1969

Pandemic influenza essentially refers to a global epidemic of influenza that occurs when a new and very different strain of influenza virus emerges and spreads across the world. The twentieth century witnessed pandemics in 1918–1920, 1957–1958, 1968–1970 and, controversially, in 1946–1948 and 1977–1978. The 1918–1919 pandemic has an unenviable reputation as a killer disease and is uppermost when considering contingency plans for an anticipated pandemic. Most experts agree that another pandemic is likely (Webster 1997), but none can predict when. Whilst pandemic planning rightly remains high on the agenda, all contingency planning needs to be based on some context of risk. Planning needs to retain a sensible perspective in terms of the cost implications and considerations of interventions that are realistic now. The progress in medicine over 10 years is formidable and it is difficult to conjecture beyond a further 10 years. The pandemic of 1969 represents a once in 50 years event rather than a once in 500 years event and this is therefore a reasonable base for contingency planning. The learning opportunity provided by the 1969 experience is considered here.

The Weekly Returns Service was established in the mid-1960s. The highest rates of influenza in its 34 year history were recorded in the winter of 1969–1970, a

period equivalent to the professional lifetime of doctors still in practice. It was due to an influenza H3N2 virus that was first isolated in July 1968 and first diagnosed in Europe in September 1968 (Potter 1998) and in England in December 1968: it continued to circulate for 2 years. The age-specific clinical incidence of ILI reported in the Weekly Returns Service in the influenza epidemic periods in 1969–1970, 1989 and 1999–2000 (figure 9) shows that influenza spreads through the community in all age groups simultaneously. The age-specific peaks were reached within 1 week of each other. These three epidemics show contrasting age-related patterns. In 1969–1970, the age groups maximally affected were 45–64 years and 15–44 years, in 1989 it was the 0–4 years and 5–14 years age groups and in 1999–2000 it was the 45–64 years and 65 years and over age groups. In 1989 the incidence of otitis media during the influenza outbreak period in children of 0–4 years was more than double that of influenza and the 5–14 years age group also exceeded it. In all other epidemics, acute otitis media was increased during the period of influenza activity, but 1989 was unique in this reverse relativity. In 1999–2000, the incidence of acute bronchitis in persons over 65 years reached a level four times that of ILI, although we do not know how much of that was attributable to influenza virus infection.

Experience of these three epidemics carries a range of lessons for pandemic planning. In 1989, the major problem was illness in the workforce; a pandemic that followed the pattern of 1989 would present the biggest problems in children (high pressure on out of hours care for children) and the pattern of 1999 would put maximum pressure on hospital beds.

The cumulative incidences of ILI and ARI reported during a 9 week period surrounding the peaks of the epidemics of 1969–1970, 1989 and 1999–2000 are presented in table 2. The estimates for ILI are equivalent to 5.6 per 100 population in 1969, 2.0 per 100 population in 1989 and 1.5 per 100 population in 1999: the equivalent estimates for ARI (regardless of diagnosis) were 12.0, 9.7 and 7.1 per 100, respectively. A rate of 5.6 per 100 is equivalent to *ca.* 3.1 million people in England and Wales and 12.0 per 100 to 6.6 million people. These numbers are suggested as those for which pandemic planning should prepare, although it is recognized that many more persons would seroconvert during a pandemic.

The maximum weekly incidence rate in 1969 was 1250 per 100 000 with ILI and 2040 with ARI, which is equivalent to 687 000 and 1 122 000 persons presenting to general practitioners in England and Wales. (25 and 41 per doctor with a list of 2000 patients). The current average contact frequency for all conditions in general practice is equivalent to *ca.* 450 000 contacts per week (160 per general practitioner with a registered list of 2000 patients). Home visits and emergency out of hours consultations are disproportionately increased during epidemics of ARI. Whereas home visits and emergency out of hours consultations currently account for *ca.* 7% of total consultations, this figure may easily rise to 20% in the pandemic situation. Contingency planning might involve the deferment of routine care by the extended use of repeat prescriptions, thus releasing consultation time in general practice surgeries. However, the need for home

Table 2. The cumulative incidence of ARI and of ILI reported during a 9 week period surrounding the peaks of the epidemics of 1969–1970, 1989 and 1999–2000.

	1969			1989			1999–2000		
	ARI	ILI	ILI %ARI	ARI	ILI	ILI %ARI	ARI	ILI	ILI %ARI
0–4 years	20 311	5408	27	35 484	4426	14	16 760	740	4
5–14 years	11 375	3432	30	13 397	2502	19	5474	406	7
15–44 years	11 147	6140	55	6972	1532	22	5174	974	19
45–64 years	11 868	6024	51	7068	1824	26	7208	1528	21
65+ years	9000	3863	43	8477	1891	22	8492	1154	14
all ages	11 986	5645	47	9663	1956	20	7092	1045	15

visits and emergency care would be critical. The training, empowerment and deployment of nurses for treating patients with ARI would be a sensible contingency arrangement.

4. ADVANCES SINCE 1969

There has been much international effort devoted in recent years to contingency planning for a pandemic (Leese & Tamblyn 1998). Perhaps we underestimate the importance of optimum management of the usual and average winter outbreak. High quality surveillance, reliable information for the public and greater flexibility of working practices are all part of an evolving strategy in relation to influenza management.

Advances over the last 30 years have occurred in the areas of diagnosis, prevention and treatment. These will be considered here with specific reference to their application in a routine winter epidemic situation, although the implications for a pandemic situation are equally relevant.

(a) *Diagnosis*

For the purpose of clinical management, influenza is diagnosed on clinical grounds. Clinical trials of neuraminidase inhibitor antiviral drugs achieved a diagnostic accuracy ranging from 53 to 78% (Monto *et al.* 1999). These rates were achieved when investigating patients presenting with classical symptoms and when influenza viruses were known to be circulating. In routine clinical practice, swabs taken from patients with clinical ILI presenting throughout the winter weeks have yielded *ca.* 30% positivity for influenza and 20% for RSV (Zambon *et al.* 2001).

During weeks of obvious influenza activity the influenza positivity rate (as measured by a polymerase chain reaction) in specimens obtained from community-dwelling persons during the four winters of 1996–1997, 1997–1998, 1999–2000 and 2000–2001 was higher than at other times (table 3). These swabs are taken from patients regardless of the duration of illness and higher positivity would be expected if samples were taken exclusively from patients in the early stage of the illness. Most of the positive swabs occurring outside the weeks of obvious influenza activity are found in the 1 or 2 weeks immediately before or afterwards. The positivity rates for RSV are *ca.* 20%, but positivity is higher outside the influenza peak periods. The influenza positivity rates are

Table 3. Positivity rate by a polymerase chain reaction for influenza and RSV in specimens submitted to Royal College of General Practitioners/Public Health Laboratory Service surveillance by influenza activity in five winters.

(The peak periods were weeks 45–3 in 1995–1996, weeks 49–9 in 1996–1997, weeks 6–13 in 1997–1998, weeks 40–6 in 1999–2000 and weeks 5–9 in 2000–2001.)

influenza activity	number of swabs	influenza positive (%)	RSV positive (%)
peak	1912	48	16
off-peak	1565	17	24
total	3477	34	19

higher than RSV in all age groups except in pre-school children. These swabs are taken from patients with a bias towards those with ILI as opposed to other respiratory syndromes and, if patients with acute bronchitis were more intensively investigated, RSV might be found more commonly (Crowcroft *et al.* 1999). Virological data from routine surveillance may influence judgement about the probability of an illness being caused by influenza. However, illnesses caused by influenza and RSV cannot be distinguished clinically and in many winters influenza and RSV are prevalent at the same time. There is a need for these two conditions to be distinguished since there are no treatments covering both conditions.

(b) *Near-patients tests*

Near-patient tests (NPTs) offer a potential rather than practical answer to the diagnostic dilemma. Several NPTs for influenza are available, although there remain several issues that currently limit their value.

(i) *Which test?*

Some NPTs only examine A or B viruses, whereas others examine both. If information from routine surveillance suggests that only one virus is circulating, then a specific test could be used. NPTs vary in their performance characteristics, but most have only been fully evaluated in circumstances where a laboratory-based person or specifically trained operative has undertaken the test. The requirements of a test for surveillance may differ from those appropriate to pre-treatment screening. For a

practising general practitioner, the emphasis will be on the reliability of a negative result in order to justify withholding treatment. Though specificity (and negative predictive value) varies between differing commercial tests and between reported studies, the specificity levels are not sufficiently high to feel confident about a negative result. A test for excluding a competitor diagnosis might be considered. A negative NPT for RSV with a high specificity and positive predictive value will provide a reasonable basis for deciding against influenza treatment. NPTs with these characteristics are available and their use has been demonstrated, but only in acutely ill, hospitalized children using nasopharyngeal aspirates. There is the further problem of patients experiencing dual influenza and RSV infections (Drews *et al.* 1997). Some tests have shown variation at the level of interpretation even by trained laboratory staff and these would be unsuitable for use in primary care.

(ii) *Which patient?*

The high influenza positivity rate in subjects recruited to clinical trials of neuraminidase antivirals suggests that the added value of NPT investigation in these cases is too small to justify their use. The same is probably true for immediate contacts of such patients.

During influenza epidemics there are substantial increases in patients consulting with less specific respiratory illnesses who may be diagnosed with otitis media or acute bronchitis or even a common cold. It would be helpful to know whether these patients have an illness due to influenza. Specimens from these patients have not been evaluated using NPTs. One would expect to find many fewer positives.

(iii) *Which specimen?*

Combined nose and throat swabs are generally used in most community-based European influenza surveillance networks and have been found to be generally acceptable. Some studies have shown a clear preference for nasopharyngeal aspirates as the specimen of choice for influenza, but there are widely diverging opinions. Nasopharyngeal aspiration is generally considered a distressing investigation and it is unlikely to receive widespread acceptance in the community (Heikkinen *et al.* 2001). In the hospital setting, nasopharyngeal aspirates are commonly taken from young children by nurses: the mother is not required to hold the baby.

The quality of specimens has been found to be a critical factor. Specimen capture in primary care will inevitably involve capture by persons relatively inexperienced in the technique. Tests dependent on a relatively high viral load, even though they may have a better performance, may thus be not as useful generally as tests with a poorer performance in optimal conditions.

(iv) *What cost?*

The major cost of health care for influenza is that of general practitioners' consultation time, i.e. 8 min per consultation. Based on an estimate of 4.2 consultations per patient per annum, the cost of general medical services equates to *ca.* £22 per consultation. Noyola *et al.* (2000) analysed the costs related to the use of the Zstat NPT and proposed a sum of £24 (\$35) as appropriate for

reimbursing a doctor for undertaking an NPT (cost of test kit included). This estimate assumes that the test will take 5 min, but makes no assumption about the time involved in explaining the need for the test or the time involved in collecting the specimen from the patient. It is based on typical consultation experience in the USA, where consultation times are longer and laboratory investigations more widely accepted than in the UK. The assessment does not consider the availability of a nurse or a technician for undertaking the test. Pressures on primary care are substantial during influenza outbreaks and primary care does not retain a reserve capacity of skilled and available persons. The Zstat test involves a wait of 30 min before reading the result. A follow-up consultation for considering the result is thus needed, particularly if the test is negative. Furthermore, the patient needs to sit in a waiting room where they might transmit the infection.

(v) *How will NPTs be reimbursed?*

General practice-based medical services are largely funded by capitation supplemented by a limited number of items of service payments. These payments involve administrative machinery with costs in time and money, that are sometimes disproportionate to the value of the item. Immunization and cervical cytology services are now reimbursed in relation to evidence of global target achievements and not individual payments. There is currently no administrative machinery for reimbursing the costs of investigations undertaken in general practice offices. Increased administrative tasks provide a powerful deterrent to innovation in general practice.

For all of these reasons, NPTs have only a limited practical application for routine use prior to treatment. However, there may well be a case for one practice in a primary care group being resourced for undertaking NPTs in order to assist with local surveillance. This would be complementary to and not a substitute for current virological surveillance by culture.

(c) *Vaccination*

Vaccination against influenza is targeted at populations at increased risk rather than the entire population, largely because annual vaccination is necessary. The targeted population in the UK includes those at risk because of comorbidity and all patients aged over 65 years. This age-related target has been reduced to 50 years in the USA. There is little doubt that influenza vaccination is sufficiently safe and effective in immune-competent persons that clinical effectiveness against influenza can be demonstrated in all such populations. Influenza epidemics continue to be associated with excess mortality in England and Wales. In the pandemic of 1969–1970 it was estimated at 28 000 (Tillett *et al.* 1983) and in 1989 it was estimated at 25 000 (Curwen *et al.* 1990; Fleming 2000). The epidemics of 1996–1997 and 1999–2000 were associated with almost as many excess deaths (27 600 and 18 500, respectively) (Fleming 2000), but the mortality was more concentrated in the elderly. The apparent paradox of high mortality in spite of increasing vaccination uptake is explained by the ever-increasing age of deaths. The immune response to vaccination declines with great age (Webster 2000) and some

sufferers die in spite of vaccination. Vaccination campaigns and a high vaccination uptake will not necessarily reduce the total pressure on hospital beds during influenza epidemics. The pressure will just come from an ever-older age group, a group who present particular problems at the point of discharge from hospital.

There is a necessary time-gap before a vaccine can be developed should a pandemic emerge. However, the 1969 experience and even that of 1918 showed that there was a considerable lead time between the emergence of the novel pandemic virus and major spread in the community. This gives some encouragement to the prospect of vaccine development within an acceptable time-frame.

The development of influenza vaccines for intranasal administration is likely to encourage a greater acceptance of vaccination amongst persons who are currently deemed at increased risk because of influenza, but, more importantly, will sharpen the debate with regard to the vaccination of children (Belshe *et al.* 1998; McIntoch & Lieu 2000).

(d) *Antiviral prophylaxis*

Amantadine was first introduced as a prophylactic against influenza infection in 1966 (Aoki 1998) and only later as a treatment. It remains an inexpensive and effective prophylactic. Use in the most elderly is limited because of neurological side-effects and problems with impaired renal function. There have not been problems with resistant viral strains where persons have received it prophylactically prior to exposure. The prophylactic use of amantadine in key workers should be considered for both long-term seasonal and immediate post-vaccination prophylaxis in the event of a pandemic or a comparatively new virus influenza A strain appearing.

The neuraminidase inhibitor antivirals have also been shown to be effective in prophylaxis. They do not have the same potential as amantadine for the development of resistant strains and their side-effects are much less. However, they are much more expensive. They are certainly preferable to amantadine if influenza B co-circulates with influenza A and are preferable in situations of post-exposure prophylaxis.

(e) *Antiviral treatments*

Amantadine (rimantadine) and the neuraminidase inhibitor antivirals have been shown to be clinically effective as treatments when given early after symptom onset. The neuraminidase inhibitor antivirals have a better safety profile, are effective against influenza B as well as influenza A and are not associated with the development of pathogenic-resistant strains. For all of these reasons, neuraminidase inhibitor antivirals are preferable to amantadine as treatments.

Clinical trials have demonstrated benefits that are comparatively small if the illness is mild but more substantial in severe illness and in illness in patients over 50 years (Fleming *et al.* 2000). This latter group of persons should be treated on the evidence available. Influenza can be a serious and even a fatal illness. It would be unjustifiable to withhold treatment from a person judged to be severely ill consulting within 48 h of symptom onset. The benefits of treatment in comparatively mild cases of influenza are small and, where treatment is not directly

financed by the sufferer, there are legitimate questions about its value. However, there is evidence that early treatment reduces the risk of spread. From the perspective of clinical practice, this will be justification for treatment in many cases. As was argued earlier, the impact of influenza in young children is under-recognized: early treatment of influenza in the parents of young children should be considered even if the illness is mild.

The neuraminidase inhibitor antivirals were not available in 1969. Their availability now considerably reduces anxieties about pandemics. However, a large manufacturing capacity will not be available as an emergency response. If the benefits of neuraminidase inhibitor antivirals are to be obtained during a pandemic, these drugs must be used in interpandemic outbreaks.

(f) *Primary health care delivery*

There have been enormous changes in primary health care since the inception of the National Health Service in 1948. In 1947, there were few true treatments and medical care in general practice was often concerned solely with the amelioration of symptoms. By 1969, general practitioners were gradually gaining direct access to laboratory facilities for haematology, microbiology and radiography; hitherto, these services were only available via specialist referral. Though preventive care in the field of hypertension was edging forward, the bulk of consultation activity was still concerned with acute episodes of illness. Patients either simply turned up at surgery premises during published hours or requested a home visit. The general practitioners responded to the demand that was set before them: there were no deputizing services and National Health Service Direct (Smith 1933) did not exist. Delays were accepted as an inevitable part of the system and the thought that the outcome might be influenced by delay was not often countenanced.

The situation today is in stark contrast to that in 1969. Patients are required to make appointments and general practitioners are less flexible because the burdens of preventive care and chronic disease management are scheduled on a continuous basis with loss of reserve capacity for sudden increased demand due to epidemic diseases. Home visits are less frequent and out of hours care is delivered by deputies. Consultations for ILIs are actively discouraged.

The availability of treatment that needs to be delivered within 48 h of symptom onset provides a challenge to health care delivery. A spirit of defeatism is evident in the reaction of some doctors, but medical practice has faced many challenges and the present challenge is no more difficult than others. Doctors need to remind themselves that *ca.* 11 million doses of influenza vaccination were delivered during October/November 2000 on top of routine demands for health care.

In a review of 909 cases presenting with ILI to general practitioners in December 1999 and January 2000, there were 31 children aged 0–4 years and 24 (77%) of these presented on the first or second day of the illness, whereas of 164 persons over 65 years, only 26 (16%) presented on the first or second day (Ross *et al.* 2000). It was also shown that, among 66 children (0–14 years), 62 (94%) were seen within 24 h of appointment request and, among 668 adults, 536 (80%) were seen in this period. These

data show that patients were registering concern for their sick children and consulting early enough to benefit from treatment (even though at that stage no neuraminidase inhibitor antivirals were licensed for use in children), but adults delayed seeking care beyond the point of effective treatment. The practices responded to requests with minimal delays. If the benefits of an antiviral treatment are to be enjoyed by the public, health care-seeking behaviour needs to change. Advice to stay at home and take paracetamol would probably be deemed medically negligent if a patient had bacterial bronchopneumonia. The clinical situation of serious influenza disease is no different and consulting behaviour would need to change if a pandemic were to be managed effectively. Effective management of influenza requires patients gaining early access to appropriate treatment. The means whereby this is achieved have not been clarified in current pandemic planning, but it is clear that it will involve much more extensive use of nurses in clinical management. National Health Service Direct is here and may well have a role to play, but it is difficult to visualize that role in the context of a service that does not prescribe. The recognition of comorbidity and risk groups for vaccination cannot be directly translated into case selection for treatment. The severity of illness is critical. Persons who are most in need of neuraminidase inhibitor antivirals probably also need to be assessed clinically.

(g) *Secondary health care delivery*

The changes in secondary care between 1969 and 1999 are no less dramatic than those in primary care. Experience in the winter of 1999–2000 brought the limitations of the National Health Service into sharp focus (Hanratty & Robinson 1999), but this was not a particularly bad winter for influenza (Goddard *et al.* 2000). The outbreak coincided with the usual winter surge in cases of ARIs of which a particularly large number were diagnosed with acute bronchitis that was possibly caused by other pathogens. The big difference between 1969 and 1999 was the degree of flexibility of hospital operation. In 1969, undue pressure for medical admissions was absorbed by using all available beds in a hospital, regardless of whether they were nominally allocated to medical or surgical specialities. At that time there were also many long-stay wards in the geriatric wings of district hospitals. These could absorb acute cases where necessary.

The situation in 1999 was diametrically opposed to that in 1969. Many beds were designated to particular care programmes and geriatric wings no longer existed. Patients in residential homes in the community often needed admission because these homes could no longer provide nursing facilities. The status of a home is dependent on its nursing complement. Where professional nursing services are minimized in the interests of cost containment, there is less capacity to cope with acute illness.

As in primary care, pandemic planning for influenza calls for flexibility of the working procedures in hospitals. There will always be pressures from respiratory illness in January and these pressures will extend to intensive care facilities. Since society no longer accepts lower prioritization of care for persons simply on the grounds of advanced age, current intensive care facilities are inadequate. One way of easing the situation is to make

January a month of minor and day case surgery, as mentioned above. Emergency surgery programmes cannot be changed, but a redistribution of surgical effort away from cases likely to require admission or intensive care could be arranged. However, operational flexibility within the health service will never be sufficient for catering for all contingencies and, thus, choices in the allocation of scarce resources such as intensive care beds are inevitable. Judgements about the anticipated quality and quantity of expected life seem the only reasonable basis for making these choices.

(h) *Management guidelines*

Clinical guidelines are a feature of current health care that did not exist in 1999. Autonomy of action was recognized as a hallmark of a professional person and little regard was given to the cost consequences of decisions. That autonomy was recently reaffirmed by the guidance on the use of zanamivir published by the National Health Service National Institute for Clinical Excellence (1999). However, autonomy of professional advice is denied when guidelines effectively control the budget. There is a deep conflict between guidelines for smoothing the operation of a health service and those derived from analysis of clinical evidence. The priority presently given to the smooth operation of the health services seems more based on opinions about the impact of influenza rather than on observations over recent years. The evidence in favour of treating those severely ill and those over 50 years of age is stronger than that based on treating the high-risk population recruited to clinical trials of neuraminidase antivirals. That such persons were not included in the recent National Institute for Clinical Excellence guidelines prompts questions about the derivation of guidelines that, by implication, are based on clinical excellence. Whilst controls on expenditure are necessary if medicine is not to consume the entire budget, it is important to reflect on the fact that the cost of the influenza vaccination programme in England and Wales in the autumn of 2000 exceeded £100 million. The maximum number of persons diagnosed with ILI during an influenza epidemic period as estimated from the incidence recorded in the Weekly Returns Service is 3.1 million in the pandemic of 1969. If all of these patients consulted sufficiently early, the cost of treatment with neuraminidase inhibitor antivirals would be less than £100 million. If half the persons diagnosed with ILI in an average winter consulted early enough and were treated with neuraminidase inhibitor antivirals (£30 per treatment) the cost would be *ca.* £6.6 million.

(i) *Over the counter medication*

In 1969, aspirin or paracetamol, a high fluid intake and bed rest were the wisdom of the day and this advice was accepted by many people. How big a difference would the substitution of neuraminidase inhibitor antivirals for paracetamol make? Neuraminidase inhibitor antivirals are currently not available over the counter and this discussion is speculative. If available at a subsidized price slightly in excess (£3) of the present prescribing fee applicable to any individual, what would be the resultant effect on the health service? The subsidy could be triggered by local surveillance information and the public

then informed. Persons with a febrile illness could choose to buy the drug and treat themselves. There would be benefits in being able to receive treatment earlier and at a cost to the health service equivalent to the subsidy with a saving of the consultation. The legal machinery could be established and this proposal be examined under pre-pandemic conditions. The benefits of early treatment would be more widely available without unduly pressurizing primary care services. The spread of illness may even be checked.

The neuraminidase inhibitor antivirals are probably safer than paracetamol, but the risk of development of resistant virus strains must be considered (Tisdale 2000). This risk is present whether the medication can be purchased over the counter or is exclusively available by general practitioner prescription. It is present wherever in the world these drugs are used in the treatment of influenza. If there were evidence of resistant virus strains of pathogenic potential, the subsidy if not the opportunity for purchase would be withdrawn. Given the specificity of these drugs against influenza, their appropriate use in respiratory illness would be reinforced by individual patient experience.

5. CONCLUSIONS

- (i) The impact of influenza on respiratory infections is more than twice that recognized clinically by general practitioners as ILI.
- (ii) Effective management of the usual winter outbreak of influenza is the key to pandemic planning.
- (iii) The experience of 1969 provides a sensible basis for pandemic planning.
- (iv) Winter pressures on hospital beds are only partially due to influenza and vaccination against influenza can make only a small contribution to dealing with this problem.
- (v) The need for early treatment with antivirals presents an unresolved challenge to health service providers.
- (vi) Neuraminidase inhibitor antivirals represent an advance in influenza management but their optimal use is not yet resolved.

6. CONFLICT OF INTEREST

The author wishes to acknowledge that he has acted as a consultant to GlaxoWellcome and as an advisor to other companies on matters relating to influenza. The content of this report and the opinions expressed in it are exclusively those of the author and not those of any organization with which he is associated.

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