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New Approaches for Managing Influenza in Primary Care

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Abstract

Influenza outbreaks occur annually on a seasonal basis, usually in the winter, and are responsible for substantial global morbidity and mortality, particularly amongst patients at high risk of complications. Influenza also places a significant clinical and economic burden on the healthcare system and management is largely the responsibility of primary-care practitioners (PCPs), who are often the first point of contact for patients. Diagnosis is usually made on clinical grounds, which is 60 to 70% accurate when influenza is known to be circulating locally. Vaccination remains the cornerstone for influenza management and protects the majority of at-risk patients, but vaccine effectiveness depends on correct prediction of the circulating strain and it is reduced in immunosuppressed and elderly patients. Until recently the options for treatment of influenza were very limited, with the primary recommendations being bedrest and treatment of symptoms only. In some countries the amantadine and rimantadine antiviral drugs have been available to treat influenza for some years, but use of these agents is limited by the incidence of adverse events, rapid development of resistance, and the fact that their activity is restricted to influenza A. Zanamivir (Relenza™, Glaxo Wellcome) is the first neuraminidase inhibitor to be approved for use in the treatment of influenza A and B. Oseltamivir (Tamiflu™, F. Hoffmann-La Roche) is similarly active against influenza A and B, and in clinical trials both drugs were shown reduce the median time to alleviation of influenza symptoms by 1 to 2.5 days (zanamivir) and 1.2 to 1.3 days (oseltamivir). Both agents were well tolerated, zanamivir having a safety profile similar to placebo and oseltamivir producing mild nausea and vomiting in some patients. Zanamivir is administered by oral inhalation delivering the drug directly to the respiratory tract, and oseltamivir, a prodrug, is taken in the form of a pill. In short-term use, no resistance to zanamivir has been seen so far, while resistance to oseltamivir is reported to be 3% in adults and 8% in children, although resistant viruses have low infectivity. While vaccines will continue to be the mainstay of the influenza pre-season management programme, the advent of neuraminidase inhibitors presents a new opportunity to manage influenza within the primary-care setting and will allow PCPs to plan ahead for their increased workload during the influenza season. Education is essential to ensure that patients consult within 48 hours, and possible practical measures to reduce the PCP's workload include developing the role of nurses to make the initial diagnosis.

Influenza is a serious respiratory infection responsible for substantial global morbidity, hospitalisations and deaths. Outbreaks occur annually during the winter months in temperate regions,[1] but have less defined seasonality in tropical and subtropical climates.[2] During a typical influenza season, up to 10% of the world population may contract symptomatic influenza.[3]

The responsibility for managing influenza lies largely with primary-care practitioners (PCPs), who are normally the first points of contact for patients with symptoms. Until recently, the management options available to PCPs were vaccination of at-risk patients, symptomatic relief and, in some countries, antiviral treatment with adamantanes, such as amantadine.[3] A breakthrough in treatment occurred in 1999, when a new class of antiviral agents – the neuraminidase (NA) inhibitors – became available [zanamivir (Relenza™, Glaxo Wellcome) and oseltamivir (Tamiflu™, F. Hoffmann-La Roche)]. Currently, only zanamivir is available in the European Union. This review examines how influenza is currently managed in the primary-care setting and considers how the advent of the NA inhibitors may influence management strategies in the future.

1. The Impact of Influenza

The true extent of influenza infection is difficult to assess because it can sometimes be mild or asymptomatic.[4] More typically, however, influenza is characterised by a range of respiratory and systemic symptoms and is a debilitating disease, even for healthy adults.

Although most patients recover from influenza within 1 to 2 weeks, complications can occur, particularly in high-risk groups such as the elderly, children and patients with underlying conditions such as chronic respiratory or cardiovascular disease, chronic renal failure, diabetes, immunosuppression or haematological disorders. Complications generally involve the respiratory tract, with acute bronchitis or pneumonia observed most frequently.[5] Pre-existing respiratory diseases [such as asthma, chronic obstructive pulmonary disease (COPD) or cystic fibrosis] are also often exacerbated.[6-8] Some complications are specific to certain groups; for example, young children and infants are at risk of acute otitis media, bronchiolitis and croup.[9] Complications may result in hospital admissions or even death, usually because of primary viral or secondary bacterial pneumonia.[10]

The burden of influenza is assessed by comparing numbers of events occurring during periods of influenza infection with numbers expected outside those periods. In 1995/1996, the number of patients consulting general practitioners (GPs) for influenza in France was estimated at >2.3 million.[11] Similarly, a 30 to 50% excess in primary-care visits compared with baseline was reported in an adult population in Portland, Oregon, USA in 1969-70 and 1972-73.[12] In the UK, where consultation rates for influenza are typically low, influenza still produces dramatic increases in the number of patients consulting their PCP during the influenza season. The largest excess observed in the UK occurred in 1989, with 832 000 additional consultations – 1.6% of the population. The impact on PCPs is illustrated by data collected in England and Wales between 1989 and 1998, when an average of 422 000 additional people presented to PCPs and were diagnosed with influenza-like illnesses each year during the influenza epidemic period.[4] The incidences of acute bronchitis, otitis media, hospital admissions and deaths associated with respiratory and cardiovascular disorders also increased during the epidemic periods (table I).[4]

2. Surveillance

Influenza is caused by two Orthomyxoviridae viruses, influenza A and influenza B, the clinical symptoms of which are indistinguishable. A third influenza virus – influenza C – has also been identified, but it does not cause clinical influenza. The two major antigenic determinants of influenza A and B are haemagglutinin (HA) and NA.[13] Mutations in the genes encoding these antigens enable the influenza viruses to change their antigenic properties and evade recognition by the immune

Table I. Average yearly impact of influenza in England and Wales from 1989-1999

Patient group	Excess compared with baseline[a]
Patients consulting and diagnosed with influenza-like illness	422 000
Patients with acute bronchitis	188 408
Patients with acute otitis media	75 251
Total number of acute respiratory infections	1 087 399
Deaths	12 554
Hospital admissions for respiratory and cardiovascular disorders (65 years and over)	9 077

a Data are the average number of excess patients treated within the influenza season, compared with the expected numbers outside the season, during 10 epidemic periods from 1989 to 1999.

system, in a process known as antigenic drift. Occasionally, influenza A viruses exhibit antigenic shift, where the change in the antigens is more dramatic, resulting from reassortment of gene segments during dual infection with different virus subtypes.[14,15] This creates antigenically novel influenza A viruses, which have the potential to cause major global pandemics.[1]

Influenza surveillance involves defining the viral subtypes in circulation and monitoring antigenic drift, to enable advice to be issued on vaccine composition. It also involves the monitoring of geographic spread and measurement of the impact on the community, to assist with management and planning in the event of a pandemic. There are two parts to influenza surveillance, which have to be used together: qualitative, laboratory-based or 'virological' surveillance, and quantitative, practice-based or 'clinical' surveillance.

Virological surveillance is conducted worldwide through a network established by the World Health Organization (WHO) in 1947, which involves health authorities, 110 national influenza centres in 82 countries and four collaborating centres (in the UK, USA, Australia and Japan).[16] On the basis of the information provided, the WHO issues advice on vaccine composition in February and September of each year for the Northern and Southern hemispheres, respectively.[17] In Europe, a total of 11 EU countries and three non-EU countries are members of the European Influenza Surveillance Scheme (EISS), each country having networks of sentinel general practitioners (http://www.eiss.org/public/present.htm). In these countries clinical surveillance of influenza in primary care is generally based on reports from these networks of sentinel practices based largely on the incidence of influenza-like illnesses or acute respiratory illnesses. This clinical surveillance data is then integrated with virological analysis of specimens submitted from the community. Together they aim to detect the early rise of influenza cases. The contribution that PCPs can make to clinical surveillance through the provision of timely information should not be underestimated.

3. Symptoms and Diagnosis

Influenza typically lasts for 1 to 2 weeks and requires bed rest and time off work or school. The onset of illness is usually rapid and the most prominent systemic features include fever (>37.8°C) or feverishness, cough, malaise, headache, sore throat, coryza and anorexia.[10] Cough and fever are observed most frequently (fig. 1).[10] Patients can continue to present with symptoms of malaise and fatigue for several weeks after infection, which may affect the workload of the PCP.

Diagnostic tests can provide valuable and accurate information on whether influenza is circulating locally.[18] Viral isolation and polymerase chain reaction (PCR) are used in clinical diagnostic laboratories for diagnosis of influenza, but their primary use is in surveillance rather than as an aid to diagnosis because they are costly, labour-intensive, and require significant technical expertise.[19] Other diagnostic tests include enzyme

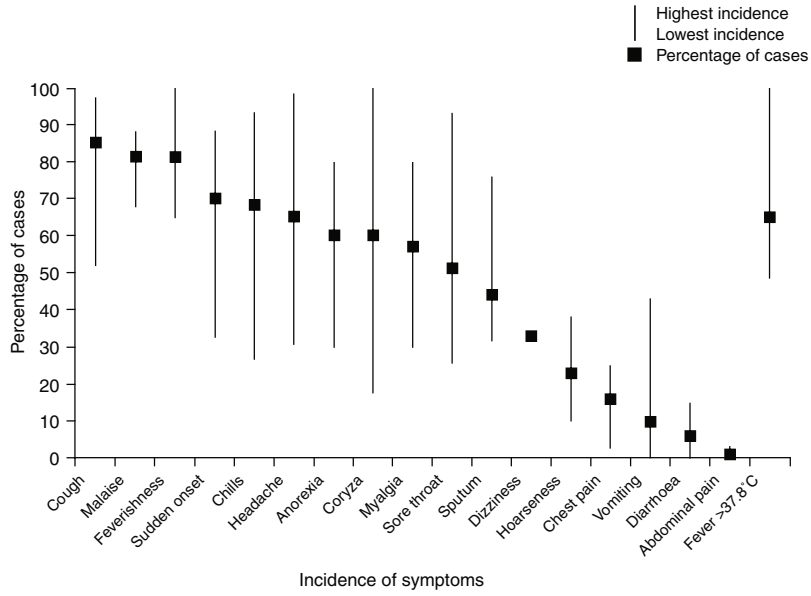

Fig. 1. Clinical symptoms of influenza. Data are overall incidence and highest and lowest incidence of symptoms from 10 studies involving 520 adults with uncomplicated influenza A (adapted with permission from Nicholson et al.[10]). For each symptom the range of percentages is shown across the 10 studies.

immunoassay (EIA) and direct immunofluorescence (DIF), but both these methods require significant time to process the samples, and whilst EIA is relatively simple to perform, DIF requires technical expertise. Thus diagnostic tests are associated with significant cost and often require considerable technical expertise. They do not currently deliver results quickly enough to direct therapy and furthermore their accuracy is generally no greater than clinical diagnosis. Diagnosis is therefore usually based on clinical symptoms and the presence of influenza in the community. Several analyses have been undertaken to identify clinical symptoms and signs that might help the PCP discriminate between influenza infection and other acute respiratory infections. When influenza is known to be circulating in the local population, clinical diagnosis based on fever plus two other symptoms (e.g. cough, sore throat, headache or myalgia) has been shown to be accurate in approximately 70% of cases.[20,21] A further study reported that fever plus cough is the best clinical predictor of influenza, with a positive predictive value of up to 79%.[22,23]

Although the range of influenza symptoms is similar in all age groups, PCPs need to be aware of certain age-specific differences.[3,10] For example, children tend to exhibit higher fever than adults, in addition to drowsiness and gastrointestinal symptoms such as abdominal pain, diarrhoea and vomiting. Influenza in the elderly is associated with a higher incidence of lower respiratory tract symptoms, such as sputum production, wheezing and chest pain.[3]

4. Pre-Season Management of Influenza

Vaccines are inexpensive, well tolerated and generally effective, and continue to be the mainstay of influenza prophylaxis. The efficacy and cost effectiveness of vaccination have been shown in healthy adults[24] and the elderly (64 to 75 years of age).[25,26] In healthy working adults, vaccination reduces the incidence of upper respiratory illness by 25% and visits to the PCP for upper respiratory

illness by 44%,[24] although recent evidence suggests that the economic benefit is not always apparent if the influenza attack rate is low or if there is a poor match between the vaccine and circulating strains.[27] It is generally recommended that those individuals considered to be at high risk of complications such as the elderly or those with chronic illnesses, nursing-home residents and professional caregivers, are vaccinated before the influenza season each year, and many countries have developed immunisation programmes in line with these recommendations.[28]

Although influenza vaccines can be highly effective, they do have certain limitations. Because of antigenic changes to the influenza virus, the vaccine composition has to be updated annually and, if the vaccine does not match the circulating virus strains closely, it provides little protection. Efficacy is also dependent on the immune response of the patient, which may be reduced to 30 to 50% in the elderly, one of the most vulnerable groups.[29] In addition, because the induced immune response begins to decline a few months after vaccination,[30] problems arise if there is a late outbreak of influenza.

Uptake of vaccination can be low for various reasons because it is often difficult to persuade patients, particularly the elderly, of the benefits. Other factors include national policies that are too timorous and a lack of awareness of the seriousness of influenza. One survey suggested that fewer than 30% of high-risk patients were vaccinated in England and Wales during the 1995-1996 influenza season.[31] Because of these limitations, in-season strategies for the management of influenza must also be available to the PCP, who plays a crucial part in increasing vaccination coverage.

5. In-Season Management of Influenza

5.1 Adamantanes

The adamantane antivirals – amantadine and rimantadine – were developed more than 30 years ago. They have been available for the treatment of influenza for many years in some countries, but are only effective against influenza A.[32] Patients receiving amantadine or rimantadine at doses of 200 mg/day have reported a number of adverse events including nausea and anorexia in 5 to 10% of patients. Other adverse events, particularly with amantadine, include central nervous system effects such as nervousness, lightheadedness, lack of concentration, insomnia, delirium, hallucinations and seizures, occurring particularly in elderly patients.[33-35] A further drawback of both amantadine and rimantadine is the rapid development of drug-resistant strains in up to 30% of patients during treatment.[36] Because of these problems, adamantanes have not been used widely in Europe.[37]

5.2 Symptomatic Relief

In practical terms, a patient presenting with the symptoms of influenza may be advised by their PCP to stay at home, take bed rest, drink plenty of fluids and take some symptomatic relief, such as aspirin or paracetamol.[3] Dealing with the resultant complications of influenza, managing patients' concerns about the duration of their symptoms and (in some countries) issuing sick notes, all affect the PCP's workload.

5.3 Neuraminidase Inhibitors

The viral surface antigens NA and HA play an essential role in influenza pathogenesis. HA is involved in the fusion of the virus envelope with the host cell membrane, while NA is critical to the release of progeny viruses from the cell surface.[3,38] The NA inhibitors are a new class of antiviral agents designed specifically to inhibit NA function and thereby prevent the release of progeny viruses from the cell.[39] They are highly selective and potent inhibitors of influenza A and B.

The first in the class to be licensed for clinical use was zanamivir. It is licensed for the treatment of influenza in patients aged 12 years or more who have been symptomatic for up to 48 hours. Another neuraminidase inhibitor, oseltamivir, has also

gained approval for the treatment of influenza in patients aged 18 years or more in a number of countries, although it is not yet licensed in the EU.

Zanamivir is administered by oral inhalation of a dry powder from a Diskhaler™ device. This route of administration targets delivery to the site of viral replication, the lungs, where the drug quickly achieves high concentrations. The onset of action is therefore rapid and systemic exposure is low.[40] In patient surveys conducted in Australia (n = 1408) and the USA (n = 13 432), 90% of those surveyed found the Diskhaler™ easy or very easy to use.[41,42] Oseltamivir has been formulated as a tablet that is well absorbed, producing peak plasma concentrations of the active metabolite oseltamivir carboxylate 3 to 4 hours after administration.[43]

5.3.1 Clinical Efficacy

A number of large, randomised, placebo-controlled trials have been conducted with zanamivir[20,21,44-46,50] in primary-care settings around the world. In all these trials, patients received the standard treatment of zanamivir 10mg inhaled twice daily for 5 days. Trials were carried out when influenza was known to be circulating and patients presenting with influenza-like illnesses started treatment within 2 days of the onset of symptoms. The primary efficacy measure was the median time from initiation of treatment until alleviation of symptoms of influenza. The severity of symptoms, use of relief medication (paracetamol and cough mixture), incidence of complications and time taken for patients to return to their normal activities were also recorded.

Two phase III oseltamivir studies[47,48] have been reported, using a standard treatment of 75mg administered twice daily for 5 days. A similar primary end-point of time to alleviation of symptoms was used in these studies – however, the two agents have not been compared directly.

With zanamivir, consistent results were seen across all clinical trials, which involved more than 4000 patients. The median time to alleviation of symptoms was reduced by up to 2.5 days compared with placebo ($p < 0.001$).[21,45,46,49] There was also a marked reduction in the severity of symptoms – for the most frequent symptom, cough, the symptom score was reduced by up to 44% ($p < 0.001$) compared with placebo.[21] In addition, patients treated with zanamivir returned to their normal daily activities up to 1.5 days earlier than those treated with placebo.[21,45,46,49]

A pooled analysis of zanamivir clinical data showed that patients aged ≥50 years, or those classified by their physician as having severe influenza at recruitment, reported a median reduction in time to alleviation of symptoms of 3 days ($p = 0.003$).[50] Furthermore, patients aged ≥50 years with severe symptoms had a much longer course of disease if untreated, and in this group zanamivir was associated with a 7-day reduction in the time to alleviation of symptoms.[51] In addition, zanamivir was associated with a 28% reduction in the use of antibiotics for complications in patients with confirmed influenza ($p = 0.006$).[50]

Studies with oseltamivir demonstrated a median reduction in the time to alleviation of symptoms of 1.2 to 1.3 days compared with placebo.[47,48] The use of relief medication and the incidence of complications were also reduced in these patients.[47,48] Patients receiving oseltamivir reported returning to their normal activities 1.9 to 2.8 days earlier than those who received placebo.[47]

Zanamivir has also been shown to be effective in individuals at high risk of complications of influenza (n = 321), reducing the time to alleviation of symptoms by 2.5 days ($p = 0.015$) and the time taken to return to normal activities by 3 days ($p = 0.022$).[52] In addition, zanamivir treatment reduced the incidence of complications requiring antibiotic use by 43% ($p = 0.045$). Oseltamivir has been shown to reduce the time to alleviation of symptoms by 1.8 days in a vaccinated population of high-risk individuals (n = 140).[53] In a study of patients with asthma or COPD, zanamivir treatment reduced the time to alleviation of symptoms by 1.5 days ($p = 0.009$) and the incidence of complications requiring both antibiotics and a change in respiratory medication by 58% ($p = 0.064$) compared with placebo.[54] Data are not currently avail-

able on the efficacy of oseltamivir in the treatment of high-risk patients.

Patient satisfaction is also improved with zanamivir. A survey of 1408 patients carried out in Australia during the 1999 influenza season revealed that 77% of the patients experienced symptom relief within 48 hours of taking zanamivir, while more than 65% returned to their normal daily activities within 72 hours of commencing treatment.[41] These responses were similar to those reported from a large survey of 13 432 patients and 896 clinicians conducted in the USA.[42] Similar studies have not been reported with oseltamivir.

5.3.2 Tolerability

The NA inhibitors have a more favourable tolerability profile than the adamantane antivirals, with fewer adverse events. Zanamivir is well tolerated, and in clinical trials has a tolerability profile similar to placebo.[55] This may be because of its high specificity for influenza A and B NA and the targeted delivery to the respiratory tract, which results in low systemic exposure to the drug.

Oseltamivir is also generally well tolerated, but nausea and vomiting have been reported to occur in up to 18% and 14% of patients, respectively, compared with 7% and 3% with placebo.[47] These adverse effects are associated with the initial administration of oseltamivir and generally resolve after 2 days. Ingesting food when taking the drug may reduce the risk of gastrointestinal adverse effects.[56]

In a large randomised study of 525 patients with asthma or COPD, zanamivir had a tolerability profile similar to placebo.[54] Zanamivir did not adversely affect pulmonary function as determined by forced expiratory volume in 1 second and peak expiratory flow rate measurements, compared with placebo. 36 (14%) zanamivir-treated patients and 53 (20%) of those who received placebo experienced at least one lower respiratory tract adverse event. Nine (3%) patients in the zanamivir group, compared with 26 (10%) patients in the placebo group, reported at least one episode of bronchitis.[54]

Precautions for use in patients with asthma or COPD were added to the product labelling following rare post-marketing reports of bronchospasm and reduced lung function in patients using zanamivir.[57] It is difficult to determine whether a causal relationship exists because influenza itself exacerbates asthma symptoms. However, it is recommended that patients with asthma or chronic lung disease keep their usual fast-acting bronchodilator available when taking zanamivir and stop taking the drug if they experience bronchospasm or a decline in respiratory function.[57]

No drug interactions have been observed with either zanamivir or oseltamivir. There is also no need to adjust dosages for the elderly, although adjustment of the oseltamivir dose is recommended for patients with renal impairment, a common problem in elderly patients.[58] Neither of the drugs seem likely to affect the normal immune response to influenza infection,[45,48] and zanamivir does not affect the antibody response to inactivated influenza vaccines;[59] the effect of oseltamivir on antibody response has not yet been reported.

5.3.3 Resistance

To date there has been no evidence of resistance to zanamivir when used in accordance with the prescribing information.[60] Only one clinical viral isolate has demonstrated reduced susceptibility following prolonged compassionate use of nebulised zanamivir for 15 days in an immunocompromised child.[61] In clinical trials up to 3% of influenza viral isolates from adult patients and over 8% from paediatric patients receiving oseltamivir in clinical trials have demonstrated resistance to the drug.[47,58] It has been possible to generate a few mutants with reduced susceptibility to zanamivir during laboratory *in vitro* studies, but strains resistant to either drug have low infectivity and virulence.[58,62,63] Continued global viral surveillance is being carried out to ascertain the incidence and importance of drug resistance in the clinical use of NA inhibitors.[64]

6. Managing Influenza in Primary Care: The Future

Vaccines will continue to be the mainstay of the influenza pre-season management programme. In addition, influenza vaccination clinics give PCPs the opportunity to educate patients, particularly those at risk of developing complications, about the importance of consulting within 48 hours if they develop symptoms of influenza, to receive a prescription for an NA inhibitor.

The advent of NA inhibitors presents a new opportunity to manage influenza within the primary-care setting and will allow PCPs to plan ahead for their increased workload during the influenza season. However, because patients need to consult their PCP within 48 hours of the onset of symptoms, education is essential, and this can be carried out in association with the influenza vaccination programme. Practical measures that might be taken include developing the role of nurses, who could make home visits where appropriate to reduce the spread of infection in surgeries. Nurses could also run triage clinics, where they would make the initial diagnosis, thereby reducing the workload of PCPs. In the longer term, the potential availability of NA inhibitors without prescription may also help to ensure patient access to these drugs as soon as possible after the onset of symptoms, whilst reducing the burden on PCPs.

Compared with the adamantanes, the added benefits of a NA inhibitor include a wide therapeutic range (influenza B as well as influenza A), fewer adverse effects (especially in the most vulnerable patients), and a much reduced likelihood of the emergence of drug-resistant strains. Thus in the area of treatment, the additional benefits of an NA inhibitor are sufficient to justify the extra cost even though the basic National Health Service (NHS) cost in the UK of 5 days' treatment is about ten times that of amantadine. Data on the impact of NA inhibitors on hospitalisation rates and mortality will be important to obtain, but evidence for this will only become available after very large numbers of influenza patients have received zanamivir or oseltamivir.

7. Conclusions

Influenza is a serious disease associated with high morbidity, hospitalisations and deaths. The majority of the burden for diagnosis and management traditionally falls on primary-care services. Until recently, the only practical management strategy in many countries was vaccination, which is usually restricted to those at most risk from infection, such as the elderly and those with pre-existing chronic disease. The introduction of the NA inhibitors provides a valuable opportunity for effective in-season management of the disease in both high risk groups and healthy persons. The appropriate education of patients and healthcare professionals, together with improved surveillance and early intervention, will ensure that optimum clinical benefit is derived from the NA inhibitors and should help PCPs to more effectively manage their workload, which inevitably increases during influenza outbreaks.

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