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Antiviral Therapy for Influenza

A Clinical and Economic Comparative Review

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Contents

Abstract

Each year influenza epidemics cause a considerable burden of disease. Vaccination against influenza A and B viruses has been and remains the cornerstone of influenza prevention, but antiviral therapy can serve as an important adjunct to vaccination in controlling the impact of the disease. Two classes of drugs are currently licensed in a large number of countries for the treatment of influenza. The M2 ion channel blockers or amantadanes (amantadine and rimantadine) are specific inhibitors of influenza A virus replication, whereas the neuraminidase inhibitors (zanamivir and oseltamivir) are active against influenza A and B viruses. Readily transmissible drug-resistant viruses develop frequently during amantadane treatment but not during neuraminidase inhibitor treatment.

In this review, efficacy and safety data from randomised controlled trials are evaluated to gain an understanding of what we can and cannot expect from antiviral treatment. All four drugs shorten the course of influenza disease by approximately 1 day and relieve symptoms to some extent, but there is still uncertainty as to whether antiviral therapy leads to a reduction of serious complications and hospitalisation. The results of cost-effectiveness analyses are very diverse, in part because of differences in methodology but also because there is no consensus on what probabilities to assign to the key risks and benefits that form the basis of these studies.

Consensus statements by advisory bodies in England and Germany recommend neuraminidase inhibitors for the therapy of influenza in high-risk individuals such as people over 65 years or under 2 years, and individuals with chronic

cardiovascular, pulmonary or renal disease, diabetes mellitus or immunosuppression. However, there is no agreement as to whether antiviral therapy can be generally recommended for otherwise healthy children and adults. The availability of safe and effective antiviral therapy options should be kept in mind by the practising clinician, while more specific recommendations and policy formulation will depend on additional efficacy data that include frequency of complications and hospitalisation as outcome measures.

Influenza is a highly infectious disease that occurs in annual seasonal epidemics, affecting 10–20% of the global population in an average year. WHO estimates that every year influenza epidemics result in 3–5 million cases of severe respiratory illness and up to 500 000 deaths. Most deaths associated with influenza in industrialised countries are due to complications of underlying diseases in people with well defined risks, such as age over 65 years or under 2 years, chronic cardiovascular, pulmonary or renal disease, diabetes mellitus, or immunosuppression.[1] In the US alone, influenza is associated with more than 50 000 excess deaths of all causes annually.[2] In addition to the enormous burden of disease in terms of morbidity and mortality, influenza epidemics also inflict a considerable economic burden, both in direct healthcare costs and in indirect costs such as productivity losses.

Vaccination against influenza A and B viruses has been and remains the cornerstone of influenza prevention. Inactivated vaccines have been successfully employed for more than 60 years and new vaccines such as live attenuated intranasal vaccines have recently become available.[3,4] Nonetheless, due mostly to insufficient vaccine coverage[5] but also to a lack of protective immunogenicity in the elderly and, in some years, a mismatch between vaccine strains and circulating strains, influenza remains a major public health problem. Therefore, effective antiviral therapies are urgently needed.

Two groups of influenza antiviral drugs are currently licensed in a large number of countries, offering clinicians a choice in the treatment and prevention of influenza. While the first group of antiviral drugs, the M2 ion channel blockers, have been on the market for a long time, the neuraminidase inhibitor group of antiviral drugs entered the market as recently as 1999. There is still considerable uncertainty as to the role of these drugs in controlling influenza epidemics and in reducing the burden of disease.

Based on a PubMed search of articles that contain at least one of the generic drug names and the term ‘influenza’, and based on additional information provided by the manufacturers of the drugs concerned, this review examines the clinical evidence for the efficacy of antiviral drugs in the treatment of influenza, and briefly summarises a number of cost-benefit analyses and recommendations for the use of antiviral therapy in inter-pandemic influenza epidemics. Chemoprophylaxis and the role of antiviral drugs in pandemic influenza have been reviewed recently[6,7] and are not included here.

1. Burden of Disease and Clinical Presentation

Annual influenza epidemics, occurring generally from November through March in the northern hemisphere and from April through September in the southern hemisphere, are the result of frequent and significant antigenic variation of influenza viruses. These variations – called antigenic drift – are most pronounced in influenza A viruses. As a result of amino acid substitutions in the two major influenza virus surface antigens (the haemagglutinin and neuraminidase proteins) the virus escapes from the host’s immune response, i.e. neutralising antibodies formed during a previous influenza infection are no longer or not completely protective. When dramatic antigenic changes – termed antigenic shift – occur, a large proportion of the population has no neutralising antibodies at all, and high attack rates with increased morbidity and mortality are inevita-

ble. Antigenic shift refers to major antigenic change in the surface antigens (haemagglutinin and neuraminidase) of influenza A viruses when compared with earlier circulating viruses. When this occurs and the resulting virus transmits readily among humans, a worldwide influenza epidemic (pandemic) may ensue. Antigenic shift has occurred through reintroduction of a human virus that has not been circulating for a long time (A/USSR [H1N1] in 1977) but usually emerges from reassortment of genes during a mixed infection with a human and an avian influenza virus in another human or lower animal with transmission to humans, or possibly by direct avian to human transmission with adaptation for spread in humans. Infections of humans with avian influenza viruses are a major concern in this respect, and the high mortality associated with H5N1 virus in Hong Kong in 1997 highlights the importance of potentially emerging novel human influenza viruses.[8]

Although pandemic influenza is much talked about, it is inter-pandemic influenza that is responsible for most of the burden of disease. However, influenza-attributable mortality and morbidity are difficult to measure. This is due partly to influenza infection often being the proximate, but not the ultimate, cause of death, for example in influenza-triggered bacterial pneumonia or congestive heart failure, and partly due to omission of laboratory confirmation of suspected influenza.[2,9] Excess mortality due to influenza is estimated to range from 20 000 to over 50 000 per year in the US alone,[9,10] and excess hospitalisation for pneumonia and influenza is estimated at 174 per 100 000 people over 65 or 49 per 100 000 overall.[11] While most clinicians are aware of the elderly being a high-risk group, other high-risk groups are often overlooked. For example, in women with acute cardiopulmonary conditions, estimated annual excess hospitalisations and deaths per 100 000 women range from 230 (15–44 years of age) to 580 (45–64 years of age).[12] Individuals with asthma and chronic obstructive pulmonary disease, chronic renal disease, diabetes mellitus or those with immunodeficiencies are also considered high-risk, as are all children aged from 6 to 23 months.[7] For people in residential care, the frequency of hospital admissions for those contracting influenza when vaccinated appears to be approximately one in eight, rising to one in five for those who have not been vaccinated.[13]

A correct clinical diagnosis of influenza depends heavily on whether influenza is circulating in the respective community. Once influenza activity is confirmed, even the simplest case definition of influenza-like illness (i.e. sudden onset fever plus nonproductive cough) is almost as accurate as most near-patient test-kits. The positive predictive value, sensitivity and the specificity of a case definition, including fever (>37.8°C) and cough, for the diagnosis of influenza infection during a 'flu season are reported at 87%, 78% and 55%, respectively.[14] However, clinical presentation of the very young and the elderly is not always as straight forward. In infants, gastrointestinal (GI) symptoms such as vomiting, diarrhoea and abdominal pain are fairly common, or influenza may present as croup or bronchiolitis, making it impossible to differentiate from parainfluenza or respiratory syncytial virus (RSV) infection. The very young infant may even appear septic and require a full workup to exclude systemic bacterial infections. In the elderly, confusion, fatigue and decreased mental acuity with or without fever are common presentations. Here, the onset of influenza is often less abrupt and the mental symptoms might be more noticeable than cough and myalgia.[15] In either case, knowledge of local influenza activity is key to a correct diagnosis.

2. Influenza Biology and Mode of Action of Antiviral Drugs

The influenza viruses are members of the orthomyxoviridae family of viruses. They are enveloped viruses with a segmented, single-stranded RNA genome of negative polarity (i.e. genomic viral RNA does not serve as mRNA). The influenza A genome encodes three transmembrane proteins, that is the haemaglutinin, neuraminidase and M2 proteins. The replication of influenza viruses is initiated by binding of the haemaglutinin protein of the virus to sialic acid (neuraminic acid) residues on the cell surface of

respiratory epithelium (and on red blood cells, hence its name). The virus then enters the cell via endocytosis. Within the acidic endosome, an influx of hydrogen ions (H^+) is mediated by the M2 ion channel and the resulting drop in pH facilitates dissociation of the matrix protein-ribonucleic protein complex so that the viral RNA may enter the nucleus where transcription takes place. Once progeny virions are assembled they bud from the cell surface membrane. Here, the viral neuraminidase protein enables the release of virus from the cell surface into the respiratory lumen by cutting the newly budded viruses off their cell surface receptors. In addition, neuraminidase prevents the clumping of viruses, thereby increasing the number of infectious particles.

The transmembrane domain of the M2 ion channel protein is the target of the amantadane group of antivirals. Amantadine (1-aminoadamantane hydrochloride) was the first specific influenza antiviral, licensed in the US in 1966 for the therapy and prophylaxis of influenza type A.[16] Studies using amantadine as an inhibitor of viral replication played an important role in defining the function of the M2 protein. The drug efficiently blocks the ion channel activity of M2 protein through allosteric inhibition and, as a result, viral uncoating cannot take place.[17] A second M2 protein inhibitor, rimantadine (methyl-1-adamantanemethylamine hydrochloride), was licensed in 1993 in the US. Its mode of action is identical to that of amantadine.

The target of the second group of antiviral drugs is the neuraminidase protein. As indicated earlier this section, the function of neuraminidase, that is, the cleavage of terminal sialic acid residues, is crucial for the virulence of influenza A and B viruses. It ensures efficient release of budded virus from infected cells, reduces viral aggregation and promotes tissue penetration and virus spread in the respiratory tract. The genetic stability of neuraminidase, most likely due to a very stringent structure-function relationship, makes this protein an attractive target for antiviral therapy. The two licensed neuraminidase inhibitors, designed to bind to the crystallography-predicted structure of the neuraminidase binding site, were amongst the first drugs to be rationally designed to fit the molecular structure of their target protein. Zanamivir and oseltamivir are the only two sialic acid analogues currently licensed as influenza antivirals, but other neuraminidase inhibitors have been described.[18]

3. Pharmacokinetic and Pharmacodynamic Properties

Amantadine (1-adamantanamine hydrochloride) and rimantadine, the α-methyl derivative of amantadine, specifically inhibit the replication of influenza A viruses. Inhibitory concentrations of the drugs range from 0.03 to 1.0 μg/mL,[19] with rimantadine being approximately 4- to 10-fold more active than amantadine.[20]

Both drugs have good oral bioavailability and very large volumes of distribution, so that local concentrations (in nasal mucus) are similar to those in plasma. Amantadine is excreted primarily unmetabolised via urine, with a terminal elimination half-life of 12–18 hours in young adults. Dosage has to be adjusted in patients with renal insufficiency and in the elderly to reduce the risk of adverse effects. Rimantadine is extensively metabolised hepatically and eliminated with a plasma half-life of 24–36 hours. Approximately 25% is excreted renally and less than 15% is excreted unmetabolised.

Zanamivir has poor oral bioavailability and, therefore, is supplied in a diskhaler, a device that contains 20 small chambers, or blisters, of zanamivir powder for inhalation. Use of the diskhaler requires a certain degree of coordination, and can be problematic in the very young and the very old. Depending on the degree of coordination, 10–20% of the inhaled drug is found in bronchi and small airways, whereas 80–90% remains in the oropharynx. Zanamivir is absorbed by respiratory epithelial cells and plasma concentrations peak within 1 hour. Plasma half-life is approximately 5 hours and only 10–20% of the drug is excreted renally. High zanamivir concentrations are found in the trachea and bronchi up to 24 hours post inhalation. Replication of laboratory strains of influenza A and B is inhibited by 50% (IC_{50}) at concentrations from 4 to

140 nmol/L, while clinical isolates exhibit IC_{50} values ranging from 2 nmol/ L to 16 μmol/L.[21] In clinical studies, zanamivir reduced both the quantity and duration of virus shedding.

Oseltamivir is readily absorbed from the GI tract and is metabolised by hepatic esterases to oseltamivir carboxylate, the only known active metabolite. Oseltamivir carboxylate is detected in plasma within 30 minutes, reaches peak plasma concentration 3–4 hours after ingestion and is excreted renally with a terminal elimination half-life of 6–10 hours. However, clearance is slower in severe renal dysfunction. The active metabolite is distributed to the surface of respiratory epithelium as well as to the middle ear and sinuses. *In vitro*, oseltamivir carboxylate inhibits replication of laboratory strains of influenza A and B at concentrations similar to those determined for zanamivir (IC_{50} 60 pmol/L to 26 μmol/L).[22] In naturally infected patients, as well as in experimentally infected volunteers, the drug was shown to reduce the quantity and duration of viral shedding.

4. Clinical Trials: Efficacy, Safety and Development of Resistance

4.1 Amantadine and Rimantadine

Clinical trials using amantadine at a dose of 200 mg/day to treat influenza type A within 48 hours of onset of symptoms showed a reduction of days with fever by approximately 1 day.[23,24] Efficacy data using a 100 mg/day dosage – the recommended dosage for the elderly – are sparse but a similar efficacy can be assumed if one considers that plasma concentrations in patients with impaired renal function receiving 100 mg/day are as high as those in young healthy adults receiving 200 mg/day.[25] Rimantadine is similar to amantadine in its antiviral activity and seems to provide a similar treatment benefit, although there are fewer trials testing the efficacy of this drug and differences in study design make a direct comparison with amantadine difficult.[26,27] In children, some trials did find a treatment benefit similar to that seen in adults, while others did not find any additional benefit of the M2 ion channel blockers compared with symptomatic use of paracetamol (acetaminophen).[28,29] There is no convincing evidence for either drug that treatment reduces complications of influenza such as pneumonia or otitis media.[30]

Resistance to amantadine and rimantadine is seen with a frequency of ≥50% in children,[31,32] the elderly and in immunocompromised patients.[33,34] In children, resistance typically occurs after 3–5 days and is associated sometimes with mild disease and sometimes with no disease at all, whereas in the immunocompromised hosts it is typically seen in less than 3 days and is associated with sometimes severe disease. Resistance poses a major problem when these drugs are used therapeutically and prophylactically at the same time in close-contact environments such as families and nursing homes.[33,35] Resistant virus develops as early as 1 day after starting treatment and is transmitted readily to individuals receiving chemoprophylaxis.[36]

The most commonly observed adverse effects seen with amantadine therapy are CNS complaints such as confusion, jitteriness, insomnia and anxiety. CNS adverse effects are the main reason for discontinuing therapy and are one reason for the hesitant attitude of many physicians towards the drug.[37] In addition, GI symptoms such as nausea and vomiting are reported adverse effects. Although confusion and other CNS symptoms are seen with a frequency of up to 30% in the elderly,[38] amantadine is generally well tolerated in children.[39] The neurotoxic effect of amantadine seems to increase with concurrent use of antihistamines, anticholinergic and psychotropic drugs.[20] Rimantadine is much less frequently associated with CNS adverse events, although GI side effects occur at a similar rate.[20]

4.2 Zanamivir

There are data on zanamivir from at least seven double-blind, placebo-controlled randomised clinical trials (RCTs) with over 2500 patients enrolled (table I). The primary endpoint in most of these studies was time to alleviation of clinically significant symptoms, for example, absence of fever or feverishness and no or only mild disease (e.g. head-

Table I. Clinical effectiveness of inhaled zanamivir in the treatment of influenza

Study (year)	No. of patients with ILI (ITT)	No. of patients with influenza (% of total)	Population characteristics (approximate mean age in years ± SD)	ITT population		Influenza-positive population		Remarks
				reduction of duration of symptoms in days (range) [p]	reduction of TRNA in days (range) [p]	reduction of duration of symptoms in days (range) [p]	reduction of TRNA in days (range) [p]	
Hayden et al.[40] (1997)	276	174 (63)	Age ≥13 (32 ± 12) Previously healthy	0.7 (0–1.4) [0.04]	NR	0.8 (0–1.7) [0.05]	1.3 (0.2–2.3) [0.02]	Symptoms ≤30h. Third arm analysed inhaled plus intranasal application
Monto et al.[41] (1999)	841	481 (57)	Age ≥13 (36 ± 14) 116 high-risk	1.0 (0–2.0) [0.01]	After 5.5 days 54% vs 45% resumed normal activity [0.005]	2.0	NR	Symptoms ≤48h. In addition 6.4mg intranasal spray bid. Third arm analysed qid treatment
MIST Study Group[42] (1998)	455	321 (71)	Age ≥12 (37 ± 13) 76 high-risk	1.5 (0.5–2.3) [0.01]	2.0 (0–4) [0.001]	1.5 (0.5–2.3) [0.004]	2.0 (0.3–4) [0.001]	Symptoms ≤36h. Benefit only if febrile at presentation. Same effect in ITT and influenza-positive population
Mäkelä et al.[43] (2000)	356	277 (78)	Age ≥12 (37) 32 high-risk	2.5 (0.8–3.5) [0.001]	NR	2.5 (1.0–4.0) [0.001]	NR	Symptoms ≤48h; temp ≥37.8°C at presentation. Same effect in ITT and influenza-positive population
Hedrick et al.[44] (2000)	471	346 (73)	Age 5–12 (8.7 ± 2.2)	0.5 (0–1.5) [0.01]	NR	1.25 (0.5–2) [0.001]	NR	Symptoms ≤36h; temp ≥37.8°C at presentation
Lalezari et al.[45] (2001)	321	227 (71)	High-risk (40)	1.5 (0–3.5) [0.046]	2.0 (0.5–4.5) [0.023]	2.5 (0.5–4.5) [0.015]	3.0 (0–8.0) [0.022]	Retrospective pooled analysis of high-risk patients in previous studies
Murphy et al.[46] (2000)	525	313 (60)	Age ≥12 (38) COPD and asthma	1.0 (NR) [0.12]	NR	1.5 (0.5–3.25) [0.009]	NR	Symptoms ≤36h. Pulmonary function unaffected. Reduction of complications not significant (p = 0.06)

bid = twice daily; **COPD** = chronic obstructive pulmonary disease; **ILI** = influenza-like illness; **ITT** = intention-to-treat; **NR** = not reported; **p** = level of significance; **qid** = four times daily; **SD** = standard deviation; **temp** = body temperature; **TRNA** = time to resume normal activity.

ache, myalgia, cough or sore throat). The majority of trials enrolled primarily previously healthy individuals between 12 and 65 years of age (table I)[40-43] with influenza-like illness (ILI) and symptoms for <48 hours. ILI was defined as presence of fever (>37.8°C) or feverishness plus at least two of the following symptoms: headache, myalgia, cough or sore throat. In the intention-to-treat (ITT) population, zanamivir consistently reduced the median duration of symptoms by approximately 1 day and by approximately 30 hours in the influenza-positive population. Mäkelä et al.[43] reported a reduction in the duration of symptoms of as much as 2.5 days. Compared with other zanamivir efficacy trials, the absolute duration of symptoms in this particular trial was slightly longer in the placebo-treated group but similar in the zanamivir-treated group (5 days), thereby resulting in a greater reduction of the duration of illness. Mäkelä et al.[43] were unable to detect a difference in the duration of symptoms between the ITT and the influenza-positive population.

An additional relevant endpoint used in two trials was time to resume normal activity. While Hayden et al.[40] observed a median 1.3 day reduction in time to resume normal activity in influenza-positive patients, the Management of Influenza in the Southern Hemisphere Trialists (MIST) group found a 2-day reduction. However, in the MIST trial no difference in this effect was observed between the ITT and the influenza-positive population (table I).[42]

The number of RCTs involving primarily high-risk individuals is very limited. Murphy et al.[46] analysed the efficacy of zanamivir treatment on time-to-alleviation of symptoms in a relatively young population (mean age 38 years; 9% >65 years) of patients with asthma (76% of subjects) and/or chronic obstructive airway disease (COPD, 23%). In the ITT population there was no significant difference in time-to-alleviation of symptoms, whereas in the influenza-positive population (60%) a significant 1.5-day reduction was observed (table I). There was no difference in the rate of hospitalisation. One retrospective pooled analysis of high-risk patients enrolled in previous efficacy studies found a significant reduction in both the ITT and the influenza-positive population with regard to time-to-alleviation of symptoms (1.5 and 2.5 days, respectively) and in the time to resume normal activity (2.0 and 3.0 days, respectively).[45]

Because of the method of administration as an inhalation powder, zanamivir RCTs in infants and young children could not be conducted. One RCT involving children aged 5–12 years was published by Hedrick et al.,[44] who found a 12- and 30-hour reduction in time-to-alleviation in their ITT and influenza-positive population, respectively.

One clinically important adverse effect reported is transient wheezing and decreased lung function in people with hyperreactive airway disease.[47] Although patients requiring asthma therapy can take their bronchodilators first and then use zanamivir, the drug is generally not recommended in patients with underlying airway disease.

4.3 Oseltamivir

Oseltamivir has been studied in experimental human infection[48] and in two large double-blind, placebo-controlled RCTs of naturally occurring influenza.[49,50] Both RCTs examined the effect of oseltamivir (in two treatment arms: 75mg and 150mg twice daily) on time to alleviation of symptoms. Nicholson et al.[50] also looked at time to resume normal activity (in two treatment arms: 75mg twice daily and 150mg twice daily) [table II]. Similar to the results obtained in zanamivir RCTs, oseltamivir treatment over 5 days, started within 48 or 36 hours after onset of symptoms, reduced the time to alleviation of symptoms by approximately 1 day in the ITT population and by approximate 33 hours in the influenza-positive population. The time to resume normal activity was reduced by 2–3 days (table II). In an open-label early versus late start-of-treatment study (not placebo-controlled) with over 1400 patients, early treatment was found to increase treatment benefit. Treatment within 12 hours of onset of symptoms reduced the total mean illness duration (from the onset of symptoms, not the start of treatment) by 3 days compared with treatment initiation 48 hours after onset of symptoms.[51]

Table II. Clinical effectiveness of oseltamivir in the treatment of influenza

Study (year)	No. of patients with ILI (ITT)	No. of patients with influenza (% of total)	Age of patients (approximate mean age in years ± SD) [years]	ITT population		Influenza-positive population		Remarks
				reduction of duration of symptoms (h) [p]	reduction of TRNA (h) [p]	reduction of duration of symptoms (h) [p]	reduction of TRNA (h) [p]	
Treanor et al.[49] (2000)	420	253 (60)	18–65 (32 ± 11)	21 [0.04]	57 [0.01]	32 [0.01]	68 [0.02]	210 patients received 75mg bid Symptoms ≤36h, median 25h Use of antibacterials reduced
Treanor et al.[49] (2000)	418	250 (60)	18–65 (33 ± 10)	23 [0.04]	28 [0.10]	33 [0.006]	45 [0.05]	206 patients received 150mg bid Symptoms ≤36h, median 27h Use of antibacterials reduced
Nicholson et al.[50] (2000)	482	319 (66)	18–65 (38 ± 11)	20 [0.05]	NR	29 [0.02]	NR	243 patients received 75mg bid Symptoms ≤36h, fever ≥38°C
Nicholson et al.[50] (2000)	483	317 (66)	18–65 (37 ± 12)	27 [0.03]	NR	35 [0.01]	NR	244 patients received 150mg bid Presentation ≤36h, fever ≥38°C
Whitley et al.[52] (2001)	695	452 (65)	1–12 (5)	NR	NR	36 [0.0001]	NR	Symptoms ≤48h, median 27h, fever ≥38°C Otitis media reduced, emesis increased in treatment group
Aoki et al.[51] (2003)	1426	958 (67)	12–70 (40)			75 [0.0001]	>75	Open-label, treatment started 12h vs 48h post-fever/feverishness; no placebo control 75mg bid

bid = twice daily; **ILI** = influenza-like illness; **ITT** = intention-to-treat; **NR** = not reported; **p** = level of significance; **SD** = standard deviation; **TRNA** = time to resume normal activity.

In children aged 1–12 years only one large RCT has been reported.[52] In this trial, oseltamivir reduced the time to alleviation of symptoms in the influenza-positive population by a median 36 hours, with a median start of treatment 27 hours after the onset of symptoms (table II).

The most commonly seen adverse effects with oseltamivir are GI symptoms such as GI discomfort, nausea and emesis (<10%). Adverse effects are generally mild and transient, and seem to occur less often when the drug is ingested with meals.

4.4 Summary

From this data, it seems fair to conclude that there is strong evidence to suggest both neuraminidase inhibitors reduce the duration of clinically significant influenza symptoms by approximately 20% (i.e. 1 day) in healthy adolescents and adults. The safety profile of both neuraminidase inhibitors is good, with oseltamivir-associated GI symptoms and zanamivir-associated respiratory symptoms in patients with reactive airway disease the only areas of concern. In high-risk individuals the benefit may be greater than in healthy young adults but data on this issue are still lacking. Evidence for a reduction of influenza complications with the use of neuraminidase inhibitors is weak, and there is no evidence supporting a reduction in hospitalisation or mortality.

Amantadine and rimantadine seem equally effective in reducing the duration of illness, but their usefulness is limited by the rapid development of resistance and the lack of efficacy in influenza B epidemics. In addition, amantadine is associated with CNS adverse effects, especially when the dose is not adjusted in patients with renal insufficiency. However, in many countries cost of the drug to the patient or the insurance company is an important concern that may favour the use of amantadine.

5. Cost-Benefit and Cost-Effectiveness Analyses

Several cost-benefit and cost-effectiveness analyses of antiviral therapy for influenza have been conducted in various populations in industrialised countries. The outcome of all these analyses depends on a number of key assumptions that need to be made at the outset.

First of all, the probability of contracting influenza during an influenza season needs to be estimated. Although reported probabilities range from 1% to 35%, a 10–20% probability can be seen as a useful estimate for an average influenza season in temperate climates. Next, an estimate for the proportional burden of disease caused by influenza type B is needed, since amantadine and rimantadine have no benefit in influenza B epidemics. In healthy working adults and in children with working parents, the largest contributor to the cost of an influenza outbreak is the loss of productivity, that is, working days lost as a result of influenza disease. Unfortunately, efficacy trials of antiviral drugs have not included working days missed as one of their endpoints. However, reduction in time to resume normal activity can be used as a surrogate for reduction in working days lost.

Naturally, decisions based on the cost effectiveness of prevention and treatment options differ when viewed from the perspective of the individual, the employer or the healthcare payer.[53] While evidence for a reduction of working days lost as a result of antiviral therapy might easily convince an employer-supported health plan to sponsor antiviral therapy in healthy working adults, quality-of-life issues such as symptom severity and utility might be of greater importance to the individual. For the practising clinician an additional important question is whether the drug is on formulary and whether it is sponsored by the patient's insurance.

A recent analysis by Lee et al.[54] in healthy working adults in the US – which assumed a 15% probability of contracting influenza, an 84% and 16% average prevalence of influenza A and B, respectively, and a loss of 2.3 versus 2.8 working days with and without antiviral treatment, respectively – suggested that while vaccination with or without antiviral treatment in case of disease was clearly cost beneficial, antiviral treatments alone had little or no net cost benefit provided the assumptions on working days gained are correct. Since the assump-

tion of 0.5 working days gained is a conservative one (an assumption of 1 working day gained may be equally valid), others might argue that antiviral treatment may well be cost-saving. To clarify this uncertainty, a head-to-head comparison of licensed antiviral drugs designed to detect small differences in working days gained is urgently needed.

Another US cost-effectiveness analysis by Muennig and Khan[55] compared oseltamivir treatment with supportive care and with vaccination in healthy adolescents and adults. Their analysis – which assumed no excess mortality, a 95% prescription rate with 95% patient compliance and 10% of patients presenting within 48 hours of onset of symptoms – suggests that, relative to supportive care and provided ILI incidence is >24% annually, the incremental cost effectiveness of oseltamivir treatment is $US27.619 per quality-adjusted life-year (QALY), while vaccination is cost saving (1997 values).

A major difficulty in comparing different cost-effectiveness models is the lack of data supporting the model assumptions for key probabilities. While the above study seems conservative (i.e. biased against antiviral treatment) in its assumption of no excess mortality and only 10% in-time presentation, the prescription and compliance rates seem very optimistic. O'Brien et al.[56] for instance, assume that, based on market research data, 50% of patients with ILI present within 48 hours. Their 'patients point of view' analysis uses data from clinical trials with oseltamivir to estimate the cost-effectiveness of oseltamivir being on formulary for Canadian primary care physicians. Effectiveness here is measured as 'influenza-days averted', and utility is estimated using a patient-completed visual analogue scale from 0 to 10 to describe states between worst possible health and perfect health. After normalisation (0 to 1), this utility measure is employed to calculate cost per QALY gained (CQG). Their cost estimate of $Can49 per influenza day averted translates into an incremental cost of $Can57 863 per QALY with oseltamivir treatment being on formulary and reimbursed (1999 values).

As Smith and Roberts[57] point out, measuring utility for short-term health states is a challenging problem. Their cost-effectiveness analysis, based on a decision model that includes all four antivirals licensed in the US with and without testing, ascribed influenza disease a utility of 0.65 untreated and 0.78 treated with antivirals, but cautioned that 0.65 might be too low an estimate and the increase in utility afforded by antiviral treatment therefore an overestimate. On the other hand their model assumed no reduction in complication rates or in mortality nor did it account for working days lost, thereby biasing the analysis against antiviral therapy. In their model, Monte Carlo analysis suggests that amantadine or no treatment is favoured if society or a third-party payer is willing to pay <$US100 per case, while zanamivir and oseltamivir are favoured in younger (rimantadine in older) patients willing to pay $US200–300 (2000 values). Testing is only favoured if the influenza likelihood is <20%. An interesting notion in this analysis is that the cost of antiviral treatment with neuraminidase inhibitors in terms of cost per quality-adjusted day gained ($US185 for zanamivir vs $US235 for oseltamivir) [2000 values] similar to the costs of migraine therapy with sumatriptan or antiviral therapy of adult chickenpox, both treatments that are routinely covered by third-party payers.

In their analysis of cost effectiveness of influenza testing and treatment strategies for adults older than 65 years of age, Rothberg et al.[58] found that, under most circumstances, empirical antiviral therapy was reasonably cost effective and within the range of other widely accepted interventions for older adults. Assuming that oseltamivir treatment prevented 33% of hospitalisations (an extrapolation from studies showing a similar reduction in complications requiring the use of antimicrobials), the cost per QALY saved in an unvaccinated 75-year-old with a 35% likelihood of ILI being influenza amounted to approximately $US10 296 (2001 value). Regardless of the treatment, vaccinated patients lived longer and incurred fewer expenses than did unvaccinated patients. Testing strategies were less effective in this base case scenario because of the lack of sensitivity

Table III. Cost (thousand GBP) of antiviral treatment per quality-adjusted life-year gained in England, Wales and Scotland.[13] In the base case (BC), 46% of influenza-like illness (ILI) is assumed to be influenza and availability of antiviral drugs on formulary assumed to not increase general practitioner (GP) consultations; in the alternative case (AC), 31% of ILI is assumed to be influenza and availability of antiviral drugs on formulary assumed to increase GP consultations for ILI from 28% to 36%

Population	Amantadine	Zanamivir		Oseltamivir	
		reduction[a]	no reduction[a]	reduction[a]	no reduction[a]
Healthy adult	BC: 13	BC: 8	BC: 30	BC: 4.3	BC: 18
	AC: 129	AC: 27	AC: 100	AC: 19	AC: 75
At-risk adult	BC: 4.3	BC: 3.7	BC: 19	BC: 3.9	BC: 26
	AC: 130	AC: 17	AC: 82	AC: 25	AC: 134
Children	NA	NA	NA	BC: 11	BC: 19
				AC: 25	AC: 45

a Assuming that drug does/does not reduce hospital admissions and mortality from complication.

GBP = British pound sterling, equivalent to approximately $US1.6; **NA** = not applicable.

of rapid testing.[58] In his review of testing and treatment strategies in children, Uyeki[59] points out that physicians need to understand the limitations of rapid tests and use clinical experience as well as local surveillance data when interpreting rapid influenza test results. He considers testing every patient with suspected influenza impractical and unnecessary, especially when an influenza outbreak is already confirmed.

The cost of treating influenza complications in the elderly, such as pneumonia, is probably the largest single contributor to the total cost of an influenza outbreak but data in this population on the effect of antivirals in preventing complications are even more limited. Mauskopf et al.[60] used a subset of data from zanamivir efficacy trials in Australia, New Zealand and South Africa to estimate the cost effectiveness of zanamivir therapy in their high-risk population for Australia (costs were estimated based on data available for ≥65-year-old patients). Here, a quality-of-well-being scale was used to measure utility, and influenza symptoms were described in terms of limitations in physical and social activity. The model employed assumed a 70% proportion of ILI being due to influenza, and further that zanamivir reduced the probability of complications from 46% to 14% and antibacterial use from 38% to 14% (as was observed in the MIST study), arriving at a CQG of $A11 715 (1995 value). This estimate has to be treated with some caution, however, since the trial results are derived from a sample of only 86 patients, all of whom presented within 36 hours after onset of symptoms. As the authors indicate, only 40% of Australians with ILI consult a physician and up to 60% of those do so outside the time window (i.e. 48 hours) for which zanamivir is indicated and shown to be effective (table III).[61]

The National Institute for Clinical Excellence (NICE) in England provides a thorough cost-effectiveness analysis that includes studies undertaken on behalf of NICE, on behalf of the Canadian Coordinating Office of Health Technology Assessment (CCOHTA), and on behalf of the manufacturers of zanamivir and oseltamivir.[13] NICE developed a base case and a more conservative alternative case scenario to analyse the available data. For the base case it was assumed that: (i) zanamivir and oseltamivir reduce the mortality from influenza complications; (ii) anyone who dies would otherwise have had an average life expectancy for their respective age; (iii) 46% of all ILI is due to influenza; and (iv) availability of antiviral drugs through the National Health System (NHS) does not increase the number of primary care physician (general practitioner [GP]) visits. The alternative case assumes an increase in GP visits from 28% to 36% for healthy adults and a 31% probability of ILI being due to influenza. Table III summarises the NICE estimates for CQG.

The NICE committee voiced three concerns relating to the sensitivity analysis in the base case scenario: (i) the assumption that GP use would not increase is probably unrealistic; (ii) the assumption that individuals dying from influenza complications

Table IV. Selected national recommendations on the use of antiviral drugs in treating influenza in patients presenting with influenza-like illness within 48 hours of onset of symptoms

Country	Population	Influenza A only		Influenza A and B	
		amantadine	rimantadine	zanamivir	oseltamivir
UK[13]	Healthy adults	No	Not licensed	No	No
	High-risk adults	No		Yes	Yes
	Healthy children	No		No	No
	High-risk children	No		yes (>12y)	Yes (>1y)
Germany[62]	Healthy adults	No	Not licensed	ns	ns
	High-risk adults	Possible[a]		Yes	Yes
	Healthy children	ns		ns	ns
	High-risk children	possible[a]		Yes (>12y)[b]	Yes (>1y)
Sweden[63]	Healthy adults	No	Not licensed	No	No
	High-risk adults	No		No	No
	Healthy children	No		No	No
	High-risk children	No		No	No
USA[7]	Healthy adults	ns	ns	ns	ns
	High-risk adults	ns	ns	ns	ns
	Healthy children	ns	ns	ns	ns
	High-risk children	ns	ns	ns	ns

a Only after diagnostic test confirms influenza type A.

b Recommended for high-risk children aged >5y, although licensure for children aged 6–12y is still in preparation.

no = not recommended; **ns** = no statement; **yes** = recommended.

would otherwise have a normal age-matched life expectancy is probably unrealistic; and (iii) the probability that ILI is true influenza might not be as high as 46%. The committee therefore concluded that on the balance of probabilities, the drugs would not be cost effective for healthy adults in England and Wales. However, it did recommend zanamivir and oseltamivir for the treatment of at-risk adults and oseltamivir for the treatment of at-risk children who present with ILI during an influenza epidemic and can start therapy within 48 hours.

6. Guidance on the Use of Antiviral Drugs for the Treatment of Influenza

Only a few countries have published national guidelines on the use of antiviral drugs for treating influenza.

Among the G7 countries, the UK has the most explicit guidance issued by NICE [table IV]. On the basis of a cost-effectiveness analysis from a government healthcare payer's perspective, NICE recommends zanamivir and oseltamivir for the treatment of at-risk adults and oseltamivir for the treatment of at-risk children older than 1 year of age who can start therapy within 48 hours of the onset of symptoms. NICE does not recommend the use of a neuraminidase inhibitor in healthy adults and children. The use of amantadine is generally not recommended by the institute.

In their analysis of cost effectiveness from a government healthcare payer's perspective, CCOHTA concludes that zanamivir could be cost effective in high-risk groups if the accuracy of diagnosing influenza was high and if hospitalisations could be prevented, but finds the evidence for these assumptions inconclusive and therefore does not recommend zanamivir for use in high-risk groups or in otherwise healthy adults.[64] A CCOHTA analysis for the use of oseltamivir in treating influenza reaches similar conclusions.[65]

A Swedish consensus document on the treatment of influenza does not recommend general use of neuraminidase inhibitors but concludes that their use can be advocated on an individual basis for patients with severe influenza. For confirmed influenza B epidemics, the Swedish consensus group

recommends giving zanamivir preference over oseltamivir, based on *in vitro* and *in vivo* susceptibility data.[63]

A German consensus report recommends the use of neuraminidase inhibitors for treating at-risk patients and their contacts.[62] Wutzler et al.[62] formulated no guideline regarding the treatment of healthy adults and children presenting with ILI; the decision is left to the attending physician. Amantadine is not viewed as an equivalent alternative to the neuraminidase inhibitors because of its limitation to influenza A, and the concerns regarding adverse effects and development of resistance.[62] Most health insurers in Germany will cover the cost of antiviral treatment if they are used to treat ILI within 48 hours of the onset of symptoms.

In Japan, no binding guidance or consensus statement exists but, similar to the situation in Germany, insurance plans cover the cost of antiviral treatment if prescribed according to the licensed indications.

The US Advisory Committee on Immunisation Practices does not provide any guidance on indications for the use of antiviral drugs to treat influenza, but it does provides specific recommendations for the use of these drugs in chemoprophylaxis and outbreak control.[7] The American Lung Association recommends that patients with ILI see their physician within 2 days after onset of symptoms, without making any recommendation for or against the use of any of the four licensed drugs.[66]

7. Conclusions

Influenza deaths have increased markedly over the past 2 decades, in part because of the aging of populations in industrialised countries, and the need for better prevention and intervention measures is obvious.[2] Vaccination programmes are and should remain the mainstay in the control of influenza epidemics. Cost-benefit analyses consistently find vaccination to be more cost effective than chemoprophylaxis or antiviral therapy. Therefore, antiviral therapy should not be seen as an alternative but as an adjunct to vaccination in our efforts to reduce the burden of influenza disease.

In the majority of countries examined, amantadine has not been used extensively in the treatment of influenza because of concerns regarding its safety profile in the elderly and because of the rapid development of antiviral resistance. However, the drug has its place in outbreak control, for example in residential care settings. Although amantadine is licensed in many countries for chemoprophylaxis, most experts would agree that it is not the drug of choice. Rimantadine has a better safety profile with regard to CNS adverse effects but the rapid development of resistance to the drug remains a concern. Rimantadine is licensed for the therapy of influenza in the US but not in the EU.

For the neuraminidase inhibitors zanamivir and oseltamivir there is good evidence for a real reduction in the duration and severity of symptoms in healthy young adults when treated within 48 hours of the onset of symptoms. Data on high-risk adults also suggest that they might benefit from antiviral treatment with neuraminidase inhibitors, but the evidence here is less conclusive and the number of high-risk individuals studied is still limited. Nonetheless, treatment of high-risk individuals is recommended in England and Germany, amongst other countries, and is covered by health insurances in a number of countries including the US, England, France, Germany and Japan. The impact of antiviral therapy in routine practice is still difficult to judge, and the efficacy observed in study populations might not be achieved in routine practice because the influenza positive rate might be considerably lower.

Cost-effectiveness studies derive variant estimates for the CQG depending on the assumed likelihood of risks and benefits as well as on whether indirect costs such as productivity losses are included. National recommendations for the use of antiviral drugs are often limited in detail but there seems to be a tendency toward recommending treatment of high-risk individuals. In choosing between antiviral therapy options, clinicians will have to consider the virus type circulating in the community, the age and risk profile of their target population, as well as the frequency of adverse effects,

efficacy, development of resistance and cost of therapy.

Ultimately, patients, physicians and healthcare payers have to decide the value they place on the benefits provided by antiviral therapy, that is, a reduction of symptom severity and a 1-day reduction in the duration of influenza illness. The two licensed neuraminidase inhibitors have a good safety profile and can, therefore, be recommended during influenza epidemics not only to patients at increased risk of developing influenza complications but also to healthy adults if they wish to reduce the severity and duration of symptoms. Whether insurers and national health systems decide to include these drugs in their sponsored formulary is a different matter altogether, and depends on a number of variables, including risk, cost and effectiveness estimates. Large trials, ideally directly comparing all licensed influenza antiviral drugs are needed to test whether antiviral therapy reduces complications, hospitalisations and deaths attributable to influenza. Such trials would certainly aid decision-making and formulation of national policies. Other areas that need to be addressed are the effects of influenza in at-risk adults and children, the feasibility of near-patient testing for influenza as well as quality-of-life issues in influenza disease.

Finally, it needs to be reiterated that annual vaccination remains the single most important intervention to reduce the burden of disease caused by influenza. Vaccination rates in populations at risk are still inadequate in most countries and many clinicians fail to convince their patients of the benefits of recommended vaccinations.[5]

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