Prescription of anti-influenza drugs for healthy adults: a systematic review and meta-analysis

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In publicly funded health systems with finite resources, management decisions are based on assessments of clinical effectiveness and cost-effectiveness. The UK National Institute for Health and Clinical Excellence commissioned a systematic review to inform their 2009 update to guidance on the use of antiviral drugs for the treatment of influenza. We searched databases for studies of the use of neuraminidase inhibitors for the treatment of seasonal influenza. We present the results for healthy adults (ie, adults without known comorbidities) and people at-risk of influenza-related complications. There was an overall reduction in the median time to symptom alleviation in healthy adults by 0·57 days (95% CI –1·07 to –0·08; p=0·02; 2701 individuals) with zanamivir, and 0·55 days (95% CI –0·96 to –0·14; p=0·008; 1410 individuals) with oseltamivir. In those at risk, the median time to symptom alleviation was reduced by 0·98 days (95% CI –1·84 to –0·11; p=0·03; 1252 individuals) with zanamivir, and 0·74 days (95% CI –1·51 to 0·02; p=0·06; 1472 individuals) with oseltamivir. Little information was available on the incidence of complications. In view of the advantages and disadvantages of different management strategies for controlling seasonal influenza in healthy adults recommending the use of antiviral drugs for the treatment of people presenting with symptoms is unlikely to be the most appropriate course of action.

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Introduction

Influenza outbreaks are usually seasonal, with heightened surveillance activity in the UK from week 40 to week 20 of the calendar year (October to May).[1] The outbreaks vary in distribution, severity, and effects on the health and wellbeing of individuals, on health-care systems, and on society at large. Multiple linear regression has been used to estimate the proportion of family doctor visits, admissions to hospital, and deaths attributable to influenza A and B each year in England and Wales. In 2007, Pitman and colleagues[2] attributed about 585 000 family doctor consultations, 19 000 hospital admissions, and 10 000 deaths from respiratory disease to influenza A, and 195 000 family doctor consultations and 1000 deaths from respiratory disease to influenza B. A study comparing family doctor consultation rates and complication rates recorded during the weeks when influenza was circulating in the community with a baseline rate when influenza was not circulating (averaged over a 9-year period), calculated that visits to a family doctor increased because of influenza by about 400% higher than the expected baseline in 1989, 300% higher in 1993, and 150% higher in 1995.[3] Calculated excess influenza-related pneumonia cases ranged from 2200 in 1995 to 12 500 in 1989, and acute bronchitis from 200 000 in 1989 and 1995 to 403 000 in 1993.[3]

Zanamivir and oseltamivir are licensed for the treatment of both influenza A and B when circulating in the community. The electronic medicines compendium lists zanamivir as licensed for individuals aged 5 years and over (treatment must be started within 48 h of onset of symptoms in adults and 36 h in children), and oseltamivir for individuals aged 1 year and over (treatment must be started within 48 h of the onset of symptoms).[4]

In publicly funded health-care systems with finite resources, such as the UK National Health Service (NHS), competing demands within the system mean that choices have to be made regarding which interventions can and cannot be supported. In England, these decisions and trade-offs are considered explicitly by the UK National Institute for Health and Clinical Excellence (NICE), and its decisions and guidance are implemented across the country to ensure equal access to health-care interventions. To assess whether antiviral treatment should be prescribed within the NHS in England, NICE commissioned a systematic review to investigate the effectiveness and cost-effectiveness of zanamivir and oseltamivir as treatments for seasonal influenza in healthy (ie, without known comorbidities) and at-risk individuals, to inform the update of NICE guidance TA58. Full results, including cost-effectiveness analyses and full consideration of the relative efficacy of oseltamavir and zanamavir, are presented elsewhere.[5]

Here we present a brief summary of the main clinical findings from the review commissioned by NICE, and discuss these in the wider context of other possible management strategies that could be adopted within the UK to deal with seasonal influenza in healthy adults. Our discussion relates specifically to the UK, but the clinical findings and our discussion of management strategies are also relevant to a wider audience. Although the research stems from data generated during seasonal outbreaks, the findings might also have some relevance to the current swine-origin influenza A H1N1 pandemic.

Methods

Search strategy and selection criteria

Detailed methods of the systematic review are reported elsewhere.[5] In brief, studies before 2001 were identified from the previous systematic review,[6] which was judged to have used comprehensive high-quality searches that did not need to be repeated. To identify new studies we searched the following databases without language restrictions from 2001 to 2007: Medline, EmBase, the Cumulative Index to Nursing and Allied Health Literature, Pascal, Science Citation Index, BIOSIS, Latin

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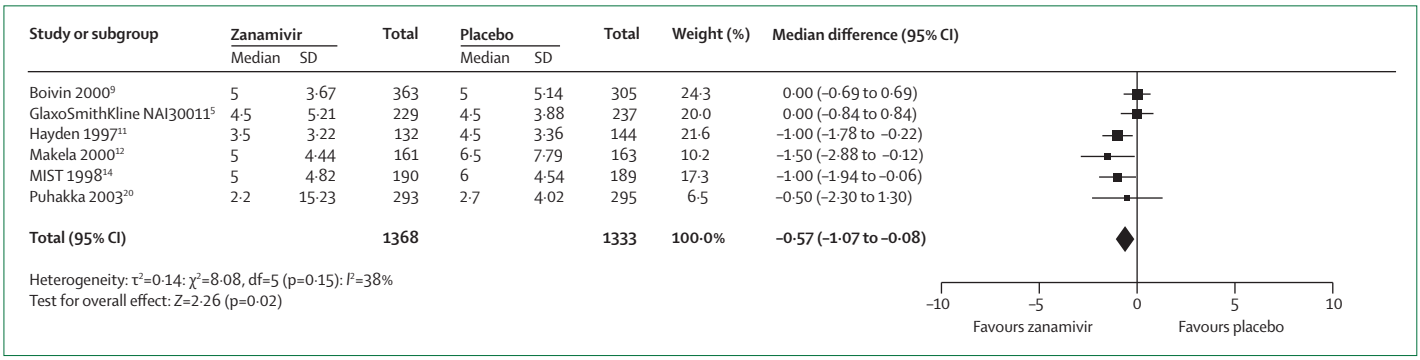

Figure 1: **Median number of days to symptom alleviation in the ITT population of healthy adults treated with zanamivir or placebo**
Median difference calculated with a random effects model.

American and Caribbean Health Sciences, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database. Toxline was also searched for studies with data on adverse events. Randomised controlled trials (RCTs) of zanamivir or oseltamivir given in their licensed doses to people presenting with symptoms typical of influenza—compared with placebo, best symptomatic care, or each other—were included. Unpublished research was identified in conference abstracts, clinical trials registers, and company websites, and through contact with manufacturers. Additional data were provided by GlaxoSmithKline for zanamivir and Roche for oseltamivir. Relevant websites and the bibliographies of included studies and relevant reviews were also searched. Studies of prophylaxis, intravenous and nebulised zanamivir, management of pandemics or epidemics of new strains of influenza, and healthy volunteers with experimentally-induced influenza, were excluded. Two reviewers (JB, MC, or CS) independently selected studies for the review, and differences were resolved by consensus or referral to a third reviewer (NW).

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Data extraction

The time to symptom alleviation (alleviating a composite of five or more symptoms, including fever), the overall complication rate, and the incidence of pneumonia, complications requiring admission to hospital, and antibiotic use (as a surrogate for bacterial infection) were extracted for both healthy and at-risk individuals on an intention to treat (ITT) basis (this population is representative of the entire population recruited in the trials) and on an ITT influenza-positive basis. This Review presents only the results for the ITT population because we judged this to be more representative of the population that will be seen in clinical practice. Data were extracted by one reviewer (JB, MC, or CS) and checked by a second (JB, MC, or CS); differences were resolved by consensus or referral to a third reviewer (NW).

Quality assessment

The quality of included RCTs was assessed in terms of randomisation, allocation concealment, masking, reporting of eligibility criteria, the recruitment of a representative population, comparability of groups at baseline, the number of patients recruited per study centre, the definition of influenza-like illness used, the use of a power calculation, and losses to follow-up. Quality was assessed by one reviewer (JB, MC, or CS) and checked by a second (JB, MC, or CS); differences were resolved by consensus or referral to a third reviewer (NW).

Data analysis

Odds ratios and 95% CI were calculated for dichotomous outcomes and differences in medians and 95% CI for continuous outcomes. Where standard errors around medians were not available, these were estimated from CI with the delta method.[7] Results from individual trials were combined to obtain an overall weighted average of treatment effect by use of a random effects model, unless there were four or fewer studies included in the analysis, in which case a fixed effect model was used, because with so few studies the estimate of the heterogeneity parameter is unlikely to be reliable.[8] All meta-analyses were done in RevMan 5.0. Heterogeneity was assessed with χ^2 and I^2; τ^2 was also calculated for continuous outcomes.

Results

26 trials met the inclusion criteria: 13 of zanamivir (reported across 23 sources of information)[5,9–25] and 13 of oseltamivir (across 14 sources).[6,26–37] Not all trials were reported individually, but for those that were, the results of the quality assessment were as follows. All reported being randomised; 11 (52%) specifically reported the use of an appropriate randomisation method and seven (33%) reported allocation concealment. 19 trials (90%) were reported as double-blind, and masking of patients was specifically reported in ten trials (48%), outcome assessors in eight trials (38%), and carers in nine trials (43%). Losses to follow-up were reported in 18 trials

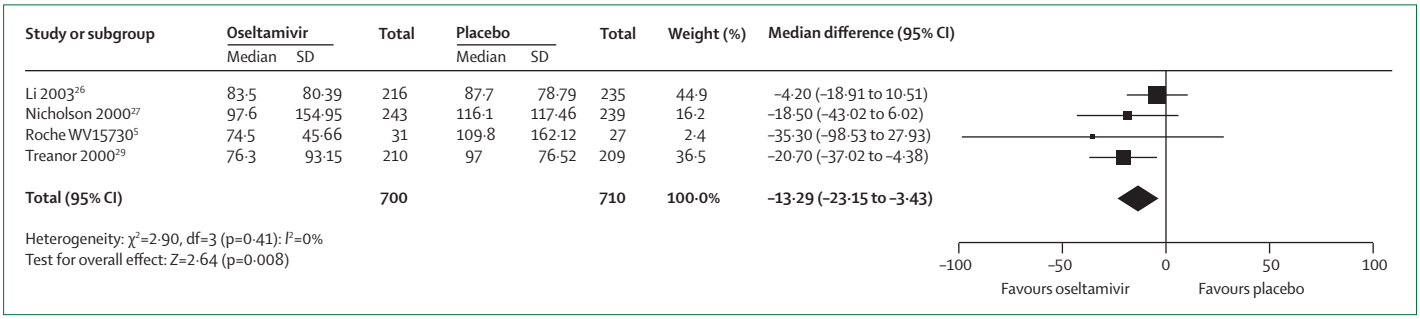

Figure 2: **Median number of hours to symptom alleviation in the ITT population of healthy adults treated with oseltamivir or placebo**
Median difference calculated with a fixed effect model.

(86%), and 11 trials (52%) had at least 95% follow-up. Several trials had many recruiting centres resulting in a very small mean number of participants recruited at any one centre, a factor that might reduce site performance;[38,39] only four trials (31%) recruited at least 15 participants at each recruiting centre.

Effectiveness in otherwise healthy adults

Six trials (figure 1), with a total of 2701 participants, compared zanamivir with placebo. Individually, two of these trials[5,9] showed no difference in the time to symptom alleviation, and four[11,12,14,20] favoured the use of zanamivir. The results were reasonably consistent (I^2=38%) and, when combined, showed a statistically significant (p=0·02) reduction in the median time to symptom alleviation of 0·57 days (95% CI –1·07 to –0·08) associated with the use of zanamivir. One study[20] reported an underlying shorter time to symptom alleviation than the other studies, most likely because of the recruitment of healthy young men (age 17–29 years) from in the Finnish Defence Force, who might have recovered more quickly.[20,21]

Four trials (figure 2),[5,26,27,29] with a total of 1410 people, compared oseltamivir with placebo. Individually, all four showed a benefit of oseltamivir in terms of reduction in time to symptom alleviation. Combined results showed a consistent (I^2=0%) statistically significant (p=0·008) reduction in the median time to symptom alleviation of 0·55 days (95% CI –0·96 to –0·14).

Effectiveness in the overall at-risk population

The results for the overall at-risk population were similar to those for healthy adults. Seven trials of zanamivir (1252 at-risk individuals) reported the time to symptom alleviation: four were in a general at-risk population,[9,12,14,16] one in at-risk children,[23] one in elderly people,[25] and one in adults with chronic obstructive pulmonary disease or asthma.[15] Only two of the trials specifically recruited an at-risk population (833 individuals),[15,25] with the remaining trials reporting results for a subgroup of at-risk patients from a mixed population. The results were consistent (I^2=0%) and, when combined, showed a statistically significant (p=0·03) reduction in the median time to symptom alleviation of 0·98 days (95% CI –1·84 to –0·11) with zanamivir.

Six trials of oseltamivir (1472 at-risk individuals) reported the time to symptom alleviation. Of these trials, two were in a general at-risk population,[34] one in children with asthma,[36] and three in elderly people.[34] The direction of effect favoured oseltamivir, and the results were consistent (I^2=0%), but there was no clear evidence of a reduction in the time to symptom alleviation (–0·74 days, 95% CI –1·51 to 0·02; p=0·06).

Complications

Overall, little information was available on the effects of either drug on the incidence of complications, and there were very few events, in both the healthy adult and at-risk populations. Furthermore, weaknesses in the available evidence limit the reliability and the ability to generalise any results relating to the effect of these drugs on the rates of complications. For example, for zanamivir the information available for healthy adults was primarily from the study in the Finnish Defence Force for which data are unlikely to be representative of complication rates seen in a populations presenting to family doctors (figure 3).[20,21] More information was available for healthy adults from oseltamivir trials, but data were still very limited (figure 4). Only a single trial (Roche NV16871) was found that assessed the effect of oseltamivir on complications in an at-risk population, and this was in children and adolescents with asthma.[36,37]

Antibiotic use, one of the most commonly reported outcomes, seemed to be reduced with both zanamivir and oseltamivir in healthy adult and at-risk populations. However, these analyses were dominated either by single trials (one analysis by a large trial done in China[33] that had an unusually high rate of antibiotic use in both arms, and another by data from a single study in children and adolescents with asthma),[37] or data were derived primarily from small subsets of patients from studies with mixed populations (only 575 people in total).[36] There were no data for zanamivir in healthy adult populations. Therefore the results of these analyses should be interpreted

Study or subgroup	Zanamivir Events	Zanamivir Total	Placebo Events	Placebo Total	Odds ratio (95% CI)
Complications needing admission to hospital					
Puhakka 2003[20,21]	48	293	37	295	1·37 (0·86 to 2·17)
Pneumonia					
Puhakka 2003[20,21]	16	293	12	295	1·36 (0·63 to 2·93)
Antibiotic use					
Hayden 1997[11]	11	132	17	144	0·68 (0·31 to 1·51)

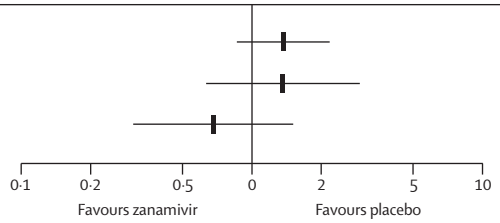

Figure 3: **Complications in the ITT population of healthy adults treated with zanamivir or placebo**
Odds ratios calculated with a Mantel–Haenszel fixed effect model.

cautiously. Overall, there is insufficient information available from which to draw conclusions on the potential of either treatment to reduce the incidence of complications in healthy adult or at-risk populations.

Discussion

Since the completion and consideration of the systematic review and associated decision modelling, NICE have continued to recommend the use of antiviral treatments only for influenza in individuals deemed to be at-risk, defined as people aged 65 years and over, and those aged 6 months and over with comorbidities that make them at risk of influenza-related complications, including chronic respiratory, cardiac, liver, and renal disorders, diabetes, and immunosuppression.[4,40] Given that in the review, neuraminidase inhibitors seem to be effective in reducing symptoms in healthy adults and at-risk populations, and few data were available on the effects on complication rates in either population, the difference between these populations in terms of this recommendation warrants further discussion.

Both zanamivir and oseltamivir reduce the time to symptom alleviation in both healthy adult and at-risk populations. Despite the statistical significance of the results, the clinical value of reducing symptom duration by between half a day and 1 day is debatable, particularly in otherwise healthy adults. The duration of symptoms before starting treatment might alter its effectiveness—starting oseltamivir within 12 h of symptom onset resulted in greater reductions in the time to symptom resolution than did starting later in the progress of the illness.[41,42] The trials included in this Review, where reported, restricted recruitment to individuals who had symptoms for less than 36 h or 48 h, as per licence. Whether those recruited into the trials began treatment within 12 h of the beginning of symptoms is unknown, but this seems unlikely. Greater benefits than found here might therefore be seen if treatment is available early in the course of illness, although delivering early treatment has logistical implications.

The decision by NICE to recommend the use of antiviral treatments in at-risk individuals is primarily on the basis of the risk of influenza-related complications.[4] There was a lack of information about the effect of zanamivir or oseltamivir on complication rates in both the healthy adult and at-risk populations included in our Review. Where data were available, there was little overall difference in complication rates associated with the use of either zanamivir or oseltamivir when compared individually with placebo. However, trials tended to be powered to detect differences of treatment effectiveness in terms of reduction of time to symptom resolution, not to detect differences in complication rates.

One of the most commonly reported outcomes was antibiotic use, which could be thought of as a proxy for the rate of secondary bacterial infections. However, the only analysis on the basis of reasonable numbers of events was of oseltamivir in healthy adults, where the evidence was derived primarily from a non-UK trial with very high antibiotic use overall,[33] and it is unlikely that the result can be generalised to clinical practice in the UK. Furthermore, antibiotic use might not be an accurate or reliable indicator of bacterial infections and complication rates, since policies for their use vary and they might have been prescribed or used inappropriately. The need to reduce the inappropriate use of antibiotics for patients with influenza has been highlighted.[43,44] Therefore, the results of these analyses need to be interpreted with caution.

At present, NICE does not take a societal perspective when evaluating interventions. However, from a wider view, consideration of the societal perspective, particularly of lost working days, is pertinent for a healthy adult population. A recent review[45] estimated that the mean number of working days lost because of influenza or an influenza-like illness ranged from less than 1·5 to 5·9 per episode, which at face value might suggest that treating influenza in healthy adults would have a positive economic effect. However, even if viewed as a public health priority, it is not clear that a recommendation for the use of antiviral treatments would be the most appropriate course of action for seasonal influenza. Given the high specificity of zanamivir and oseltamivir to the influenza virus, the clinical effectiveness and cost-effectiveness of these treatments is likely to be highly dependent on the true positive rate (the number of people who definitely have

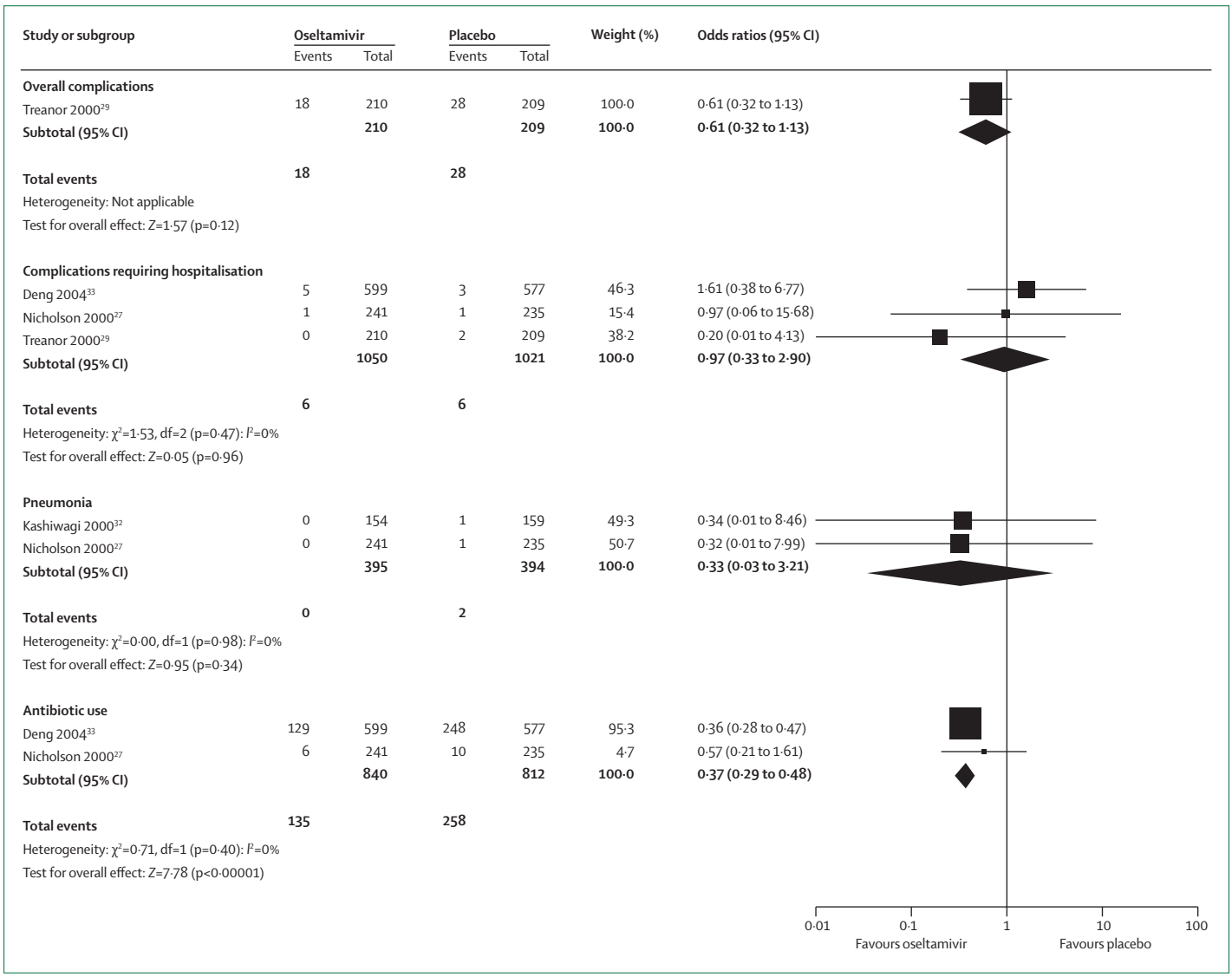

Figure 4: **Complications in the ITT population of healthy adults treated with oseltamivir or placebo**
Odds ratios calculated with a Mantel–Haenszel fixed effect model.

influenza divided by the number presenting with influenza-like illnesses) for influenza in the population presenting to a family doctor. There is some evidence that the accuracy of clinical diagnosis might be improved with increased prevalence of influenza when it has been declared to be circulating in the community.[46] However, if these treatments were made available to healthy adults and their availability publicised, this might lead to an increased number of family doctor consultations during a normal seasonal outbreak, many of which would have an influenza-like illness and not influenza. The increased numbers of influenza-like illness consultations would affect the point at which influenza is declared to be circulating in the community, since this occurs when the number of patients presenting to family doctors with an influenza-like illness crosses a predefined threshold (currently 30 consultations per 100 000), which could, in turn, increase the rate of antiviral-drug use.[47,48]

Several other approaches might be more effective clinically, and in terms of cost, than treating individuals when they present with influenza symptoms. These include vaccination, postexposure prophylaxis (treating people with antiviral drugs after they have been in contact with influenza), expectant treatment (people that have been in contact with influenza are prescribed antiviral drugs to be taken as and when symptoms present), making the drugs available over the counter for purchase, and the introduction of rapid testing in the family doctor surgery before prescription (to allow the treatment only of people who have influenza). There would be advantages and disadvantages to each of these options.

Search strategy and selection criteria

These are described in detail in the Methods section.

Vaccination and postexposure prophylaxis have the advantage of being preventive measures. Vaccination with highly purified subunits (haemagglutinin) of inactivated influenza viruses stimulates the production of antibodies. The vaccine contains components of two types of influenza A and one type of influenza B; these vary each year depending on which are expected to be circulating in the community. In 2008–09 the vaccine components included A/Brisbane/59/2007 (H1N1)-like strain, A/Brisbane/10/2007 (H3N2)-like strain, and B/Florida/4/2006-like strain.[49] A review of reviews[50] concluded that vaccination provided substantial protection against influenza in healthy and at-risk individuals, both children and adults—efficacy against laboratory confirmed influenza ranged from 26% to 87% depending on the vaccine match and age of the individual. An observational study[51] in people with a first diagnosis of lower respiratory tract infection in primary care in the UK, showed a decrease in respiratory infection-related mortality with influenza vaccination (hazard ratio 0·75, 95% CI 0·65–0·87). The main disadvantage of vaccination is that the components in the vaccine might not match the influenza virus in circulation.[50,52,53] Poorly matched vaccines tend to provide reduced protection against influenza.[50] Therefore, although vaccination is effective, a management strategy of vaccination alone might not be sufficiently reliable to control seasonal influenza outbreaks.

If a vaccination programme for healthy adults were to be introduced into the UK, the economic effect would need to be assessed. There is little research into the cost-effectiveness of vaccination for influenza in a UK-based population. A single-blind RCT done in community-dwelling people aged 65–74 years who visited family doctors in Liverpool for influenza-like illnesses during the 1999–2000 influenza season, reported no economic benefit of vaccination.[54] However, the study did not continue for a second year as planned because of the extension of the vaccination policy to all people aged 65 years and over in 2000, therefore the study was underpowered and detected no influenza-related deaths or admissions to hospital during the study period.[54] A more recent study investigated the cost-effectiveness of extending the vaccination policy to healthy adults aged 50–64 years.[55] This study estimated that vaccination prevented 4508 cases of influenza (95% CI 2431–7606) per 100 000 vaccinations per influenza season, which translated to a net cost to the NHS of £653 221 (95% CI £354 575–1 072 257), and £1 139 069 (£27 052–2 030 473) when non-NHS costs were included. The associated costs per quality-adjusted life-year (QALY) were £6174 and £10 766, respectively, illustrating an extension to the vaccination policy is a cost-effective strategy.[55]

A systematic review and meta-analysis showed oseltamivir and zanamivir to be effective in postexposure prophylaxis in households with both adults and children (relative risk 0·19, 95% CI 0·08–0·45 and 0·21, 0·13–0·33, respectively).[56] The cost-effectiveness assessment showed that, in healthy adults, postexposure prophylaxis with zanamivir yielded fewer QALYs, either at a greater cost (dominated) or a greater incremental cost-effectiveness (extendedly dominated). The incremental cost effectiveness of postexposure prophylaxis with oseltamivir was around £34 000 per QALY gained in unvaccinated healthy adults and about £104 000 in previously vaccinated healthy adults.[56]

Expectant treatment and over-the-counter antiviral drugs would likely reduce the time from the onset of symptoms to the giving of drugs and, therefore, might increase their effectiveness in people with influenza.[41,42] This hypothesis needs further investigation. Making drugs available over the counter would offset the cost to the NHS, both in terms of the cost of the drugs and reductions in the need for visits to a family doctor. The reduction in visits to a family doctor might in turn reduce exposure of other people to the influenza virus, and those people with influenza-like illness to other illnesses while they are more vulnerable to secondary infections. However, both of these strategies are likely to increase the volume of drugs being consumed, with much of this increased consumption likely to be by people who do not have influenza.

Any strategy that increases the availability of the drugs to the general public, consequently increasing the rates of inappropriate use, could increase the chances of viral strains developing resistance. Surveillance showed a substantial increase in the rate of resistance of the H1N1 subtype of type A influenza to oseltamivir across Europe over the 2007–08 influenza season. During weeks 1–4 of the 2008–09 influenza season (Dec 28 to Jan 24), 1291 of 1362 isolates (95%) collected from across 30 countries, showed resistance to oseltamivir.[57] The rates of resistance ranged from 14% (China) to 100% (Canada, Morocco, France, Italy, Japan, and the South Korea); in the UK the rate of resistance was 98%. In the USA, resistance was at 12·3% during the 2007–08 influenza season, which increased to 98·5% during the first half of the 2008–09 season.[58] However, the numbers of swabs on which these figures are based are small, and although H1N1 was the prevalent strain circulating in the UK in 2007–08, this was not the case in the previous five seasons, or in 2008–09, and might not be the case in subsequent influenza seasons. It is also worth noting that H1N1 is often associated with milder illness than other influenza subtypes, and the oseltamivir-resistant subtypes remain sensitive to zanamivir.[59,60]

The reason for this sudden increase in the rate of resistance remains uncertain. Sales of oseltamivir to pharmacies, nursing homes, and hospitals in Norway, one of the first countries to show high rates of resistance, showed a high rate of sales in 2005 and 2006, but a low rate of sales before the increase in resistance seen in the 2007–08 season.[61] The higher rates of sales in 2005 and 2006 were attributed to stockpiling in fear of a pandemic,

and were not thought to represent actual use, therefore overuse, or inappropriate use, might not be the cause of the observed increase in resistance.[61] In response to the recent outbreak of swine-origin influenza A H1N1, in May 2009, oseltamivir was made available over the counter in New Zealand. This is the first country to make antiviral drugs available to the public without prescription, and should show the effect of increasing availability of influenza drugs and the rate of oseltamivir resistance.

The use of rapid diagnostic tests would ensure that neuraminidase inhibitors were only prescribed to people with confirmed influenza, reducing inappropriate use. There are a range of tests available that detect influenza but do not distinguish between types, detect one or other influenza type, or can distinguish between influenza A and B. Most rapid tests are immunoassays, which detect influenza viral antigen. According to the US Centers for Disease Control and Prevention, the sensitivity and specificity of rapid tests compared with viral culture vary, median sensitivities are about 70–75% and specificities are about 90–95%, but might be lower in elderly people where viral shedding might be lower.[62] A high specificity and low sensitivity ensures that people who do not have influenza are more likely to have a negative result (so someone who does not have influenza is unlikely to be prescribed antiviral drugs) but means some patients with influenza are likely to be missed. The cost-effectiveness of the use of rapid diagnostic testing has not been investigated; therefore whether savings on the costs of oseltamivir and zanamivir and potential reduction in complications would offset the cost of the rapid diagnostic tests is unclear. Furthermore, the use of rapid diagnostic tests would require seeing a family doctor at their surgery, increasing exposure to and transmission of the virus, and also increasing exposure of those people with the influenza-like illnesses to other illnesses while they are vulnerable to secondary infections.

Conclusion

Although the evidence for clinical effectiveness in healthy and at-risk populations is similar, and the data relating to complications is lacking in both groups, it is reasonable to recommend precautionary treatment to people who are at an increased risk of suffering influenza-related complications. Even if active management of seasonal influenza in healthy adults is deemed a public health priority, recommending the use of antiviral drugs for the treatment of people presenting with symptoms is unlikely to be the most appropriate course of action, given the high specificity of zanamivir and oseltamivir to the influenza virus, and the debatable clinical importance of their affect on symptom duration. Extension of the vaccination policy might be a more appropriate choice for healthy adults, and an assessment of cost-effectiveness that includes societal costs of extending the UK vaccination policy to all working-age adults seems desirable.

Contributors

JB, MC, and CS were responsible for study selection, data extraction, quality assessment, data analysis, and preparation of the article. KN provided clinical advice. AJE provided data from the Royal College of General Practitioners Weekly Return Service and advice on influenza surveillance. SD devised the search strategy and did the searches for published and unpublished work. MW, SP, and LS provided input and managerial support at all stages of the Review. All authors assisted with data interpretation and commented on drafts of the article. JB had full access to all data.

Conflicts of interest

AJE has received funding from the pharmaceutical industry to attend an influenza-related conference. KN participated in advisory board meetings for Novartis Vaccines and for GlaxoSmithKline, he also participated in a Baxter-sponsored symposium on pandemic influenza vaccines, and his research group has received funding from Novartis and Roche. The other authors declare no conflicts of interest.

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