Reducing antibiotic use in influenza: challenges and rewards

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ABSTRACT

Respiratory tract infections are a frequent cause of medical consultations. Although the majority of such infections are viral in aetiology, they account for three-quarters of all antibiotic consumption, since bacterial infections of the upper and lower respiratory tract, notably bronchitis, sinusitis and pneumonia, are the most frequent complications resulting from virus infections, especially influenza in adults and children. The resulting widespread use of antibiotics is a primary factor that drives the emergence of antibiotic resistance at both the local and regional levels. Recent surveys suggest that the proportion of patients with influenza-like illness who receive antibiotics is at least double the actual incidence of the infections for which the treatment is intended. Inappropriate prescribing needs to be tackled by encouraging more rigorous diagnosis, prevention and treatment of viral infections, specifically influenza. Although accurate diagnosis of influenza is challenging, rapid tests to identify the causative pathogen, e.g., RT-PCR tests for influenza viruses, are becoming more reliable and affordable. The use of antiviral drugs, particularly neuraminidase inhibitors, is a specific and effective way of preventing and treating influenza, and has been shown to reduce the incidence of complications and associated antibiotic use. In contrast to bacterial resistance to antibiotics, viral resistance to neuraminidase inhibitors is low, and their high specificity means that they cannot exert selection pressure on any other species. The widespread adoption of these principles may have a significant effect on antimicrobial use and resistance.

Keywords Antibiotic use, influenza, neuraminidase inhibitors, resistance, respiratory tract infection, review

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INTRODUCTION

The number of antibiotic-resistant microorganisms has increased in the past decade as a result of increased use of antibiotics in children and the excessive use of antibiotics in adults. The majority of antibiotics prescribed to adults in ambulatory practice are for acute respiratory tract infections (RTIs), particularly acute sinusitis, acute pharyngitis, acute bronchitis and non-specific upper respiratory tract infections (URTs), including the common cold [1]. Influenza is associated with excess rates of hospitalisation and mortality during disease outbreaks, particularly in the elderly and in children [2,3]. This burden stems largely from secondary complications arising from the primary viral infection, the most common of which are bacterial infections of the respiratory tract, notably pneumonia and bronchitis. In children, otitis media is the most common complication of infection. The level of antibiotic prescribing in patients with influenza still appears to be seriously out of proportion to the number of bacterial infections that actually occur. This review considers the challenge of appropriate antimicrobial prescribing in patients with influenza infection.

SECONDARY BACTERIAL INFECTIONS IN INFLUENZA

The most commonly encountered bacterial infections following primary influenza infection in adults principally affect the respiratory system. Susceptibility to secondary infection of the lungs and bronchi by bacteria, e.g., Streptococcus pneumoniae and Haemophilus influenzae, seems to result from increased binding of bacteria to the basal membrane of the respiratory epithelium [4]. This
may be the result of direct viral damage [5] or viral activation of receptors on the epithelial cell that can directly bind bacteria, e.g., the receptor for platelet-activating factor [6]. Influenza virus has also been shown to increase susceptibility by reducing neutrophil function [7] and by increasing the production of cytokines such as interleukin-10 [8]. A pneumococcal enzyme, neuraminidase, improves colonisation by cleaving N-acetylneuraminic acid from mucin, thereby decreasing the viscosity of the mucus. Neuraminidase also cleaves glycolipids, glycoproteins and oligosaccharides, and is thus thought to bring about exposure of N-acetylglycosamine receptors on the host epithelial cells [9]. The neuraminidase activity of viruses such as influenza and parainfluenza viruses might thereby contribute to the increased adherence of pneumococci that can be observed during viral infections [10].

Estimates of the incidence of influenza-associated RTIs vary considerably, depending on factors such as country, season, age group and viral strain. A comparison of infection rates in over 140,000 cases of influenza and influenza-like illness (ILI) with matched controls in adults and children in the UK General Practice Research Database revealed an excess of influenza-associated bacterial infections [11]. The great majority of these were URTIs and acute bronchitis (incidence of 5.51% and 1.48%, respectively), followed by otitis media (1.05%) and pneumonia (0.38%). A pooled analysis of >2400 patients infected with influenza virus who took part in ten clinical studies revealed higher incidence values of 8.2% for bronchitis and 1.8% for pneumonia [12]. In contrast, an incidence of 19% was estimated for acute bronchitis during the 1989 UK influenza epidemic [13], and another general practice survey of patients with influenza or ILI during the Italian winter epidemic of 1998–1999 revealed that 15% had bronchitis, and a further 15% had URTIs, while sinusitis and pneumonia were reported in 3.2% and 1.4% of patients, respectively [14].

Although much less common than bronchitis, bacterial pneumonia, often occurring in tandem with viral pneumonia, has more serious consequences. The infecting species is typically Staphylococcus aureus, but Strep. pneumoniae and H. influenzae are also commonly isolated [15]. Patients with bacterial pneumonia are very likely to need hospital treatment, and the mortality rate is high, particularly in patients who are elderly or who have cardiovascular or respiratory illness [3], in whom pneumonia is much more frequent than in other adults. Of 178 elderly individuals residing in a group of Canadian nursing homes who were infected with influenza during the 1999–2000 outbreak, 37 (21%) had bacterial pneumonia [16].

Secondary bacterial respiratory tract infections are a frequent complication in children as well as adults, but the most common bacterial infection associated with childhood influenza is otitis media. In a clinical study of children aged 1–12 years, tympanometrically confirmed otitis media was found in 37 (18.5%) of 200 children in the placebo group [17], which is the same incidence as reported in influenza-positive children up to 14 years of age during two consecutive seasons [18]. In a study of vaccine efficacy, 20 (21%) of 95 children aged 1–5 years in the placebo group had influenza-associated otitis media [19]. Secondary infections in children with influenza increase the demand for antibiotics, accounting, on aggregate, for up to 30% of all excess use during the influenza season [20]. During the 1918–1919 pandemic, a second wave of infection spread globally between September and November 1918, and had a high fatality rate [21,22]. Many deaths were the result of secondary bacterial pneumonia [23].

THE NEED TO REDUCE INAPPROPRIATE ANTIBIOTIC USE

Since their discovery during the 20th century, antimicrobial agents have substantially reduced the threat posed by infectious diseases. These gains are now seriously jeopardised by the emergence and spread of microbes that are resistant to effective first-choice drugs. Reducing resistance rates by limiting and optimising therapy of RTIs is an important strategy.

Strep. pneumoniae is the most common bacterial pathogen in RTIs, being implicated each year in >500,000 cases of pneumonia and >7 million cases of otitis media in the USA alone [24]. Worldwide, pneumococcal disease is one of the leading causes of mortality, particularly among children, the elderly and those with co-morbid illnesses. Increasing resistance to penicillins and macrolides, reaching 30–40% among isolates in many areas, is therefore of considerable concern [25]. Macrolide resistance in Strep. pneumoniae now
exceeds penicillin resistance in some regions, and continues to increase. Pneumococcal fluoroquinolone resistance remains rare, but will inevitably increase as these agents are employed more widely to treat RTIs.

The selection of antibiotic resistance is inevitable. The overall volume of antibiotic prescribing is the primary factor driving resistance at both the local and regional levels, although other influences, notably clonal spread, complicate epidemiological analysis. It is therefore necessary to educate prescribers concerning the need to avoid antibiotic therapy when there is no clinical indication. The problems of resistance to penicillins and macrolides, arising from antibiotic misuse and overuse, are well-established [26–31], and advice on how to counter these trends is readily available in treatment guidelines [32–35]. Whether such advice has brought about changes in prescribing practice is a moot point. For example, a large general practice survey during the Italian winter epidemic of 1998–1999 found complications in c. 35% of patients with influenza or ILI. However, c. 36% of the patients received antibiotics, suggesting that the rate of prescribing was appropriate [14]. A survey in the UK of >100 primary-care practices showed that antibiotic use for respiratory infections fell by 45% between 1994 and 2000, but that this was more the result of a reduction in consultations than a reduction in inappropriate prescription [36]. The National Ambulatory Medical Care Surveys (NAMCS) in the USA showed a reduction in prescribing rates for common respiratory infections in children and adolescents during 1990–2000 [37], but the picture was less clear in adults, with decreases in the use of penicillins, cephalosporins and erythromycin between 1992 and 2000, but large increases in the use of other macrolides and quinolones [38]. During the same decade, antibiotic use in France, which is the biggest consumer of antibiotics per capita in Europe, increased slightly [39]. In Canada, although the prevalence of penicillin non-susceptibility stabilised in association with a reduction in β-lactam use, an increase in amoxycillin non-susceptibility was observed, beginning in 2001. This was caused by the proliferation of the 19F-14 clone (a vaccine serotype). Erythromycin resistance was correlated strongly with use of azithromycin and clarithromycin, while an inverse relationship existed for erythromycin. Non-susceptibility to tetracyclines continued to increase in Canada during the surveillance period, despite decreasing use of these agents. This finding has been noted in previous surveillance studies, and may be best explained by co-selection of the tetracycline resistance gene tet(M) with the macrolide resistance gene erm(B). Fluoroquinolone resistance rates have stabilised in Canada since 1998, despite increasing use of these agents. A possible explanation is the increase in the use of fluoroquinolones that have greater activity for the treatment of RTIs caused by pneumococci (46th Interscience Conference on Antimicrobial Agents and Chemotherapy, abstract C2-433).

Antibiotic misuse

The use of antibiotics to treat a viral infection such as influenza is doubly misguided, since antibiotics have no effect on an infection of solely viral origin, and the use of antibiotics will exert selection pressure on bacteria carried by the treated individual, adding to the risk of generating resistance. A survey of US primary-care patients who received an antibiotic for a respiratory tract infection reported no overall improvement in several patient-reported outcomes or follow-up clinic visits [40]. Similar findings were reported for patients with ILI during the 1999–2000 influenza epidemic in France [41]; those who received antibiotics did not benefit in terms of symptom relief, absence from work or avoidance of follow-up visits.

The evidence of continuing misuse of antibiotics in an attempt to treat viral respiratory infections such as influenza is of particular concern. An analysis of NAMCS data from 1992 revealed that acute rhinosinusitis and acute bronchitis, which are nearly always caused by viruses, accounted for 21% of all antibiotic prescriptions for adults [42]. Despite a call in 1997 to address inappropriate prescribing [43], a survey of >15 000 adults making outpatient visits in North Carolina, USA in 2000–2001 for influenza or acute URTIs, bronchitis, pharyngitis or nasopharyngitis revealed that 63% received oral antibiotics [44]. A nationwide US survey published a year later showed that 38% of >6.5 million visits (primary practice, outpatient and emergency room) by children and adults aged 5–49 years with a sole diagnosis of influenza were associated with an antibiotic prescription [45].
America. The majority of antibiotics prescribed in France during 1992–2000 were for URTIs, i.e., conditions very likely to be viral in origin [39]. A survey of a large general practitioner database in Italy by Mazzaglia et al. [46] reported a high rate of antibiotic prescribing to adolescents, adults and elderly patients for acute respiratory infections (63%) and, more disturbingly, for influenza, croup and common cold (44%). Even higher rates were revealed by a survey of hospital emergency departments in Spain [47], in which an expert panel judged that >70% of prescriptions for influenza, croup or colds were inappropriate.

Studies in children provide a similarly discouraging picture. Although 18.5% of 392 children with confirmed influenza in Greece during the influenza season were found to have otitis media, antibiotics were prescribed to 39.5% of these children, most commonly to those aged <2 years [18]. Similar levels of prescribing were revealed by a representative survey (using 1992 NAMCS data) of US children, which found that antibiotics were given to 44% of children and adolescents aged <18 years who had colds, and to 46% of those with URTIs [48]. During the 2002 epidemic in France, a survey of children aged <3 years admitted to emergency departments with ILI considered that >80% of the prescriptions for antibiotics were inappropriate [49].

Diagnostic challenges

One factor leading to the inappropriate prescribing of antibiotics for influenza is the difficulty of making a reliable diagnosis of the disease. Distinguishing between viral and bacterial respiratory infections on the basis of clinical features alone is very difficult. Scoring systems for sore throat symptoms have been tested and validated [50], but have not proved easy to use in practice [51]; thus, avoiding needless use of an antibiotic requires tests to identify the infecting pathogen. For example, treatment of sore throats with penicillin V is only effective in those individuals who test positive for group A streptococci (GAS) [52], so rapid tests for detection of GAS that are highly sensitive and specific can improve the efficiency of prescribing. Increased levels of C-reactive protein can also indicate the presence of bacterial infection, and use of rapid tests for C-reactive protein has been shown to reduce antibiotic prescribing in patients with sinusitis [53].

Eliminating the possibility of bacterial infection still leaves the challenge of identifying whether influenza virus is the cause of an illness, since patients infected with other respiratory viruses, e.g., respiratory syncytial virus, present with clinical features very similar to those of influenza, including complications such as secondary infections [18]. The sensitivity and predictive value of a given clinical definition of influenza vary according to how widely influenza and other respiratory pathogens are circulating in the community [54], and the clinical features of ILI are usually not sufficiently specific to confirm or exclude influenza [55]. A case-definition including cough and fever was 78% sensitive and 55% specific (and had 87% predictive value) for laboratory-confirmed influenza during the Canadian influenza season of 1998–1999 [56]; similarly, the combination of cough and fever had a positive predictive value of 79% in a retrospective analysis of subjects in international clinical trials [57]. The inaccuracy inherent in the clinical diagnosis of influenza underlines the importance of laboratory tests to confirm the identity of the pathogen. Rapid tests based on immunoassays or neuraminidase activity can detect influenza A and B viruses, but the sensitivity and, to a lesser extent, specificity of immunoassays is inferior to that of viral culture or RT-PCR assays [58]. RT-PCR is more sensitive [59], and may be adopted routinely as it becomes more affordable. Serology and viral culture have greater value for retrospective confirmation of infection, e.g., in surveillance studies.

ANTIVIRAL THERAPY

The neuraminidase inhibitors (NIs) zanamivir and oseltamivir are antiviral agents that were developed during the 1990s specifically for the treatment and prophylaxis of influenza. These agents have a therapeutic advantage over older antiviral drugs, e.g., rimantadine and amantadine, in that they are active against influenza B as well as influenza A viruses, they are tolerated much more readily, and the emergence of resistance occurs infrequently. Clinical trials have established that NIs are effective in reducing the severity and duration of influenza in adults and adolescents [60–63] as well as in children [17,64]. Several large controlled studies of the use of NIs for disease prevention have demonstrated that zanamivir and oseltamivir are effective in
preventing the clinical symptoms of influenza in healthy adults when the drugs are used either as prophylaxis for close contacts, e.g., household members after exposure, or as seasonal prophylaxis in the community. These studies revealed that the incidence of both influenza A and influenza B infections was reduced by 70–90% when NIs were used for prophylaxis either before or after exposure to the virus [65].

An additional benefit of treating influenza with NIs is the reduction in the need for antibiotics to treat secondary infections. An early randomised controlled study in southern hemisphere countries revealed that zanamivir treatment reduced the relative risk of antibiotic use by 13% as compared with a placebo, and that the risk reduction was 65% in a subgroup of high-risk patients [66]. These findings were confirmed in a later pooled analysis of seven clinical studies of the use of zanamivir for the treatment of adults and adolescents with influenza, which showed a relative risk reduction of 26% as compared with a placebo [61]. A similar degree of reduction in antibiotic use (26.7%) was seen in a pooled analysis of ten treatment studies of the use of oseltamivir in adults, adolescents and the elderly [12]; in addition, only 4.6% of influenza patients treated in this study reported bronchitis, lower respiratory tract infections or pneumonia, as compared with 10.3% of those receiving a placebo [12]. These benefits have also been shown in clinical practice. A retrospective cohort survey, using claims data from a US health insurance database [67], investigated antibiotic use in individuals diagnosed with IILI, and showed a relative risk reduction of 11% for the oseltamivir group as compared with the no-antiviral group; the incidences of pneumonia in the two groups were 1.3% and 2.6%, respectively, representing a risk reduction following treatment of 28% (Table 1) [67].

As described above, elderly patients and adults with influenza and a co-existing illness, e.g., lung or heart disease, have more frequent infections and are heavier users of antibiotics. Treatment with NIs has been shown to be particularly beneficial in this group. For example, in a pooled analysis of high-risk adults and children, mostly with chronic respiratory conditions, who took part in clinical trials of zanamivir [68], the incidences of complications requiring antibiotic treatment in the influenza-positive patients in this analysis were 13% for the treated group and 24% for those receiving a placebo, representing a reduction in relative risk of 43%. Similar results were seen in a study of nursing home residents taking antiviral agents as treatment or prophylaxis for influenza [16]. Despite the small number of individuals included in the analysis, residents who received oseltamivir within 48 h of the onset of symptoms, or who were taking oseltamivir as prophylaxis, had significantly lower rates of antibiotic use and fewer complications and deaths than individuals in the other groups. Children with influenza accrue similar benefits from NI treatment to adults. Oseltamivir reduced the incidence of complications requiring antibiotics in children by 40% as compared with placebo, and reduced the relative risk of otitis media by 44% [17].

The level of success achieved in shortening the duration of influenza episodes with NI treatment depends very closely on how early treatment can be initiated, reflecting the importance of inhibiting viral replication as soon as possible after infection. This was first reported in a phase III clinical study of zanamivir, which, whether administered by inhalation or by a combination of the inhaled and intranasal routes, resolved major influenza symptoms in 4 days (median) when given within 30 h of the onset of symptoms, as compared with a median of 5 days when given later [60]. Minimising the delay before the initiation of treatment also improves treatment effectiveness for oseltamivir; this was first shown in the study by Nicholson et al. [62] and then subsequently confirmed in the IMPACT study [69]. The latter study specifically analysed the effect of treatment initiation time (ranging from 0–8 h after symptom onset to 36–48 h) on

<table>
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<th>Reference</th>
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<tr>
<td>MIST Study Group [66]</td>
<td>Randomised, controlled trial</td>
<td>Zanamivir</td>
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<td>Kaiser et al. [12]</td>
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<td>Nordstrom et al. [67]</td>
<td>Retrospective cohort study</td>
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Table 1. Reductions in the relative risk of antibiotic use in treatment studies of oseltamivir or zanamivir as compared with placebo in patients with influenza-like illness.
outcome in 1426 adults and adolescents; the largest reductions in illness duration and symptom severity were seen in those with the earliest treatment initiation (Fig. 1). The same relationship was also demonstrated in a study of over 3000 Japanese adults and adolescents [70].

Although the possibility exists of triggering the development of resistant viral strains with antiviral treatments, the risk is much lower than that for the generation of resistance in bacteria following the use of antibiotics and is easily outweighed by the treatment benefits. Furthermore, the high specificity of NIs for influenza viruses means that these agents cannot exert selection pressure on any other viruses. Administration of sub-potent doses of an antiviral agent in the presence of the target pathogen may trigger resistance, as is the case for antibiotics; however, the resulting mutant virus usually has reduced fitness (e.g., reduced infectivity, reduced transmissibility) [71–74].

PATHS TO IMPROVEMENT

There are two ways of responding to the challenge posed by influenza infections and the misuse of antibiotics: first, by using NIs to either minimise the severity and length of the influenza illness or to prevent influenza in the first place; and second, by the use of clinical and diagnostic tests to identify a patient who has influenza and does not require an antibiotic. Experience in Finland and Iceland has already shown that bacterial resistance rates decrease following a reduction in antibiotic use on a national scale. In Finland, the use of macrolides decreased by 42% between 1991 and 1992, and then remained steady for the next 4 years; during 1991–1996, the incidence of erythromycin resistance in GAS isolated from throat swabs decreased by c. 50% [75]. Preliminary data have indicated that a similar programme in Iceland resulted in a decrease in the incidence of penicillin-resistant pneumococci, from 20% in 1993 to 16.9% in 1994 (K. Kristensson, M. A. Hjamasdottir and T. H. Gudnason, unpublished results).

The number of antibiotic courses prescribed appropriately for cases of URTI, bronchitis, otitis media and other infections could also be limited by preventing the infections themselves. It is evident that shortening the duration and severity of influenza illness in more patients through wider adoption of effective antiviral therapy with NIs should also cause the incidence of secondary bacterial infection to decrease, thereby directly reducing the number of antibiotic courses prescribed to these patients. This dual approach could potentially reduce the risk of antibacterial resistance while more effectively treating influenza and its complications.

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REFERENCES


