

Influenza infection and COPD

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Abstract: Influenza is a disease with global impact that causes enormous morbidity and mortality on an annual basis. It primarily infects the respiratory tract and causes a broad range of illness ranging from symptomless infection to fulminant primary viral and secondary bacterial pneumonia. The severity of infection depends on both the virus strain and a number of host factors, primarily age and the presence of comorbid conditions such as cardiopulmonary disease. The mortality and utilization of healthcare resources associated with influenza is concentrated in the elderly and those with coexisting disease such as chronic obstructive pulmonary disease (COPD). Increasing use of vaccination and the development of new antiviral drugs hold out hope that the burden of disease associated with influenza can be reduced. However the constant emergence of new influenza strains and the current risk of avian influenza pandemic serve as warnings that influenza will remain a serious pathogen for the foreseeable future.

Keywords: COPD, influenza, exacerbations.

Introduction

Viral infections of the respiratory tract are the commonest disease syndrome in humans. A number of different viruses can infect the human respiratory tract. Most of them cause self-limiting illnesses such as the common cold or acute bronchitis. The severity of illness depends on the particular virus and on host factors. In patients with airway diseases such as chronic obstructive pulmonary disease (COPD), the morbidity caused by respiratory virus infection is considerably greater. Among respiratory viruses, influenza has the greatest impact in terms of both the morbidity and mortality that it causes. Although influenza affects all age groups, much of the morbidity and mortality are concentrated in high-risk groups such as the elderly and those with comorbid disease, particularly cardiovascular and pulmonary disease. In this review we will consider the impact of influenza in one particular high-risk group, ie, patients with COPD.

Pathoepidemiology of influenza virus infections

Influenza infections typically occur in both pandemic and inter-pandemic forms. Pandemics occur infrequently and are associated with enormous mortality on a worldwide scale whereas epidemic influenza occurs every winter in the temperate zones of the northern and southern hemispheres. While less dramatic than the impact of a pandemic, epidemic influenza is still the cause of considerable mortality, and as it occurs on an annual basis, the total cumulative burden of disease is higher than for the more infrequent pandemics.

Pandemics

Influenza pandemics are believed to have occurred throughout history with the first recorded documentation of a probable influenza pandemic occurring in the 16th

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century (Potter 2001). There have been 3 pandemics in the 20th century with the last one occurring in 1968. The most dramatic pandemic occurred in 1918–1920 caused by the H1N1 influenza strain or the so-called ‘Spanish flu’. Although accurate figures are not available for many parts of the world, the pandemic is estimated to have infected 50% of the world’s population, with 25% suffering a clinical infection and to have caused 40–50 million deaths (Palese 2004). Nearly half of the influenza-related deaths during the pandemic occurred among young, healthy adults for reasons that remain obscure but are suspected to be related to secondary bacterial infection and poor sanitary conditions due to the First World War.

A second pandemic occurred in 1957 when a new influenza virus H2N2 with two unknown surface proteins to which there was little or no pre-existing immune protection in the human population appeared. The pathogenicity of the 1957 strain was less than the one responsible for the 1918 pandemic and in addition antibiotics were available to treat complications such as bacterial pneumonia. Most deaths occurred in the very young and very old and estimates suggest that 2 million people died (Lipatov et al 2004). In 1968 another change in the surface glycoproteins led to the emergence of a H3N2 strain that again caused the virus to become pandemic, resulting in an estimated global excess mortality of around 1 million.

Many scientists believe it is only a matter of time until the next influenza pandemic occurs. Fears of a further pandemic have been heightened by the emergence of a highly pathogenic strain of avian influenza (H5N1) in Asia, and the occurrence of cases of transmission of this virus from birds to humans. In 1997 this strain of avian influenza virus began circulating in poultry populations in Hong Kong and was halted only by the slaughter of 1.5 million chickens in the territory. Eighteen humans were infected with the virus and of these 6 died. From December 2003 to August 2004, outbreaks of highly pathogenic avian influenza A occurred among poultry in nine countries in Asia (Republic of Korea, Vietnam, Japan, Thailand, Cambodia, Laos, Indonesia, China, and Malaysia). This was followed by spread to other continents with reports of H5N1 influenza in both domestic and wild birds from Russia (July 2005), Kazakhstan and Mongolia (August 2005), Turkey and Romania (October 2005), and Africa and Western Europe (February 2006). Since the avian influenza outbreak, the main concern has been that the virus will either mutate to allow efficient transmission to mammals, or reassort gene segments with human influenza viruses during the coinfection of a single

host, resulting in a new virus that would be easily transmissible from person to person. Such events are believed to have preceded the previous influenza pandemics. To date avian to human transmission has occurred in those heavily exposed to infected birds, but only isolated cases of human-to-human infection have been reported (Normile 2006). As reported by the World Health Organization (2006), the total number of human cases of avian influenza is 244, with 143 deaths. These figures give a mortality rate in humans for this influenza strain of 57%, however a recent report has suggested that significant numbers of mild human infections may have occurred and therefore the actual mortality rate may be much less (Thorson et al 2006).

Epidemics

Annual influenza epidemics occur in the temperate zones and are associated with a considerable burden of disease. Accurate assessment of the impact of epidemic influenza on mortality and morbidity is difficult for a number of reasons. The symptoms of influenza infection are nonspecific and clinically it cannot be distinguished from other respiratory viruses such as parainfluenza virus and respiratory syncytial virus (RSV) that circulate at the same time of year. Laboratory confirmation of influenza virus infection is rarely available in routine clinical practice. In addition many influenza-associated deaths occur from secondary complications in patients with significant underlying comorbidity so influenza is rarely mentioned as a cause of death on death certificates. Consequently the impact of influenza has been determined indirectly using statistical models with two approaches commonly used. The first approach calculates excess mortality during influenza seasons, excess mortality being defined as the sum of deaths during the influenza season that exceeds a baseline of expected deaths in the absence of influenza. This has the disadvantage that deaths may be due to other factors such as other winter viruses and cold temperatures that are present at the same time as the influenza season. An alternative approach has been to use hospitalization and death certificate statistics for pneumonia and influenza, on the assumption that the majority of pneumonia is influenza-related in the influenza season. The downside of this approach is that many influenza-related deaths may not be classified as either pneumonia or influenza and so it underestimates the total burden of disease attributable to influenza. An American study of monthly mortality reports over a 40-year period reported excess mortality in four disease classes (pneumonia and influenza, ischemic heart disease, cerebrovascular disease, and diabetes) that accounted for approximately 80% of

excess all-cause mortality during winter seasons (Reichert et al 2004). Seasonal variations have also been noted in the incidence of stroke (Lanska and Hoffmann 1999) and an association between respiratory tract infection and myocardial infarction reported (Meier et al 1998). Therefore the excess mortality associated with influenza is likely to extend beyond deaths reported as due to influenza and pneumonia only. It has long been recognized that total mortality increases markedly during the influenza season (Ivan and Duda 1977). Surveillance data from a number of countries has shown a strong correlation between the incidence of reports of influenza-like illness and death rates. Influenza-associated excess mortality in the USA in six epidemics from the winters of 1972/73 to 1980/81 was estimated to be 200,000, with 80%–90% of excess mortality occurring in persons over 64 years old (Lui and Kendal 1987). Similar data have been obtained from other countries. In the UK it is estimated that influenza is associated with 12,500 excess deaths per year (Fleming 2000).

More sophisticated models have been used that attempt to correct for other factors associated with winter mortality to obtain a more accurate picture of influenza-associated mortality. A close relation between excess winter-season mortality and clinical reports of influenza-like illness has been reported that was independent of the effect of temperature (Tillett et al 1983).

A study using national mortality and viral surveillance data to estimate annual influenza- and RSV-associated deaths in the USA estimated that in the 1990–1991 through 1998–1999 seasons, influenza alone was associated with an annual mean of 8097 pneumonia and influenza deaths (9.8% of these deaths). For underlying respiratory and circulatory deaths, there was an annual mean of 36,155 influenza-associated deaths, (3.1% of these deaths) and for all-cause deaths there was an annual mean of 51,203 influenza-associated deaths, representing 2.2% of all mortality (Thompson et al 2003). This study also found that influenza-associated deaths in the USA increased substantially from the 1976–1977 through 1998–1999 seasons, probably due to the aging of the population. Persons in the over 85 age group are 16 times more likely to die of an influenza-associated all-cause death than persons aged 65 to 69 years (Thompson et al 2003). Other studies have also shown that influenza-attributable mortality rates increase with age among persons aged 65 years or older (Nordin et al 2001), and mortality is higher in those with underlying medical conditions such as COPD, congestive cardiac failure, and diabetes.

Although the mortality associated with influenza is undoubtedly considerable, mortality figures represent only a fraction of influenza's total health burden in a population. The effect of influenza on healthcare utilization such as hospitalizations, office visits, and medication use in adults has been less well documented than the impact on mortality. A study of 26 consecutive influenza seasons from 1969–1970 through 1994–1995, estimated that 3 million excess hospitalizations due to pneumonia and influenza occurred in the USA (Simonsen et al 2000). Although average rates of excess hospitalizations were higher in the elderly (174/100,000 population) than in those aged <65 years (33/100,000 population), the younger age group accounted for more than half of the total number of influenza-related hospitalizations. In addition, the average number of excess hospitalizations was 50% higher during seasons when more pathogenic strains of influenza A were the predominant circulating virus, compared with those dominated by influenza B or milder strains of influenza A. The effect of influenza on healthcare utilization and medication use was assessed in a study of respiratory illnesses in cohorts of healthy elderly patients (65 years of age) and high-risk adults (those with chronic heart or lung disease) over 4 consecutive winters. Among the healthy adults, 42% of those with a confirmed influenza infection required an office visit, 8% an emergency room visit, and 33% an antibiotic. In the high-risk group the corresponding figures were 60%, 10%, and 60% respectively. Twenty percent required hospitalization (Falsey et al 2005). These figures reflect the greater impact of influenza in high-risk groups, which includes patients with COPD.

Virology

Influenza viruses are negative stranded, segmented, enveloped RNA viruses belonging to the *Orthomyxoviridae* family and 3 virus types: A, B, and C exist. Influenza A and B are the main human pathogens whereas influenza C is rarely pathogenic for man and has no animal reservoir. Virus particles consist of three major components: the viral envelope, the matrix protein (M1), and the viral ribonucleocapsid. Three transmembrane envelope proteins: hemagglutinin (HA), neuraminidase (NA), and M2 are anchored in the lipid bilayer of the viral envelope. HA provides the receptor-binding site and elicits neutralizing antibodies. Cleavage of HA is essential for fusion and virus infectivity. NA removes the cell surface receptor (sialic acid) and is critical for the release of virus particles from the cell surface and spread of virus. M2 is a minor protein component of the viral envelope that functions as an ion channel crucial during uncoating. Influenza viruses

are further classified into subtypes depending on the arrangements of the HA and NA surface glycoproteins. To date 16 HA subtypes (H1–H16) and 9 NA subtypes (N1–N9) have been identified. Human influenza viruses are limited to three HA (H1, H2, and H3) and two NA (N1 and N2) subtypes, whereas birds are the predominant hosts for the other subtype strains. Variations in these surface glycoproteins mean that new antigenic strains of influenza are continually appearing and account for the occurrence of yearly epidemics and pandemics. Variation can arise through the two processes of antigenic drift and antigenic shift. Antigenic drift occurs in both influenza A and B and involves the accumulation of point mutations in the surface glycoproteins, leading to the evolution of new strains of virus. The new strains are related to those circulating during preceding epidemics, but once evolved far enough away from preceding strains, the virus evades immune recognition which leads to repeated outbreaks. Antigenic shift occurs when mixed infection in animal hosts allows mixing of genes between different subtypes and therefore occurs with influenza A only, as B has no animal host. This process can result in major changes in the surface glycoproteins and emergence of a virus that is antigenically distinct from previous human viruses, allowing escape from herd immunity. As pigs can be infected with both human and avian influenza viruses, it is believed that this may be the source of new virus subtypes derived by antigenic shift. This can also occur in humans exposed to high levels of avian flu, or by gradual adaptation of an avian strain through repeated minor ‘forays’ into humans before it finally adapts sufficiently to ‘take off’. Antigenic shift is the process underlying the occurrence of influenza pandemics in human populations. Human influenza A viruses in the first half of this century carried H1N1 surface antigens but in 1957 the virus acquired the genes for the H2 and N2 antigens by reassortment of its genome with an avian virus. As the human population had no immunity to these new antigens the virus caused the ‘Asian flu’ pandemic. A similar antigenic shift gave rise to the H3N2 virus and the pandemic of 1968. The arrangement of the membrane proteins also influences the virulence of influenza strains. The H3N2 strain of influenza A is the most virulent of the recently circulating influenza viruses and the predominance of this strain during the 1990s may have been another important factor contributing to the increase in influenza-associated deaths.

Influenza and COPD

Chronic obstructive pulmonary disease affects an estimated 600,000 people in the UK and accounts for 30,000 deaths per

year. In the USA it is estimated to affect 24 million people and is the 4th leading cause of morbidity and mortality (Renard et al 2002). On a worldwide basis, it is estimated that COPD will be the 3rd leading cause of mortality by the year 2020 (Murray and Lopez 1997). Much of the morbidity and mortality associated with COPD are due to acute exacerbations. In the USA, COPD is responsible for an estimated 1.4 million emergency department visits and almost 662,000 hospitalizations (1.9% of total hospitalizations). An additional 2.5 million hospitalizations (7.0% of total hospitalizations) had COPD listed as a contributing cause. However the burden of disease of COPD is proportionately even greater in the elderly. In patients aged 65 to 75 years and ≥ 75 years, COPD was a primary or contributing cause of hospitalization in 19.9%, and 18.2%, respectively, of total hospitalizations (Mannino 2002). In the USA, 64% of the direct costs of COPD are accounted for by hospitalizations and emergency room visits (Sullivan et al 2000). In the UK, exacerbations are the largest single cause of acute respiratory admissions. In 2003 there were almost 100,000 hospital admissions for acute exacerbations of COPD with a mean hospital stay of 10 days resulting in almost 1,000,000 bed days (Donaldson and Wedzicha 2006).

Exacerbations can be caused by a number of factors but the commonest cause is infection of the tracheo-bronchial tree. Historically COPD exacerbations have been considered as being predominantly caused by bacteria, however recent evidence has suggested that respiratory viruses are associated with 40%–60% of COPD exacerbations (Seemungal et al 2001; Rohde et al 2003; Tan et al 2003). There is little evidence published to date regarding the specific role of influenza virus infection in COPD, but studies of influenza in patients with a nonspecific diagnosis of chronic lung disease have provided evidence of the impact of influenza in COPD.

Indirect studies of influenza in COPD exacerbations

Much of the evidence of an association between influenza infection and adverse outcomes in COPD is derived from studies of influenza in the elderly and in patients with chronic lung diseases. These studies include patients with a number of diagnoses, including asthma and bronchiectasis, so the results cannot be extrapolated to COPD alone. Many of these studies have had the primary aim of evaluating the efficacy of influenza vaccination but the outcome measures in the nonvaccinated group provide valuable data on the

impact of influenza in COPD. Among patients hospitalized with acute respiratory disease during an influenza epidemic chronic pulmonary disease is the most common underlying disease (Glezen et al 1987), suggesting that pulmonary disease including COPD is the most important risk factor for an adverse outcome with influenza infection.

A US study used viral surveillance to evaluate the contribution of influenza to rates of hospitalization, mortality, outpatient visits, and antibiotic courses among those enrolled in Medicaid over 4 years. Among patients with chronic lung disease there were an estimated 13 and 23 excess hospitalizations per 1000 persons per year due to influenza in the age groups 50 to 64, and 65 years or older, respectively. Among those with chronic lung disease 65 years or older, there were 23.8 (95% confidence interval [CI], 10.1–37.5) deaths due to influenza per 10,000 persons. The estimated increase in antibiotic prescriptions attributed to influenza ranged from 64 to 108 prescriptions per 1000 persons with chronic lung disease. Influenza virus and RSV together accounted for 9% of deaths in those 65 years or older (Griffin et al 2002). Another study of adults aged 65 with a diagnosis of chronic lung disease enrolled in a health maintenance organization found that among those not vaccinated for influenza the rate of hospitalization for pneumonia and influenza doubled from 55 per 1000 person years during the noninfluenza season to 110 hospitalizations per 1000 person-years during the influenza season (Nichol et al 1999). A study from Hong Kong estimated the excess of hospital admissions attributable to influenza in patients over 65 years with cardiorespiratory disease, but differentiated COPD from asthma. Influenza activity was an independent significant factor affecting hospital admission rates for COPD but not for asthma (Yap et al 2004). This would suggest that in this age group the impact of influenza in patients with chronic respiratory disease occurs predominantly in COPD patients.

Direct studies of Influenza in COPD exacerbations

Older studies of the role of respiratory viruses in COPD exacerbations suggested that they are responsible for a minority of exacerbations only, with viruses detected in 18% of episodes of acute respiratory illness (Smith et al 1980). However more recent studies using modern diagnostic methods such as polymerase chain reaction (PCR) have achieved much higher viral detection rates and the association of virus infections with COPD is much higher than previously suspected. The first report using PCR detected a virus in 39% of COPD

exacerbations in a cohort of patients with moderate to severe COPD (Seemungal et al 2001). The most common viruses detected were rhinoviruses (58% of viruses) and influenza was detected in 16% of virus-associated exacerbations. 64% of the exacerbations were preceded by colds so the proportion of virus-associated exacerbations may be even higher than the 39% virus detection rate. Seventy-four percent of study patients had received influenza vaccination. In a study from Germany of more severe exacerbations that resulted in hospitalization, viruses were detected in 56% of exacerbations, compared with an detection rate of 19% in a control group with stable COPD (Rohde et al 2003). Again picornaviruses were the most common virus detected, accounting for 36% of viruses detected, and influenza was detected in 25% of exacerbations. In 14 patients hospitalized with an acute exacerbation of COPD in Singapore a virus was detected in 64% of patients (Tan et al 2003). In this study the commonest virus detected was influenza (36%), but patients had not received influenza vaccination. A study from the USA of a mixture of exacerbations treated both as inpatients and outpatients detected a respiratory virus in 41.8% of exacerbations. However this was likely an underestimate as in some of the patients PCR was not used for virus detection. Influenza viruses were detected in 8.2% of exacerbations (Beckham et al 2005). In a study of influenza vaccination in COPD patients, influenza accounted for 16% of all cases of acute respiratory illness during the winter season (Neuzil et al 2003).

These studies have focused solely on the role of virus infection. However, bacterial infection is common in COPD both at exacerbation and in stable disease. There is epidemiological and experimental evidence that viral respiratory infections, particularly those caused by influenza virus, increase the incidence of secondary bacterial infection such as pneumonia. Therefore there is potential for significant virus–bacteria interaction in COPD but little data is available regarding this. A study using serological evidence of virus infection did report a significant association between influenza infection and infection with both *Streptococcus pneumoniae* and *Haemophilus influenzae* (Smith et al 1976). A more recent study using PCR detected a viral infection in 48% of exacerbations in a population of COPD patients (Papi et al 2006). Consistent with other published studies rhinovirus infections were the most common and influenza was second, accounting for 23% of virus-associated exacerbations. In 25% of exacerbations there was evidence of co-infection with a virus and bacteria and these were

associated with greater impairment in lung function and longer hospitalization.

Avian influenza and COPD

To date most human infections with the H5N1 avian influenza strain have occurred in young adults and children. If spread to the wider population does occur it remains unknown what the impact of this influenza virus will be in the elderly and those with chronic cardiorespiratory diseases such as COPD. Mortality in the 1918 pandemic was greater in young adults, but the proportion of the population who were elderly or had chronic diseases would have been much lower than the present. The mortality and morbidity of epidemic influenza is greater among these groups and therefore avian influenza has the potential to impose an enormous strain on healthcare resources. Recent studies have also re-evaluated the role of bacterial infection in the 1918 pandemic. It is now thought that much of the mortality may have been due to bacterial pneumonia with organisms such as *S. pneumoniae* and *H. influenzae*, rather than primary viral pneumonia (Brundage 2006). These organisms are common colonizing organisms in COPD patients. In addition the mortality and requirement for intensive care of community acquired bacterial pneumonia is higher in COPD patients (Restrepo et al 2006). Therefore there is considerable potential for high mortality and mortality in COPD patients in the event of an avian influenza pandemic. To date planning for a pandemic has focused on stockpiling antiviral drugs. A better understanding of the potential impact of avian influenza infection in high-risk groups such as the elderly and COPD patients is urgently required. This will allow planning of other healthcare resources such as vaccination, antibiotics, intensive care beds, and assisted ventilation that may have an impact on the morbidity and mortality associated with such a pandemic.

Management options

The current options for prevention and treatment of influenza are among the most advanced for any respiratory virus. Vaccination is the cornerstone of attempts to control influenza, however the frequent changes in viral antigens means that annual re-vaccination is required. Vaccination does not result in complete protection and therefore there is still a role for drug therapy. The determination of the molecular structure of the influenza virus has led to the identification of the key proteins involved in viral replication and subsequently the development of drugs to target these.

Vaccination

Influenza vaccination has proved to be efficacious and safe and currently represents the mainstay for influenza prevention. Because of the constantly changing antigenic make-up of the virus, vaccination must be repeated on an annual basis to cover the predominant virus strains circulating in the community. Each year the World Health Organization (WHO) Global Influenza Program recommends the composition of the influenza vaccine for the next season based on surveillance data from a worldwide network of national influenza centers and WHO collaborating centers. There is now extensive evidence that vaccination reduces the incidence of adverse outcomes associated with influenza. However debate continues regarding the extent of this protection and the populations that should receive vaccination. The development of antibodies directed against the hemagglutinin and neuraminidase glycoproteins are associated with protection against infection and amelioration of illness. Both inactivated and live virus vaccines are available. Most influenza vaccines are either split vaccines that are produced from the disrupted highly purified influenza virus, or surface antigen vaccines containing predominantly purified hemagglutinin and neuraminidase. Most inactivated vaccines are trivalent, containing two influenza A subtypes (H1N1 and H3N2) and one influenza B strain and following vaccination 90% of subjects achieve serum hemagglutinin-inhibition titres of >1:40, a level generally associated with protection of about 50% of the population.

Vaccination and COPD

A number of international and national respiratory societies have published guidelines for the optimal management of COPD (Pauwels et al 2001; Celli et al 2004). These guidelines universally recommend annual influenza vaccination but there is actually very little evidence regarding the efficacy of vaccination specifically in COPD patients. A Cochrane systematic review of randomized controlled trials that have been reported on the effects of influenza vaccination in COPD identified 11 papers (Poole et al 2006). Of these, 3 studies were performed on subjects with chronic bronchitis and only 3 enrolled subjects solely with documented COPD. The other 5 trials included were conducted in subjects of whom a proportion, varying from 5% to 32%, had chronic lung disease. Where possible, data from the lung disease subgroup were included but in none of these studies was it possible to ascertain what proportion of the chronic lung disease subgroup had COPD. Of the 3 trials in COPD patients only 1 was a placebo-controlled trial whereas the

other 2 compared the effect of different influenza vaccination regimes. Based mainly on data from one old study in patients with chronic bronchitis (Howells and Tyler 1961) and one recent study in COPD (Wongsurakiat et al 2004) influenza vaccination did reduce exacerbation rates in COPD patients, but there was no evidence of any effect on hospitalization rates and mortality. In the study in COPD patients, none of the vaccinated patients required mechanical ventilation because of influenza-related respiratory illness, whereas all the unvaccinated patients with moderate-to-severe COPD who were hospitalized because of influenza-related respiratory illness needed mechanical ventilation. However the reduction in the numbers of hospitalizations and need for mechanical ventilation did not reach statistical significance (Wongsurakiat et al 2004).

Indirect evidence of a benefit of vaccination in COPD patients has come from studies in patients with nonspecific chronic pulmonary disease. These studies have provided evidence that influenza vaccination reduces both hospitalizations and mortality. A study of persons over 65 years and older with chronic lung disease found that influenza vaccination was associated with a 52% reduction in hospitalization rate for influenza and pneumonia and a 70% reduction in mortality. Vaccination was also associated with fewer outpatient visits for all respiratory conditions (Nichol et al 1999). Other studies of high-risk groups that included patients with both cardiac and pulmonary disease have had similar findings (Nichol et al 1994, 1998).

The evidence base is not large despite the universal recommendation that COPD patients receive influenza vaccination. The evidence that is available does suggest that vaccination reduces exacerbations and studies in elderly patients with chronic lung disease (a high proportion of whom can be assumed to have COPD) would favor a reduction in mortality with vaccination. In view of this it is unlikely that further placebo-controlled trials of influenza vaccination will be carried out. Despite the expert recommendations there is evidence that influenza vaccination among COPD patients remains suboptimal (Garcia-Aymerich et al. 2000) and every effort should be made to increase uptake of vaccination in this high-risk population.

Drug treatments

Even where uptake of vaccine is high, influenza outbreaks with associated complications and mortality continue to occur (Bowles et al 2002). Therefore alternative management options for influenza are required and a number of antiviral drugs are available for the treatment of influenza.

M2 Inhibitors

M2 is a membrane protein found in influenza A but not influenza B that is required for nucleocapsid release after viral fusion. Two compounds are available that inhibit function of the M2 protein and prevent viral uncoating following endocytosis. In the USA, both amantadine and rimantadine are licensed for the treatment and prophylaxis of influenza A infections, whereas in the UK only amantadine is licensed. A number of clinical studies assessing the efficacy of the M2 inhibitors have been published. A Cochrane review published in 2004 (Jefferson et al 2004) and a more recent systematic review (Jefferson et al 2006) have analyzed the results of these trials. Both amantadine and rimantadine are effective at preventing influenza when used as prophylaxis, with efficacy rates of 61% and 72% respectively. When used to treat established influenza both drugs reduce the duration of fever and symptoms in patients by 24-h, when started within 48-h of onset of illness. However their effectiveness (the capacity to prevent influenza) is much less than their efficacy (the ability to prevent influenza-like illnesses). Neither drug has an effect on reducing viral shedding. Side effects are common with the adamantanes and are a major limiting factor in their use. Side effects involving the central nervous system occur in 5%–29% of patients treated with amantadine, and include headache, light-headedness, dizziness, difficulty in concentrating, and insomnia. Central nervous system adverse effects and withdrawal from trials are significantly more common among amantadine recipients than rimantadine recipients. There are no trials of M2 inhibitors in COPD patients; therefore their effectiveness in this population group is unknown.

Another significant concern with the M2 inhibitors is the high frequency of resistance to these drugs in H3N2 influenza (Bright et al 2005). A recent report detected increasing incidence of H3N2 viruses with a particular M2 protein mutation that confers high-level resistance to both amantadine and rimantadine from countries participating in WHO's global influenza surveillance network. Adamantane resistance increased in frequency from 0.4% of influenza A viruses isolated in 1994–1995 to 12.3% in 2003–2004. Resistant strains were detected in a wide range of geographical sites, but 61% of resistant viruses isolated since 2003 originated from Asia. If resistance continues to increase at this rate the M2 inhibitors will have little efficacy as anti-influenza agents. Of concern is the fact that the currently circulating strains of avian H5N1 influenza are highly resistant, thus if human infections do become more frequent, the M2 inhibitors will have no useful therapeutic role.

Neuraminidase inhibitors

Neuraminidase is an enzyme expressed on the surface of influenza A and B that is essential for release of newly formed viruses from an infected cell. NA cleaves the cellular-receptor sialic acid residues to which the newly formed viral particles are attached, releasing the viruses to invade new cells. Neuraminidase may also cleave the sialic acid moieties on airway mucin, facilitating viral invasion of airway epithelial cells. Inhibition of NA therefore limits infection to one round of replication, greatly reducing viral reproduction. The active site of NA is a highly conserved region among influenza A and B viruses and determination of its 3 dimensional structure led to the development of compounds capable of binding to and inhibiting the active catalytic site (Colman et al 1983). There are two licensed neuraminidase inhibitors, zanamivir and oseltamivir, and a third, RWJ-270201 which is in Phase II clinical studies. All three compounds are highly active against a broad range of influenza A and B viruses and also inhibit amantadine and rimantadine resistant strains of influenza A.

Zanamivir has a low oral bioavailability and so is delivered in inhaled form whereas oseltamivir is available orally. Studies of zanamivir in influenza have shown that it reduces symptoms by 24-h, decreases the number of nights of disturbed sleep, and reduces use of over the counter medications. There is little data available regarding the efficacy of zanamivir specifically in COPD. There is one study of zanamivir in patients with respiratory disease that included patients with both asthma and COPD (Murphy et al 2000). In the influenza-positive population (313 patients) the median time to alleviation of influenza symptoms was significantly shorter by 1.5 days (95% CI 0.50 to 3.25 days, $p = 0.009$) in the zanamivir group compared with placebo. In addition, there was a significant reduction in the mean total symptom score ($p = 0.001$) in zanamivir-treated patients compared with placebo during the treatment period (days 1 to 5). Influenza-related complications requiring both the use of antibiotics and a change in respiratory medication were reduced by 58% (relative risk 0.42, 95% CI 0.18 to 0.96; $p = 0.064$) with zanamivir treatment compared with placebo. Patients treated with zanamivir had a small but significantly increased mean peak expiratory flow rate compared with placebo during the treatment period. The only data quoted in the study that was specific to the COPD group was for alleviation of symptoms. In 64 patients with COPD the median time to alleviation of symptoms was shorter by 1.5 days in the zanamivir group (6.0 days) compared with placebo (7.5 days). A retrospective analysis of 'high-risk' patients (mainly patients with chronic

respiratory disease) enrolled in trials of zanamivir found that the benefit is even greater in these patient groups (Lalezari et al 2001). Use of zanamivir in high-risk patients resulted in a 2.5-day reduction in time to alleviation of symptoms, a 3-day reduction in the time to returning to usual activity and a 43% risk reduction in antibiotic use. This study did not report a higher incidence of adverse effects in high-risk patients treated with zanamivir and the incidence of asthma exacerbation or increase in symptoms was 14% in the placebo group and 7% in the treatment group.

Oseltamivir has shown a similar efficacy to zanamivir in healthy adults and children with reductions in illness severity and duration, viral shedding, and lower respiratory tract complications. An analysis of data from subjects enrolled in trials of oseltamivir treatment that included both healthy adults and high-risk individuals including COPD has been published (Kaiser et al 2003). In adults with a proven influenza illness, oseltamivir treatment reduced overall antibiotic use and the incidence of influenza-related lower respiratory tract complications by 55%. In high-risk individuals there was a 34% reduction in lower respiratory tract illness leading to antibiotic use. There was also a 50% reduction in hospitalizations associated with use of oseltamivir in the high-risk group. A randomized, open-label trial in Chinese patients with chronic respiratory and cardiac diseases reported that oseltamivir significantly reduced the duration of influenza symptoms, the incidence of complications and antibiotic use (Lin et al 2006). A study of oseltamivir in asthmatic children reported improvements in lung function and reduced asthma exacerbations during influenza infection (Johnston et al 2005).

From the currently available evidence it is difficult to make specific recommendations regarding the treatment of influenza in COPD, beyond the universal recommendation that COPD patients receive annual influenza vaccination. Trials of NA inhibitors in high-risk patients that have included COPD patients have demonstrated benefit with reductions in symptoms, lower respiratory tract complications, and antibiotic use. Further trials are required to more precisely determine the role of NA inhibitors in COPD patients. Treatment recommendations will need to address specific clinical problems such as their role in vaccinated patients, their use where a laboratory diagnosis of influenza is not available, and the cost effectiveness of drug treatment.

Conclusions

Despite much research progress in recent years, influenza remains a pathogen associated with considerable morbidity

and mortality, especially in high-risk groups such as patients with COPD. However there has been little research into the specific role of influenza in causing acute exacerbations of COPD. Vaccination remains an effective measure to reduce the burden of disease associated with influenza, but cannot completely prevent disease. Effective anti-influenza agents are now available but their use is tempered by issues of cost and patient selection. Studies of the NA inhibitors have shown that their benefit is greater in high-risk patients, but use of these drugs is not common in COPD. Further research is required to determine the most efficient and cost-effective strategies to combat influenza infection, including studies in high-risk groups such as COPD patients in whom the burden of disease associated with influenza is greater.

References

- Beckham JD, Cadena A, Lin J, et al. 2005. Respiratory viral infections in patients with chronic, obstructive pulmonary disease. *J Infect*, 50:322–30.
- Bowles SK, Lee W, Simor AE; Oseltamivir Compassionate Use Program Group. 2002. Use of oseltamivir during influenza outbreaks in Ontario nursing homes, 1999–2000. *J Am Geriatr Soc*, 50:608–16.
- Brundage JF. 2006. Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness. *Lancet Infect Dis*, 6:303–12.
- Celli BR, MacNee W; American Thoracic Society and the European Respiratory Society. 2004. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J*, 23:932–46.
- Colman PM, Varghese JN, Laver WG. 1983. Structure of the catalytic and antigenic sites in influenza virus neuraminidase. *Nature*, 303:41–4.
- Donaldson GC, Wedzicha JA. 2006. COPD exacerbations. 1: Epidemiology. *Thorax*, 61:164–8.
- Falsey AR, Hennessey PA, Formica MA, et al. 2005. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med*, 352:1749–59.
- Fleming DM. 2000. The contribution of influenza to combined acute respiratory infections, hospital admissions, and deaths in winter. *Commun Dis Public Health*, 3:32–8.
- Garcia-Aymerich J, Barreiro E, Farrero E, et al. 2000. Patients hospitalized for COPD have a high prevalence of modifiable risk factors for exacerbation (EFRAM study). *Eur Respir J*, 16:1037–42.
- Glezen WP, Decker M, Perrotta DM. 1987. Survey of underlying conditions of persons hospitalized with acute respiratory disease during influenza epidemics in Houston, 1978–1981. *Am Rev Respir Dis*, 136:550–5.
- Griffin MR, Coffey CS, Neuzil KM, et al. 2002. Winter viruses: influenza and respiratory syncytial virus-related morbidity in chronic lung disease. *Arch Intern Med*, 162:1229–36.
- Howells CHL, Tyler LE. 1961. Prophylactic use of influenza vaccination in patients with chronic bronchitis. *Lancet*, 1428–32.
- Ivan A, Duda R. 1977. Excess mortality—influenza epidemiological surveillance indicator. *J Hyg Epidemiol Microbiol Immunol*, 21:136–44.
- Jefferson T, Deeks JJ, Demicheli V, et al. 2004. Amantadine and rimantadine for preventing and treating influenza A in adults. *Cochrane Database Syst Rev*, 3:CD001169.
- Jefferson T, Demicheli V, Rivetti D, et al. 2006. Antivirals for influenza in healthy adults: systematic review. *Lancet*, 367:303–13.
- Johnston SL, Ferrero F, Garcia ML, et al. 2005. Oral oseltamivir improves pulmonary function and reduces exacerbation frequency for influenza-infected children with asthma. *Pediatr Infect Dis J*, 24:225–32.
- Kaiser L, Wat C, Mills T, et al. 2003. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med*, 163:1667–72.
- Lalezari J, Campion K, Keene O, et al. 2001. Zanamivir for the treatment of influenza A and B infection in high-risk patients: a pooled analysis of randomized controlled trials. *Arch Intern Med*, 161:212–17.
- Lanska DJ, Hoffmann RG. 1999. Seasonal variation in stroke mortality rates. *Neurology*, 52:984–90.
- Lin JT, Yu XZ, Cui DJ, et al. 2006. A multicentre, randomized, controlled trial of oseltamivir in the treatment of influenza in a high-risk Chinese population. *Curr Med Res Opin*, 22:75–82.
- Lipatov AS, Govorkova EA, Webby RJ, et al. 2004. Influenza: emergence and control. *J Virol*, 78:8951–9.
- Lui KJ, Kendal AP. 1987. Impact of influenza epidemics on mortality in the United States from October 1972 to May 1985. *Am J Public Health*, 77:712–16.
- Mannino DM. 2002. COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. *Chest*, 121(Suppl):121S–126S.
- Meier CR, Jick SS, Derby LE, et al. 1998. Acute respiratory-tract infections and risk of first-time acute myocardial infarction. *Lancet*, 351:1467–71.
- Murphy KR, Eivindson A, Pauksens K, et al. 2000. Efficacy and safety of inhaled zanamivir for the treatment of influenza in patients with asthma or chronic obstructive pulmonary disease: a double-blind, randomised, placebo-controlled, multicentre study. *Clin Drug Invest*, 20:337–49.
- Murray CJ, Lopez AD. 1997. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet*, 349:1498–504.
- Neuzil KM, O'Connor TZ, Gorse GJ, et al. 2003. Recognizing influenza in older patients with chronic obstructive pulmonary disease who have received influenza vaccine. *Clin Infect Dis*, 36:169–74.
- Nichol KL, Baken L, Nelson A. 1999. Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. *Ann Intern Med*, 130:397–403.
- Nichol KL, Margolis KL, Wuorenma J, et al. 1994. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *N Engl J Med*, 331:778–84.
- Nichol KL, Wuorenma J, Von Sternberg T. 1998. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. *Arch Intern Med*, 158:1769–76.
- Nordin J, Mullooly J, Poblete S, et al. 2001. Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: data from 3 health plans. *J Infect Dis*, 184:665–70.
- Normile, D. 2006. Avian influenza. Human transmission but no pandemic in Indonesia. *Science*, 312:1855.
- Palese P. 2004. Influenza: old and new threats. *Nature Med*, 10(12 Suppl): S82–7.
- Papi A, Bellettato CM, Braccioni F, et al. 2006. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med*, 173:1114–21.
- Pauwels RA, Buist AS, Calverley PM. The GOLD Scientific Committee. 2001. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med*, 163:1256–76.
- Poole P, Chacko E, Wood-Baker R, et al. 2006. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 1:CD002733.
- Potter CW. 2001. A history of influenza. *J Appl Microbiol*, 91:572–9.
- Reichert TA, Simonsen L, Sharma A, et al. 2004. Influenza and the winter increase in mortality in the United States, 1959–1999. *Am J Epidemiol*, 160:492–502.
- Rennard S, Decramer M, Calverley PM, et al. 2002. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. *Eur Respir J*, 20:799–805.

- Restrepo MI, Mortensen EM, Pugh JA, et al. 2006. COPD is associated with increased mortality in patients with community-acquired pneumonia. *Eur Respir J*, 28:346–51.
- Rohde G, Wiethege A, Borg I, et al. 2003. Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. *Thorax*, 58:37–42.
- Seemungal T, Harper-Owen R, Bhowmik A, et al. 2001. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 164:1618–23.
- Simonsen L, Fukuda K, Schonberger LB, et al. 2000. The impact of influenza epidemics on hospitalizations. *J Infect Dis*, 181:831–7.
- Smith CB, Golden C, Klauber MR, et al. 1976. Interactions between viruses and bacteria in patients with chronic bronchitis. *J Infect Dis*, 134:552–61.
- Smith CB, Golden CA, Kanner RE, et al. 1980. Association of viral and Mycoplasma pneumoniae infections with acute respiratory illness in patients with chronic obstructive pulmonary diseases. *Am Rev Respir Dis*, 121:225–32.
- Sullivan SD, Ramsey SD, Lee TA. 2000. The economic burden of COPD. *Chest*, 117(Suppl):5S–9S.
- Tan WC, Xiang X, Qiu D, et al. 2003. Epidemiology of respiratory viruses in patients hospitalized with near-fatal asthma, acute exacerbations of asthma, or chronic obstructive pulmonary disease. *Am J Med*, 115:272–7.
- Thompson WW, Shay DK, Weintraub E, et al. 2003. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA*, 289:179–86.
- Thorson A, Petzold M, Nguyen TK, et al. 2006. Is exposure to sick or dead poultry associated with flulike illness? A population-based study from a rural area in Vietnam with outbreaks of highly pathogenic avian influenza. *Arch Intern Med*, 166:119–23.
- Tillett HE, Smith JW, Gooch CD. 1983. Excess deaths attributable to influenza in England and Wales: age at death and certified cause. *Int J Epidemiol*, 12:344–52.
- Wongsurakiat P, Maranetra KN, Wasi C, et al. 2004. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study. *Chest*, 125:2011–20.
- World Health Organisation. 2006. Avian influenza [online]. Accessed on 8 September 2006. URL: http://www.who.int/csr/disease/avian_influenza/en/
- Yap FH, Ho PL, Lam KF, et al. 2004. Excess hospital admissions for pneumonia, chronic obstructive pulmonary disease, and heart failure during influenza seasons in Hong Kong. *J Med Virol*, 73:617–23.