

# Bacterial and viral infections associated with influenza

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Influenza-associated bacterial and viral infections are responsible for high levels of morbidity and death during pandemic and seasonal influenza episodes. A review was undertaken to assess and evaluate the incidence, epidemiology, aetiology, clinical importance and impact of bacterial and viral co-infection and secondary infection associated with influenza. A review was carried out of published articles covering bacterial and viral infections associated with pandemic and seasonal influenza between 1918 and 2009 (and published through December 2011) to include both pulmonary and extra-pulmonary infections. While pneumococcal infection remains the predominant cause of bacterial pneumonia, the review highlights the importance of other co- and secondary bacterial and viral

infections associated with influenza, and the emergence of newly identified dual infections associated with the 2009 H1N1 pandemic strain. Severe influenza-associated pneumonia is often bacterial and will necessitate antibiotic treatment. In addition to the well-known bacterial causes, less common bacteria such as *Legionella pneumophila* may also be associated with influenza when new influenza strains emerge. This review should provide clinicians with an overview of the range of bacterial and viral co- or secondary infections that could present with influenza illness.

**Keywords** Co-infection, epidemiology, incidence, influenza, secondary infection.

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## Introduction

Bacterial secondary infections or co-infections associated with cases of influenza are a leading cause of severe morbidity and mortality, especially among high-risk groups such as the elderly and young children. Vaccines and antiviral and antibiotic therapies are now readily available to clinicians for control and prevention of primary and secondary bacterial infections. Thus, information on the overall range, incidence and severity of influenza co-infections and secondary infections associated with different influenza strains, aetiological agents, different age groups and their underlying risk conditions is very important contextually for clinicians and public health specialists involved in implementing policy and treatment regimes for this disease spectrum.

Bacterial infection may be concurrent with influenza viral infection, and the resulting co-infection can lead to an enhanced pneumonic illness or may occur shortly after influenza virus has been largely cleared from the lungs, when the host appears to be more susceptible to bacterial infection.<sup>1,2</sup> Morbidity and mortality are recognised to be greater in cases of influenza-associated bacterial infection compared with bacterial pneumonia without influenza infection<sup>3</sup> with all age groups affected by this synergistic process. The annual increase in influenza activity during winter months is usually accompanied by an increase in cases of community-acquired pneumonia (CAP). The most com-

mon causes of CAP are *Streptococcus pneumoniae* (*S pneumoniae*), *Staphylococcus aureus* (*S aureus*) and *Haemophilus influenzae* (*H influenzae*). *S pneumoniae* is the most frequently isolated pathogen associated with influenza<sup>4</sup>, although deaths, especially in children are also associated with *S aureus* infection, as highlighted by the recent emergence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA).<sup>5</sup>

The objective of this review is to assess and evaluate the incidence, epidemiology, aetiology, clinical importance and impact of co-infection and secondary infection associated with influenza. As there are few review articles on this topic, it also aims to integrate some newly published reports. The main focus of this review is pulmonary infection while some less common extra-pulmonary complications as shown by case reports are also included.

Information in this review should supplement the information available to clinicians on antimicrobial treatment therapies, including antibiotic sensitivity information, local guidelines and local antimicrobial susceptibility data as well as local availability of medicines. Bacterial outcomes have been extensively studied in both influenza pandemic and epidemic periods and latterly within the context of available viral and bacterial vaccines that protect against primary and secondary infection. In addition to prevention strategies, treatment of influenza complications has also become available through antiviral and antibiotic therapies. The goal

of combined therapies for prevention and treatment must surely be a reduction in the proportion of bacterial infections associated with influenza. However, the wider use of antibiotics for treatment of bacterial influenza needs to be considered alongside the corresponding requirement for appropriate use of antibiotics, in order to reduce the increasing burden of antibiotic resistance of bacterial strains implicated in co-infection with influenza.

## Background

### Mechanisms of co/secondary infection

The mechanisms by which co-infection and secondary infection take place are complex. Reports from past influenza pandemics show an extremely high frequency of lung colonisation by bacterial species that are commonly found in the nasopharynx. Most evidence suggests that virus-induced changes in the respiratory tract prime the upper airway and lung for subsequent bacterial infection. Secondary bacterial infections are facilitated by virus-induced cytopathology and resulting immunological impairment, which may be caused in part by the overproduction of inflammatory cytokines.<sup>6</sup> Modification of the immune response either by diminishing the ability of the host to clear bacteria or by amplification of the inflammatory cascade is likely to contribute to the severity of the resulting infection.<sup>7</sup> Animal studies using murine models have shown that influenza predisposes to bacterial pneumonia.<sup>6,8–10</sup> Lag times of 7–21 days have been calculated in studies for onset of bacterial infection following seasonal influenza<sup>11</sup> although much shorter times from onset to death have been recorded in pandemic periods.<sup>12–14</sup>

Influenza A is the dominant strain associated with co/secondary bacterial infection with evidence that specific N2 seasonal subtypes cause more severe infection than other subtypes.<sup>15</sup> Influenza B, although generally regarded as having less impact on morbidity and mortality in healthy persons can also cause severe secondary bacterial infection during seasonal influenza episodes, especially within younger age groups.<sup>5,16,17</sup>

## Methods

### Search strategy and selection criteria

We searched the National Library of Medicine through PubMed using the search terms: ('influenza' and 'secondary infection'), ('influenza' and 'pneumonia') and ('influenza' and 'co-infection'). We also searched the references of the identified articles for additional articles. We included studies on both influenza type A and B, and also seasonal and pandemic influenza. The search was limited to studies of disease in humans that were published in English from 1918 to the end of 2011. We only selected studies in which

pathogens were identified. We then reviewed abstracts and titles and selected studies that were relevant to the topic of interest.

### Key terms

- *Bacterial co-infection* – a bacterial pneumonia occurring simultaneously with onset of influenza virus illness
- *Secondary bacterial infection* – a bacterial pneumonia occurring after influenza illness onset or clearance of influenza virus
- *Viral co-infection* – Influenza virus and one or more other respiratory viruses detected simultaneously by microbiological examination of respiratory samples.

## Influenza and co-infection

### Pandemic influenza and bacterial infections

The three influenza pandemics of the 20th century (1918 H1N1, 1957 H2N2 and 1968 H3N2) are all associated with secondary bacterial pneumonia.<sup>18</sup>

#### 1918 H1N1 pandemic

This pandemic has been extensively researched, mainly due to its global impact and estimated 40–50 million deaths in an era of unknown virological cause and absence of antibiotic therapy, in order to understand its aetiological and epidemiological features. British and French army camps in 1916/17 were the initial setting for major outbreaks of purulent bronchitis associated with *Haemophilus influenzae*, pneumococcus, streptococcus and staphylococcus. Over a period of 2 months in 1918 at 37 large American army camps, secondary bacterial infection occurred in approximately 17% of those diagnosed with influenza of which approximately 35% were fatal.<sup>4</sup> Oxford describes these army camp outbreaks as progenitors of the ensuing H1N1 pandemic of 1918.<sup>19</sup> Overall, it has been estimated that in the US military, the mean influenza attack rate during the course of the 1918/1919 pandemic was 23%, the mean percentage of influenza cases that developed pneumonias was 16% and the mean percentage of pneumonia cases that were fatal was 34%.<sup>4</sup> Recent re-analyses of post-mortem lung cultures from 1918 showed evidence of bacterial infection in >90% of the specimens.<sup>18,20</sup>

Experts now support the sequential infection hypothesis and believe that bacteria were secondary invaders to pulmonary tissues weakened by the influenza virus. They suggest that the scale and range of bacterial invaders was random, and in the case of large group outbreaks, depended on the occurrence of particular bacteria in the respiratory tract of persons at the time of infection and on their occurrence in contacts. The fatal outcome of influenza pneumonia was therefore determined partly by virally depressed local and general pulmonary resistance and partly by the virulence and

nature of the invading bacteria.<sup>12</sup> Brundage explains the high transmission rates in military camps and other crowded settings as due to 'cloud adults' – affected persons who increased the aerosolisation of colonising strains of bacteria to other susceptible persons. Military personnel were deemed to be highly susceptible because of their closed community style living and their physically weakened state. In American civilian populations, attack rates and deaths were similar among younger adults and overall were approximately 28% for influenza with 30% of associated pneumonias being fatal.<sup>21</sup> Studies also show that, in all age groups, deaths were strongly correlated with pneumonia cases than with influenza clinical cases alone. Children had the highest rates of clinical influenza infection, whereas young adults had the highest influenza pneumonia rates and associated fatality rates.<sup>20,22,23</sup>

#### 1957 H2N2 pandemic

The Asian influenza pandemic was similarly characterised by waves of influenza followed by an increase in hospitalisations and deaths from pneumonia. One US study showed these were associated with *S pneumoniae*, *H influenzae* and *S aureus*<sup>24</sup>, while a Dutch study of 158 Asian influenza deaths documented that *S aureus* and pneumococci were recovered from 59% and 15% of lung cultures, respectively.<sup>25</sup> A British study of 140 hospitalised cases of pneumonia over a two-month period in 1957, a high proportion of whom also had evidence of confirmed influenza A infection, showed that *S aureus* was isolated from 27% of the cases and pneumococci and *H influenzae* from 15% and 4%, respectively.<sup>26</sup> Mortality was 47% in the staphylococcal group compared with 16% in the non-staphylococcal group: eight of the 18 staphylococcal deaths were in persons with no previous disease while seven were in cases with chronic chest disease.

#### 1968 H3N2 pandemic

In the 1968 H3N2 Hong Kong pandemic, a three-fold increase in the incidence of staphylococcal pneumonia was found in one hospital study compared with the number of pneumonic cases in the previous year. Of 128 patients with pneumonia during the pandemic influenza period, 26% were proven staphylococcal pneumonia cases and a high correlation between pneumonia and influenza infection was documented.<sup>27</sup> In England and Wales, the national experience of the Hong Kong influenza in 1968/69 reported that mortality was substantially lower than in previous influenza winters.<sup>28</sup> However, excess respiratory deaths were recorded in the second wave of the pandemic in 1969/70 and increased by approximately 55% and circulatory system deaths by 4%. Deaths in the elderly increased by 10%, in those aged 40–60 years by 8% and in younger adults by 4%.<sup>29</sup> In the United States, significant excess pneumonia-influenza mortality occurred in all nine geographical areas of the country in

the first wave in 1968/69 and followed influenza activity by several weeks.<sup>30</sup>

#### 2009 H1N1 pandemic

The first pandemic of the 21st century in 2009 is still being researched but so far has shown a similar pattern to previous pandemics with a high proportion of cases and deaths occurring in younger age groups compared with non-pandemic influenza seasons. A study of the first 47 deaths in New York City showed 13 (28%) had evidence of invasive bacterial co-infection. *S pneumoniae* was most commonly identified [8 patients (17%)], followed by *S pyogenes* [3 patients (6%)]. One paediatric case had post-mortem evidence of both bacteria.<sup>13</sup> A multi-centre review of 77 deaths in another US study between May and August 2009 found evidence of concurrent bacterial infection in specimens from 22 (29%) of the 77 patients, including 10 caused by *S pneumoniae*.<sup>31</sup>

An analysis of 631 patients admitted to hospital over the five-month pandemic period in 2009 in the UK with confirmed pandemic influenza infection reported that 102 cases had radiological evidence of pneumonia and that mortality in cases with radiographic pneumonia was significantly higher than in cases without ( $P = 0.0008$ ). Four cases of pneumonia (4%) had positive bacteriological findings, three of whom died – two children with methicillin-resistant *Staphylococcus aureus* (MRSA) and one adult with *S pneumoniae* in sputum. One adult had *S aureus* bacteraemia and survived.<sup>32</sup> In a study of 68 autopsy reports from a total of 457 pandemic influenza deaths in the UK, 28 (41%) reported that bacterial secondary infection was the significant complication; pneumococcus was the most common agent identified (25%).<sup>33</sup>

In Argentina, nasopharyngeal swab samples from 199 cases of confirmed H1N1 pandemic infection were tested for 33 additional microbial agents using MassTag PCR methods. At least one additional agent of potential pathogenic importance was detected in 152 samples, including *S pneumoniae* (41%); *H influenzae* (68.4%); *S aureus* (23%); and methicillin-resistant *S aureus* (MRSA, 4%). Other viruses such as RSV, and influenza B were found in 20 samples and other bacterial pathogens in five. The presence of *S pneumoniae* was strongly correlated with severe disease and was present in 56.4% of severe cases versus 25% of mild cases ( $P = 0.0004$ ). In subjects 6–55 years of age, the adjusted odds ratio (OR) of severe disease in the presence of *S pneumoniae* was highly significant ( $P = 0.0001$ ). This study demonstrated that the presence of *S pneumoniae* in nasopharyngeal swab samples could predict severe disease outcome, the risk being more acute in persons aged between 6 and 55 years. In this low-risk age group, severity of disease could be predicted with 90.97% accuracy via a multivariable logistic regression model.<sup>34</sup> In the United States, those aged 5–19 years

experienced overall the largest relative increase in pneumococcal hospitalisations during the 2009 pandemic influenza period compared with seasonal baseline estimates for this age group and mirrored both temporal and geographical influenza activity across the country.<sup>35</sup> No national relative increase occurred in persons aged <5 years or aged 65 years or more, suggesting that the pandemic influenza virus was the likely cause of the increase in the younger age group.

A prospective, observational, multicenter study conducted in 148 Spanish intensive care units (ICU) and with 645 patients, all of whom had confirmed H1N1 pandemic influenza infection showed that co-infection occurred in 113 (17.5%) of patients. *S pneumoniae* was identified as the most prevalent bacteria (54.8%). Co-infection was associated with increased ICU mortality (26.2% versus 15.5%), but Cox regression analysis adjusted by potential confounders did not confirm a significant association between co-infection and ICU mortality.<sup>36</sup> A study of 100 fatal cases of H1N1 influenza in the United States showed 26% overall were due to bacterial co-infection, mainly caused by *S. pneumoniae*.<sup>37</sup> Similarly, a study of paediatric H1N1-associated mortality in the United States demonstrated that 28% of fatal cases had evidence of co-infection<sup>38</sup> while a study in England of 70 H1N1 paediatric deaths confirmed bacterial co-infection in 20% of the cases.<sup>14</sup>

A French study measured levels of procalcitonin (PCT) – a recognised marker of bacterial infection, in patients with H1N1 influenza pneumonia admitted to hospital and was able to conclude that levels of 0.8 µg/l or more discriminated well between isolated viral and mixed bacterial and viral pneumonia.<sup>39</sup> This information together with clinical judgement may help to identify patients for whom antibiotic therapy may be inappropriate.

The overall conclusion to date from epidemiological and clinical studies of the 2009 H1N1 pandemic is that worldwide incidence was low and infection was mostly mild. The fact that much of the 2009 pandemic occurred outside the regular season for pneumococcal disease in temperate regions may help to explain the lack of a marked increase in risk of pneumococcal infection at this time.<sup>40</sup> Death rates although low, were more prevalent in younger age groups than the elderly and excess deaths were recorded in children by one international European study<sup>41</sup> and in England where the childhood mortality rate was six per million population compared with an estimate of two per million population for seasonal influenza among children aged <14 years.<sup>14</sup> As in the pandemics of the 20th century, *S pneumoniae*, *H influenzae* and *S aureus* were the main bacterial infections associated with severe infection or death in this pandemic. Measures to prevent and treat their adverse impact on pandemic influenza cases in the future should now be incorporated into pandemic plans.<sup>42</sup>

### Pandemic influenza and other viral co-infections

The literature on co-infections with other viruses during pandemic periods is sparse in comparison with that available for influenza-associated bacterial infections. There are no reports documenting solely viral co-infections during the 1957 and 1968 pandemics, possibly because these infections were not sufficiently severe to merit hospitalisation and/or enhanced microbiological investigation. The 2009 pandemic first appeared in some countries during their normal seasonal activity. As a result, national virological surveillance schemes were able to demonstrate the emergence of the new H1N1 strain against a background and subsequent decline of circulating seasonal H1N1 and H3N2 strains. In New Zealand, 13 cases of pandemic H1N1 cases co-infected with seasonal H1N1 were detected, all with mild disease.<sup>43</sup> In Argentina, 20 of 199 persons investigated with pandemic disease were co-infected with another respiratory virus including RSV (A or B), rhinovirus and coronavirus. Seven of these cases were classed as having severe disease (hospitalisation or death with no other risk factors related to underlying disease) and 13, mild disease (ambulatory cases).<sup>34</sup> A US study of 173 cases of pandemic H1N1 found co-infection with other viruses in 20 cases (11.6%), rhinovirus being the most common agent.<sup>44</sup> In England and Wales, the Health Protection Agency's national virological surveillance scheme for community cases of influenza<sup>45</sup> detected 14 (3%) specimens where cases had evidence of pandemic H1N1 infection together with RSV, human metapneumovirus (hMPV), rhinovirus or parainfluenza virus (personal communication J Field).

### Seasonal influenza and co/secondary bacterial infection

Seasonal influenza activity provides more opportunities for monitoring the changing epidemiology and microbiological features of influenza-related co/secondary infection but essentially mirrors that of findings in recent pandemics. Maxwell first noted that bacterial pneumonia could occur during interepidemic periods when sporadic cases of influenza were investigated.<sup>46</sup> McCullers shows that from 1968 to 1999 excess deaths directly attributed to pneumonia and influenza (P&I deaths) from selected US cities data were more commonly associated with influenza A(H3N2) rather than H1N1 or influenza B infections.<sup>7</sup> Meningococcal infections were observed to increase in the presence of both influenza A<sup>47,48</sup> and influenza B<sup>49</sup>, but no causal relationship was identified in a later study.<sup>50</sup> In Sweden, pneumococcal infections were calculated to increase by 12–20% per influenza season over a ten-year study period with a lag time of 1–3 weeks for pneumococcal disease following peaks in influenza incidence.<sup>11</sup> In Canada, a recent observational study showed that the seasonality and time lag of

pneumococcal disease was only partially related to influenza seasonality. Other factors such as reduced temperatures and daylight hours were important for the regular appearance of pneumococcal disease each winter. However, the study did find that influenza increased the risk of pneumococcal disease through enhancing pneumococcal invasion in colonised individuals, but had minimal impact on the transmission dynamics of pneumococcal infection.<sup>40</sup> Transmission studies using animal models show increased incidence and severity of bacterial pneumonia after influenza infection is pneumococcal strain dependent. Different strains may increase the duration of pneumococcal carriage and enhance the bacterial pneumonia.<sup>10</sup> In another study using infant mice, influenza virus was shown to be essential for pneumococcal transmission in a co-housed group although other indirect effects by which the virus altered the immune response of the mice were also considered to be important reasons in the dynamics and synergism between influenza and pneumococcal infection.<sup>9</sup> The introduction of a seven-valent pneumococcal conjugate vaccine (PCV7) for infants has been shown in the United States to lead to a reduction in pneumococcal infections in vaccinated children and in adults through herd immunity effects.<sup>51</sup> A significant fall in influenza-associated pneumonia hospitalisations was observed among vaccinated children and unvaccinated adults; the vaccine acted to prevent the secondary pneumococcal pneumonia that followed influenza infection.<sup>51</sup> A nine-valent pneumococcal conjugate vaccine (PncCV) in South Africa was shown to prevent 31% of pneumonias associated with any of seven respiratory viruses in hospitalised children. The study concluded that a significant proportion of viral pneumonia is due to bacterial co-infection and is preventable by a bacterial vaccine.<sup>52</sup>

A study of influenza-related paediatric deaths in the United States over the 2003/04 influenza season found 24 of 102 deaths to have a bacterial cause, mainly *S aureus*.<sup>53</sup> Other US studies of that season also noted a rise in reports of community-acquired *S aureus* infections in children and young adults, a significant proportion being MRSA infections.<sup>54</sup> Similar findings were obtained for the 2006/07 influenza season in the United States<sup>55</sup> and by Kallen who reported 51 cases of influenza-related *S aureus*, 37 of which were MRSA infections in young adults. Where outcome of illness was known, deaths occurred in 24 of 47 cases.<sup>56</sup> Finelli notes that the proportion of influenza-related *S aureus* paediatric deaths increased fivefold between 2004 and 2007.<sup>5</sup>

Although less common than influenza A-associated mortality, deaths do result from influenza B infection, and awareness is growing of the role influenza B co-infection may play in severity of influenza-related illness. A review of influenza surveillance data in the United States from 2004 to 2007 revealed that anywhere from 23 to 38% of the annually reported paediatric deaths attributable to influenza were

from influenza B, and many of the fatal cases had evidence of bacterial co-infection.<sup>5</sup> A description of 19 cases of invasive Group A streptococcal (iGAS) infection in South East England during the seasonal outbreak of influenza in 2010/2011 included four cases of influenza B infection, of which three were fatal.<sup>17</sup> Case reports of three healthy women with no known risk factors and severe co-infections of *S. pyogenes* in two and *S. pneumoniae* in the third that required intensive resuscitation measures recently in Switzerland<sup>16</sup>, further underscore the potential impact bacterial co-infection with influenza B can have on morbidity and mortality.

### Seasonal influenza and viral co-infection

Multi-viral co-infections have mainly been identified in paediatric studies. Between two and six viral co-infections were reported per child in China,<sup>57</sup> a mix of influenza A H1 and H3 with influenza B in Japanese children<sup>58</sup> and co-infection with influenza and human metapneumovirus (hMPV) in two successive winters 2002–2004, also in Japan.<sup>59</sup> A one-year study in Peru found 5.5% of virological surveillance samples to be positive for influenza plus additional respiratory viruses<sup>60</sup> while a similar finding of 3% was obtained from the community-based virological surveillance data in England and Wales for the 2010/11 winter season (personal communication J Field). None of these reports suggested that the cases had severe disease.

### Influenza and less common co-infections (pandemic and seasonal)

The 2009 pandemic is the first pandemic where virological and microbiological tests for the disease have been conducted intensively at a global level. As a consequence, a wide range of less common pathogen pairings were encountered. In South Africa, co-infection with HIV or active tuberculosis was a common finding among the investigated early fatal cases, signifying that these conditions could be associated with increased mortality risk.<sup>61</sup> From a TB endemic area, it has been reported that an immunocompromised cancer patient was co-infected with both TB and pandemic H1N1 – a rare finding.<sup>62</sup> In Mexico, a study of 126 HIV patients with respiratory symptoms found that in the 30 patients co-infected with pandemic H1N1 virus, illness opportunistic infections were more severe and involved longer hospital stays ( $P = 0.0013$ ), higher hospitalisation rates ( $P < 0.0001$ ) and increased deaths ( $P = 0.026$ ). Deaths were also associated with delayed administration of oseltamivir ( $P = 0.0022$ ).<sup>63</sup> In the United States, Hopkins *et al.* reported six cases of bacterial tracheitis (BT) that were isolated in conjunction with influenza A (H1N1). No previous H1N1 cases have presented as BT in the literature to date.<sup>64</sup> Six cases of bacterial co-infection due to *Legionella pneumophila* were reported from Italy; the authors commenting on the fact that bacterial co-infections associated with the influenza

A H1N1 pandemic have not been well described yet because of lack of data.<sup>65</sup> The first case of Panton-Valentine leukocidin (PVL) necrotising pneumonia due to influenza A (H1N1) and community-acquired methicillin-resistant *Staphylococcus aureus* was reported from Spain,<sup>66</sup> the authors recommend that other clinicians become aware of this co-infection. Similarly, co-infection with dengue virus and pandemic influenza H1N1 is likely to be a feature in tropical countries where seasonal patterns of these two viruses were contemporaneous, as documented in a case report from Puerto Rico.<sup>67</sup> During seasonal influenza activity in 2006, influenza A H3N2 infection was associated with a fatal paediatric case of *Campylobacter jejuni* infection in Malaysia.<sup>68</sup> Co-infection with *Campylobacter* spp. has not been previously described together with influenza virus.

## Discussion

This review has documented the adverse impact of co/secondary bacterial infection with influenza infection, and the higher rates of severe morbidity or mortality that subsequently occur in all age groups. *Streptococcus pneumoniae* continues to be the dominant pathogen involved in this synergistic process<sup>7</sup> followed mainly by *Staphylococcus aureus*<sup>5</sup> and *Haemophilus influenzae*.<sup>12,18</sup> *Legionella pneumophila* a less common bacterium was also found to be associated with influenza infection in the 2009 H1N1 pandemic.<sup>65</sup>

Pneumonia remains the single commonest cause of death in children <5 years.<sup>69</sup> Clinicians and public health officials now have several means by which influenza-associated pneumonias can be prevented or ameliorated. Control and prevention, through viral and bacterial vaccines, and prophylaxis and treatment, through the application of antiviral and antibiotic therapies all contribute to reducing the global burden of these infections. All of these measures however have limitations which impede their effectiveness. Antibiotic resistance has been recognised as a growing concern for many years and during the 2009 pandemic, an increasing number of oseltamivir-resistant influenza strains were detected, particularly among immunocompromised patients with influenza infection.<sup>70,71</sup> Other threats to combating influenza epidemics or pandemics in the future might include timely production and administration of effective vaccines and logistical issues associated with stockpiling and distribution of antiviral and antibiotic drugs.<sup>42,72</sup>

Most vaccine effectiveness studies select high-risk groups within which to show enhanced protective effects and typically present data on levels of protection against hospital admissions or mortality associated with influenza rather than prevention of secondary infections as a clinical end point.<sup>73</sup> Pneumococcal vaccine effectiveness studies also focus on prevention of invasive pneumococcal disease and may or

may not include information on influenza vaccine status as a confounding variable.<sup>74</sup> Some studies have focused on the protective effect of dual influenza and pneumococcal vaccinations in the elderly. In Sweden, influenza and pneumococcal polysaccharide vaccines together reduced hospital admissions for influenza, pneumonia and invasive pneumococcal disease by 32, 22 and 54%, respectively. Overall mortality was also reduced by 27%.<sup>75</sup> A study of prior influenza vaccination in relation to its effect on severity and mortality in patients with CAP during seasonal influenza periods showed that prevention of the predisposing viral illness reduced the risk for more severe secondary pneumonia. However, outside the influenza season, no significant influence of influenza vaccination status on CAP severity was found.<sup>76</sup> Most of the subjects in this study were elderly and therefore in the risk group for influenza vaccination. Increasing the uptake of influenza vaccination in younger age groups could contribute to the overall prevention of influenza-attributable pneumococcal disease either directly or through protection from influenza via herd effects on other individuals.<sup>40</sup>

The 2009 pandemic provided the first opportunity for significant international use of antivirals to prevent the spread of influenza and to treat infected individuals. Given prophylactically, antivirals aid prevention of infection either in the absence of vaccine protection or within high-risk groups and may also prevent transmission within closed communities or households. When used for treatment, observational studies have confirmed that oseltamivir given within 48 hours of symptom onset (the recommended time for maximum effectiveness) improves survival in patients with severe influenza and may reduce secondary bacterial infection.<sup>77</sup> Of 70 paediatric deaths related to the 2009 pandemic and investigated in one study, 45 (64%) had received antiviral therapy but only seven (10%) within 48 hours of onset.<sup>14</sup> 21% of the deaths in this cohort occurred in healthy children. The authors recommend that vaccination of children should be extended to include non-risk groups and that antiviral treatment should be given as early as possible after symptom onset.<sup>14</sup>

Antibiotic treatment should be guided by information on the likely bacterial pathogens associated with the influenza virus circulating in the community. Recommendations should also defer to local CAP management practice because inappropriate use of antibiotics increases antibiotic resistance. If invasive bacterial infection is suspected, early antiviral treatment and appropriate use of antibiotics should be administered. Aggressive use of antimicrobial therapy early in the course of infection may reduce severe morbidity and mortality of influenza-associated bacterial infection.<sup>6</sup>

The articles in this review suggest that influenza-related bacterial infections overall may account for up to 30% of CAP

cases, mainly in the elderly.<sup>42</sup> In the developing world, this percentage is much higher, but children are the main sufferers, and pneumonic infections are the leading cause of death in children aged <5 years. Many of these deaths are preventable through immunisation, treatment and access to health care. The recent initiative of the Global Alliance on Vaccines and Immunisation, which supports global coverage of conjugate Hib and pneumococcal vaccines in childhood programmes, estimates that the incidence of severe pneumonia and associated mortality in children in developing countries may be reduced by 50% through this programme.<sup>69</sup> However, other inequities are likely to persist between developed and developing countries with reference to access to adult respiratory vaccines, the ability to stockpile antivirals and antibiotics as part of pandemic planning and remain a major obstacle to global-improved public health goals.

Antibiotic usage to combat bacterial infection is recognised as adversely contributing to changes in sensitivity and resistance of these drugs with evidence that community-acquired MRSA infections are leading to high levels of morbidity and mortality in individuals with influenza, especially children.<sup>5</sup> If influenza vaccine coverage was extended to all children and low-risk adults aged <65 years, protection against influenza infection would be enjoyed by a larger proportion of the population, overall attack rates should fall, there should be an associated reduction in the incidence of secondary bacterial infections, a subsequent fall in the number of antibiotic prescriptions for these infections and therefore a slowing down in the rise of antibiotic resistance. Obviously, this simplistic approach overlooks the vast organisation of economic and human resources needed to achieve these outcomes, but nevertheless, they remain a public health goal. Interventions through vaccination have been shown to be cost saving and of cost benefit in influenza epidemic and pandemic settings,<sup>78</sup> but again, depend on staying one step ahead of the viruses and bacteria they seek to eradicate.

The co-infections with more than one strain or subtype of influenza virus reported in this review have not yet provided any evidence of re-assortment threats or the emergence of new influenza strains. In 2001/02, a re-assortment between H1N1 and H3N2 produced a small number of cases of H1N2 infection in some countries, but circulation of the new strain was not sustained the following winter and did not confer more severe levels of illness compared with other subtypes. However, drifted strains occur on a regular basis and give rise to high levels of primary and secondary infection, particularly when there is a mismatch to strains contained within the seasonal vaccine.

In conclusion, ample evidence exists to show that severe bacterial infection can be a consequence of influenza infection, both in pandemic and seasonal episodes. Planning for future pandemics must therefore give equal emphasis to prevention and treatment of both these conditions, partic-

ularly in high-risk groups such as the very young and the elderly.

## Competing interests

The authors have no competing interests.

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