Use of Antibiotics in an Influenza Pandemic

Scientific Evidence Base Review

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Use of Antibiotics in an Influenza Pandemic

Scientific Evidence Base Review

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Executive summary

Acute influenza infection causes pharyngitis, rhinitis, sinusitis, otitis media, exacerbation chronic obstructive pulmonary disease (COPD), bronchitis and, occasionally focal pneumonia or severe lung injury with widespread damage to the alveoli, leading to respiratory failure.

Influenza infection predisposes to secondary bacterial infection due to a combination of respiratory mucosal damage and a reduced capacity to mount an immune response to bacterial invasion.

Common secondary infections include sinusitis, otitis media, bronchitis and exacerbation of COPD; less commonly, bacterial pneumonia, or blood-borne infection with common respiratory pathogens occurs; rarely, an unexpected severe infection such as meningococcal disease, is precipitated by influenza when the viral infection coincides with a period of throat colonisation with a potentially virulent pathogen.

The incidence of secondary bacterial infection varies with the age and infirmity of the patient and the strain of infecting influenza virus: while individuals in recognised risk groups have the highest risk of bacterial infections, younger patients and children also have a significantly increased risk.

Patients whose illness is relatively mild and who remain in the community have a low risk of secondary bacterial infection, ranging from zero to around 1%.

Among patients admitted to hospital with influenza, rates of secondary bacterial pneumonia have varied from 0.6% to 46%, with lower incidence tending to be seen in younger adults, but relatively higher incidence in young children (who are too young to have developed firm immunity to some of the bacteria concerned).

Among patients admitted with influenza who have respiratory failure and require intensive care or suffer fatal infections, the incidence of bacterial lung infections has ranged from 28 to 55%.

The commonest bacterial pathogens identified in secondary bacterial infections are: *Streptococcus pneumoniae*, accounting for half or more of all infections, *Staphylococcus aureus, Streptococcus pyogenes* and, more rarely, *Haemophilus influenzae*. Healthcare-acquired infections may also occur, particularly in patients in intensive care, with reported rates of 10-25%.

In young children, *Haemophilus influenzae* and *Streptococcus pneumoniae* tend to be the predominant pathogens; occasional severe *Streptococcus pyogenes* (group A streptococcus, or GAS) infections are seen (and also rarely occur in young adults): *Staphylococcus aureus* infections have been relatively less often reported.

In the United Kingdom, high levels of antibiotic resistance are uncommon in community-acquired secondary bacterial infections, though community-acquired meticillin-resistant *Staphylococcus aureus* is occasionally identified.

The prevalence of penicillin-resistance in *Streptococcus pneumoniae* in the UK is below 5%; for erythromycin, it is 5-10% (ECDC European antimicrobial Surveillance System 2008 report: *www.rivm.nl/earss).*

The prevalence of meticillin-resistant *S. aureus* is mainly related to healthcare-acquired invasive infections, and has more than halved since the high level (just under 50%) in 2008 (mandatory HCAI surveillance report June 2010: *www.hpa.org.uk*): community-acquired MRSA reports remain rare in the UK.

For milder pandemics, such as the 1968 and 2009 events, the clinical effects of the influenza infection were similar to those of seasonal flu, but with an increase in the numbers of cases of viral pneumonitis in younger patients. Bacterial infections tended to be focussed in older patients and those with risk factors for severe flu.

Increases in antibiotic use, in these recent pandemics, were driven by numbers of infected persons, rather than a major alteration in clinical features.

For pandemics more like the 1957 and 1918 events, and for a possible avian-related human influenza, the clinical features of the illness may also depend on severe respiratory tract

damage and significant temporary impairment of immunological responses; this is likely to result in a greater number of secondary bacterial infections in the two weeks from onset of symptoms.

While *S. pneumoniae* infections will generally be addressed, in the community or in hospital by most recommended antibiotics, such as amoxicillin and clindamycin, there will be a lesser but still significant, increase in *Staphylococcus aureus* infections some of which will be meticillin-resistant, or toxin-producing. In these more severe pandemics, the increase in demand for antibiotics will again depend on the influenza attack rate in the population.

GP prescribing and patient demand for antibiotic-treatment of respiratory infections in general has fallen steadily over the last decade, whilst the proportion of lower respiratory infections for which GPs prescribe antibiotics has remained fairly stable. Many such infections, including bacterial bronchitis, exacerbations of chronic obstructive pulmonary disease and uncomplicated mild pneumonias are treated with oral antibiotics in the community; more severe infections may also remain in the community if there is severe pressure on healthcare provision during an influenza pandemic.

During a severe influenza pandemic, the number of patients who can be treated in inpatient (particularly intensive) care will have an approximate ceiling. A tenfold or greater increase in inpatient care could be envisaged if non-urgent work is discontinued and lengths of stay are curtailed (especially if peaks in demand were separated in time over different areas of the country). This increase in throughput would include patients of whom a high proportion required antibiotic treatment. Finally, the use of both antivirals is known to reduce secondary complications and, therefore, the use of antibiotics.

1. Background and Introduction

Virally-induced damage to the respiratory tract predisposes to bacterial invasion and infection.

1. Bacterial infections are a recognised complication of both seasonal and pandemic influenza.

2. Seasonal influenza is usually a self-limiting acute infection, associated with viral invasion of the upper and lower respiratory tract, particularly the ciliated epithelium of the pharynx, trachea and bronchial tree. Clinical features of pharyngitis, rhinitis, sinusitis, tracheitis, laryngitis, croup (pharyngo tracheo laryngitis), exacerbation of chronic obstructive pulmonary disease (COPD), bronchitis and bronchiolitis are reported for both adults and children. Rare, more severe cases are associated with pneumonia or evidence of acute lung injury (ALI, diffuse alveolar damage, or DAD), causing respiratory difficulty with low blood oxygen levels and widespread air-space opacities on chest imaging.

3. The immune response to the infection causes death and shedding of the respiratory epithelium, with consequent clearance of the viruses. The exposed sub-epithelial surface of the lower respiratory tract is susceptible to colonisation and infection with bacterial flora derived from the mouth and pharynx.

The immune response to bacterial infection is significantly reduced by influenza virus infection.

4. In common with all pathogenic viruses, influenza viruses are able to reduce the host's ability to mount an effective immune response to infection. This is achieved by a mixture of inhibition of innate immune reactions, such as interferon production and killer cell mobilisation, and a virus-induced early and intense activation of the programmed cell death (or apoptosis) of immunocytes (a normal host function used to terminate immune and inflammatory reactions after an immune response). These immunological changes increase the risk of secondary infections particularly those caused by *S. pneumoniae*[1, 2] during and following acute influenza by:
   - Reducing the host's ability to resist a subsequent infection

- Altering the balance of colonisation versus infection by bacteria in the respiratory tract
- Exacerbating or revealing pre-existing low-grade infection of the respiratory tract

5. Furthermore, the detection of *S pneumoniae* in patients with influenza has been shown to be associated with severe disease and a poor outcome[3].

6. However, other pathogens are also involved in the aetiology of influenza-related pneumonia, and increase in frequency in the population during periods of high influenza activity[4, 5].

7. These immunological effects are more likely to be seen in patients whose respiratory tract is already susceptible to bacterial colonisation, eg patients with chronic obstructive pulmonary disease, chronic asthma or lungs damaged by chronic heart failure. As well as increasing the risk of bacterial pneumonia, they also predispose to bacterial sinusitis and acute suppurative otitis media. Influenza infection increases the likelihood of meningococcal disease in individuals who are carrying meningococci in the throat, and probably of clinical streptococcal disease in carriers of Group A streptococci[6, 7].

2. Influenza-related deaths and bacterial respiratory infection

8. Every year in the UK, there is a seasonal rise in death rates during the winter, caused almost exclusively by excess cardiovascular and respiratory deaths (Figure 1).

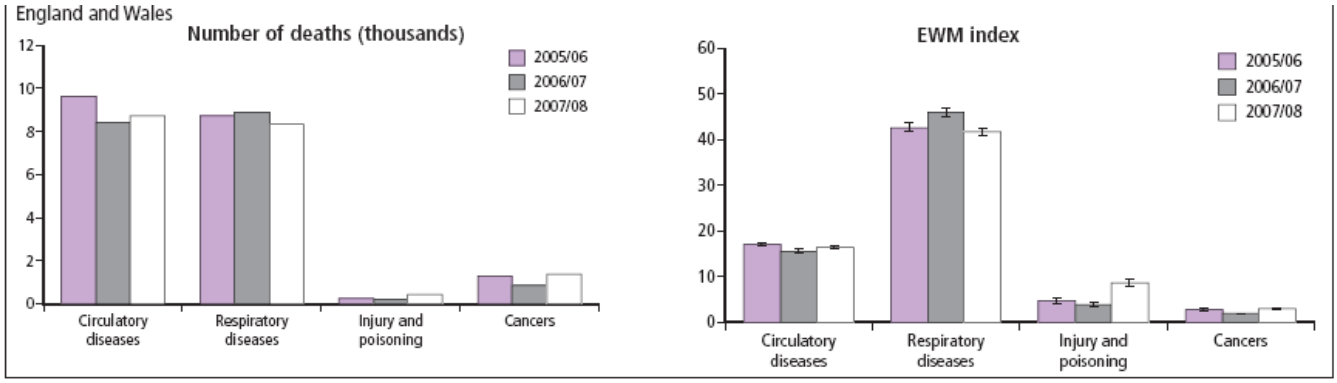

Figure 1 (from: Figure 6 in: Excess winter mortality in England and Wales: 2008/09 (provisional) and 2007/08 (final). ONS Statistical bulletin. © Crown copyright 2009).

9. As well as from population statistics, cohort studies of the UK population show that excess winter mortality in people aged 75 years or older is mainly due to respiratory and cardiovascular causes, and that the only predispositions for these deaths that remain significant after adjustment for co-variables are female gender and pre-existing respiratory disorders[8].

10. A large cohort study of 24,535 patients was designed to negate confounding factors[9]. It showed that increased deaths during a surge of seasonal influenza were not seen in an influenza- vaccinated cohort, but were strongly evident in the unvaccinated. Deaths attributed to influenza infection during outbreaks of influenza, taking all causes of mortality into account, was 13.4% in the unvaccinated versus 2.2% in the vaccinated. The probability that the protection was due to vaccination was particularly strong for respiratory deaths (P=0.002). It also highlights the contribution of influenza to the surge in deaths.

11. A meta-analysis of 20 studies suggested that this effect is detectable over a wider age-range, including somewhat younger patients[10].

12. Children are commonly carriers of *S. pneumoniae* and other important pathogens, and are highly susceptible to secondary bacterial infection after severe viral infections, including influenza[11, 12]. A prospective study of antibiotic use in children up to the age of 12 in general practice showed that, for influenza, but not for other acute viral respiratory infections, antibiotic treatment was associated with reduction in the duration of fever in around 20% of cases [13]. Antibiotic treatment did not alter parents' perception of a child's recovery, but the finding suggests that there is a significant incidence of mild secondary bacterial infections, even in self-limiting influenza cases outside hospital.

13. An examination of influenza-related deaths over the whole population age-range, in the pandemic of 1918-19[14] suggested that the association between bacterial secondary infections and pandemic influenza is not a feature of only one pandemic virus, or even solely of pandemic viruses. The authors argued that the majority of influenza-related deaths in the 1918-19 pandemic were associated with bacterial secondary infections, and that viral pneumonia alone was a much less common cause of mortality, most often seen in young adults. They refer to several public health reports showing that deaths were more related to pneumonia rates, which varied from community to community, than to influenza attack rates, which were less variable. Although neither antibiotic treatment nor intensive care were available at the time, many studies were performed on sputum, lungs and blood, and the authors review the findings, which showed that *Streptococcus pneumoniae, Haemophilus influenzae, Streptococcus pyogenes* (Group A streptococcus or GAS), and *Staphylococcus aureus* were the most common isolates.

14. In keeping with the variability of the prevalence of pathogens in different countries and communities, the likelihood of secondary infection with these four pathogens was different in different areas studied, but *S. pneumoniae* was the predominant pathogen in most studies. In the pandemic of 2009-10, individual cases of meticillin-resistant *Staphylococcus aureus* have been reported from various parts of the world [15, 16].

In summary

15. Bacterial secondary infections are well-recognised in association with both seasonal and pandemic influenza. Community-acquired secondary bacterial infections are related to the carriage and prevalence of bacterial species in the affected community. Common pathogens remain, as in the last century, *S. pneumoniae, S. pyogenes, H. influenzae* and *S. aureus.* Other pathogens include community-acquired, meticillin-resistant *S. aureus* (CA-MRSA) and the uncommon *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Moraxella catarrhalis* and gram-negative enterobacterial pathogens.

3. The incidence of bacterial secondary infection

Post-mortem evidence of community and healthcare-acquired bacterial infections

16. The most precise information on bacterial infections in pandemic influenza has come from post mortem/autopsy examinations of fatal influenza cases. The 2009-10 Influenza A (H1N1) pandemic was relatively mild, with a case-fatality rate similar to that of recent seasonal influenza viruses.

17. Numbers of prescriptions for medicines commonly used for lower respiratory infections in England (Figure 2), show that antibiotic prescribing in the second and third quarters of 2009 was not distinguishably different compared with the same period in the years preceding and following. Although these figures need to be interpreted with some caution as the data is not age-stratified, this may suggest that there was not great pressure on prescribing in primary care, as a result of the relatively mild pandemic. This is in contrast to the pressures reported from acute hospital trusts and ICU services in areas most affected by the pandemic surge.

18. Recent data on prescribing in primary care show that antibiotic prescriptions for upper respiratory tract infections have fallen significantly in numbers over the late 1900s and early 2000s, because of both fewer GP visits and a lower percentage of visits resulting in a prescription. However, there has been much less change in the total numbers of prescriptions for antibiotic-treatment of lower respiratory infections[18]. Antibiotic prescriptions for infections in primary care may therefore be a useful indicator of the numbers of bacterial lower respiratory infections being seen in the community.

19. Nevertheless, among the deaths investigated in the 2009 pandemic, there was a high prevalence of secondary bacterial infection with pathogens that were likely to have been community-acquired. Predominant among these was *S. Pneumoniae*, followed by *S. pyogenes*.

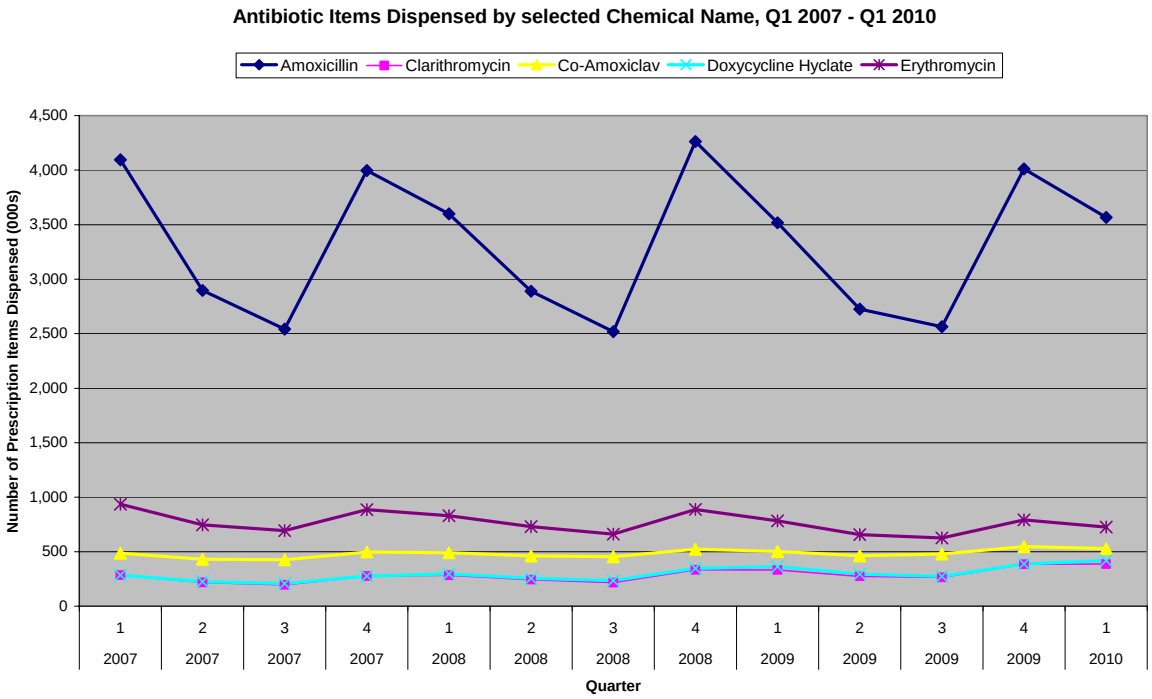

Figure 2. Source: Prescription Cost Analysis: The Health and Social Care Information Centre, Prescribing Support Unit.

20. Examples from published reports include:
    - From the USA [5], secondary bacterial infection was identified in 22 of 77 cases (28%), of which 10 were caused by *S. pneumoniae*, six *S. pyogenes*, and seven with *S. aureus*. Another series reported 18 of 34 cases (55%) with bacterial infections, of which 10 had *S. pneumoniae and one each* S, pyogenes, *S. aureus* and MRSA, plus one with both *S, pneumoniae* and *S. aureus* [19].
    - From Brazil, eight of 21 cases (38%), of which six had *S. pneumoniae* [20].
    - From the United Kingdom, 28 of 68 cases (41%) with bacterial infection, of which 7 were *S. pneumoniae*, four were *S, pyogenes* and two each were *S. Aureus* and *H. influenzae*. Seven of nineteen deaths in children under the age of 16 years were related to secondary bacterial infections, including *S.pneumoniae*, *S. pyogenes, H. influenzae* and *S. aureus* [21].

21. Among those cases who received intensive care prior to death, a number of cases of infection with healthcare-acquired and ventilator-associated pathogens were additionally identified. These included MRSA, *Klebsiella* species, *Serratia* species, pseudomonads and *Acinetobacter* species, including antibiotic-resistant *A. baumanii*.

Evidence from patients admitted to hospital

22. There are relatively few reports of bacterial secondary infections with influenza in surviving hospital patients. Evidence from the recent A (H1N1) pandemic is based on a rather mild pandemic virus, with an estimated case-fatality rate of around 26 per 100,000 in UK cases [22]. Nevertheless, a study in Utah [23] showed that there was a significant increase in the admission of children with empyema during the pandemic surge, compared with the same season in the last four years. The main pathogens were *S. pneumoniae* and *S. pyogenes*.

23. A three-year prospective study in Finland [24] showed that 30 percent of cases of bacterial pneumonia in children were associated with a viral infection, most commonly respiratory syncytial virus or rhinovirus. However, during a seasonal influenza outbreak in 2000-2001, the percentage of respiratory infections in children caused by influenza rose from 5% to 20% [25]. Although this does not provide a figure for the percentage of influenza cases accompanied by bacterial pneumonia, it suggests that a significantly more severe influenza

pandemic, such as the 1918-19 pandemic, with mortality rates in various countries estimated at 0.2 to 8% [26], might result in large numbers of influenza-infected children who, even with a low percentage requiring antibiotic treatment, would place an increased demand on antibiotic supplies. It has been estimated that in Copenhagen, in the summer of 1918, the demand for hospital admissions among all age-groups rose about 300-fold compared with previous years in the decade, though this was exceptionally high compared with other cities in Denmark[27].

24. The pandemics of 1957 and 1968 were considerably less severe than that of 1918-19 but would still pose a severe pressure on secondary and tertiary care and, by extrapolation, on antibiotic supplies. In a Royal Society of Medicine symposium, an overview from the World Health Organization included the information that the case-fatality rate in the 1957 pandemic was probably around 18-50 per 100,000 overall, but in some areas, perhaps as high as 300 per 100,000 infections. Most of the deaths in a wide range of countries had been associated with bacterial secondary infection [28]. A detailed study of hospital admission in New York in 1957-58 [29], showed that 15 of 33 patients (45%), and half of ten fatal cases, had evidence of secondary bacterial lung infection. In the 1950s, antibiotic resistance in *S aureus* (particularly to tetracycline and streptomycin) was becoming widespread, and this may have led to relatively high numbers of infections with this organism. Nowadays, resistance to tetracycline is much less common.

25. In the 1968-69 pandemic, in the USA, staphylococcal pneumonia incidence was increased by around 2.5-fold and caused severe infections with fatality rates as high as 33% [30].

26. An observational study of invasive *S. pneumoniae* infections in New Zealand [31] showed a significant correlation between numbers of *S. pneumoniae* infections and influenza incidence over a 10-year period. A one-year survey of 304 patients with community-acquired pneumonia showed that 45 patients had a mixed viral and bacterial diagnosis, most often including influenza or rhinovirus[32].

27. In Spain, eight percent of 96 patients admitted to hospital with respiratory failure and proven influenza A (H1N1) in 2009 had a community-acquired bacterial infection, and 25% of patients later developed a healthcare-acquired bacterial infection [33].

28. Of 631 hospital admissions with proven influenza A (H1N1) in Britain, 349 had x-ray evidence of pneumonia, but only four (0.6% of all admissions) had a proven bacterial coinfection [34].

29. During the influenza seasons of 2003-2008, a USA-wide survey of children in hospital with influenza-related pneumonia [35] showed that pneumonia was present in 41-45% of children aged 6-23 months with influenza, 36-44% aged 2 years to under 7 years and 20 to 40% of older children. Of these cases, there was co-existing bacterial infection in 2% overall; just under half of isolated bacteria were *S. aureus,* (one-third of these were MRSA).

In summary

30. Bacterial secondary infections are uncommon in mild influenza. Many are probably minor and self-limiting, or easily treated with antibiotics recommended for use in primary care, particularly amoxicillin or clarithromycin.

31. With more severe influenza illness, bacterial secondary infections become progressively more common, and in secondary care, high dependency and intensive care, rates of bacterial secondary infection rise to between 8 and 55%. In a pandemic caused by a more virulent virus strain, secondary bacterial infection is likely to be more common, and would be likely to severely affect known high-risk groups in the community.

32. The nature of the infecting organisms in the community has not changed over the years since pandemics have been medically documented. *Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus* and, less commonly, *Haemophilus influenzae* are the main bacterial invaders in adult cases, while *Haemophilus influenzae, Streptococcus pneumoniae* and *Sreptococcus pyogenes* tend to predominate in children. In all age groups, *Staphylococcus aureus* becomes a more prevalent respiratory pathogen in infections caused by more virulent influenza viruses, and in more severely ill cases.

33. The antibiotic sensitivities of these pathogens are predictable. In the United Kingdom, the antibiotics most likely to be effective against all, or most, of these pathogens remain co-amoxyclav and doxycycline. Macrolides (clarithromycin and erythromycin) are effective as second choices, but with a small risk of being less effective against *Staphylococcus aureus*

(meticillin-sensitive). Erythromycin is less active against *Haemophilus influenzae* than clarithromycin, which is nowadays the recommended macrolide agent for treating respiratory infections in the community [36], and severe respiratory infections in inpatient care.

34. For patients with penicillin sensitivity, or with suspected mixed infections which may include atypical organisms, levofloxacin is recommended as an alternative choice [36]. A small proportion of community-acquired infections is caused by meticillin-resistant *S. aureus*. A proportion of these would be sensitive to doxycycline, which is the first-choice recommendation for treating non-severe community-acquired influenza-related bacterial pneumonia during a pandemic[37]. In cases where doxycycline would not be appropriate, useful oral medicines might include clindamycin or linezolid. Ensuring the availability of small stocks of these may be appropriate.

35. Finally, numerous studies demonstrate that the use of antivirals to treat influenza infections also reduces the number of secondary complications and, in particular, the use of antibiotics[38, 39].

4. Conclusions

36. Depending on the nature and severity of a pandemic strain of influenza A virus, an increased demand for orally-administered antibiotics in primary care services may occur. However, a more severe pandemic would inevitably cause a higher demand for antibiotics, even if the incidence of influenza-related bacterial pneumonia were low[28].

37. In secondary care, there is more likely to be an increased demand for antibiotics to be used by the intravenous (or intramuscular) route. Co-amoxyclav, macrolides and broader-spectrum antibiotics such as levofloxacin and cefalosporins would be the likely requirement. In a severe pandemic, outpatient injectable antibiotics, such as daily ceftriaxone, may occasionally be used as one-off dosage to assist patients who are moderately to severely ill but not likely to gain admission to hospital.

38. The number of patients cared for in critical care services will be limited by availability of facilities. These patients are more likely to require treatment for ventilator-associated pneumonias, with antibiotics such as ceftazidime, meropenem or ertapenem, as well as vancomycin or teicoplanin for MRSA and enterococcal infections. In the majority of cases, alternatives may be used but for healthcare-acquired infections with highly resistant pathogens, especially if outbreaks were seen, supply problems could occur.

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