Epidemiology, etiology, and risk factors of bacterial pneumonia

Epidemiology

Hospital-acquired pneumonia

Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection after urinary tract infections. The incidence of HAP ranges from 5 to 15 cases per 1000 hospital admissions, and is a frequent problem in general wards (incidence ranging from 1.6 to 3.67 cases per 1000 admissions) [1–3]. In the case of patients admitted to an intensive care unit (ICU), HAP occurs in up to 25% of patients [4], with approximately 70 to 80% of episodes occurring during mechanical ventilation (MV) [5] (Figure 2.1).
The incidence of HAP in the ICU varies by geographic area (Table 2.1). In the United States, the National Nosocomial Infection Surveillance data found that 31% of all nosocomial infections in combined medical–surgical ICUs were due to pneumonia, with 83% of cases being ventilator-associated pneumonia (VAP) [6]. In Europe, a large Italian study in 125 ICUs (which included 34,472 patients) reported that 9.1% of all admitted patients developed nosocomial infections, and pneumonia (specifically VAP) was the most prevalent (48.7%) ICU-acquired infection [7]. In a prevalence study of 254 ICUs in Mexico, 23.2% of patients had an ICU-acquired infection, and VAP was the most prevalent infection (41.2%) [8]. According to a study in Asian hospitals, the proportion of ICU-acquired respiratory infections ranges from 9 to 23% [9].

Most of the currently available studies on HAP have focused on ventilated patients; there are few studies on HAP in nonventilated ICU-acquired pneumonia (NV-ICUAP). One study that compared VAP and NV-ICUAP in a population of 315 patients with ICU-acquired pneumonia, found that 52% of patients had VAP and 48% had NV-ICUAP [5].

With all the data available relating to HAP in the ICU we can say that HAP represents one of the most common nosocomial infections worldwide and VAP is the most common nosocomial infection diagnosed in the ICU. The true incidence of NV-ICUAP remains uncertain.

**Community-acquired pneumonia**

Since community-acquired pneumonia (CAP) is not a reportable disease, its true incidence remains uncertain. Only 20 to 50% of patients with CAP require hospitalization. The overall annual incidence of CAP in adults in Europe ranges between 1.07 and 1.20 per 1000 person-years and 1.54 and 1.70 per 1000 population and increases with age (14 per 1000 person-years in adults aged ≥65 years) [22] (Table 2.2). CAP most frequently affects individuals at extremes of age and those with any type of coexisting illness [22–24]. The study by Torres et al [22] reported an increased risk of CAP in men (compared with women) and in patients ≥65 years of age.

Based on data from a systematic literature review, Said et al [28] estimated that the proportion of pneumococcal pneumonia that is
| Study            | Country/Year of publication                                           | Study period                                   | Population | Incidence                                                                 |
|------------------|------------------------------------------------------------------------|------------------------------------------------|------------|---------------------------------------------------------------------------|
| Torres et al [10]| Spain/1991                                                             | April 1987 to May 1988                         | VAP        | 78 (24%) per 322 cases                                                   |
| Rello et al [11] | Spain/1991                                                             | January 1988 to November 1989                  | VAP        | 58 (21.9%) per 264 cases                                                 |
| Joseph et al [12]| India/2009                                                             | October 2006 to December 2007                  | VAP        | 22.94 per 1000 ventilator days                                            |
| Blot et al [13]  | Belgium, France, Germany, Greece, Italy, Ireland, Portugal, Spain, and Turkey/2014 | The period of data collection was 6 months     | VAP        | 14.6% in patients 45 to 64 years of age                                   |
|                  |                                                                        |                                                |            | 17.0% in patients 65 to 74 years of age                                   |
|                  |                                                                        |                                                |            | 12.8% in patients ≥75 years of age                                       |
| Suka et al [14]  | Japan/2007                                                             | July 2002 and June 2004                        | VAP        | 53.4%                                                                     |
|                  |                                                                        |                                                |            | 6.5 cases per 1000 patient-days                                          |
| Sopena et al [15]| Spain/2014                                                             | January 2006 and April 2008                    | Non-ICU    | 2.45 cases per 1000 hospital admissions (95% CI, 2.04–2.92)              |
| Barreiro-Lopez et al [16]| Spain/2005                             | November 1997 to January 1999 | Non-ICU    | 3.35 cases per 1000 hospital admissions                                  |
| Franzetti et al [17]| Italy/2006                                      | January 1988 and December 2002                | NBP (HIV)  | 24 cases per 1000 inpatient/year                                         |
| Weber et al [18] | USA/2007                                                               | 2000 to 2003                                  | HAP/VAP    | 0.37 cases per 1000 hospital admissions                                  |
| Diouf et al [19] | France/2006                                                            | January to December 2002                       | VAP        | 7.16 per 100 admitted patients and 50 per 100 ventilated patients       |
| Koulenti et al [20]| Belgium, France, Germany, Greece, Italy, Ireland, Portugal, Spain, and Turkey/2009 |                                                | HAP/VAP    | 75.9% NP                                                                 |
|                  |                                                                        |                                                |            | 20.5% HAP                                                                |
|                  |                                                                        |                                                |            | 42.7% VAP                                                                |
|                  |                                                                        |                                                |            | 12.7% VE-VAP                                                             |
| Japoni et al [21]| Iran/2011                                                              | June 2008 and March 2009                      | HAP/VAP    | 6.9% NP, of which 72% were VAP                                           |

Table 2.1 Incidence of hospital-acquired pneumonia. HAP, hospital-acquired pneumonia; HIV, human immunodeficiency virus; ICU, intensive care unit; NBP, nosocomial bacterial pneumonia; NP, nosocomial pneumonia; VAP, ventilator-associated pneumonia; VE- VAP, very early-onset ventilator-associated pneumonia. Data extracted from [10–21].
bacteremic to be approximately 25%, and the ratio of nonbacteremic pneumococcal pneumonia to bacteremic pneumococcal pneumonia to be approximately 3:1.

Estimates of mortality among patients with CAP range from 1 to 5% in outpatients, from 5.7 to 14.0% in general wards, and from 34 to 50% in the ICU setting (especially in ventilated patients) [29,30]. Medium- and long-term mortality of patients with CAP who were enrolled in the Pneumonia Patient Outcomes Research Team (PORT) cohort study was 8.7% within 90 days after presentation, 29.2% in 1 year, and 25.4% in 5 years [31].

In the case of pneumococcal pneumonia, the mortality rate is about 5%, and in the case of bacteremic pneumococcal pneumonia the mortality rates vary significantly, ranging from 6 to 30% in the adult population [32,33].

### Table 2.2 Epidemiology of community-acquired pneumonia in Europe

| Study            | Country | Study period             | CAP incidence (95% CI)                                                                 |
|------------------|---------|--------------------------|---------------------------------------------------------------------------------------|
| Rodriguez et al  | UK      | 1 January 2000 to        | Primary care patients, per 1000 person-years:                                         |
| [25]             |         | 31 December 2005         | • Overall, 1.07 (1.04 to 1.09)                                                        |
|                  |         |                          | • Women, 0.93 (0.89 to 0.96)                                                          |
|                  |         |                          | • Men, 1.22 (1.18 to 1.26)                                                           |
| Vila-Corcoles et | Spain   | 1 January 2002 to        | Age ≥65 years, per 1000 person-years:                                                 |
| al [26]          |         | 30 April 2005            | • Overall, 14.0 (12.7 to 15.3)                                                        |
|                  |         |                          | • Men, 19.2 (17.1 to 21.6)                                                           |
|                  |         |                          | • Women, 10.0 (8.6 to 11.5)                                                          |
| Viegi et al [27] | Italy   | 15 February 1999 to      | Annual incidence per 1000 population:                                                 |
|                  |         | 14 February 2000         | • Overall, 1.703                                                                      |
|                  |         |                          | • Males, 1.692                                                                       |
|                  |         |                          | • Females, 1.713                                                                     |
Microbial etiology

Etiology of hospital-acquired pneumonia

Knowledge of pathogens associated with HAP is critical for empirical antibiotic therapy. Most data concerning the microbial etiology of HAP refer specifically to the VAP population; data on microbial etiology of NV-ICUAP and non-ICU HAP remain limited.

The principal sources of pathogens in HAP cases are the health care environment and the patient’s own microbial flora. The microbial etiology of HAP in the ICU varies according to patient population, hospital ICU settings, the country, and the type of presentation (early- or late-onset).

A review of published studies of the causes of pneumonia in hospitalized patients and the results of the SENTRY Antimicrobial Surveillance Program in the United States [34] concluded that six pathogens cause approximately 80% of HAP cases (Figure 2.2): *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella* species, *Escherichia coli*, *Acinetobacter* species, and *Enterobacter* species.

![Figure 2.2 Microbial etiology of hospital-acquired pneumonia (SENTRY study). Data extracted from Jones [35].](image-url)

- Staphylococcus aureus
- Pseudomonas aeruginosa
- Klebsiella species
- Escherichia species
- Acinetobacter species
- Enterobacter species
- Serratia species
- Stenotrophomonas maltophilia
- Streptococcus pneumoniae
- Haemophilus influenzae
Gram-negative pathogens
The most frequent Gram-negative pathogens associated with HAP include:

- *P. aeruginosa*;
- *Acinetobacter baumannii*;
- *Haemophilus influenzae*; and
- *Enterobacteriaceae* (*Klebsiella pneumoniae*, *E. coli*, *Enterobacter* species, *Serratia* species, *Proteus* species, etc).

Gram-negative bacteria are implicated in 50 to 80% of the cases of HAP in an ICU [10].

Gram-positive pathogens
The most common Gram-positive pathogens isolated from patients with HAP include *S. aureus* (methicillin-sensitive and methicillin-resistant), *Streptococcus* species, and *Streptococcus pneumoniae*. Gram-positive pathogens account for 20 to 30% of HAP cases.

Polymicrobial etiology
Polymicrobial etiology is defined as pneumonia caused by more than one potentially pathogenic microorganism, and around 30 to 70% of VAP cases are polymicrobial [36,37]. Combes et al [37] demonstrated that the epidemiology and outcomes of patients with pneumonia of monomicrobial or polymicrobial etiology did not differ significantly.

Etiology of early- and late-onset pneumonia
Early-onset HAP in patients with no prior antibiotic exposure is often caused by community-acquired pathogens such as *H. influenzae*, *S. pneumoniae*, or methicillin-sensitive *S. aureus* (MSSA), and in these cases pathogens with antibiotic resistance are rarely causative. Patients with prior antibiotic exposure are susceptible to the above microorganisms plus some *Enterobacteriaceae* (*Serratia* species and *Proteus* species).

Patients with late-onset HAP have the most severe form of infection and are at an increased risk of infection by multidrug-resistant (MDR) microorganisms such as *P. aeruginosa*, methicillin-resistant *S. aureus* (MRSA), *A. baumannii*, and *Enterobacteriaceae* expressing extended
spectrum β-lactamases (ESBL) and AmpC β-lactamases, which confer resistance to penicillins and cephalosporins. Polymicrobial etiology may also be seen in patients with late-onset HAP. Prior antibiotic therapy or prior hospitalization within 90 days of infection predisposes to colonization and infection with MDR pathogens [38] (Figure 2.3).

**Multidrug-resistant pathogens**
Pathogens such as *P. aeruginosa*, *S. aureus* (MRSA), *A. baumannii*, and ESBL-producing enteric Gram-negative bacilli continue to increase in frequency and in resistance profiles in ICUs around the world.

Goossens [39] in the MYSTIC study reported that 12% of isolates from 33 European ICUs were *P. aeruginosa* MDR (resistant to ceftazidime, ciprofloxacin, and gentamicin). The prevalence of *P. aeruginosa* is due to its ability to acquire antibiotic resistance, especially in cases of previous colonization, previous infection with MDR *P. aeruginosa*, and prior antibiotic therapy during an ICU stay. VAP caused by *P. aeruginosa* is associated with a high mortality [40].
HAP caused by *A. baumannii* represents approximately 20% of all episodes of HAP in ICUs in Europe [20]. The success of *A. baumannii* is due to its high environmental resistance, limited virulence, and an extraordinary facility for the development of antimicrobial resistance.

**Etiology of community-acquired pneumonia**

The differing percentages of causative microorganisms associated with CAP that have been reported in studies are likely to be due to a number of factors, including diversity in local epidemiology, setting (outpatients, hospitalized, or ICU), pneumonia severity, and patient characteristics (eg, sex, age, and comorbidities). However, *S. pneumoniae* is widely accepted as being the most common CAP-causing pathogen across a range of severities and patient ages [41–44]. In Europe and the United States, *S. pneumoniae* accounts for about 30 to 35% of cases [41,45,46].

The frequencies of atypical bacteria varies according to the epidemic year, but are still considered common causes of CAP [44]. Among these, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* are the most frequently reported. *M. pneumoniae* accounts for up to 37% of CAP in patients treated as outpatients and 10% of cases requiring hospitalization [41,47]. *C. pneumoniae* accounts for 5 to 15% of cases

| Outpatients | Hospitalized (Non-ICU) | ICU patients |
|-------------|------------------------|--------------|
| Streptococcus pneumoniae | Streptococcus pneumoniae | Streptococcus pneumoniae |
| Mycoplasma pneumoniae | Mycoplasma pneumoniae | Legionella pneumophila |
| Haemophilus influenzae | Chlamydia pneumoniae | Gram-negative bacilli |
| Chlamydia pneumoniae | Haemophilus influenzae | Staphylococcus aureus |
| Respiratory viruses: influenza A and B, adenovirus, RSV, parainfluenza virus | Legionella pneumophila | Respiratory viruses |
| Respiratory viruses | Haemophilus influenzae | Pseudomonas aeruginosa |
| Polymicrobial etiology | Respiratory viruses | (the frequency is determined by the presence or absence of specific risk factors) |
| Polymicrobial etiology | Polymicrobial etiology | Polymicrobial etiology |

*Table 2.3 Microbial etiology of community-acquired pneumonia by site of care.* Adapted from Cillóniz et al [41]. ICU, intensive care unit; RSV, respiratory syncytial virus.
cases of CAP [41], and *L. pneumophila* pneumonia accounts for 2 to 6% of CAP in immunocompetent patients (especially serogroup 1) [48].

In the case of respiratory viruses, data show a viral presence in 10 to 30% of immunocompetent adults hospitalized with CAP [41,49,50]. Influenza virus A/B, respiratory syncytial virus, adenovirus, rhinovirus, and parainfluenza virus are most often responsible for CAP in immunocompetent adults.

The incidence of polymicrobial etiology in CAP varies from 5.7 to 13.0% depending on the population and the microbiological diagnostic test used [41,50,51]. Table 2.3 shows the principal pathogens involved in CAP.

**Antibiotic resistance**

Antibiotic resistance among *S. pneumoniae*, the most common cause of CAP, has increased worldwide in the last two decades [52–54]. However, mortality rates related to antibiotic-resistant *S. pneumoniae* have not increased due to interventions such as conjugated pneumococcal vaccine, which covers the serotypes that are most likely to express resistance [55]. In a study of macrolide-resistant *S. pneumoniae*, Daneman et al [56] found that resistance, and therefore risk of macrolide failure, was independent of the underlying resistance mechanism.

Pneumococcal strains have developed resistance to several antibiotics including penicillins, cephalosporins (β-lactams), macrolides, and fluoroquinolones. Currently, 20 to 30% of pneumococcal disease cases worldwide are MDR (resistant to more than three classes of antibiotics) [57,58] (Table 2.4).

It is broadly recognized that risk factors for infection caused by antimicrobial-resistant *S. pneumoniae* include extremes of age (age <2 years or >65 years), antimicrobial treatment within the previous 3 months, community or household exposure to resistant isolates, institutionalization, alcoholism, comorbidity, and immunosuppression [60,61]. A prospective cohort study of invasive pneumococcal infection conducted in Canada aimed to investigate the relative risk of infection with macrolide- or fluoroquinolone-resistant *S. pneumoniae* on the basis of antibiotic use in the previous 3 months [62]. The prevalence of macrolide resistance among infecting isolates increased from 7% to 10% (when no antibiotic,
### Community-acquired pneumonia

| Pathogens                  | Antibiotic resistance | Principal mechanisms of resistance                                                                 | Risk factors of resistance                                                                       |
|----------------------------|-----------------------|------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| *Streptococcus pneumoniae* | Penicillins           | Mutations in PBPs 2x, 2b, and 1a                                                                      | Prior antibiotic treatment                                                                         |
|                            |                       | Methylation of the 23S ribosomal target site, encoded by the *erm(B)* gene                            | Age <5 years                                                                                       |
|                            | Macrolides            | Active (proton-dependent) efflux, encoded by the *mefE* (macrolide efflux) or *mefA* genes           | Attendance to daycare centers                                                                      |
|                            | Fluoroquinolones      | Mutations in the QRDR of *gyrA* and/or *parC*                                                        | Residence in long-term care facilities                                                               |
| *Mycoplasma pneumoniae*    | Macrolides            | Mutation in the 23S gene rRNA                                                                       | Recent hospitalization                                                                             |
|                            |                       |                                                                                                      | Chronic pulmonary disease                                                                         |
|                            |                       |                                                                                                      | Nosocomial acquisition                                                                             |

### Hospital-acquired pneumonia

| Pathogens                  | Antibiotic resistance | Principal mechanisms of resistance                                                                 | Risk factors of resistance                                                                 |
|----------------------------|-----------------------|------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| *Staphylococcus aureus*    | Methicillin (MRSA)    | Gene *mecA*                                                                                            | Hospital environment (ICU)                                                                     |
|                            | Vancomycin (VRSA)     | Presence of transposon Tn1546                                                                         | Prolonged hospitalization (>5 days)                                                               |
|                            | Daptomycin            | *mprF* and the *yyFG* components of the *yyFGHI* operon                                              | Recent hospitalization for 2 days in the preceding 90 days                                      |
| *Pseudomonas aeruginosa*   | Penicillins           | Reduced access to bacterial targets                                                                  | Recent antibiotic therapy                                                                        |
|                            | Aminoglycosides       | Presence of efflux mechanisms                                                                         | Residence in a nursing home or extended care facility                                           |
|                            | Fluoroquinolones      | Production of enzymes that inactivate and degrade antibiotics                                        | Immunosuppressive therapy or disease                                                               |
| *Acinetobacter baumannii*  | Penicillins           | Antimicrobial-inactivating enzymes                                                                    |                                                                                                |
|                            | Carbapenems           | Reduced access to bacterial targets                                                                  |                                                                                                |
|                            | Colistin              | Mutations that change targets or cellular functions                                                  |                                                                                                |
|                            | Tigecycline           |                                                                                                      |                                                                                                |
|                            | Fluoroquinolones      |                                                                                                      |                                                                                                |

Table 2.4 Antibiotic resistance and risk factors associated with common pathogens causing pneumonia. Adapted from Lynch and Zhanel [52] and Feldman et al [59]. *Erm(B)*, erythromycin ribosome methylation; *mprF*, multipepoxide resistance factor; PBPs, penicillin-binding proteins; QRDR, quinolone resistance determinant region.
an antibiotic from another class, or erythromycin had previously been used) to 53% if azithromycin had previously been used. Similarly, the prevalence of fluoroquinolone resistance among pneumococci recovered from adults with community-acquired infection was <1% if no fluoroquinolone had been used in the previous 3 months, rising to approximately 4% if a fluoroquinolone had previously been used [62].

*S. pneumoniae* was reported to be the etiological agent in 2 to 35% of cases of CAP treated in the outpatient setting [42,63,64]. It is estimated that 0.14 to 1.90% of outpatients with bacterial pneumonia have pneumococcal infections with levels of resistance high enough to warrant consideration of alternative treatment [65].

Approximately 10% of CAP cases are caused by MDR pathogens (*S. aureus* and *P. aeruginosa* were most frequently isolated) [66,67]. In a European study of pathogens isolated from hospitalized patients with CAP, MDR pathogens were the cause of CAP in 3.3 to 7.6% of patients in which a pathogen could be identified, with MRSA being the most common MDR pathogen [68].

Hospital environments, especially ICUs, are important reservoirs of resistant pathogens. The risk of developing infection with MDR pathogens in HAP depends on the presence of some risk factors such as prolonged hospitalization (>5 days), recent hospitalization for 2 days in the preceding 90 days, recent antibiotic therapy, residence in a nursing home or extended care facility, immunosuppressive therapy, or comorbidity.

MDR pathogens are mostly involved in late-onset HAP due mainly to antibiotic selective pressure, cross-transmission, and colonization from ICU environmental sources. *S. aureus* (especially MRSA) accounts for up to 30% of cases of HAP [69], compared to less than 10% of CAP cases [48].

Colonization (nasal and skin) is the major source for pneumonia; 30 to 50% of healthy adults carry pneumonia-causing pathogens transiently in the anterior nares, and health care workers may have higher carriage rates. Patients who develop MRSA pneumonia have nasal colonization on admission in 67% of cases, whereas noncolonized patients have less than a 5% risk of subsequent MRSA pneumonia. This pathogen is easily transferred from person to person by direct hand contact.
Community-acquired MRSA (CA-MRSA) has become an important CAP pathogen. Community and hospital MRSA share a mecA gene that confers universal methicillin- and β-lactam-resistance, but CA-MRSA presents broader antibiotic susceptibility than hospital MRSA. CA-MRSA carries the gene for the Panton-Valentine leukocidin (PVL) toxin, which causes leukocyte destruction and tissue necrosis [70]. The clinical presentation of CA-MRSA pneumonia has been described as the presence of a cavitary lung lesion. CA-MRSA is susceptible to clindamycin, TMP-SMX, daptomycin, and doxycycline [71].

*P. aeruginosa* in CAP is rare; patients with underlying diseases such as cystic fibrosis, chronic obstructive pulmonary disease (COPD), and bronchiectasis are the most likely to be affected by this pathogen. *P. aeruginosa* is a leading cause of HAP and particularly frequent cause of VAP [72]. Prolonged endotracheal intubation and prior antibiotic therapy, especially with broad-spectrum antibiotics, are the primary risk factors for *Pseudomonas* VAP. A French study of patients with VAP noted that patients with prior antimicrobial therapy had markedly increased rates of *P. aeruginosa* or *Acinetobacter* infection (65%) compared with patients with VAP without prior antibiotic therapy (19%) [73].

*A. baumannii* exhibits a high level of antimicrobial resistance but with a low virulence [74] and can cause CAP and HAP. *A. baumannii* is a frequent cause of pneumonia in Southeast Asia; hot climates especially dry [75] and humid [76,77] are the preferred environment of this pathogen. Infections caused by *A. baumannii* presented similar epidemiologic patterns in CAP and HAP, with a seasonal variation and a peak in the late summer. CAP caused by *A. baumannii* has a mortality rate of 50% [76], and in the case of HAP the severity of the underlying disease determines the fatality rate. Garnacho-Montero et al [74] noted that antibiotic exposure was the only independent risk factor associated with VAP caused by *A. baumannii*. The mortality rate of VAP caused by *A. baumannii* infection was no higher than VAP caused by other pathogens.
Risk factors

Risk factors related to hospital-acquired pneumonia

Factors that increase the risk of HAP include two main categories and are detailed in Table 2.5.

Intubation and mechanical ventilation increases the risk of VAP by 6- to 21-fold, and the risk is greatest in the first 5 days of intubation [38]. The endotracheal tube allows direct entry of bacteria into the lower respiratory tract, interferes with normal host defense mechanisms, and becomes a reservoir for pathogenic microorganisms.

Oropharyngeal colonization is the main mechanism responsible for development of HAP; colonization will be present upon admission or acquired in the ICU. Feldman et al [59] found that colonization and biofilm formation were present within 12 hours of patient intubation and present in almost all patients after 96 hours. In the same study it was also demonstrated that colonization in patients undergoing mechanical ventilation occurred first in the oropharynx and stomach, then lower respiratory tract, and finally in the endotracheal tube [59].

| Patient-related factors | Hospital- and treatment-related factors |
|------------------------|----------------------------------------|
| Male sex               | Colonization of the oropharynx by virulent microorganisms |
| Age 60 years or above  | Prior antibiotic therapy |
| Malnutrition           | Conditions that promote pulmonary aspiration or inhibit coughing |
| Severe acute or chronic illnesses | • thoracoabdominal surgery |
| Immunosuppression      | • endotracheal intubation |
| Recent hospitalization | • insertion of nasogastric tube |
| Burns, trauma, post surgery | • inadequate endotracheal tube cuff pressure |
| Severity of Illness (APACHE II or SAPS II score) | • repeated reintubation |
| Acute respiratory distress syndrome (ARDS) | • supine position |
|                        | Exposure to contaminated respiratory equipment |

Table 2.5 The factors that increase the risk of developing hospital-acquired pneumonia. Adapted from Sopena and Sabria [1] and Masterton et al [78].
Risk factors related to community-acquired pneumonia

Age and sex

Pneumonia can occur at any age, but its incidence increases significantly with advanced age. Old age is therefore an important risk factor for pneumonia, which is a leading cause of illness and death in the elderly. A recent study that investigated the influence of age and comorbidity on microbial patterns in patients over 65 years of age with CAP found that age does not significantly affect pathogen patterns, whereas comorbidities were associated with specific causes [23]. The main factors associated with mortality in this analysis were neurologic diseases, the presence of potential MDR pathogens, and very advanced age (>85 years) [23]. Advanced age is associated with a decline in the integrity of physical barriers and protection against invading pathogens, as well as age-related changes in the immune system. Declines in the sensitivities of airway protective cough and swallowing reflexes are age-related and important risk factors for the development of pneumonia [79].

The difference of susceptibility to infections such as pneumonia between males and females is multifactorial. During the development of infection there is an interaction between sex-specific immune responses and immune responses to specific pathogens. A clear example of this relationship is the sex differences in the incidence and outcome of influenza virus A infections. In 2010 the WHO published a report detailing evidence that sex and gender should be considered when evaluating exposure to and the outcome of influenza virus infection [80]. The report concluded that the outcome of pandemic influenza H1N1 is generally worse for young adult females.

Health care settings

The number of patients who receive care outside the hospital setting (eg, in nursing homes) is increasing with the aging population, implying an increase in the risk of pneumonia [22,81,82]. In addition, 10 to 18% of all patients hospitalized for pneumonia are nursing home residents, with mortality rates potentially as high as 55% [81,83].
Comorbidities and lifestyle factors

**Chronic obstructive pulmonary disease**

COPD is one of the most common comorbidities associated with CAP. Patients with COPD have a 2- to 4-fold increased risk of CAP [22]. Data from a Spanish study conducted in patients with CAP compared the outcome of patients with and without COPD and revealed that the presence of COPD was an independent risk factor for mortality [84].

**Diabetes mellitus and obesity**

The prevalence of diabetes is increasing rapidly and is predicted to increase further, in parallel with the trends observed for obesity [85,86]. Diabetic patients may have increased susceptibility to pneumonia for several reasons: increased risk of aspiration, hyperglycemia, decreased immunity and impaired lung function, and coexisting morbidity.

Kornum et al [87] reported that Type 1 and Type 2 diabetes were risk factors for pneumonia-related hospitalization in a cohort of 34,239 patients with pneumonia in Denmark [87]. Similarly, Yende et al [88] reported that pre-existing diabetes was associated with a higher risk of death after hospitalization for CAP compared to those hospitalized for noninfectious illnesses. Furthermore, the risk of developing severe pneumococcal bacteremia is higher in diabetic patients [89].

**Chronic renal disease**

Several studies have demonstrated that chronic renal failure is a significant risk factor for mortality in patients with CAP [90,91]. In patients on dialysis, the mortality rate from pneumonia is 14- to 16-fold higher than in the general population [92].

**Chronic liver disease**

Bacterial infections occur in 32 to 34% of patients with cirrhosis who are admitted to the hospital, of which approximately 15% are pneumonia (the third leading cause of infection in these patients). Cillóniz et al [93] reported that chronic liver disease was a risk factor for pulmonary complication in patients hospitalized due to pneumococcal pneumonia [93].
**Human immunodeficiency virus**
CAP is a frequent respiratory complication in patients infected with human immunodeficiency virus (HIV), even in the highly active antiretroviral therapy era [94–96]. Patients infected with HIV are 25 times more likely to develop pneumonia than uninfected patients; the depletion of CD4+ lymphocytes and high levels of HIV-RNA in HIV-infected persons occurs in parallel to the risk of developing pulmonary infections [97].

**Exposure to cigarette smoke**
Smoking is associated with colonization by pathogenic bacteria and an increased risk of lung infections, especially in the case of pneumococcal pneumonia [98]. In a study of bacterial pneumonia in patients with HIV, current smokers had a >80% higher risk of developing pneumonia compared with never-smokers [33,99]. Bello et al [100] showed that current smokers with pneumococcal CAP often develop severe sepsis and require hospitalization at a younger age despite having fewer comorbid conditions. Almirall et al [101] found that passive smoking at home is a risk factor for CAP in older adults (65 years of age or more).

**Alcohol abuse**
Samokhvalov et al [102] performed a meta-analysis that showed that the consumption of 24, 60, and 120 g of pure alcohol daily resulted in a relative risk for incident CAP of 1.12 (95% CI 1.02–1.23), 1.33 (95% CI 1.06–1.67), and 1.76 (95% CI 1.13–2.77), respectively, relative to non-drinkers.

**Poor oral hygiene**
A hundred million bacteria (oral and respiratory bacteria) are contained in every cubic millimeter of dental plaque. Oral and respiratory bacteria in the dental plaque are shed into the saliva and are then aspirated into the lower respiratory tract and the lungs to cause infection. Aspiration pneumonia is one of the most serious problems in the elderly population.

**Contact with children**
Regular contact with children is associated with an increased risk of developing CAP [103]. Two studies have reported that the presence of
children in the household increased the adjusted odds ratio (OR) from 1.0 for ‘no children’ to 3.2 [104] or 3.41 [105] for three or more children.

**Summary points**

- CAP is a serious health problem associated with high morbidity and mortality in all age groups worldwide.
- HAP is the second most frequent nosocomial infection and is associated with significant impact on patient morbidity and mortality.
- *Streptococcus pneumoniae* remains the most common cause of CAP across all severities.
- Six pathogens cause approximately 80% of HAP: *S. aureus*, *P. aeruginosa*, *Klebsiella* species, *E. coli*, *Acinetobacter* species, and *Enterobacter* species.
- Pathogens involved in HAP differ significantly from those typically responsible for CAP.
- The etiological microorganisms associated with early-onset and late-onset HAP in patients with no prior antibiotic exposure are often the same as those responsible for CAP.
- MDR pathogens (*P. aeruginosa*, *A. baumannii*, and MRSA) are the most common pathogens in patients with late-onset HAP with prior antibiotic exposure.
- Older age, male sex, chronic comorbidities, exposure to cigarette smoke, alcohol abuse, malnutrition, conditions that promote pulmonary aspiration or inhibit coughing, and exposure to contaminated respiratory equipment are the principal risk factors for pneumonia.

**References**

1. Sopena N, Sabria M. Multicenter study of hospital-acquired pneumonia in non-ICU patients. *Chest*. 2005;127:213–219.
2. Everts RJ, Murdoch DR, Chambers ST, et al. Nosocomial pneumonia in adult general medical and surgical patients at Christchurch Hospital. *N Z Med J*. 2000;113:221–224.
3. Louie M, Dyck B, Parker S, Sekla L, Nicolle LE. Nosocomial pneumonia in a Canadian tertiary care center: a prospective surveillance study. *Infect Control Hosp Epidemiol*. 1991;12:356–363.
4. Safdar N, Dezfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit Care Med*. 2005;33:2184–2193.
5. Esperatti M, Ferrer M, Theessen A, et al. Nosocomial pneumonia in the intensive care unit acquired during mechanical ventilation or not. *Am J Respir Crit Care Med*. 2010;182:1533–1539.
Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in combined medical-surgical intensive care units in the United States. *Infect Control Hosp Epidemiol.* 2000;21:510–515.

Malacarne P, Boccalatte D, Acquarolo A, et al. Epidemiology of nosocomial infection in 125 Italian intensive care units. *Minerva Anestesiol.* 2010;76:13–23.

Ponce de Leon-Rosales SP, Molinar-Ramos F, Domínguez-Cherit G, Rangel-Frausto MS, Vazquez-Ramos VG. Prevalence of infections in intensive care units in Mexico: a multicenter study. *Crit Care Med.* 2000;28:1316–1321.

Rozaidi SW, Sukro J, Dan A. The incidence of nosocomial infection in the Intensive Care Unit, Hospital Universiti Kebangsaan Malaysia: ICU-acquired nosocomial infection surveillance program 1998–1999. *Med J Malaysia.* 2001;56:207–222.

Torres A, Aznar R, Gatell JM, et al. Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *Am Rev Respir Dis.* 1990;142:523–528.

Joseph NM, Sistla S, Dutta TK, Badhe AS, Rasitha D, Parija SC. Ventilator-associated pneumonia in a tertiary care hospital in India: role of multi-drug resistant pathogens. *J Infect Dev Ctries.* 2010;4:218–225.

Blot S, Koulenti D, Dimopoulos G, et al. Prevalence, risk factors, and mortality for ventilator-associated pneumonia in middle-aged, old, and very old critically ill patients*. *Crit Care Med.* 2014;42:601–609.

Suka M, Yoshida K, Uno H, Takezawa J. Incidence and outcomes of ventilator-associated pneumonia in Japanese intensive care units: the Japanese nosocomial infection surveillance system. * Infect Control Hosp Epidemiol.* 2007;28:307–313.

Sopena N, Heras E, Casas I, et al. Risk factors for hospital-acquired pneumonia outside the intensive care unit: A case-control study. *Am J Infect Control.* 2014;42:38–42.

Barreiro-Lopez B, Tricas JM, Mauri E, Quintana S, Garau J. [Risk factors and prognostic factors in nosocomial pneumonia outside the intensive care units setting]. *Enferm Infecc Microbiol Clin.* 2005;23:519–524.

Franzetti F, Grassini A, Piazza M, et al. Nosocomial bacterial pneumonia in HIV-infected patients: risk factors for adverse outcome and implications for rational empiric antibiotic therapy. *Infection.* 2006;34:9–16.

Weber DJ, Rutala WA, Sickbert-Bennett EE, Samsa GP, Brown V, Niederman MS. Microbiology of ventilator-associated pneumonia compared with that of hospital-acquired pneumonia. *Infect Control Hosp Epidemiol.* 2007;28:825–831.

Diouf E, Beye MD, Diop NM, et al. [Nosocomial ventilator-associated pneumonia in a tropical intensive care unit]. *Dakar Med.* 2006;51:81–88.

Koulenti D, Lisboa T, Brun-Buisson C, et al. Spectrum of practice in the diagnosis of nosocomial pneumonia in patients requiring mechanical ventilation in European intensive care units. *Crit Care Med.* 2009;37:2360–2368.

Japoni A, Vazin A, Davarpanah MA, et al. Ventilator-associated pneumonia in Iranian intensive care units. *J Infect Dev Ctries.* 2011;5:286–293.

Torres A, Peetermans WE, Vieggi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax.* 2013;68:1057–1065.

Cillóniz C, Polverino E, Ewig S, et al. Impact of age and comorbidity on cause and outcome in community-acquired pneumonia. *Chest.* 2013;144:999–1007.

Marrie TJ. Community-acquired pneumonia in the elderly. *Clin Infect Dis.* 2000;31:1066–1078.

Rodriguez LA, Ruigomez A, Wallander MA, Johansson S. Acid-suppressive drugs and community-acquired pneumonia. *Epidemiology.* 2009;20:800–806.

Vila-Corcoles A, Ochoa-Gondar O, Rodriguez-Blanco T, Raga-Luria X, Gomez-Bertomeu F. Epidemiology of community-acquired pneumonia in older adults: a population-based study. *Respir Med.* 2009;103:309–316.
Viegi G, Pistelli R, Cazzola M, et al. Epidemiological survey on incidence and treatment of community acquired pneumonia in Italy. *Respir Med*. 2006;100:46–55.

Said MA, Johnson HL, Nonyane BA, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. *PLoS One*. 2013;8:e60273.

Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. *JAMA*. 1996;275:134–141.

Alkhayer M, Jenkins PF, Harrison BD. The outcome of community acquired pneumonia treated on the intensive care unit. *Respir Med*. 1990;84:13–16.

Mortensen EM, Kapoor WN, Chang CC, Fine MJ. Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. *Clin Infect Dis*. 2003;37:1617–1624.

Lin SH, Lai CC, Tan CK, Liao WH, Hsueh PR. Outcomes of hospitalized patients with bacteremic and non-bacteremic community-acquired pneumonia caused by *Streptococcus pneumoniae*. *Epidemiol Infect*. 2011;139:1307–1316.

Garcia-Vidal C, Ardanuy C, Tubau F, et al. Pneumococcal pneumonia presenting with septic shock: host- and pathogen-related factors and outcomes. *Thorax*. 2010;65:77–81.

Nair GB, Niederman MS. Nosocomial pneumonia: lessons learned. *Crit Care Clin*. 2013;29:521–546.

Jones RN. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Clin Infect Dis*. 2010;51 (Suppl 1):S81–S87.

Torres A, Carlet J. Ventilator-associated pneumonia. European Task Force on ventilator-associated pneumonia. *Eur Respir J*. 2001;17:1034–1045.

Combes A, Figliolini C, Trouillet JL, et al. Incidence and outcome of polymicrobial ventilator-associated pneumonia. *Chest*. 2002;121:1618–1623.

American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171:388–416.

Goossens H. Susceptibility of multi-drug-resistant *Pseudomonas aeruginosa* in intensive care units: results from the European MYSTIC study group. *Clin Microbiol Infect*. 2003;9:980–983.

Fujitani S, Sun HY, Yu VL, Weingarten JA. Pneumonia due to *Pseudomonas aeruginosa*: part I: epidemiology, clinical diagnosis, and source. *Chest*. 2011;139:909–919.

Cillóniz C, Ewig S, Polverino E, et al. Microbial aetiology of community-acquired pneumonia and its relation to severity. *Thorax*. 2011;66:340–346.

Cillóniz C, Ewig S, Polverino E, et al. Community-acquired pneumonia in outpatients: aetiology and outcomes. *Eur Respir J*. 2012;40:931–938.

Cillóniz C, Torres A, Polverino E, et al. Community-acquired lung respiratory infections in HIV-infected patients: microbial aetiology and outcome. *Eur Respir J*. 2014;43:1698–1780.

Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44 (Suppl 2):S27–S72.

Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. The Canadian Community-Acquired Pneumonia Working Group. *Clin Infect Dis*. 2000;31:383–421.
49 Jokinen C, Heiskanen L, Juvonen H, et al. Microbial etiology of community-acquired pneumonia in the adult population of 4 municipalities in eastern Finland. Clin Infect Dis. 2001;32:1141–1154.

50 Jennings LC, Anderson TP, Beynon KA, et al. Incidence and characteristics of viral community-acquired pneumonia in adults. Thorax. 2008;63:42–48.

51 Johansson N, Kalin M, Tiveljung-Lindell A, Giske CG, Hedlund J. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. Clin Infect Dis. 2010;50:202–209.

52 Lynch JP III, Zhanel GG. Streptococcus pneumoniae: does antimicrobial resistance matter? Semin Respir Crit Care Med. 2009;30:210–238.

53 Song JH, Chung DR. Respiratory infections due to drug-resistant bacteria. Infect Dis Clin North Am. 2010;24:639–653.

54 Van BF, Reinert RR, Appelbaum PC, Tulkens PM, Peetermans WE. Multidrug-resistant Streptococcus pneumoniae infections: current and future therapeutic options. Drugs. 2007;67:2355–2382.

55 Stephens DS, Zughaier SM, Whitney CG, et al. Incidence of macrolide resistance in Streptococcus pneumoniae after introduction of the pneumococcal conjugate vaccine: population-based assessment. Lancet. 2005;365:855–863.

56 Daneman N, McGeer A, Green K, Low DE. Macrolide resistance in bacteremic pneumococcal disease: implications for patient management. Clin Infect Dis. 2006;43:432–438.

57 Draghi DC, Jones ME, Sahm DF, Tillotson GS. Geographically-based evaluation of multidrug resistance trends among Streptococcus pneumoniae in the USA: findings of the FAST surveillance initiative (2003–2004). Int J Antimicrob Agents. 2006;28:525–531.

58 Whitney CG, Farley MM, Hadler J, et al. Increasing prevalence of multidrug-resistant Streptococcus pneumoniae in the United States. N Engl J Med. 2000;343:1917–1924.

59 Feldman C, Kassel M, Green K, Powis JE, McGeer A. Predicting antimicrobial resistance in invasive pneumococcal infections. Clin Infect Dis. 2005;40:1288–1297.

60 Berntsson E, Lagergard T, Strannegard O, Trollfors B. Etiology of community-acquired pneumonia in out-patients. Eur J Clin Microbiol. 1986;5:446–447.

61 Berti S, Cillóniz C, Chalmers JD, et al. Multidrug-resistant pathogens in hospitalised patients coming from the community with pneumonia: a European perspective. Thorax. 2013;68:997–999.
70 Otto M. Basis of virulence in community-associated methicillin-resistant Staphylococcus aureus. *Ann Rev Microbiol.* 2010;64:143–162.
71 Rice LB. Antimicrobial resistance in gram-positive bacteria. *Am J Med.* 2006;119 (Suppl 1):S11–S19.
72 Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am Respir Crit Care Med.* 2002;165:867–903.
73 Fagon JY, Chastre J, Domart Y, et al. Nosocomial pneumonia in patients receiving continuous mechanical ventilation. Prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques. *Am Rev Respir Dis.* 1989;139:877–884.
74 Garnacho J, Sole-Violan J, Sa-Borges M, Diaz E, Rello J. Clinical impact of pneumonia caused by Acinetobacter baumannii in intubated patients: a matched cohort study. *Crit Care Med.* 2003;31:2478–2482.
75 Scott P, Deye G, Srinivasan A, et al. An outbreak of multidrug-resistant Acinetobacter baumannii-calcoaceticus complex infection in the US military health care system associated with military operations in Iraq. *Clin Infect Dis.* 2007;44:1577–1584.
76 Chen MZ, Hsueh PR, Lee LN, Yu CJ, Yang PC, Luh KT. Severe community-acquired pneumonia due to Acinetobacter baumannii. *Chest.* 2001;120:1072–1077.
77 Leung WS, Chu CM, Tsang KY, Lo FH, Lo KF, Ho PL. Fulminant community-acquired Acinetobacter baumannii pneumonia as a distinct clinical syndrome. *Chest.* 2006;129:102–109.
78 Masterton R, Craven D, Rello J, et al. Hospital-acquired pneumonia guidelines in Europe: a review of their status and future development. *J Antimicrob Chemother.* 2007;60:206–213.
79 Ebihara S, Ebihara T, Kohzuki M. Effect of aging on cough and swallowing reflexes: implications for preventing aspiration pneumonia. *Lung.* 2012;190:29–33.
80 Klein SL, Passaretti C, Anker M, Olukoya P, Pekosz A. The impact of sex, gender and pregnancy on 2009 H1N1 disease. *Biol Sex Differ.* 2010;1:5.
81 Polverino E, Dambrava P, Cillóniz C, et al. Nursing home-acquired pneumonia: a 10 year single-centre experience. *Thorax.* 2010;65:354–359.
82 Gutierrez F, Masia M, Mirete C, et al. The influence of age and gender on the population-based incidence of community-acquired pneumonia caused by different microbial pathogens. *J Infect.* 2006;53:166–174.
83 Sund-Levander M, Ortvist A, Grodzinsky E, Klefsgard O, Wahren LK. Morbidity, mortality and clinical presentation of nursing home-acquired pneumonia in a Swedish population. *Scand J Infect Dis.* 2003;35:306–310.
84 Molinos L, Clemente MG, Miranda B, et al. Community-acquired pneumonia in patients with and without chronic obstructive pulmonary disease. *J Infect.* 2009;58:417–424.
85 Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care.* 2004;27:1047–1053.
86 Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. *Int J Obes (Lond).* 2008;32:1431–1437.
87 Kornum JB, Thomsen RW, Riis A, Lervang HH, Schonheyder HC, Sorensen HT. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. *Diabetes Care.* 2008;31:1541–1545.
88 Yende S, Van Der PT, Lee M, et al. The influence of pre-existing diabetes mellitus on the host immune response and outcome of pneumonia: analysis of two multicentre cohort studies. *Thorax.* 2010;65:870–877.
89 Kang CI, Song JH, Kim SH, et al. Risk factors and pathogenic significance of bacteremic pneumonia in adult patients with community-acquired pneumococcal pneumonia. *J Infect.* 2013;66:34–40.
90 From S, Targowski T. [The risk factors of death in community-acquired pneumonia]. *Pol Merkur Lekarski.* 2002;12:455–457.
91 Chidiac C, Che D, Pires-Cronenberger S, et al. Factors associated with hospital mortality in community-acquired legionellosis in France. *Eur Respir J.* 2012;39:963–970.
92 Slinin Y, Foley RN, Collins AJ. Clinical epidemiology of pneumonia in hemodialysis patients: the USRDS waves 1, 3, and 4 study. *Kidney Int.* 2006;70:1135–1141.
93 Cillóniz C, Ewig S, Polverino E, et al. Pulmonary complications of pneumococcal community-acquired pneumonia: incidence, predictors, and outcomes. Clin Microbiol Infect. 2012;18:1134–1142.

94 Feikin DR, Feldman C, Schuchat A, Janoff EN. Global strategies to prevent bacterial pneumonia in adults with HIV disease. Lancet Infect Dis. 2004;4:445–455.

95 Benito N, Moreno A, Miro JM, Torres A. Pulmonary infections in HIV-infected patients: an update in the 21st century. Eur Respir J. 2012;39:730–745.

96 Madeddu G, Porqueddu EM, Cambosu F, et al. Bacterial community acquired pneumonia in HIV-infected inpatients in the highly active antiretroviral therapy era. Infection. 2008;36:231–236.

97 Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. N Engl J Med. 1995;333:845–851.

98 Kohlhammer Y, Schwartz M, Raspe H, Schafer T. [Risk factors for community acquired pneumonia (CAP). A systematic review]. Dtsch Med Wochenschr. 2005;130:381–386.

99 Gordin FM, Roediger MP, Girard PM, et al. Pneumonia in HIV-infected persons: increased risk with cigarette smoking and treatment interruption. Am J Respir Crit Care Med. 2008;178:630–636.

100 Bello S, Menendez R, Torres A, et al. Tobacco smoking increases the risk for death from pneumococcal pneumonia. Chest. 2014;146:1029–1037.

101 Almirall J, Serra-Prat M, Bolibar I, et al. Passive smoking at home is a risk factor for community-acquired pneumonia in older adults: a population-based case-control study. BMJ Open. 2014;4:e005133.

102 Samokhvalov AV, Irving HM, Rehm J. Alcohol consumption as a risk factor for pneumonia: a systematic review and meta-analysis. Epidemiol Infect. 2010;138:1789–1795.

103 Almirall J, Bolibar I, Serra-Prat M, et al. New evidence of risk factors for community-acquired pneumonia: a population-based study. Eur Respir J. 2008;31:1274–1284.

104 Schnoor M, Klante T, Beckmann M, et al. Risk factors for community-acquired pneumonia in German adults: the impact of children in the household. Epidemiol Infect. 2007;135:1389–1397.

105 Teepe J, Grigoryan L, Verheij TJ. Determinants of community-acquired pneumonia in children and young adults in primary care. Eur Respir J. 2010;35:1113–1117.