18

Acute lower respiratory infections

Introduction

Key points

- Community-acquired pneumonia is the most frequent cause of death from infection in Europe.
- The majority of patients with pneumonia are treated at home, but about 1 million are hospitalised annually in the EU.
- On average, in Europe, approximately 80% of isolates of *Streptococcus pneumoniae*, the most frequently identified cause of pneumonia, are now resistant to commonly used penicillin and macrolide antibiotics.
- Influenza usually affects the very young and the old, but the H1N1 pandemic hit younger adults particularly hard.

Acute lower respiratory infections are a leading cause of sickness and mortality both in children and adults worldwide. Unfortunately, acute lower respiratory infections are not uniformly defined and this may hamper a true appreciation of their epidemiological importance. From an epidemiological point of view, the definition of acute lower respiratory infections usually includes acute bronchitis and bronchiolitis, influenza and pneumonia.

Acute bronchitis can be defined as an acute illness that occurs in a patient without chronic lung disease. Symptoms include cough (productive or otherwise) and other symptoms or clinical signs that suggest lower respiratory tract infection with no alternative explanation (*e.g.* sinusitis or asthma).

Bronchiolitis is the most common lower respiratory tract infection and the most common cause of admission to hospital in the first 12 months of life (see chapter 16).

Incidence

The incidence of acute bronchitis in adults is high, between 30 and 50 per 1000 people per year. This means that in Europe, approximately 16 500 000 adult cases are seen each year in primary care. The clinical syndrome lasts approximately 2 weeks and has a clear impact on daily activities.

Age-standardised admission rates for acute bronchitis and bronchiolitis in Europe are shown in figure 1.

Attack rates during seasonal influenza epidemics can vary considerably, but usually 5–20% of the population is affected

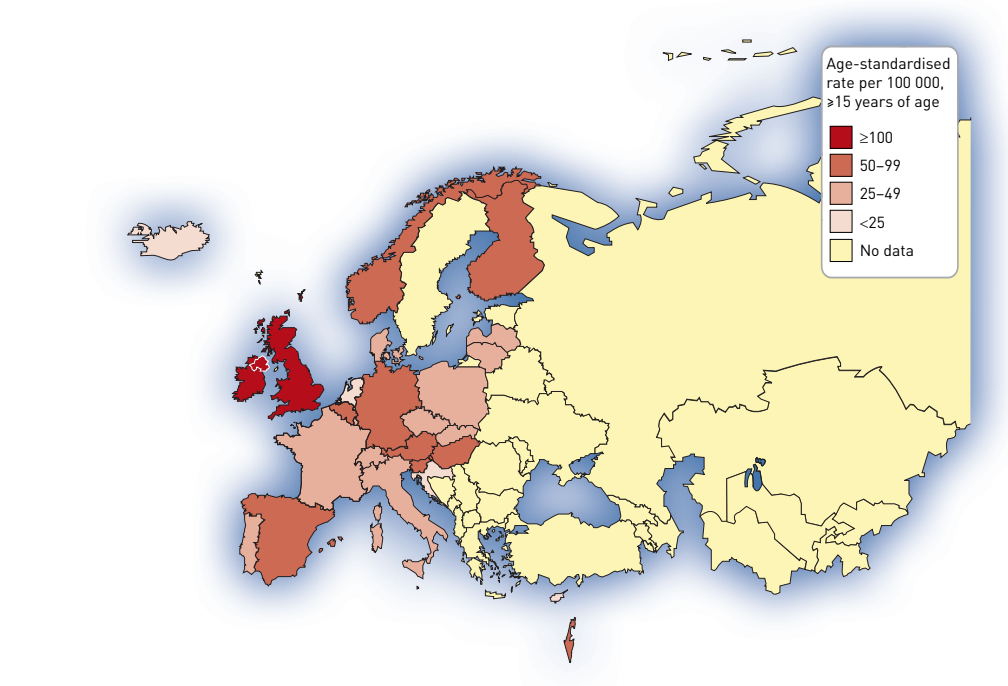
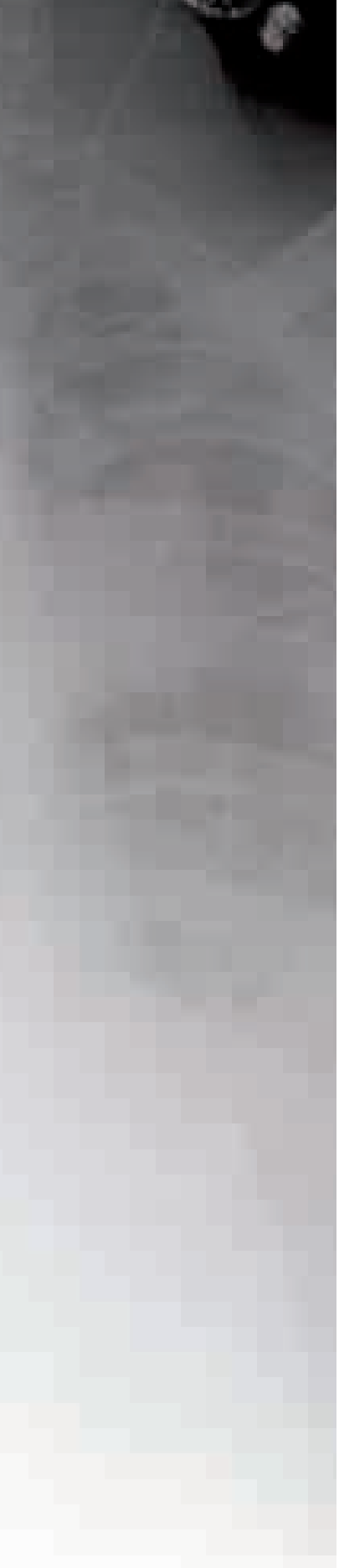


Figure 1 – Hospital admission rate for acute lower respiratory infections (including acute bronchitis and bronchiolitis but excluding pneumonia) in adults. Data from the World Health Organization Hospital Morbidity Database, October 2011 update, and Eurostat, March 2012 update.

Causes and pathogenesis

Identifying causative pathogens for acute bronchitis is quite difficult and most clinical studies report identification in less than 30% of cases. Almost 90% of cases are related to viruses – such as adenovirus, coronavirus, parainfluenza, influenza and rhinovirus – and less than 10% to bacteria, such as *Bordetella pertussis*, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*.

Respiratory syncytial virus (RSV) is the most common cause of severe acute respiratory infection (*i.e.* bronchiolitis) in children (see chapter 16). Despite the generation of RSV-specific adaptive immune responses, RSV infection does not confer protective immunity in humans and recurrent infections are common.



Clinical manifestations and consequences

Acute bronchitis is a self-limiting infection in most cases, with symptoms typically lasting about 2 weeks.

RSV bronchiolitis is usually mild and self-limiting; however, some children experience more severe illness and require hospital admission, and some will need ventilatory support. Differences in innate immune function in response to the respiratory virus, as well as differences in the geometry of the airways, may explain some of the variability in clinical pattern (see chapter 16).

Management

European Respiratory Society (ERS)/European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines indicate that cough suppressants, expectorants, mucolytics, antihistamines, inhaled corticosteroids and bronchodilators should not be prescribed in acute bronchitis in primary care.

Antibiotics are not usually indicated for the treatment of acute bronchitis, especially in younger patients in whom bacterial infection is not suspected (see chapter 16).

Influenza

Influenza usually occurs during annual epidemics and occasional pandemics, the most recent pandemic being in 2009. Rates of infection are highest among children, with rates of serious illness and death highest in individuals over 65 years of age, children under 2 years of age, and persons of any age who have medical conditions that predispose to increased risk of complications from influenza. More than 90% of influenza-related deaths occur in patients in the older age group. Underlying medical conditions that increase the risk of hospitalisation with seasonal influenza include diabetes and cardiovascular, neurological and chronic respiratory diseases, such as asthma.

Incidence

There are varying estimates of the number of people infected by influenza every year, the resulting burden of ill health and premature death, and the degree to which these burdens can be reduced, but it is agreed that influenza is a significant threat to public health.

The attack rates during seasonal influenza epidemics can vary considerably from year to year, but usually some 5–20%

of the population is affected. The impact of influenza in different age groups varies considerably between epidemics. Usually, winter epidemics affect each country for 1–2 months and, across Europe, epidemics last for about 4 months. The epidemiology and clinical features of influenza can differ during pandemics, depending on the characteristics of the virus and on the level of immunity to a virus that by definition is different from those circulating in previous influenza seasons. This was the case during the 2009 influenza A (H1N1) pandemic, where the highest incidence of infection and disease was in younger individuals (*i.e.* those less than 65 years of age).

Figure 2 shows the case-load during the H1N1 pandemic in Europe.

Post-influenzal bacterial pneumonia is a major cause of morbidity and mortality associated with both seasonal and pandemic influenza.

Causes and pathogenesis

Influenza in humans is caused by three major families of RNA viruses: influenza A, B and C. They are usually classified according to differences in the antigenic properties of their external coat. Influenza A viruses, clinically the most important, are further divided into subtypes based on two proteins on the external coat, the haemagglutinin (HA) (H1–H16) and neuraminidase (NA) (N1–N9) proteins. Type B viruses cause somewhat less severe illness, and type C viruses do not cause significant human disease, so only type A and B viruses are of concern. Another important challenge is the emergence of influenza virus strains resistant to antivirals.

Clinical manifestations and consequences

Influenza viruses can cause disease among persons in any age group but the frequency of infection is highest in children. Rates of serious illness and death are highest among individuals over 65 years of age, children less than 2 years of age and persons of any age who have medical conditions that increase the risk of complications from influenza. Uncomplicated influenza is characterised by the abrupt onset of constitutional and respiratory signs and symptoms (*e.g.* fever, myalgia (muscle pain), headache, malaise, nonproductive cough, sore throat and rhinitis). Among children, otitis media, nausea and vomiting are also commonly reported with influenza infection. Uncomplicated influenza typically resolves after 3–7 days in most people. However, influenza virus can cause primary influenza viral pneumonia, exacerbate underlying medical conditions (*e.g.* pulmonary or cardiac disease), lead to secondary bacterial pneumonia, sinusitis and otitis media, or contribute to co-infections with other viral or bacterial pathogens.

Management

Two classes of antivirals, the adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors (laninamivir, oseltamivir, peramivir, and zanamivir), are currently approved for the prevention and treatment of influenza; several other classes of antivirals and immune modulators are also under investigation.

Pneumonia

Community-acquired pneumonia (CAP) is a major respiratory disease with a high prevalence in the general population, clinical heterogeneity and variable severity. Both

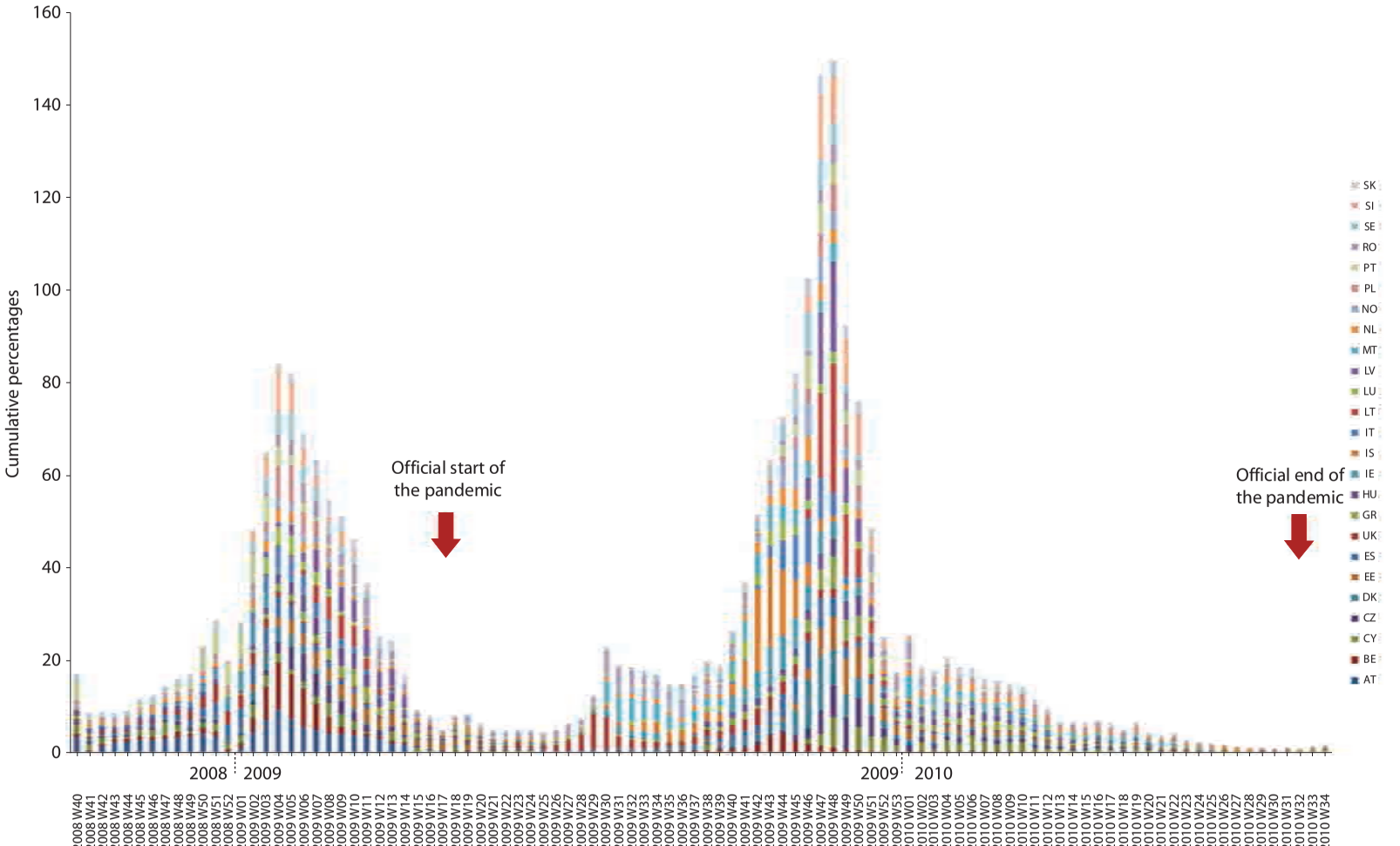


Figure 2 – Aggregate percentages of weekly reported influenza-like illness for 25 European Union member states, from week 40, 2008, to week 34, 2010. Data for each country are presented as the percentage of total cases over the whole 100-week period reported in a given week. Reproduced from European Centre for Disease Prevention and Control, 2010.

in the USA and in Europe, CAP is the most frequent cause of death due to infection and it has implications for healthcare systems worldwide. Pneumonia usually causes symptoms for 3–4 weeks, and daily activities may be impaired for a further 3 weeks on average. The reported incidence of pneumonia varies considerably from country to country and study to study, with a consistently higher incidence in very young children and elderly adults. In Europe, the mean age of the population is increasing sharply, and this is likely to lead to a significant increase in pneumonia hospital admissions and costs.

Pneumonia that occurs 48 h or more after hospital admission, and which was not incubating at the time of admission, is defined as hospital-acquired pneumonia (HAP), while pneumonia that arises more than 48–72 h after endotracheal intubation is defined as ventilator-associated pneumonia (VAP).

Incidence

The overall incidence of CAP in general practice in Europe is reported to range 1.7–11.6 cases per 1000 people per year in adults (table 1). In the European Union (EU), about

Country	Study period	Age years	Cases per 1000 population
Finland	1981–1982	15–29	4.2 M; 4.6 W
		30–44	5.6 M; 5.9 W
		45–59	9.8 M; 7.0 W
		60–74	25.0 M; 9.0 W
		>75	65.2 M; 19.6 W
		>60	33.0 M; 11.8 W
Spain	1993–1995	15–39	1.2 M; 1.0 W
		40–64	1.8 M; 1.4 W
		>64	5.2 M; 1.9 W
		All ages	1.6
	1999–2001	15–44	0.8 M; 0.6 W
		45–64	1.4 M; 0.7 W
		65–74	3.2 M; 1.6 W
		>75	8.7 M; 3.0 W
		All ages	1.6 M; 0.9 W
	2002–2005	65–74	3.0 M; 2.2 W
		75–84	5.3 M; 2.8 W
		>85	10.0 M; 7.9 W
		All ages	4.2 M; 2.9 W
Italy	1999–2000	15–44	0.9
		45–64	1.6
		>64	3.3
		All ages	1.7 M; 1.7 W
Germany	2003	>18	8.7

Table 1 – Pneumonia incidence in Europe in the outpatient setting. M: men; W: women. Reproduced and modified from Welte *et al.*, 2012, with permission from the publisher.

3 370 000 cases are expected annually. Hospitalisation rates differ widely between European countries, ranging from 20–50%, meaning that there are about 1 million hospital admissions for CAP per year in the EU. Age-standardised hospital admission rates for pneumonia are shown in figure 3. It is important to note that while most patients are treated on an outpatient basis, most studies are based on hospitalised patients and the true extent of pneumonia is not known.

The incidence of HAP is ~0.5–2.0% among all hospitalised patients, and while it is the second-commonest nosocomial infection, it is first in terms of mortality (ranging from 30% to more than 70%). The incidence in different hospitals and different wards of the same hospital varies considerably.

“Almost 90% of cases of acute bronchitis are related to viruses such as adenovirus, coronavirus, parainfluenza, influenza and rhinovirus”

Causes and pathogenesis

The main organisms causing CAP in Europe are shown in figure 4. *Streptococcus pneumoniae* is the most frequent causative agent of pneumonia in Europe.

Antibiotic resistance is one of the major threats undermining the treatment of respiratory infections, with potentially important clinical and economic implications. Data from the European Antimicrobial Resistance Surveillance Network (EARS-net) show that in Europe almost 10% of *S. pneumoniae* strains are resistant to penicillin and 15% to macrolide antibiotics (figure 5). Moreover, new difficult-to-treat bacteria are emerging in pneumonia, *e.g.* methicillin-resistant *Staphylococcus aureus* (MRSA) and several Gram-negative bacteria (*e.g.* multidrug-resistant *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*), particularly in elderly patients living in long-term care facilities. However, data from European studies generally suggest a low frequency of multidrug-resistant organisms (< 10%) in patients from the community with pneumonia. Viral and mixed viral–bacterial infections are reported in about 10–20% of CAP cases.

Gram-negative pathogens are the main cause of HAP. *P. aeruginosa*, *Acinetobacter baumannii*, microorganisms belonging to the family *Enterobacteriaceae* (*Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *etc.*) and, under certain conditions, microorganisms such as *Haemophilus influenzae*, are involved in HAP aetiology. Among Gram-positive pathogens, *S. aureus*, *Streptococcus* spp. and *S. pneumoniae* are the most common agents, accounting for 35–39% of all cases. Nonbacterial pathogens such as *Aspergillus* spp. and viruses (cytomegalovirus) have been described. There are significant geographical differences in the rates of antibiotic resistance between European areas and even within countries, from one hospital to another.

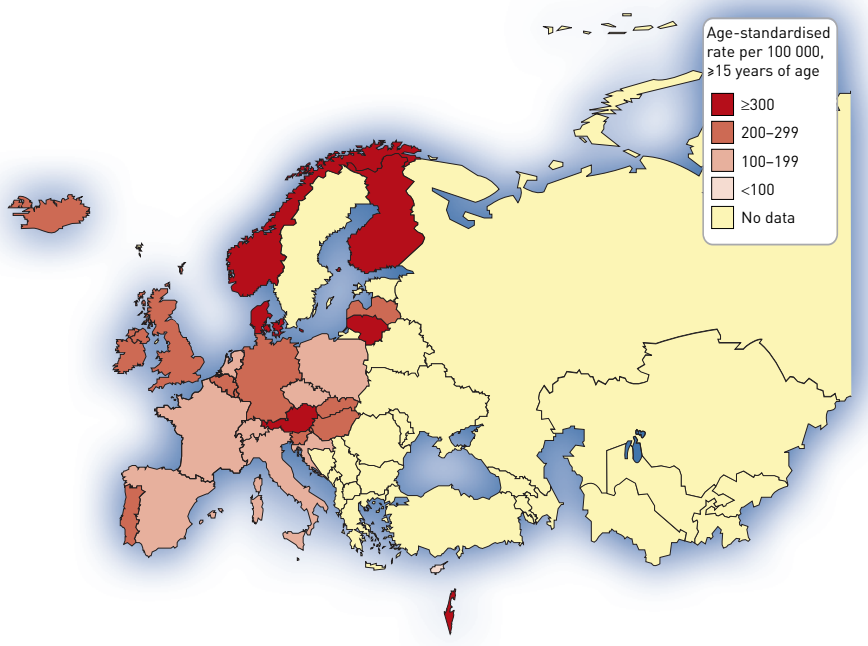


Figure 3 – Hospital admission rate for pneumonia in adults. Data from the World Health Organization Morbidity Database, October 2011 update, and Eurostat, March 2012 update.

In neutropenic patients, Gram-negative bacteria are the main pathogens, being responsible for about 70% of cases; fungal and mixed infections are involved in about 10% and 10–15% of cases, respectively.

HIV infection impairs humoral immunity by causing quantitative and functional defects in CD4+ lymphocytes, leading to an increased risk of bacterial infections, with *S. pneumoniae* and *H. influenzae* being the most frequent pathogens. The incidence of fungal infections, mainly caused by *Pneumocystis jiroveci*, increases when the patient's CD4+ count is below 200 cells·mL^{-1}.

In the past decade, outbreaks of new infectious agents have been reported. One of these outbreaks was caused by the severe acute respiratory syndrome (SARS)-coronavirus (CoV), a pathogenic coronavirus that emerged from a zoonotic reservoir and was associated with severe respiratory syndromes with a high mortality rate. The prompt global response to this outbreak, which stopped the spread of the disease, demonstrated the importance of intensive international collaborative efforts as well as timely and thorough investigations.

Clinical manifestations and consequences

Pneumonia is defined as an acute illness with cough and at least one of the following: new focal chest signs; fever of more than 4 days' duration or dyspnoea/tachypnoea, without other obvious cause; and radiographic evidence of lung shadowing that is likely to be new. Sepsis and cardiovascular complications are the main cause of early treatment failure, *i.e.* in the first 3 days after admission. Early and appropriate antibiotic treatment is associated with a better outcome.

The dramatic shortage of new antibiotics, together with the increasing number of resistant bacteria, is a threat to the global population

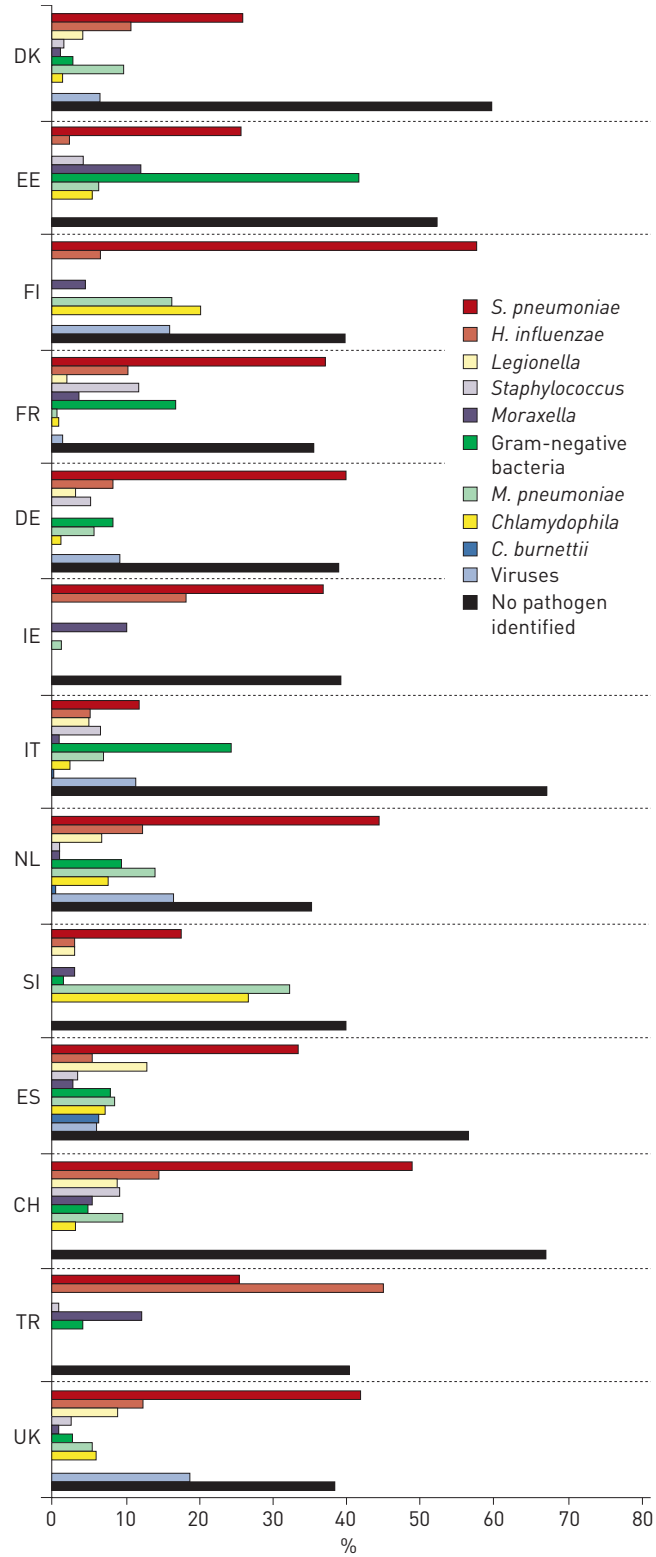


Figure 4 – Frequency of isolation of causative organisms of community-acquired pneumonia in selected European countries. *S. pneumoniae*: *Staphylococcus pneumoniae*; *H. influenzae*: *Haemophilus influenzae*; *M. pneumoniae*: *Mycoplasma pneumoniae C. burnettii*: *Coxiella burnetii*. Data from Welte *et al.*, 2010.

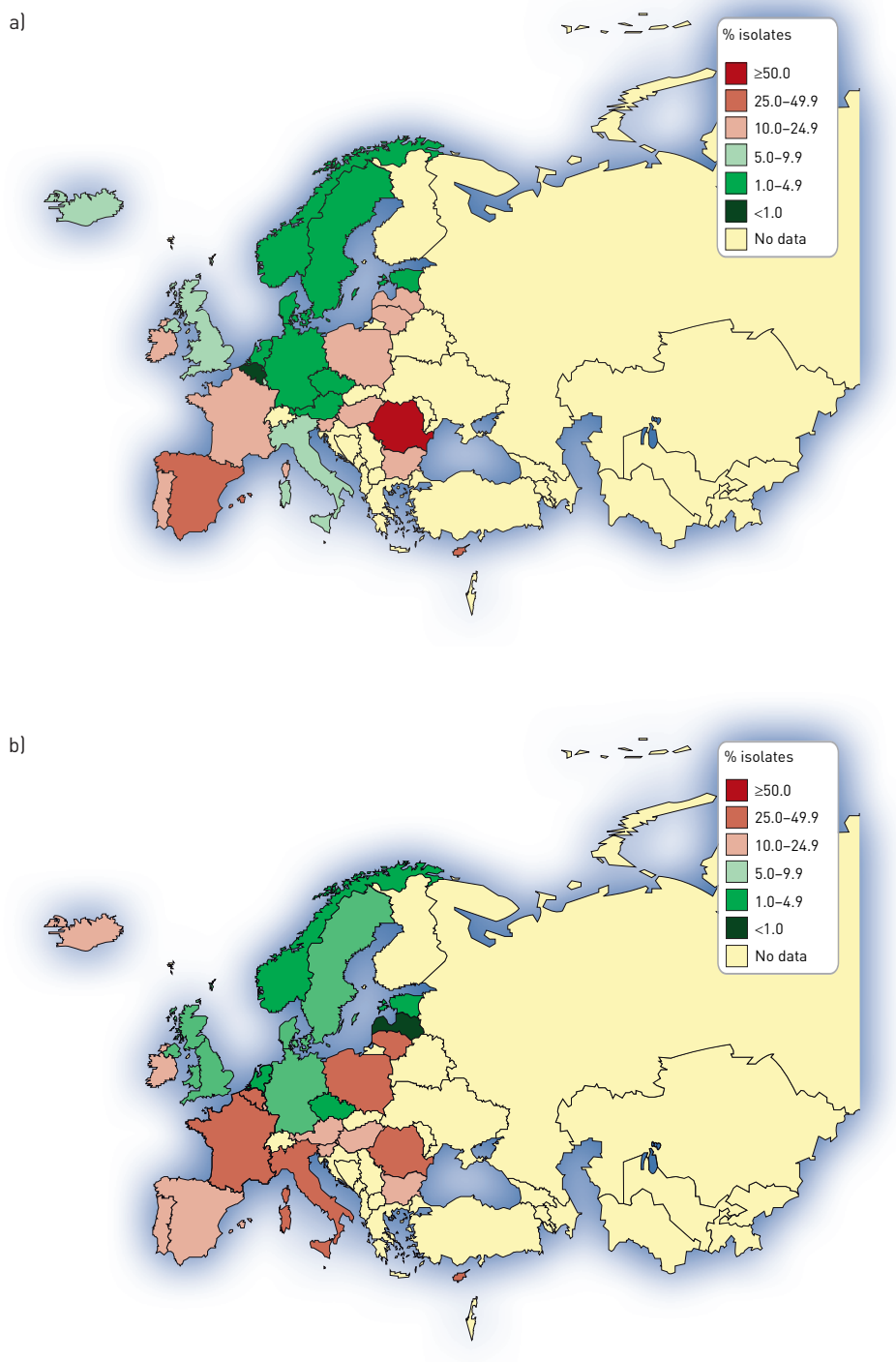


Figure 5 – Percentage of *Streptococcus pneumoniae* isolates resistant to a) penicillin and b) macrolides. Data from European Centre for Disease Prevention and Control, 2011 data (accessed January 2013).

Management

Antibiotics are the treatment of choice for pneumonia, both in the outpatient and hospital setting. The ERS/ESCMID guidelines indicate different antibiotic approaches according to setting, risk factors and severity. The appropriate use of antibiotics is a vitally important intervention in the effort to reduce antibiotic resistance rates.

Prognosis

Age-standardised mortality rates for pneumonia are shown in figure 6. The risk of death from pneumonia increases with age. A Finnish study showed a six-fold increase in incidence between the ages of 30–44 years and 75 years or older. In Portugal, case fatality rates were 4.5% for patients aged 18–50 years, 19.4% for those aged more than 50 years and 24.8% for those aged more than 75 years. A UK study reported case-fatality rates of 5.6% in those aged less than 65 years and 47.2% for those aged more than 85 years. The study also found a 12-fold greater likelihood of death within 30 days of hospital admission for adults aged more than 85 years compared with those aged less than 65 years.

Over the past century, human life expectancy has increased dramatically in developed countries. In 2004, the EU had approximately 455 million inhabitants, of whom one-sixth were over 65 years of age (Eurostat 2004). If current trends in fertility, mortality and migration rates continue, the population is expected to peak in 2023, at which time one-third of the population will be over 65 years old. Clearly, the burden of pneumonia will be even more important in the years to come.

Variables associated with pneumonia mortality

- Over 65 years of age
- Female sex
- Use of oral corticosteroids
- Pneumonia due to more than one organism
- Pleural effusion
- Intensive care unit admission
- Atypical pneumonia
- Hospital-acquired pneumonia
- Recent hospitalisation
- Serious underlying disease
- Acute renal failure
- Bacteraemic pneumonia
- Ineffective initial therapy
- Multilobar involvement
- Impaired alertness
- Septic shock

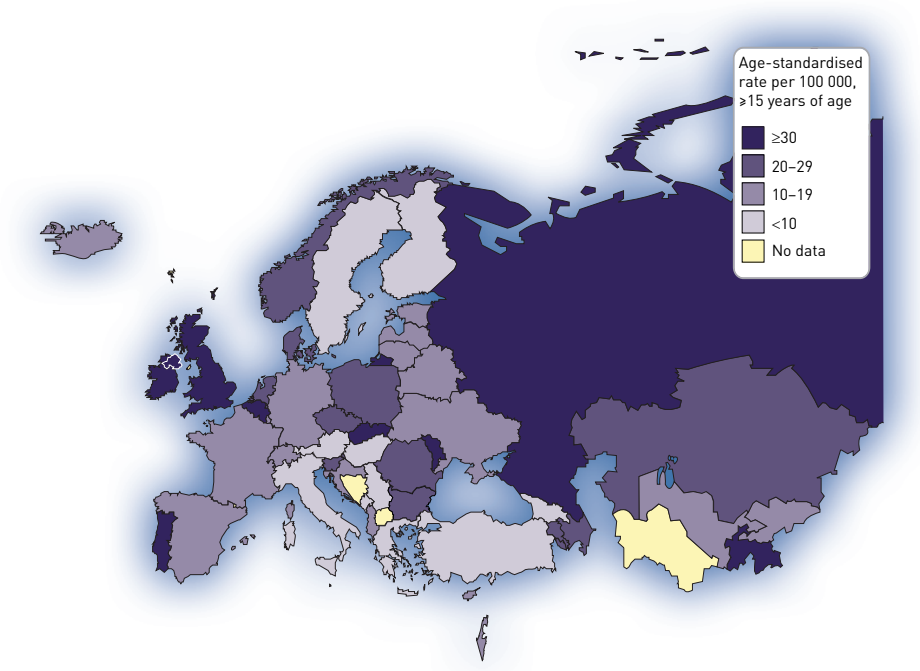


Figure 6 – Mortality rate for pneumonia in adults. Data from the World Health Organization World and Europe Mortality Databases, November 2011 update.

The risk of pneumonia-related mortality increases three-fold if pneumonia is due to *S. pneumoniae*, with a mortality rate ranging from 6.4% to more than 40% in the different settings of out-, in- and intensive care unit patients. Mortality does not seem to be related to antibiotic resistance. Pneumococcal pneumonia is accompanied by bacteraemia (bacteria detectable in the blood) in 10–30% of cases.

Patients with pneumonia who survive hospitalisation may still experience adverse outcomes after discharge, including readmission and death due to a relapse of pneumonia or other causes. Early readmission rates range 8–46%, with readmission particularly occurring in patients who show signs of instability at discharge and contributing considerably to medical resource use and costs. In patients with pneumonia, the mortality rate within 90 days after discharge can be as high as 14%; even at 1 year, mortality is still considerably higher after hospitalisation with pneumonia than in the general population or in those hospitalised for other reasons. CAP is also associated with a significant increase in the risk of cardiovascular events and death from cardiac causes.

Intensive care unit admission criteria for pneumonia patients are highly variable between European countries, and the admission rate ranges 3–5% in Italy to more than 10% in Belgium.

Prevention

Population protection by immunisation against infection has been one of the major achievements of public health. The importance and role of influenza and *S. pneumoniae* immunisation are discussed in chapter 26. Currently, there is no immunisation available for RSV, although a number of vaccines have been tested and/or are currently under consideration.

Future developments

There is a need to develop new or more effective immunisations against respiratory bacteria and viruses, particularly for the prevention of RSV and pneumococcal infections.

Only a few new families of antibiotics are in the pipeline for bacterial respiratory infections. The dramatic shortage of new antibiotics, together with the increasing number of antibiotic-resistant bacteria, is a worrying threat to the global population and a critical challenge for healthcare institutions. New therapeutic strategies, such as monoclonal antibodies acting against different strains of multidrug-resistant bacteria, must be developed.

The future of microbiology will determine many of the advances in respiratory medicine. For example, molecular bacteriology is being revolutionised by the next generation of sequencing methodologies; molecular virology should follow.

Areas of focus in the future should be the development of mechanisms for boosting host defence and innate immunity so that antivirals and antibacterials will be less necessary.

Further reading

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