Pneumococcal empyema and complicated pneumonias: global trends in incidence, prevalence, and serotype epidemiology

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Abstract This review evaluates the serotype epidemiology of complicated pneumococcal pneumonia (CPP) during the period 1990–2012. PubMed and EMBASE were searched using the terms “empyema”, “complicated pneumonia”, “pleural infection”, “necrotizing pneumonia”, “pleural effusion”, “parapneumonic effusion”, “pneumatocele”, or “lung abscess”; “pneumococcal” or “Streptococcus pneumoniae”; and “serotype” for studies on the epidemiology of complicated pneumonias published from January 1, 1990 to October 1, 2013. Studies with data on incidence and serotypes were included; reviews, case reports, and conference abstracts were excluded. Of 152 papers, 84 fitted the inclusion criteria. A few pneumococcal serotypes were predominant causes of CPP, particularly serotypes 1, 19A, 3, 14, and 7F. CPP was a more common manifestation of pneumococcal disease among older (>2 years old) than younger children. The data support increases in both reported incidence rates and proportions of CPP in children and adults during the period 1990–2012; specific increases varied by geographic region. The proportions of serotype 3 and, particularly in Asia, serotype 19A CPP have increased, whereas most studies show declines in serotype 14. Serotype 1 has been a predominant cause of CPP since 1990, while antibiotic resistance was infrequent among serotype 1 isolates. The reported incidence and proportions of CPP among pneumonia cases steadily increased from 1990 to 2012. Several factors might account for these increases, including enhanced disease detection due to a higher index of suspicion, more sophisticated diagnostic assays, and changes in the prevalence of serotypes with capacity to invade the pleural space that were not targeted by the 7-valent pneumococcal conjugate vaccine (PCV7).

Introduction

Streptococcus pneumoniae is the most common cause of pneumonia in children and a major cause of pneumonia in adults worldwide [1, 2]. Among patients with pneumonia, as many as half may develop pleural effusions (i.e., fluid in the pleural space); of these, 5–10 % may progress to empyema [3]. In general, “complicated pneumonia” refers to pneumonia accompanied by pleural effusion. Empyema is a serious complication characterized by pus and bacteria in the pleural space [3, 4], which may progress to necrosis, cavitation, or fistulas in the thoracic cavity. S. pneumoniae is the most common cause of complicated pneumonia in children and a common cause in adults [5, 6]. Other bacteria associated with acute complicated pneumonias include S. pyogenes, S. milleri, Staphylococcus aureus, Haemophilus influenzae, Mycoplasma pneumoniae, Pseudomonas aeruginosa, other Streptococcus species, and, less commonly, Klebsiella, Enterobacter, Proteus, Salmonella, and Yersinia species [5].

The reported incidence and proportion of cases of complicated pneumococcal pneumonia (CPP) in children and adults have increased in recent decades [7–19]. This trend has been described both before and after the introduction in 2000 of the 7-valent pneumococcal conjugate vaccine (PCV7; serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to CRM197) for pediatric vaccination. A 23-valent pneumococcal polysaccharide vaccine (PPV23) containing pneumococcal capsular polysaccharides (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V,
10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) was introduced in 1983 for the vaccination of children and adolescents at high risk of pneumococcal disease, but primarily older adults. Unlike the pneumococcal conjugate vaccines, PPV23 is not approved for children aged <2 years. PPV23 in adults has been shown to have an impact on bacteremic pneumococcal pneumonia, but not all-cause pneumonia [20, 21]. More recently, the 10-valent pneumococcal conjugate vaccine (PCV10; serotypes 1, 4, 5, 6B, 7F, 9V, 14, and 23F conjugated to non-typeable \textit{H. influenza} protein D, serotype 18C conjugated to tetanus toxoid, and serotype 19F conjugated to diphtheria toxoid) and the 13-valent pneumococcal conjugate vaccine (PCV13; serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F conjugated to CRM197) were introduced beginning in 2009 (Table 1).

A limited number of pneumococcal serotypes have been associated with CPP and pneumococcal empyema (PnEmp). Changes in the serotype epidemiology of invasive pneumococcal disease (IPD) and pneumococcal pneumonia have been reported in recent years, with significant declines in incidence and in the proportion of disease caused by PCV7 serotypes and increases in the proportion of non-PCV7 serotype disease [22–27]. Although these changes are suggestive of serotype replacement, similar trends have also been reported in some countries prior to the introduction of PCV7 [28, 29, 68].

The purpose of this review is to evaluate the serotype epidemiology of CPP during the period 1990–2012.

**Methods**

PubMed and EMBASE were searched for studies on the epidemiology and incidence of CPP published from January 1, 1990 through October 1, 2013 using the terms: “empyema”, “complicated pneumonia”, “pleural infection”, “necrotizing pneumonia”, “pleural effusion”, “parapneumonic effusion”, “pneumatocole”, or “lung abscess”; “pneumococcal” or “\textit{Streptococcus pneumoniae}”; and “serotype”. Studies with data on incidence, prevalence (i.e., proportion of cases), or serotypes were included; reviews, case reports, and conference abstracts were excluded. In addition, the references sections of relevant review articles were checked for studies not identified during the online search.

The base population used for analyses varied by study. For example, among studies of incidence or proportion of complicated pneumonias or empyema, the base populations included: hospitalized patients [13] or hospitalized patients with community-acquired pneumonia (CAP) [19, 30–32]; pneumococcal pneumonia [9, 16, 32–40]; IPD [10, 12, 17, 18, 41–49]; complicated pneumonia [7, 13, 50–54]; complicated pneumonia with positive cultures [14]; CPP [55]; empyema [56–61]; or empyema with fistula [62].

| Country        | Vaccine  | Start of the immunization programa |
|----------------|----------|-----------------------------------|
| North America  |          |                                   |
| Canada         | PCV7     | 2001b                             |
| USA            | PCV13    | 2010                              |
| South America  |          |                                   |
| Mexico         | PCV7     | 2007                              |
| Uruguay        | PCV7     | 2008                              |
| Europe         |          |                                   |
| France         | PCV7     | 2006                              |
| Germany        | PCV7     | 2006c                             |
|                | PCV10    | 2009c                             |
|                | PCV13    | 2009c                             |
| Italy          | PCV7     | 2005–2007b                        |
| Portugal       | PCV7     | 2006d                             |
| Spain          | PCV7     | 2002–2006d                        |
|                | PCV13    | 2010                              |
| Middle East/North Africa | |        |
| Israel         | PCV7     | 2009                              |
|                | PCV13    | 2010                              |
| Asia-Pacific   |          |                                   |
| Australia      | PCV7     | 2001f                             |
|                | PCV13    | 2010                              |
| China          | PCV7     | 2008f                             |
|                | PCV13    | No                                |
| India          | PCV7     | 2010d                             |
|                | PCV13    | 2012d                             |
| Philippines    | PCV7     | No                                |
|                | PCV10    | 2012                              |
|                | PCV13    | 2013                              |
| Singapore      | PCV7     | No                                |
|                | PCV13    | 2011                              |
| South Korea    | PCV7     | 2003d                             |
|                | PCV13    | 2010d                             |
| Taiwan         | PCV7     | 2005d                             |
|                | PCV13    | 2011d                             |
Table 1 (continued)

| Country   | Vaccine | Start of the immunization program¹ |
|-----------|---------|-----------------------------------|
| Vietnam   | PCV7    | No                                |
|           | PCV13   | No                                |

PCV7, 7-valent pneumococcal conjugate vaccine; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine

¹Dates refer to a national immunization program, unless otherwise specified

Regional (city) mass vaccination programs

Some studies described the clinical methodologies used to identify pleural effusion or empyema prior to microbiological identification. Retrospective studies used: diagnostic coding [16, 19, 30, 31, 35, 52, 61]; records of chest radiographs [9, 33, 48, 50]; computed tomography (CT) [7, 9, 34, 50]; ultrasound [7, 34, 50, 56]; microbiologic culture records [13]; or results at surgery [56]. One study reviewed “pleural effusion data”, although no other details were specified [48]. Prospective studies used: thoracocentesis [39, 51, 53, 54]; CT, ultrasound, or chest radiograph plus clinical signs [58]; CT, ultrasound, or chest radiograph [32]; or physical examination and chest radiograph [37, 60, 63]. One study did not specify the diagnostic methodology [49].

Studies varied in the methodologies used to isolate *S. pneumoniae*, including: culture of samples from the pleural cavity [7, 13, 49–51, 54, 58, 62, 64–66], blood [32, 68–71], blood and pleural cavity [9, 10, 14, 15, 17, 18, 30, 31, 34–36, 38, 41–48, 52, 53, 56, 57, 63, 72–90], or unspecified sites [33, 40, 91]; and, more recently, investigators used polymerase chain reaction (PCR) or real-time PCR to identify pneumococcal-specific genes (e.g., *ply, LytA, rpoB, or wza [cpsA]*) in samples from the pleural cavity [43, 46, 49, 51, 53–55, 58, 60, 64, 67, 87, 88, 90, 92–94], blood [15, 32, 37, 75, 95], blood and pleural cavity [88], or nasopharyngeal aspirate [96]. A few studies applied immunochromatographic pneumococcal antigen detection (Binax NOW®) from blood or urine [15, 38, 51, 74, 77, 84].

Pneumococcal serotypes in blood or pleural fluid were identified with the Quellung reaction (also referred to as capsular swelling) [7, 12, 14, 15, 17, 18, 30, 31, 34–38, 40, 42–49, 56, 68, 69, 71, 73, 77, 82, 85–88, 90–93], dot blot [47, 71, 93], slide or latex agglutination [8–10, 40, 63, 65, 70, 72, 77, 80, 81, 83, 84, 97, 98], enzyme-linked immunoassays [55, 99], real-time PCR [32, 37, 43, 44, 46, 49, 51, 64, 65, 87, 88, 90, 93, 95], or multiplex PCR [54, 58, 60, 67, 74, 84, 92, 94, 97]. The Quellung reaction may include up to all the known serotypes, whereas PCR is typically more limited in the serotypes that can be identified. Some studies used more than one methodology (e.g., initial serotyping of cultured isolates, followed by PCR in culture-negative samples) [37, 65, 87, 88, 93, 94].

Definitions of penicillin susceptibility varied; some studies used breakpoints established by the Clinical and Laboratory Standards Institute (CLSI) in 2009 [53, 74, 83, 88, 90, 100], whereas others used pre-2009 breakpoints [7, 9, 15, 17, 30, 34, 63, 73].

Results

A total of 152 papers were initially identified; 68 were excluded because there were no data on incidence or serotypes, or they were case reports; consequently, 84 were included in this analysis.

Table 2 presents data on the incidence and proportion of CPP [7, 9, 10, 12–14, 16–19, 30–47, 49–62]. Trends and age-related differences in the studies are discussed below.

Incidence

The incidence of any-cause empyema among children aged <19 years in Utah (USA) (1994–2007) [30, 31] and Australia (1998–2010) [19] ranged from 0.9 to 12.5 per 100,000 population, and tended to increase over time; the incidence was highest in children aged 0–4 years (Table 2) [19]. Likewise, in Spain from 1997–2001 to 2002–2006, the PnPem incidence was lower in children aged 5–17 years (0.5–1.3 per 100,000 population) as compared to younger children [12]. In 1996–2001 and 2006–2009, the adult PnPem incidence was higher in those aged >65 years (3.5–4.8 per 100,000) than other adult age groups (0.5–1.8 per 100,000) (Table 2) [17].

The incidence for PnPem tended to increase from the late 1990s to the mid-2000s in children in the USA [10, 16] and Spain [12], but remained lower in children aged 5–17 years compared with younger children (Table 2) [12]. For example, the PnPem incidence among children aged <18 years in Utah (USA) increased from 10.3 per 100,000 population in 1996–2000 to 14.3 per 100,000 population in 2001–2003 [10], and increased in children aged 2–4 years in the USA from 1.1 to 2.5 per 100,000 population from 1996-1998 to 2005–2007, respectively [16]. In Spain from 1997–2001 to 2002–2006, the PnPem incidence increased from 2.2 to 9.2 per 100,000 population in children aged <2 years and from 1.5 to 9.2 per 100,000 population in children aged 2–4 years [12]. Of note, two studies from Spain showed significant declines in the PnPem incidence following the introduction of PCV13 into the pediatric immunization program: in one, from 6.73 to 4.14
| Years [ref] | Country/ages, status | Methodology | Complicated pneumonia-specific outcome (i.e., cases with CPP) | Clinical presentation in patient population (i.e., cases in the patient population) | Proportion of cases | IR (cases of complicated pneumonia-specific outcome/100,000 population-years) |
|------------|----------------------|-------------|---------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------|--------------------------------------------------------------------------------|
| 1993–1999 [30] | USA/<19 years, hospitalized | Retrospective, single, tertiary care hospital database, Utah | Empyema | CAP | 1993–1999 | 28.3 % (153/540) | 1994 | 1 |
| | | | | | | | | 1994 | 13 % (n/a) | 1999 | 5 |
| | | | | | 1997 | 41 % (n/a) | |
| Last year of surveillance: 2000 | USA/0–26 years, hospitalized | Retrospective, participants in 8 children’s hospitals | CPP | Pneumococcal pneumonia | 0–26 years | 36.1 % (133/368) | n/a |
| | | | | | 0–12 months | 26.4 % (19/72) | |
| | | | | | 13–24 months | 28.6 % (22/77) | |
| | | | | | 25–36 months | 28.1 % (16/57) | |
| | | | | | 37–48 months | 29.0 % (11/38) | |
| | | | | | 49–60 months | 50.0 % (9/18) | |
| | | | | | ≥61 months | 53.0 % (56/106) | |
| Last year of surveillance: 2001 | USA/4 months to 16.5 years, hospitalized | Retrospective, single hospital database, Tennessee | S. pneumoniae-positive complicated parapneumonic effusions | 1996–2001 | 40.8 % (31/76) | n/a |
| Last year of surveillance: 2003 | USA/<18 years, hospitalized | Retrospective, regional medical database, Utah | S. pneumoniae-positive parapneumonic empyema | IPD | 1996–2003 | 22 % (52/234) | 1996–2000 | 10.3 |
| | | | | | 1997–2000 | 16 % (21/129) | n/a |
| | | | | | 2001–2003 | 30 % (31/105) | n/a |
| | | | | | 2000–2003 | 15.1 % (38/251) | n/a |
| Last year of surveillance: 2006 | Canada/<18 years, hospitalized | Retrospective, university hospital databases (8 hospitals across Canada) | S. pneumoniae-positive empyema | Empyema | 2000–2003 | 15.1 % (38/251) | n/a |
| | | | | | 2000–2003 | 15.1 % (38/251) | n/a |
| Last year of surveillance: 2006 | USA/<18 years, hospitalized | Retrospective, single, tertiary care hospital database, Utah | S. pneumoniae-positive necrotizing pneumonia | Pneumococcal pneumonia | 1997–2006 | 26.6 % (33/124) | n/a |
| | | | | | 1997–2000 | 12.8 % (5/39) | |
| | | | | | 2001–2006 | 32.9 % (28/85) | |
Table 2 (continued)

| Years [ref] | Country/ages, status | Methodology | Complicated pneumonia-specific outcome (i.e., cases with CPP) | Clinical presentation in patient population (i.e., cases in the patient population) | Proportion of cases | IR (cases of complicated pneumonia-specific outcome/100,000 population-years) |
|-------------|-----------------------|-------------|---------------------------------------------------------------|-----------------------------------------------------------------|-------------------|---------------------------------------------------------------|
| 1996–1999 and 2001–2007 | USA/<2 years, hospitalized | Retrospective, national inpatient database | S. pneumoniae-positive empyema | Pneumococcal pneumonia | 1996–1999 and 2001–2007 | 7.92 % | 1996–1998 1% | 2005–2007 1.3% |
| 2001–2007 [31] | USA/<18 years, hospitalized | Retrospective, single, tertiary care hospital database | Empyema | Pneumonia | 2001–2007 | 24.8% | (62/250) | 2001 8.5% |
| 1997–2007 [50] | Canada/<17 years, hospitalized | Retrospective, single hospital database, Alberta | S. pneumoniae-positive complicated pneumonia | Complicated pneumonia | 1997–2002 2002–2007 | 20.6% 26.5% | (7/34) (18/68) | n/a |
| 1997–2010 [18] | USA/<18 years, hospitalized | Retrospective, regional medical database, Utah | CPP | IPD | 1997–2000 2001–2010 | 17.2% 33.0% | (22/128) (127/385) | n/a |
| Central/South America | 2005–2010 [45] | Mexico/1 month to 16 years, hospitalized | Prospective, single hospital (Tijuana) active surveillance | S. pneumoniae-positive empyema | 2005–2010 | 46.4% | (13/28) | n/a |
| 2003–2008 [36] | Brazil/<15 years, hospitalized | Retrospective, single hospital database | S. pneumoniae-positive pleural fluid | Pneumococcal pneumonia | 2003–2008 | 29.9% | (32/107) | n/a |
| Europe | Last year of surveillance: 2003 | 1997–2003 [55] | UK/<17 years, hospitalized | Retrospective and prospective, single tertiary care center | S. pneumoniae-positive cavitatory disease | Empyema or parapneumonic effusion | 16.0% | (12/75) | n/a |
| Last year of surveillance: 2006 | 1990–2006 [57] | UK/<15 years, hospitalized | Retrospective, single hospital database, Scotland | S. pneumoniae-positive empyema | 1990–2006 | 14.3% | (4/28) | n/a |
| 1997–2006 [12] | Spain/<2 years, hospitalized | Prospective, regional children’s hospital | S. pneumoniae-positive pneumonia with empyema | IPD | 1997–2006 | 6.9% 17.9% | (2/29) (12/67) | 2007–2006 2.2% | 2005–2007 9.2% |
| Year of surveillance | Country/age, status | Methodology | Clinical presentation in patient population | Complicated pneumonia-specific outcome (i.e., cases with CPP) | IS (cases of complicated pneumonia-specific outcome/100,000 population-years) | Proportion of cases | Time periods or subgroups | Time periods or subgroups |
|----------------------|--------------------|-------------|---------------------------------------------|-------------------------------------------------------------|--------------------------------------------------------------------------|--------------------|--------------------------|--------------------------|
| 2000–2006 [52]       | France/0–18 years, hospitalized | Retrospective, regional medical database, Limousin | Pleural effusion, empyema, or pneumonia | Pneumonia with empyema | 3.3% (39) | 46.2% (12.7) | 2000–2006 | n/a                      |
| 2002–2009 [62]       | UK/0–17 years, hospitalized | Retrospective, single hospital database | Empyema with fistula | S. pneumoniae-positive empyema | 14.2% (44.310) | 14.2% (44.310) | 2002–2009 | n/a                      |
| 2006–2009 [51]       | Spain/children, hospitalized | Prospective, single tertiary care center, children with parapneumonic effusion requiring thoracocentesis | Parapneumonic effusion | S. pneumoniae-positive parapneumonic effusion | 6.54% (838/285) | 6.54% (838/285) | 2006–2009 | n/a                      |
| 2007–2009 [43]       | Spain/a 15 years, hospitalized | Prospective, single hospital | Parapneumonic effusion | IPD | S. pneumoniae-positive parapneumonic effusion | 30.3% (19/63) | 587/285 | 2007–2009 | n/a                      |
| 2000–2009 [52]       | France/0–18 years, hospitalized | Retrospective, regional medical database, Limousin | Pneumonia with empyema | S. pneumoniae-positive empyema | 3.3% (39) | 46.2% (12.7) | 2000–2009 | n/a                      |
| 2002–2009 [62]       | Turkey/0–18 years, hospitalized | Retrospective, single hospital database | Empyema with fistula | S. pneumoniae-positive empyema | 14.2% (44.310) | 14.2% (44.310) | 2002–2009 | n/a                      |
| Last year of surveillance: 2011 |                   |                          |                             |                             |                           |                     |                          |                          |
| 2010–2011 [60]       | Spain/children, hospitalized | Prospective, single hospital | Parapneumonic effusion | IPD | S. pneumoniae-positive empyema | 3.3% (39) | 46.2% (12.7) | 2010–2011 | n/a                      |
| 2000–2006 [52]       | Spain/3–60 months, hospitalized | Prospective, single hospital | Parapneumonic effusion | S. pneumoniae-positive parapneumonic effusion | 6.54% (838/285) | 6.54% (838/285) | 2000–2006 | n/a                      |
| 2002–2009 [62]       | Turkey/0–18 years, hospitalized | Retrospective, single hospital database | Empyema with fistula | S. pneumoniae-positive empyema | 14.2% (44.310) | 14.2% (44.310) | 2002–2009 | n/a                      |
| 2006–2009 [51]       | Spain/children, hospitalized | Prospective, single tertiary care center, children with parapneumonic effusion requiring thoracocentesis | Parapneumonic effusion | S. pneumoniae-positive parapneumonic effusion | 6.54% (838/285) | 6.54% (838/285) | 2006–2009 | n/a                      |
| 2007–2009 [43]       | Spain/a 15 years, hospitalized | Prospective, single hospital | Parapneumonic effusion | IPD | S. pneumoniae-positive parapneumonic effusion | 30.3% (19/63) | 587/285 | 2007–2009 | n/a                      |
| Years [ref] | Country/ages, status | Methodology | Complicated pneumonia-specific outcome (i.e., cases with CPP) | Clinical presentation in patient population (i.e., cases in the patient population) | Proportion of cases | IR (cases of complicated pneumonia-specific outcome/100,000 population-years) |
|------------|----------------------|-------------|-------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------|-------------------------------------------------------------|
| 2008–2011 [37] | Italy≤5 years, hospitalized | Prospective, 5 regional hospitals | CPP, pleural effusion, empyema, necrotizing pneumonia, or atelectasia | Pneumococcal CAP | CPP | 26.0% (19/73) |
|             |                      |             |                                                             | Pleural effusion | 21.9% (16/73) |
|             |                      |             |                                                             | Emphyema | 5.5% (4/73) |
|             |                      |             |                                                             | Necrotizing pneumonia | 0% (0/73) |
|             |                      |             |                                                             | Atelectasia | 5.5% (4/73) |
|             |                      |             | Parapneumonic pneumococcal empyema | IPD | 2007–2011 | 34.0% (209/614) |
|             |                      |             | Parapneumonic pneumococcal empyema (PCV13 serotypes) | IPD (PCV13 serotypes) | 2007–2008 | 30.7% (50/163) |
|             |                      |             |                                                             | 2008–2009 | 29.9% (50/167) |
|             |                      |             |                                                             | 2009–2010 | 39.6% (67/169) |
|             |                      |             |                                                             | 2010–2011 | 36.5% (42/115) |
|             |                      |             |                                                             | 2007–2008 | 31.2% (39/125) |
|             |                      |             |                                                             | 2008–2009 | 33.6% (45/134) |
|             |                      |             |                                                             | 2009–2010 | 40.7% (55/135) |
|             |                      |             |                                                             | 2010–2011 | 40.4% (36/89) |
| 2007–2011 [46] | Spain<15 years, hospitalized | Prospective, regional (Madrid) active clinical surveillance | Parapneumonic pneumococcal empyema | IPD | 2007–2008 | 30.7% (50/163) |
|             |                      |             | Parapneumonic pneumococcal empyema (PCV13 serotypes) | IPD (PCV13 serotypes) | 2007–2008 | 31.2% (39/125) |
| Last year of surveillance: 2012 | |             |                                                             | 2008–2009 | 33.6% (45/134) |
| 2007–2010, 2011–2012 [49] | Spain<12 months, hospitalized | Prospective, regional (Madrid) active clinical surveillance | *S. pneumoniae*-positive parapneumonic pneumococcal empyema (any serotype) | IPD | 2007–2010 | 3.7% (4/107) |
|             |                      |             |                                                             | 2011–2012 | 5.0% (1/20) |
| ≥12–24 months, hospitalized | |             |                                                             | 2011–2012 | 33.7% (30/89) |
| ≥24 to<60 months, hospitalized | |             |                                                             | 2007–2010 | 18.2% (2/11) |
| ≥60 months to 15 years, hospitalized | |             |                                                             | 2011–2012 | 67.9% (19/28) |
| <15 years, hospitalized | |             |                                                             | 2007–2010 | 37.7% (43/114) |
| Middle East/North Africa | |             |                                                             | 2011–2012 | 50.0% (10/20) |
| Last year of surveillance: 1997 | |             |                                                             | 2007–2010 | 33.5% (167/499) |
| 1986–1997 [33] | Israel0–16 years, hospitalized | Retrospective, regional medical database | Pulmonary complications of pneumococcal pneumonia | Pneumococcal pneumonia | 2011–2012 | 40.5% (32/79) |

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| Years [ref] | Country/ages, status | Methodology | Complicated pneumonia-specific outcome (i.e., cases with CPP) | Clinical presentation in patient population (i.e., cases in the patient population) | Proportion of cases | IR (cases of complicated pneumonia-specific outcome/100,000 population-years) |
|------------|----------------------|-------------|-------------------------------------------------|---------------------------------------------------------------------------------|-------------------|---------------------------------------------------------------|
| 1990–2002 [14] | Israel/0–18 years, hospitalized | Retrospective, primary/tertiary hospital database | S. pneumoniae-positive empyema | Empyema with positive cultures | 45.8% (11/24) | n/a |
| Asia-Pacific | Last year of surveillance: 2003 | | | | |
| 1995–2003 [9] | Taiwan/<15 years, hospitalized | Retrospective, single hospital database | CPP | Pneumococcal pneumonia | 1995 25.0% (14) | n/a |
| | | | | | 1996 25.0% (14) | |
| | | | | | 1997 42.9% (3/7) | |
| | | | | | 1998 57.1% (47) | |
| | | | | | 1999 50.0% (6/12) | |
| | | | | | 2000 71.4% (10/14) | |
| | | | | | 2001 61.5% (8/13) | |
| | | | | | 2002 70.0% (7/10) | |
| Last year of surveillance: 2004 | | | | | |
| 1995–2004 [13] | China/<16 years, hospitalized | Retrospective, representative sample from tertiary care hospital | S. pneumoniae-positive empyema or pleural effusion | Empyema or pleural effusion | 1.1% (5/461) | n/a |
| 1995–2004 [13] | Korea/<16 years, hospitalized | Retrospective, representative sample from tertiary care hospital | S. pneumoniae-positive empyema or pleural effusion | Empyema or pleural effusion | 6.7% (9/134) | n/a |
| 1997–2004 [41] | Singapore/3 months to 19.5 years, hospitalized | Retrospective, single hospital database | S. pneumoniae-positive empyema | IPD | 14.3% (21/147) | n/a |
| Last year of surveillance: 2005 | | | | | |
| 1996–2005 [13] | Vietnam/<16 years, hospitalized | Retrospective, representative sample from tertiary care hospital | S. pneumoniae-positive empyema or pleural effusion | Empyema or pleural effusion | 0.5% (3/665) | n/a |
| 2000–2005 [13] | Taiwan/<16 years, hospitalized | Retrospective, representative sample from tertiary care hospital | S. pneumoniae-positive empyema or pleural effusion | Empyema or pleural effusion | 55.5% (66/119) | n/a |
| Last year of surveillance: 2009 | | | | | |
| 2008–2009 [53] | Taiwan/<18 years, hospitalized | Prospective, observational, limited enrollment (~100) | S. pneumoniae-positive empyema or parapneumonic pleural effusion | Empyema or parapneumonic pleural effusion | 27.3% (12/44) | n/a |
| | | | | | S. pneumoniae-positive empyema | 27.3% (12/44) | |
| | | | | | S. pneumoniae-positive parapneumonic pleural effusion | 0% (0/45) | |
| 2007–2009 [58] | Australia/<16 years, hospitalized | Prospective, nationwide empyema surveillance network | S. pneumoniae-positive empyema | Empyema | Blood culture 12.5% (19/152) | n/a |
| | | | | | Pleural fluid culture 7.5% (12/160) | |
| | | | | | Pleural fluid PCR 51.0% (74/145) | |
| Years [ref] | Country/ages, status | Methodology | Complicated pneumonia-specific outcome (i.e., cases with CPP) | Clinical presentation in patient population (i.e., cases in the patient population) | Proportion of cases | IR (cases of complicated pneumonia-specific outcome/100,000 population-years) |
|------------|----------------------|-------------|---------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------|--------------------------------------------------------------------------------|
| 2007–2009 [59] | Australia/<16 years, hospitalized | Prospective, nationwide empyema surveillance network | *S. pneumoniae*-positive empyema via PCR (lytA testing) of pleural fluid | Empyema | 54.4 % (43/79) | n/a |
| Last year of surveillance: 2010 | | | | | | |
| 1998–2010 [19] | Australia/0–19 years, hospitalized | Retrospective, national database | Empyema | Pneumonia | n/a | 1998–2004 0.9 2005–2010 1.2b |
| | | | | | | 1998–2004 2.3 2005–2010 3.5 |
| | | | | | | 1998–2004 1.6 2005–2010 2.7b |
| | | | | | | 1998–2004 0.5 2005–2010 0.5 |
| | | | | | | 1998–2004 0.4 |
| | | | | | | 1998–2004 0.9 2005–2010 0.8 |
| 2003–2010 [54] | Korea/children aged 29–124.5 months, hospitalized | Prospective, 2 hospitals (Seoul) | *S. pneumoniae*-positive empyema | Parapneumonic effusion | 21.0 % (13/62) | n/a |
| B. Adults | | | | | | |
| North America | | | | | | |
| Last year of surveillance: 2010 | | | | | | |
| 2000–2010 [40] | Texas, USA/adults, hospitalized | Retrospective, hospital, all cases with chest X-ray available | *S. pneumoniae*-positive necrotizing pneumonia | Pneumococcal pneumonia | Overall 6.6 % (23/351) | n/a |
| | | | | | PPV23 vaccinated 6.6 % (10/151) |
| | | | | | Not vaccinated 6.5 % (13/200) |
| Europe | | | | | | |
| Last year of surveillance: 2002 | | | | | | |
| 1999–2002 [38] | Barcelona, Spain/ >16 years, hospitalized | Prospective, single tertiary care hospital, all cases during study period | *S. pneumoniae*-positive pleural effusion or empyema | Pneumococcal CAP | Pleural effusion 15.2 % (19/125) | n/a |
| | | | | | Empyema 6.4 % (8/125) |
| Last year of surveillance: 2009 | | | | | | |
| 1996–2009 [17] | Spain/ >18 years, hospitalized | Prospective, 2 university hospitals (Barcelona), ongoing observational study | *S. pneumoniae*-positive empyema | IPD | 1996–2001 12.2 % (62/508) 2005–2009 11.5 % (66/572) | 1996–2001 1.6 2006–2009 1.8 |
Table 2 (continued)

| Years [ref] | Country/ages, status | Methodology | Complicated pneumonia-specific outcome (i.e., cases with CPP) | Clinical presentation in patient population (i.e., cases in the patient population) | Proportion of cases | IR (cases of complicated pneumonia-specific outcome/100,000 population-years) |
|-------------|----------------------|-------------|---------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------|
| 18–50 years |                      |             |                                                               |                                                                                  |                   |                                                                                  |
| 2001–2009 [39] | Spain/adults, hospitalized | Prospective, single tertiary care hospital (Barcelona), all cases during study period | S. pneumoniae-positive pleural effusion or empyema | Pneumococcal pneumonia | Pleural effusion | 19.5 % (122/626) |
| 2001–2009 [39] | Spain/adults, hospitalized | Prospective, single tertiary care hospital (Barcelona), all cases during study period | S. pneumoniae-positive pleural effusion or empyema | Pneumococcal pneumonia | Pleural effusion | 19.5 % (122/626) |
| Last year of surveillance: 2010 | | | | | | |
| 1996–2010 [47] | Spain/18–64 years, hospitalized | Retrospective, single university hospital (Barcelona) | S. pneumoniae-positive empyema | IPD | Emphyema | 2.9 % (18/626) |
| 1996–2008 [61] | USA/all ages, hospitalized | Retrospective, national inpatient database | S. pneumonia empyema -positive | Emphyema | n/a | n/a |
| C. All ages | | | | | | |
| North America | | | | | | |
| 1996–2008 [61] | USA/all ages, hospitalized | Retrospective, national inpatient database | S. pneumonia empyema -positive | Emphyema | n/a | n/a |
| Last year of surveillance: 2008 | | | | | | |
| 1996–2008 [61] | USA/all ages, hospitalized | Retrospective, national inpatient database | S. pneumonia empyema -positive | Emphyema | n/a | n/a |
| | | | | | | |
| CAP, community-acquired pneumonia; CPP, complicated pneumococcal pneumonia; IPD, invasive pneumococcal disease; IR, incidence rate; n/a, not applicable; PCV13, 13-valent pneumococcal conjugate vaccine; PCR, polymerase chain reaction; PPV23, 23-valent pneumococcal polysaccharide vaccine; RT-PCR, reverse transcriptase PCR

\( ^a \) \( n \) indicates the number of cases with CPP

\( ^b \) \( N \) indicates the number of cases in the patient population

\( ^c \) \( p<0.01 \) for increase

\( ^d \) \( p<0.05 \) vs. 2010–2011

\( ^e \) \( p<0.05 \) for decrease

\( ^f \) \( p<0.01 \) for decrease

\( ^g \) \( p<0.05 \) for increase

\( ^h \) Lower 95 % confidence interval of incidence rate ratio >1

\( ^i \) \( p\leq0.001 \) for increase
Proportion of cases with CPP

Outcomes used as numerators for proportions of cases with CPP ranged from more general (e.g., pulmonary complications, complicated pneumonia) to more specific (e.g., empyema, cavitatory disease). Denominators varied, including hospitalized patients, hospitalized patients with CAP, hospitalized patients with pneumococcal CAP, or children with parapneumonic PnEmp. In addition, the assessment methods varied in sensitivity, which may have affected the reported proportions. For example, in hospitalized children with empyema in Australia, only 7.5% of pleural fluid cultures, but 51.0% of pleural fluid PCRs, were pneumococcal-positive [58].

The proportion of cases of CPP or PnEmp among hospitalized children with pneumococcal pneumonia or IPD ranged from 7.9 to 71.4% (Table 2) and tended to increase over time [9, 10, 12, 16, 18, 32–37, 41, 44–46, 49]. For example, the proportions of cases of CPP or PnEmp in hospitalized children with IPD in Spain increased from 6.9% in 1997–2001 [12] to 65.4% during 2007–2009 [10, 18, 41, 44–46, 49]. Among hospitalized children with CAP in Utah (USA), the proportion of cases of complicated pneumonia and empyema increased from 13% in 1994 to 41% in 1997 [30]. Among children with complicated pneumonia or empyema, the proportion of cases of PnEmp as reported in several countries ranged from 0 to 54.4%, although the sample sizes were often small [7, 13, 14, 49, 50, 52–60, 62].

Among hospitalized adults with pneumococcal CAP, the proportions of cases with pleural effusion (PE) (15.2–19.5%, Spain) [38, 39] were higher than those for PnEmp (6.4%, Spain) [38] or necrotizing pneumonia (6.5–6.6%, USA) [40]. Among hospitalized adults with IPD in Spain, 6.9–15.0% were diagnosed with PnEmp (Table 2) [17, 47].

Effect of age on the incidence and proportion of cases of CPP

The effect of age on CPP was not consistent across studies, and age effects for incidence differed as compared to proportion. In most studies, older children comprised a larger proportion of those with CPP or PnEmp relative to other pneumococcal diseases. In Utah (USA) (1997–2010), children with CPP were significantly older than those with other forms of IPD (37 months vs. 25 months; p<0.001) [18]. Among children with pneumococcal pneumonia in the USA (1993–2000), the proportion of cases with CPP increased with age from 26.4% (ages 0–12 months) to 53.0% (ages >61 months) [34]. In contrast, in a study of children from four Asian countries (Vietnam, China, Korea, and Taiwan), empyema and PE were most common in the younger age groups, particularly those ≤4 years of age [13].

The pattern of age-specific incidence may differ from that of the proportion of cases. For example, among hospitalized children with IPD in Spain (1997–2006), the proportion of cases with PnEmp increased with age from 6.9–17.9% (ages <2 years) to 21.4–33.3% (ages 5–17 years), whereas the PnEmp incidence declined with age from 2.2–9.2 per 100,000 population (ages <2 years) to 0.5–1.3 per 100,000 population (ages 5–17 years), which seems to parallel the pattern of IPD incidence among children [12]. In particular, in another study in Spain (2007–2012), the PnEmp incidence was greater among children aged ≥24 to <60 months (8.55–13.81 per 100,000 population) than among younger (<12 months: 1.78–1.36 per 100,000 population) or older (5–15 years: 1.53–2.36 per 100,000 population) children [49].

In Spain (1996–2009), although adults aged 50–65 years had a higher proportion of cases of PnEmp (17.3%) than adults aged ≥65 years (12.7%), the PnEmp incidence was lower among adults aged 50–65 years than those aged ≥65 years (1.4 vs. 4.8 per 100,000 population, respectively) [17], which is consistent with the trend of age-specific incidence of IPD with aging.

Serotype epidemiology

Table 3 presents data on serotype epidemiology [7–9, 14, 15, 17, 18, 30–35, 37, 39–41, 43, 44, 46, 47, 49, 51–60, 62, 64, 66–69, 72, 73, 75–84, 86–91, 93, 94, 97, 99, 101, 102]. Globally, serotypes 1 and 19A exhibited strong associations with pneumococcal PE [15, 52, 66, 69, PnEmp] [10, 31, 43, 46, 49, 54, 57, 58, 60, 68, 72, 81, 83, 88, 90, 93, 101], or both [32, 39, 44].

In Utah (USA) (2001–2010), CPP in children was caused mainly by serotypes 1, 7F, 19A, and 3 (Table 3). Compared with other serotypes, serotype 1 was significantly more likely to cause CPP than other pneumococcal diseases (86% vs. 29%; odds ratio [OR], 14.0; p<0.001) [18]. Among children with IPD in Spain (2002–2006), serotype 1 caused 29.6% of cases of PnEmp, compared with 11.1% caused by PCV7 serotypes (NB, which were all serotype 14 isolates) (Table 3) [101]. Similarly, among adults during 2006–2009 in Spain, serotype 1 caused 32.7% of cases of PE [39].

Serotype 19A also appears to be important, particularly in the Asia-Pacific region. For example, serotype 19A caused 69.2% and 71.0% of cases of pneumococcal necrotizing pneumonia and PnEmp, respectively, in children in Taiwan [83], 46.2% of PnEmp cases in children in Korea [54], and 36.4% of PnEmp cases in children in Australia [58].

Serotypes varied in their prevalence as complicated versus uncomplicated pneumonia. In children in Utah (USA) (1997–
| Years, country[ref] | Serotype assessment methodology/source/diagnosis | Isolates | Number serotyped | Serotypes or serotypes |
|---------------------|-----------------------------------------------|----------|------------------|-----------------------|
|                     |                                               |          | Age range/ subgroup | PCV7 serotypes/ serogroups (％) | 6 additional<sup>b</sup> serotypes/serogroups in PCV13 (％) | 11 additional<sup>c</sup> serotypes/serogroups in PPV23 (％) | Non-vaccine serotypes/serogroups, or other (％) |
|                     |                                               |          |                  | Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F | Serotypes 1, 3, 5, 6A, 7F, and 19A | Serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F | Non-typeable (％) |
| A. Children         |                                               |          |                  |                                    |                                |                                |                                |
| North America       |                                               |          |                  |                                    |                                |                                |                                |
| Last year of surveillance: 1999 |                                               |          |                  |                                    |                                |                                |                                |
| 1993–1999, USA[30]  | Capsular swelling/bl, pl/pneumococcal empyema | <19 years | 26               | 9 (15.4 %) | 1 (50.0 %) | 12 (3.8 %) | 29 (3.8 %) | Non-typeable (3.8 %) |
|                     |                                               |          |                  | 14 (15.4 %) |                                |                                |                                |                                |
|                     |                                               |          |                  | 18 (3.8 %)  |                                |                                |                                |                                |
|                     |                                               |          |                  | 19 (3.8 %)  |                                |                                |                                |                                |
|                     |                                               |          |                  | 38.5 %      | 50.0 %  | 3.8 %   | 7.7 %   |                                |
| Subtotal<sup>d</sup> |                                               |          |                  | 38.5 %      | 50.0 %  | 3.8 %   | 7.7 %   |                                |
| Last year of surveillance: 2000 |                                               |          |                  |                                    |                                |                                |                                |
| 1993–2000, USA[34]  | Quellung/bl and/or pl/ CPP                     | Children | 133              | 14 (29.1 %) | 1 (24.4 %) | 0 | Other (5.5 %) |
|                     |                                               |          |                  | 19 (9.0 %)  | 3 (8.4 %)  |                                |                                |                                |
|                     |                                               |          |                  | 6 (8.4 %)   | 5 (3.4 %)   |                                |                                |                                |
|                     |                                               |          |                  | 9 (5.0 %)   |                                |                                |                                |                                |
|                     |                                               |          |                  | 4 (3.4 %)   |                                |                                |                                |                                |
|                     |                                               |          |                  | 23 (3.4 %)  |                                |                                |                                |                                |
|                     |                                               |          |                  | 58.3 %      | 36.2 %  | 0 %     | 5.5 %   |                                |
| Subtotal<sup>d</sup> |                                               |          |                  | 58.3 %      | 36.2 %  | 0 %     | 5.5 %   |                                |
| Last year of surveillance: 2001 |                                               |          |                  |                                    |                                |                                |                                |
| 1996–2001, Tennessee, USA[7] | Quellung/bl, pl/CPP | 4 months to 16.5 years | 20       | 14 (35.0 %) | 1 (25.0 %) | 12 (5.0 %) |                                |                                |
|                     |                                               |          |                  | 23F (10.0 %) | 19A (15.0 %) | 22 (5.0 %) |                                |                                |
|                     |                                               |          |                  | 9V (5.0 %)  |                                |                                |                                |                                |
|                     |                                               |          |                  | 50.0 %      | 40.0 %  | 10.0 %  | 0 %     |                                |
| Subtotal<sup>d</sup> |                                               |          |                  | 50.0 %      | 40.0 %  | 10.0 %  | 0 %     |                                |
| Last year of surveillance: 2003 |                                               |          |                  |                                    |                                |                                |                                |
| 2000–2003, Canada[56] | Quellung/bl, pl/lt/pneumococcal empyema | <18 years | 35               | 14 (28.6 %) | 3 (25.7 %) |                                |                                |                                |
|                     |                                               |          |                  | 6B (8.6 %)  | 1 (22.9 %) |                                |                                |                                |
|                     |                                               |          |                  | 9V (5.7 %)  | 6A (2.9 %) |                                |                                |                                |
|                     |                                               |          |                  | 4 (2.9 %)   | 23F (2.9 %) |                                |                                |                                |
|                     |                                               |          |                  | 48.6 %      | 51.4 %  | 0 %     | 0 %     |                                |
| Subtotal<sup>d</sup> |                                               |          |                  | 48.6 %      | 51.4 %  | 0 %     | 0 %     |                                |
| Last year of surveillance: 2005 |                                               |          |                  |                                    |                                |                                |                                |
| 1996–2005, USA[73]  | Capsular swelling/bl, pl/pneumococcal empyema | <18 years/1996–2000 | 24       | 14 (12.5 %) | 1 (45.8 %) |                                |                                | Not tested (8.3 %) |
|                     |                                               |          |                  | 6B (8.3 %)  | 6A (4.2 %) |                                |                                |                                |
|                     |                                               |          |                  | 19F (8.3 %) | 19A (4.2 %) |                                |                                |                                |
| Years, country/[ref] | Serotype assessment methodology/source/diagnosis | Isolates | Serogroups or serotypes |
|----------------------|--------------------------------------------------|----------|------------------------|
|                      | Age range/subgroup | Number serotyped | Number serotyped | PCV7 serotypes/serogroups (%a) | Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F | 6 additionalb serotypes/serogroups in PCV13 (%)a | 11 additionalf serotypes/serogroups in PPV23 (%)a | Non-vaccine serotypes/serogroups, or other (%)a |
| 2001–2005            | 50                  | 9V (4.2 %)              | 23F (4.2 %)                 |
|                      |                     | 37.5 %                  | 54.2 %                  | 0 %                        | 8.3 %                      |
| 1997–2000            | 5                   | 6B (4.0 %)              | 9V (4.0 %)                | 4 (2.0 %)                  | 19A (14.0 %)               |
|                      |                     | 19F (6.0 %)             | 9N (2.0 %)                | 19A (14.0 %)               | Not tested (8.0 %)         |
| 2001–2006            | 27                  | 4 (2.6 %)               | 19F (2.6 %)              | 6A (2.6 %)                 | 18 (2.6 %)                |
|                      |                     | 8 (2.6 %)               | 17 (2.6 %)               | 7 (2.6 %)                  | 28 (2.6 %)                |
|                      |                     | 6A (2.6 %)              | 6A (2.6 %)                | 7 (2.6 %)                  | 29/38/42 (2.6 %)           |
|                      |                     | 19V (2.0 %)             | 1 (33.3 %)                | 17 (2.0 %)                 | Others (11.5 %)            |
| 2001–2007            | 51                  | 9V (2.0 %)              | 50.0 %                   | 0 %                       | 11.5 %                    |
|                      |                     | 38.4 %                  | 3 (33.3 %)                | 17 (2.0 %)                 | 38 (2.0 %)                |
|                      |                     | 14 (15.4 %)             | 50.0 %                   | 0 %                       | 11.5 %                    |
|                      |                     | 9V (15.4 %)             | 1 (50.0 %)                | Others (11.5 %)            |
|                      |                     | 19F (3.8 %)             | 40.0 %                   | 0 %                       | 0 %                       |
|                      |                     | 18C (3.8 %)             | 40.0 %                   | 0 %                       | 0 %                       |
|                      |                     | 3 (3.7 %)               | 4 (3.7 %)                 | NG (3.7 %)                | NT (7.4 %)                |
|                      |                     | 19A (14.8 %)            | 17 (3.7 %)                | NG (3.7 %)                | NT (7.4 %)                |
|                      |                     | 3 (7.4 %)               | 3 (7.4 %)                 | NG (3.7 %)                | NT (7.4 %)                |
|                      |                     | 3.7 %                   | 63.0 %                   | 74 %                      | 25.9 %                    |
|                      |                     | 14 (15.4 %)             | 1 (50.0 %)                | Others (11.5 %)            |
|                      |                     | 9V (15.4 %)             | 4 (2.0 %)                 | 11.5 %                    |
|                      |                     | 19F (3.8 %)             | 7 (2.6 %)                 | 28 (2.6 %)                |
|                      |                     | 18C (3.8 %)             | 19 (2.6 %)                | 29/38/42 (2.6 %)           |
|                      |                     | 3.7 %                   | 63.0 %                   | 74 %                      | 25.9 %                    |
|                      |                     | 14 (15.4 %)             | 1 (50.0 %)                | Others (11.5 %)            |
|                      |                     | 9V (15.4 %)             | 4 (2.0 %)                 | 11.5 %                    |
|                      |                     | 19F (3.8 %)             | 7 (2.6 %)                 | 28 (2.6 %)                |
|                      |                     | 18C (3.8 %)             | 19 (2.6 %)                | 29/38/42 (2.6 %)           |
|                      |                     | 3.7 %                   | 63.0 %                   | 74 %                      | 25.9 %                    |
|                      |                     | 14 (15.4 %)             | 1 (50.0 %)                | Others (11.5 %)            |
|                      |                     | 9V (15.4 %)             | 4 (2.0 %)                 | 11.5 %                    |
|                      |                     | 19F (3.8 %)             | 7 (2.6 %)                 | 28 (2.6 %)                |
|                      |                     | 18C (3.8 %)             | 19 (2.6 %)                | 29/38/42 (2.6 %)           |
|                      |                     | 3.7 %                   | 63.0 %                   | 74 %                      | 25.9 %                    |
|                      |                     | 14 (15.4 %)             | 1 (50.0 %)                | Others (11.5 %)            |
|                      |                     | 9V (15.4 %)             | 4 (2.0 %)                 | 11.5 %                    |
|                      |                     | 19F (3.8 %)             | 7 (2.6 %)                 | 28 (2.6 %)                |
|                      |                     | 18C (3.8 %)             | 19 (2.6 %)                | 29/38/42 (2.6 %)           |
|                      |                     | 3.7 %                   | 63.0 %                   | 74 %                      | 25.9 %                    |
| Years, country/[ref] | Serotype assessment methodology/source/diagnosis | Isolates | Serogroups or serotypes |
|----------------------|--------------------------------------------------|----------|------------------------|
|                      |                                                  | Age range/subgroup | Number serotyped | PCV7 serotypes/serogroups (%)<sup>a</sup> | 6 additional<sup>b</sup> serotypes/serogroups in PCV13 (%)<sup>a</sup> | 11 additional<sup>c</sup> serotypes/serogroups in PPV23 (%)<sup>a</sup> | Non-vaccine serotypes/serogroups, or other (%)<sup>a</sup> |
|                      |                                                  |                      |                  | Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F | Serotypes 1, 3, 5, 6A, 7F, and 19A | Serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F | |
| Last year of surveillance: 2009 |                                                  |                      |                  |                                            |                                            |                                            | |
| 2007–2009, USA/[67] | Multiplex immunoassay/pl/CPP                      | 0.4–15 years        | 49               | 6B (2.0 %) | 3 (26.5 %) | 19A (22.4 %) | 7F/7A (14.3 %) | 1 (12.2 %) | 19A (25.5 %) | 7F (3.9 %) | 90.2 % | 4.0 % | 4.0 % |
| Subtotal<sup>f</sup> |                                                  |                      |                  |                                            |                                            |                                            | |
| 2009, Utah, USA/[64] | Real-time PCR/pl/pneumococcal empyema             | <18 years           | 45               | 7F (46.7 %) | 19A (13.3 %) | 3 (13.3 %) | 1 (4.4 %) | 75.5 % | 4.0 % | 18.4 % | 0 % | 77.8 % | 0 % | 22.2 % |
| Subtotal<sup>f</sup> |                                                  |                      |                  |                                            |                                            |                                            | |
| 1997–2010, Utah, USA/[18] | Capsular swelling/bl/pl/CPP                      | <18 years/1997–2000 | 22               | PCV7 (40.9 %) | 0 % | 1 (19.7 %) | 22F (3.9 %) | 7F (18.9 %) | 19A (17.3 %) | 3 (16.5 %) | 59.1 % | 0 % | 40.9 % |
| Subtotal<sup>f</sup> |                                                  |                      |                  |                                            |                                            |                                            | Other (59.1 %) | |
| 2001–2010            |                                                  |                      | 127              | PCV7 (5.5 %) | 1 (19.7 %) | 22F (3.9 %) | 7F (18.9 %) | 19A (17.3 %) | 3 (16.5 %) | 5.5 % | 72.4 % | 3.9 % | 19.7 % |
| South America        |                                                  |                      |                  | PCV7 (40.9 %) | 0 % | 1 (19.7 %) | 22F (3.9 %) | 7F (18.9 %) | 19A (17.3 %) | 3 (16.5 %) | 59.1 % | 0 % | 40.9 % |
| Last year of surveillance: 2004 |                                                  |                      |                  |                                            |                                            |                                            | Other (59.1 %) | |
| 1998–2004, Uruguay/[76] | Latex agglutination/bl/pl/pneumococcal empyema  | Children            | 237              | 9V (3.8 %) | 5 (23.2 %) | 9N (0.8 %) | 7 (0.4 %) | 6B (2.1 %) | 3 (10.1 %) | 12 (0.4 %) | 14 (2.1 %) | 1 (23.6 %) | 8 (0.8 %) | 18B (0.4 %) |
|                      |                                                  |                      |                  | 6B (2.1 %) | 3 (10.1 %) | 12 (0.4 %) | 14 (2.1 %) | 1 (23.6 %) | 8 (0.8 %) | 18B (0.4 %) | 6B (2.1 %) | 3 (10.1 %) | 12 (0.4 %) | 14 (2.1 %) | 1 (23.6 %) | 8 (0.8 %) | 18B (0.4 %) |
|                      |                                                  |                      |                  | 19F (0.8 %) | 4 (23.2 %) | 9N (0.8 %) | 7 (0.4 %) | 6B (2.1 %) | 3 (10.1 %) | 12 (0.4 %) | 14 (2.1 %) | 1 (23.6 %) | 8 (0.8 %) | 18B (0.4 %) | 6B (2.1 %) | 3 (10.1 %) | 12 (0.4 %) | 14 (2.1 %) | 1 (23.6 %) | 8 (0.8 %) | 18B (0.4 %) |
|                      |                                                  |                      |                  | 4 (0.4 %) | 19F (0.8 %) | 10A (0.4 %) | 15 (0.4 %) | 6A (0.8 %) | 22 (0.4 %) | 33 (0.4 %) | 6B (2.1 %) | 3 (10.1 %) | 12 (0.4 %) | 14 (2.1 %) | 1 (23.6 %) | 8 (0.8 %) | 18B (0.4 %) | 6B (2.1 %) | 3 (10.1 %) | 12 (0.4 %) | 14 (2.1 %) | 1 (23.6 %) | 8 (0.8 %) | 18B (0.4 %) |
| Subtotal<sup>f</sup> |                                                  |                      |                  | 31.2 % | 64.1 % | 3.8 % | 0.8 % | 31.2 % | 64.1 % | 3.8 % | 0.8 % |
| Years, country/[ref] | Serotype assessment methodology/source/diagnosis | Isolates | Serotypes or serotypes |
|---------------------|-----------------------------------------------|----------|------------------------|
|                     | Age range/subgroup | Age range | PCV7 serotypes/serogroups (%\(a\)) | 6 additional\(^b\) serotypes/serogroups in PCV13 (%\(c\)) | 11 additional\(^c\) serotypes/serogroups in PPV23 (%\(c\)) | Non-vaccine serotypes/serogroups, or other (%\(c\)) |
|                     | Number serotyped | Number | Serotype 4, 6B, 9V, 14, 18C, 19F, and 23F | Serotypes 1, 3, 5, 6A, 7F, and 19A | Serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F |
|                     | 0–14 years | 191 | n/a | 1 (26.2 %)\(^f\) | n/a | n/a |
| 2002–2004, Uruguay/[66] Subtotal\(^d\) | Latex agglutination; ELISA (PCV13 serotypes)/pl/pneumococcal empyema | 0.6–16.9 years | 43 | 14 (11.6 %) | 1 (39.5 %) | Negative (23.2 %) |
| Europe Last year of surveillance: 2001 | 11.6 % | 46.5 % | 0 % | 41.9 % |
| 1997–2001, England/[8] Subtotal\(^d\) | Latex agglutination; ELISA (PCV13 serotypes)/pl/pneumococcal empyema | 0.5–16.9 years | 11 | 14 (18.2 %) | 1 (36.4 %) | 3 (7.0 %) |
| Last year of surveillance: 2003 | 36.4 % | 63.7 % | 0 % | 0 % |
| 1997–2003, England/[55] Subtotal\(^d\) | EIA (PCV13 serotypes)/bl, pl/pneumococcal cavitory empyema | <15 years | 30 | 14 (13.3 %) | 19A (26.7 %) | 7F (3.3 %) |
| Last year of surveillance: 2004 | 30.0 % | 70.0 % | 0 % | 0 % |
| 2002–2004, France/[72] Subtotal\(^d\) | Latex agglutination/bl, pl/pneumococcal empyema | 0.8–14.8 years | 27 | 4 (14.8 %)\(^f\) | 1 (66.7 %) | 7F (3.7 %) |
| Last year of surveillance: 2006 | 22.2 % | 77.8 % | 0 % | 0 % |
| 2003–2004, England/[99] Subtotal\(^d\) | ELISA (PCV13 serotypes)/pl/pneumococcal empyema | 0–14 years | 6 | n/a | 1 (50.0 %)\(^f\) | Not tested (50.0 %) |
| Last year of surveillance: 2006 | n/a | 50.0 % | n/a | n/a |
Table 3 (continued)

| Years, country[ref] | Serotype assessment methodology/source/diagnosis | Isolates | Serotypes or serotypes |
|---------------------|-------------------------------------------------|----------|------------------------|
|                     |                                                 | Age range/| Number               | PCV7 serotypes/serogroups (%)<sup>b</sup> | 6 additional<sup>c</sup> serotypes/serogroups in PCV13 (%)<sup>a</sup> | 11 additional<sup>d</sup> serotypes/serogroups in PPV23 (%)<sup>e</sup> | Non-vaccine serotypes/serogroups, or other (%)<sup>f</sup> |
|                     |                                                 | subgroup  |                     | Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F | Serotypes 1, 3, 5, 6A, 7F, and 19A | Serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F |                      |
| 2004–2006, Spain[101] | MLST/pl/pneumococcal empyema | <14 years | 27 | 14 (11.1 %) | 1 (29.6 %) | 19A (3.7 %) | Other serotypes not confirmed (55.6 %) |
| Subtotal<sup>d</sup> |                                                 |          |                     | 11.1 % | 33.3 % | 0 | 55.6 % |
| 2003–2006, Spain[87] | Quellung, real-time PCR/bl, pl/pneumococcal empyema | <18 years | 111 | 14 (8.1 %) | 9V (1.8 %) | 19F (0.9 %) | 9V (1.8 %) | 7F (12.6 %) | 3 (10.8 %) | 5 (8.1 %) | 19A (7.2 %) | 6A (1.8 %) | 1.8 % | 3.7 % | 19A (7.4 %) | 6A (3.7 %) | 7F (3.7 %) | 0 % | 0 |
| Subtotal<sup>d</sup> |                                                 |          |                     | 10.8 % | 89.1 % | 0.9 % | 0 |
| 2003–2006, Spain[15] | Quellung/bl, pl/pneumococcal parapneumonic pleural effusion | <18 years | 27 | 14 (11.1 %) | 6B (3.7 %) | 9V (3.7 %) | 19F/B/C (1.5 %) | 1 (37.0 %) | 3 (14.8 %) | 5 (14.8 %) | 19A (7.4 %) | 6A (3.7 %) | 7F (3.7 %) | 0 |
| Subtotal<sup>d</sup> |                                                 |          |                     | 18.5 % | 81.5 % | 0 | 0 |
| 2003–2006, Spain[93] | Real-time PCR/pl/pneumococcal empyema | Children | 67 | 14 (4.5 %) | 19F/B/C (1.5 %) | 1 (34.3 %) | 7F/7A (16.4 %) | 3 (11.9 %) | 19A (4.5 %) | 5 (3.0 %) |
| Subtotal<sup>d</sup> |                                                 |          |                     | 6.0 % | 70.1 % | 1.5 % | 22.4 % |
| Last year of surveillance: 2007 |                                                 |          |                     |                     | | | |
| 2007, France[97] | Latex agglutination/pl, hospitalized patients with pneumococcal disease | 1 month to 12.6 years | 10 | 14 (50.5 %) | 19A (50.5 %) | 0 % | 100 % | 0 % | 0 % | 19A (0) | n/a | Other (100 %) | 0 % |
| Subtotal<sup>d</sup> |                                                 |          |                     | 6.0 % | 70.1 % | 1.5 % | 22.4 % |

<sup>a</sup> Numbers in parentheses are percentages, unless otherwise specified.
<sup>b</sup> MLST = multilocus sequence typing.
<sup>c</sup> Additional serotypes/serogroups in PCV13.
<sup>d</sup> Subtotal.
<sup>e</sup> Additional serotypes/serogroups in PPV23.
<sup>f</sup> Other serotypes/serogroups, or other.
<sup>g</sup> N/A.
| Years, country/[ref] | Serotype assessment methodology/source/ diagnosis | Isolates | Serotypes or serotypes | Age range/subgroup | Number serotyped | PCV7 serotypes/serogroups (%)<sup>a</sup> | 6 additional<sup>a</sup> serotypes/serogroups in PCV13 (%)<sup>a</sup> | 11 additional<sup>a</sup> serotypes/serogroups in PPV23 (%)<sup>a</sup> | Non-vaccine serotypes/serogroups, or other (%)<sup>a</sup> |
|----------------------|--------------------------------------------------|----------|------------------------|-------------------|-----------------|-------------------------------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------------------------|
| 2005–2009, Spain/[88] | Quellung/bl, other sterile sites/ pneumococcal empyema | <14 years | 2002–2004: 13 2005–2007: 34 | 68 n/a | 1 (41.2 %) n/a | 19A (7.7 %)<sup>e</sup> | 19A (17.6 %)<sup>e</sup> | 19A (17.6 %)<sup>e</sup> | Other (92.3 %) |
| Last year of surveillance: 2009 | | | | | | | | | |
| 2000–2006, France/[52] | Not specified/bl, pl/ pneumococcal pleural effusion | 6 months to 15 years<sup>g</sup> | 4 | 0 % | 19A (50.0 %) | 1 (25.0 %) | 5 (25.0 %) | 1 (25.0 %) | Unknown (66.7 %) |
| Subtotal<sup>d</sup> | | | | | | 41.2 % | n/a | n/a | |
| Last year of surveillance: 2009 | | | | | | | | | |
| 2006–2009, Italy/[32] | Real-time PCR/bl/CPP | 0–16 years | 2000–2006 3 | 8 | 33.3 % | n/a | n/a | n/a | Unknown (12.5 %) |
| Subtotal<sup>d</sup> | | | | | | 87.5 % | n/a | n/a | |
| 2007–2009, Italy/[32] | Real-time PCR/bl/CPP | 0–16 years | 36 | n/a | 14 (5.6 %) | 18 (5.6 %) | 6 (2.8 %) | 9V (2.8 %) | 18 (5.6 %) |
| Subtotal<sup>d</sup> | | | | | | 16.7 % | 77.8 % | 2.8 % | 2.8 % | Non-typeable (2.8 %) |
| 2005–2009, Spain/[88] | Quellung; PCR of culture-negative specimens/bl, pl/ pneumococcal empyema | <14 years/2005–2009 | 104 | 14 (2.9 %) 9V (1.0 %) 19F (1.0 %) | 16.7 % | 77.8 % | 2.8 % | 2.8 % | 12A (1.0 %) |
| Subtotal<sup>d</sup> | | | | | | 16.7 % | 77.8 % | 2.8 % | 2.8 % | 12A (1.0 %) |
### Table 3 (continued)

| Years, country/ref | Serotype assessment methodology/source/diagnosis | Isolates | Serogroups or serotypes |
|--------------------|--------------------------------------------------|----------|-------------------------|
|                    | Age range/subgroup | Number serotyped | PCV7 serotypes/serogroups (%)<sup>a</sup> | 6 additional<sup>b</sup> serotypes/serogroups in PCV13 (%)<sup>a</sup> | 11 additional<sup>c</sup> serotypes/serogroups in PPV23 (%)<sup>a</sup> | Non-vaccine serotypes/serogroups, or other (%)<sup>a</sup> |
|                    |                    |          | Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F | Serotypes 1, 3, 5, 6A, 7F, and 19A | Serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F |

**Subtotal<sup>d</sup>**

|                  | 2005–2007 | 53 | 4.8 % | 94.2 % | 0 % | 1.0 % |
|------------------|-----------|----|-------|--------|-----|------|
|                  |           |    | 14 (3.8 %) | 1 (43.4 %) | 7F (26.4 %) | 6A (19.0 %) |
|                  |           |    | 19F (1.9 %) | 3 (15.1 %) | 19A (3.8 %) | 5 (3.8 %) |
|                  |           |    |       |       |       | 6A (1.9 %) |

**Subtotal<sup>d</sup>**

|                  | 2007–2009 | 51 | 5.7 % | 94.3 % | 0 % | 0 % |
|------------------|-----------|----|-------|--------|-----|------|
|                  |           |    | 14 (2.0 %) | 1 (41.2 %) | 7F (17.6 %) | 12A (2.0 %) |
|                  |           |    | 9V (2.0 %) | 3 (13.7 %) | 19A (11.8 %) |      |
|                  |           |    |       |       |       | 5 (9.8 %) |

**Subtotal<sup>d</sup>**

|                  | Real-time PCR/pl/ pneumococcal empyema | Children (mean age 6.5 years) | 28 | 3.9 % | 94.1 % | 0 % | 2.0 % |
|------------------|----------------------------------------|-----------------------------|----|-------|--------|-----|------|
|                  |                                        |                             |    | 6B (7.1 %) | 1 (35.7 %) | n/a | Unknown serotype (14.3 %) |
|                  |                                        |                             |    | 9V (7.1 %) | 7F (10.7 %) |      |      |
|                  |                                        |                             |    | 14 (3.8 %) | 19A (10.7 %) |      |      |
|                  |                                        |                             |    | 23F (3.8 %) | 3 (7.1 %) |      |      |
|                  |                                        |                             |    |       |       |      |      |

**Subtotal<sup>d</sup>**

|                  | Quellung; real-time PCR if culture-negative/bl, pl/ pneumococcal empyema | 3–59 months | 189 | 21.4 % | 64.3 % | n/a | n/a |
|------------------|------------------------------------------------------------------------|-------------|-----|-------|--------|-----|------|
|                  |                                                                        | Specific PVC7 serotypes were not specified (2.6 %) |    | 6B (7.1 %) | 1 (24.9 %) | n/a | Other serotypes not specified (39.7 %) |
|                  |                                                                        |                                           |    | 9V (7.1 %) | 3 (14.8 %) |      |      |
|                  |                                                                        |                                           |    | 14 (3.8 %) | 19A (14.3 %) |      |      |
|                  |                                                                        |                                           |    | 23F (3.8 %) | 7F (3.7 %) |      |      |

**Subtotal<sup>d</sup>**

|                  | Quellung, PCR/bl, pl/ pneumococcal empyema | <15 years | 100 | 2.6 % | 57.7 % | n/a | n/a |
|------------------|------------------------------------------|-----------|-----|-------|--------|-----|------|
|                  |                                          | Specific PVC7 serotypes were not specified (2.6 %) |    | 6B (7.1 %) | 1 (38.0 %) | n/a | Other serotypes not specified (19.0 %) |
|                  |                                          |                                           |    | 9V (7.1 %) | 5 (15.0 %) |      |      |
|                  |                                          |                                           |    | 14 (3.8 %) | 19A (11.0 %) |      |      |
|                  |                                          |                                           |    | 23F (3.8 %) | 7F (9.0 %) |      |      |
|                  |                                          |                                           |    |       |       |      |      |

**Subtotal<sup>d</sup>**

|                  | Latex agglutination bl, CSE, pl, synovial fluid, peritoneal | <16 years | 22 | n/a | 81.0 % | n/a | n/a |
|------------------|-----------------------------------------------------------|----------|----|-----|--------|-----|------|
|                  |                                                          | Specific PVC7 serotypes were not specified (2.6 %) |    | 6B (7.1 %) | 1 (38.0 %) | n/a | Other serotypes not specified (19.0 %) |
|                  |                                                          |                                           |    | 9V (7.1 %) | 5 (15.0 %) |      |      |
|                  |                                                          |                                           |    | 14 (3.8 %) | 19A (11.0 %) |      |      |
|                  |                                                          |                                           |    | 23F (3.8 %) | 7F (9.0 %) |      |      |

**Subtotal<sup>d</sup>**

|                  |                           | <16 years | 22 | n/a | 19A (13.6 %)<sup>e</sup> | n/a | n/a |
|------------------|---------------------------|----------|----|-----|--------------------------|-----|------|
|                  |                           | Specific PVC7 serotypes were not specified (2.6 %) |    | 6B (7.1 %) | 1 (38.0 %) | n/a | Other serotypes not specified (19.0 %) |
|                  |                           |                                           |    | 9V (7.1 %) | 5 (15.0 %) |      |      |
|                  |                           |                                           |    | 14 (3.8 %) | 19A (11.0 %) |      |      |
|                  |                           |                                           |    | 23F (3.8 %) | 7F (9.0 %) |      |      |

**Subtotal<sup>d</sup>**

|                  |                           | <16 years | 22 | n/a | n/a | n/a | n/a |
|------------------|---------------------------|----------|----|-----|-----|-----|------|
|                  |                           | Specific PVC7 serotypes were not specified (2.6 %) |    | 6B (7.1 %) | 1 (38.0 %) | n/a | Other serotypes not specified (19.0 %) |
|                  |                           |                                           |    | 9V (7.1 %) | 5 (15.0 %) |      |      |
|                  |                           |                                           |    | 14 (3.8 %) | 19A (11.0 %) |      |      |
|                  |                           |                                           |    | 23F (3.8 %) | 7F (9.0 %) |      |      |

**Subtotal<sup>d</sup>**

|                  |                           | <16 years | 22 | n/a | n/a | n/a | n/a |
|------------------|---------------------------|----------|----|-----|-----|-----|------|
|                  |                           | Specific PVC7 serotypes were not specified (2.6 %) |    | 6B (7.1 %) | 1 (38.0 %) | n/a | Other serotypes not specified (19.0 %) |
|                  |                           |                                           |    | 9V (7.1 %) | 5 (15.0 %) |      |      |
|                  |                           |                                           |    | 14 (3.8 %) | 19A (11.0 %) |      |      |
|                  |                           |                                           |    | 23F (3.8 %) | 7F (9.0 %) |      |      |

**Subtotal<sup>d</sup>**

|                  |                           | <16 years | 22 | n/a | n/a | n/a | n/a |
|------------------|---------------------------|----------|----|-----|-----|-----|------|
|                  |                           | Specific PVC7 serotypes were not specified (2.6 %) |    | 6B (7.1 %) | 1 (38.0 %) | n/a | Other serotypes not specified (19.0 %) |
|                  |                           |                                           |    | 9V (7.1 %) | 5 (15.0 %) |      |      |
|                  |                           |                                           |    | 14 (3.8 %) | 19A (11.0 %) |      |      |
|                  |                           |                                           |    | 23F (3.8 %) | 7F (9.0 %) |      |      |

**Subtotal<sup>d</sup>**

|                  |                           | <16 years | 22 | n/a | n/a | n/a | n/a |
|------------------|---------------------------|----------|----|-----|-----|-----|------|
|                  |                           | Specific PVC7 serotypes were not specified (2.6 %) |    | 6B (7.1 %) | 1 (38.0 %) | n/a | Other serotypes not specified (19.0 %) |
|                  |                           |                                           |    | 9V (7.1 %) | 5 (15.0 %) |      |      |
|                  |                           |                                           |    | 14 (3.8 %) | 19A (11.0 %) |      |      |
|                  |                           |                                           |    | 23F (3.8 %) | 7F (9.0 %) |      |      |
| Years, country/[ref]     | Serotype assessment methodology/source/diagnosis | Isolates | Serogroups or serotypes                                                                                                                                 |
|-------------------------|-------------------------------------------------|----------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
|                         | Serotypes                                        | Number   | PCV7 serotypes/serogroups (%)<sup>a</sup>                                                                                                               |
|                         |                                                  |          | 6 additional<sup>b</sup> serotypes/serogroups in PCV13 (%)<sup>a</sup>                                                                                  |
|                         |                                                  |          | 11 additional<sup>c</sup> serotypes/serogroups in PPV23 (%)<sup>a</sup>                                                                               |
|                         | Non-vaccine serotypes/serogroups, or other (%)<sup>a</sup> |          |                                                                                                                                                        |
| 2008–2009, UK/[62]      | Not specified/pl/pneumococcal empyema with or without fistula | 13       | n/a                                                                                                                                                    |
|                         |                                                  |          | 3 (76.9 %)                                                                                                                                            |
|                         |                                                  |          | 19 (7.7 %)                                                                                                                                            |
|                         |                                                  |          | Unidentified (7.7 %)                                                                                                                                   |
|                         |                                                  |          | Not tested (7.7 %)                                                                                                                                     |
| Subtotal<sup>f</sup>    |                                                 | n/a      | 84.6 %                                                                                                                                                |
| Last year of surveillance: 2010 | 0.8–14.7 years | 11       | 1 (46.7 %)                                                                                                                                            |
| 2009–2010, France/[84]  | Latex agglutination; multiplex PCR/bl, pl/pneumococcal empyema | 0.8–14.7 years | 19A (54.5 %)                                                                                                                                          |
|                         |                                                  |          | 1 (18.2 %)                                                                                                                                            |
|                         |                                                  |          | 7F/A (18.2 %)                                                                                                                                          |
|                         |                                                  |          | 3 (9.1 %)                                                                                                                                             |
| Subtotal<sup>f</sup>    |                                                 | n/a      | 60.0 %                                                                                                                                                |
| Last year of surveillance: 2011 | 0 % | 1   | 100 %                                                                                                                                                |
| 2006–2010, Spain/[89]   | Latex agglutination/bl, pl, br pneumococcal empyema | Children (age range not otherwise specified) | 0 %                                                                                                                                                   |
|                         |                                                  |          | 7F (100 %)                                                                                                                                            |
| Subtotal<sup>f</sup>    |                                                 | n/a      | 100 %                                                                                                                                                |
| Last year of surveillance: 2011 | 0–16 years | 136 | 0 %                                                                                                                                                   |
| 2006–2011, UK/[94]      | Multiplex polysaccharide antigen detection assay/pl (culture-negative)/pneumococcal empyema | 0–16 years | 1 (43 %)                                                                                                                                              |
|                         |                                                  |          | 3 (21 %)                                                                                                                                               |
|                         |                                                  |          | 7 (11 %)                                                                                                                                               |
|                         |                                                  |          | 19A (10 %)                                                                                                                                              |
| Subtotal<sup>f</sup>    |                                                 | n/a      | 85 %                                                                                                                                                    |
| 2009–2011, UK/[75]      | RT-PCR/pl/pneumococcal empyema                  | ≤16 years | n/a                                                                                                                                                    |
|                         |                                                  |          | 1 (38.9 %)                                                                                                                                              |
|                         |                                                  |          | 3 (27.8 %)                                                                                                                                              |
|                         |                                                  |          | 19A (22.2 %)                                                                                                                                            |
|                         |                                                  |          | 7A/F (5.6 %)                                                                                                                                           |
### Table 3 (continued)

| Years, country/[ref]     | Serotype assessment methodology/source/diagnosis | Isolates | Serogroups or serotypes | 6 additional<sup>a</sup> serotypes/serogroups in PCV13 (%<sup>a</sup>) | 11 additional<sup>a</sup> serotypes/serogroups in PPV23 (%<sup>a</sup>) | Non-vaccine serotypes/serogroups, or other (%<sup>a</sup>) |
|--------------------------|-------------------------------------------------|----------|------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
|                           | Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F      |          |                        | Serotypes 1, 3, 5, 6A, 7F, and 19A              | Serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F |
|                           | Number serotyped                                |          |                        | (%)                                              | (%)                                              | (%)                                              |
|                           | Age range/subgroup                              |          |                        | (%)                                              | (%)                                              | (%)                                              |
| Subtotal<sup>d</sup>      |                                                 |          |                        |                                                  |                                                  |                                                  |
| 2008–2011, Italy/[37]     | Real-time PCR                                   | ≤5 years | 18                     | 0 %                                              | 94.4 %                                           | 5.6 %                                            |
|                           | (PCV13 serotypes)/bl/CPP                        |          |                        | 4 (5.6 %)                                        | 19A (33.3 %)                                     | Untypeable or other serotype (33.3 %)          |
|                           |                                                  |          |                        | 14 (5.6 %)                                       | 3 (11.1 %)                                        |                                                  |
|                           |                                                  |          |                        |                                                  | 7F (5.6 %)                                        |                                                  |
|                           |                                                  |          |                        |                                                  | 1 (5.6 %)                                        |                                                  |
| Subtotal<sup>d</sup>      | Quellung; real-time PCR                         | <15 years| 209                    | 11.2 %                                           | 55.6 %                                           | 33.3 %                                           |
|                           | PCR/bl, pl/bacteremic pneumococcal empyema      |          |                        |                                                  |                                                  |                                                  |
| 2010–2011, Turkey/[60]   | Multiple antigen testing (PCV13 serotypes/     | 0–18 years | 55                     | 0 %                                              | 41.6 %<sup>c</sup>                               | n/a                                             |
|                           | serogroups and serotype 8)/pneumococcal empyema|          |                        | 19F (5.5 %)                                      | 1 (14.5 %)                                       | n/a                                             |
|                           |                                                  |          |                        | 6B (3.6 %)                                       | 5 (12.7 %)                                       | n/a                                             |
|                           |                                                  |          |                        | 14 (3.6 %)                                       | 3 (9.1 %)                                        | n/a                                             |
|                           |                                                  |          |                        | 9V (1.8 %)                                       | 7F (1.8 %)                                       | n/a                                             |
|                           |                                                  |          |                        | 23F (1.8 %)                                      | 19A (1.8 %)                                      | n/a                                             |
| Subtotal<sup>d</sup>      | Quellung, real-time PCR                         | <15 years/2007-2010 | 167                  | 16.4 %                                           | 40.0 %                                           | 38.2 %                                           |
|                           | Individual PCV7 serotypes not specified (42 %) |          |                        |                                                  |                                                  |                                                  |
| Last year of surveillance: 2012 |                                                          |          |                        |                                                  |                                                  |                                                  |
| 2007–2012, Spain/[49]    |                                                 |          |                        |                                                  |                                                  |                                                  |
|                           | Quellung, real-time PCR                         | <15 years | 167                    | Individual PCV7 serotypes not specified (42 %)  | 1 (39.5 %)                                       | Other serotypes not specified (16.8 %)          |
|                           |                                                  |          |                        | 19A (15.6 %)                                     | 5 (9.6 %)                                        |                                                  |
|                           |                                                  |          |                        | 3 (9.0 %)                                        | 7F (5.4 %)                                       |                                                  |
| Subtotal<sup>d</sup>      |                                                 |          |                        |                                                  |                                                  |                                                  |
| 2011–2012                 |                                                 |          |                        |                                                  |                                                  |                                                  |
|                           |                                                 |          |                        |                                                  |                                                  |                                                  |
|                           |                                                 |          |                        |                                                  |                                                  |                                                  |
| Subtotal<sup>d</sup>      |                                                 |          |                        |                                                  |                                                  |                                                  |
| Middle East/North Africa  |                                                 |          |                        |                                                  |                                                  |                                                  |
| Last year of surveillance: 1997 |                                                          |          |                        |                                                  |                                                  |                                                  |
| 1986–1997, Israel/[33]    | Not specified/not specified/CPP                 | 0–16 years | 22                     | n/a                                              | 1 (31.8 %)<sup>f</sup>                           | n/a                                             |

<sup>a</sup> Serotypes and serogroups listed in the table are based on the serology of the isolates. For the years 2007–2012 and 2008–2011, Italy, the serotyped serotypes include additional serotypes/serogroups in PCV13 and PPV23. For the years 2007–2012, Spain and 2010–2011, Turkey, the serotyped serotypes do not include additional serotypes/serogroups in PCV13 and PPV23.

<sup>b</sup> The number of additional serotypes/serogroups in PPV23 is based on the serology of the isolates.

<sup>c</sup> The number of additional serotypes/serogroups in PCV13 is based on the serology of the isolates.

<sup>d</sup> The subtotal values include data from multiple surveillance years.

<sup>e</sup> The total number of serotypes/serogroups not specified is based on the serology of the isolates.

<sup>f</sup> The total number of non-classified serotypes/serogroups is based on the serology of the isolates.
| Years, country/[ref] | Serotype assessment methodology/source/diagnosis | Isolates | Age range/ subgroup | Number serotyped | Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F (%) | 6 additional<sup>a</sup> serotypes/serogroups in PCV13 (%)<sup>d</sup> | 11 additional<sup>a</sup> serotypes/serogroups in PPV23 (%)<sup>d</sup> | Non-vaccine serotypes/serogroups, or other (%)<sup>d</sup> |
|----------------------|--------------------------------------------------|----------|---------------------|------------------|-----------------------------------------------|---------------------------------------------|---------------------------------------------|--------------------------------------------|
|                      | Serogroups or serotypes                           |          |                     |                  |                                               |                                              |                                              |                                            |
|                      | PCV7 serotypes/serogroups (%)<sup>a</sup>        |          |                     |                  |                                               |                                              |                                              |                                            |
|                      | Serotypes 1, 3, 5, 6A, 7F, and 19A (%)<sup>d</sup> |          |                     |                  |                                               |                                              |                                              |                                            |
|                      | 11 additional<sup>a</sup> serotypes/serogroups in PPV23 (%)<sup>d</sup> |          |                     |                  |                                               |                                              |                                              |                                            |
|                      | Non-vaccine serotypes/serogroups, or other (%)<sup>d</sup> |          |                     |                  |                                               |                                              |                                              |                                            |
| Subtotal<sup>d</sup> |                                                  |          |                     |                  |                                               |                                              |                                              |                                            |
| Last year of surveillance: 2002 |                                   |          |                     |                  |                                               |                                              |                                              |                                            |
| 1990–2002, Israel<sup>[14]</sup> | Quellung/bl, pl/CPP                             | 0–18 years | 11                  |                  | 4 (25.0 %)                                    | 1 (62.5 %)                                  | 5 (12.5 %)                                  |                                            |
| Subtotal<sup>d</sup> |                                                  |          |                     |                  |                                               |                                              |                                              |                                            |
| Last year of surveillance: 2009 |                                   |          |                     |                  |                                               |                                              |                                              |                                            |
| 2000–2009, Israel<sup>[69]</sup> | Quellung/bl/ pneumococcal bacteremic pneumonia with pleural effusion | <18 years | 28                  |                  | 14 (14.3 %)                                   | 1 (53.6 %)                                  | 5 (17.9 %)                                  | 19A (7.1 %)                                 |
| Subtotal<sup>d</sup> |                                                  |          |                     |                  |                                               |                                              |                                              |                                            |
| Last year of surveillance: 2009 |                                   |          |                     |                  |                                               |                                              |                                              |                                            |
| 2000–2009, Israel<sup>[79]</sup> | Not specified/pl, bl/ pneumococcal empyema       | 2 months to 18 years | 8                  |                  | 17.9 %                                       | 82.1 %                                      | 0 %                                        | 0 %                                        |
| Subtotal<sup>d</sup> |                                                  |          |                     |                  |                                               |                                              |                                              |                                            |
| Last year of surveillance: 2003 |                                   |          |                     |                  |                                               |                                              |                                              |                                            |
| 1995–2003, Taiwan<sup>[9]</sup> | Slide agglutination/bl, pl/CPP                   | 9–144 months | 19                  |                  | 14 (68.4 %)                                   | 6 (21.1 %)                                  | 23 (10.5 %)                                 |                                            |
| Subtotal<sup>d</sup> |                                                  |          |                     |                  |                                               |                                              |                                              |                                            |
| Last year of surveillance: 2004 |                                   |          |                     |                  |                                               |                                              |                                              |                                            |
| 1997–2004, Singapore<sup>[41]</sup> | Quellung/bl, pl/ invasive pneumococcal pneumonia or empyema | 3 months to 19.5 years | 62<sup>i</sup> |                  | 14 (33.9 %)                                   | 6A (8.1 %)                                  | 6B (17.7 %)                                 | 19A (4.8 %)                                 |
| Subtotal<sup>d</sup> |                                                  |          |                     |                  |                                               |                                              |                                              |                                            |
| Years, country/[ref] | Serotype assessment methodology/source/diagnosis | Isolates | Serogroups or serotypes | Age range/subgroup | Number serotyped | PCV7 serotypes/serogroups (%) | 6 additional\(^c\) serotypes/serogroups in PCV13 (%) | 11 additional\(^d\) serotypes/serogroups in PPV23 (%) | Non-vaccine serotypes/serogroups, or other (%) |
|-----------------------|--------------------------------------------------|----------|-------------------------|-------------------|-----------------|-------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Last year of surveillance: 2009** | | | | | | | | | |
| 2007–2009, Australia\([58]\) | Multiplex PCR/bl, pl/pneumococcal empyema | 0.4–15.5 months | 55\(^i\) | 14 (1.8 %) | 19A (36.4 %) | 22F/22A (3.6 %) | 6C (1.8 %) |
| | | | | 9V/A (1.8 %) | 3 (32.7 %) | | |
| | | | | | 1 (14.5 %) | | |
| | | | | | 7F/7A (3.6 %) | | |
| | Subtotal\(^d\) | | | 3.6 % | | 87.3 % | 3.6 % | 5.5 % |
| 2007–2009, Australia\([59]\) | Multiplex PCR/pl/pneumococcal empyema | ≤16 years | 29 | 9V/9A (3.4 %) | 19A (41.4 %) | 22F/22A (6.9 %) | None |
| | | | | | 3 (31.0 %) | 1 (13.8 %) | |
| | | | | | 7F/7A (3.4 %) | | |
| | Subtotal\(^d\) | | | 3.4 % | | 89.7 % | 6.9 % | 0 % |
| 2006–2009, Taiwan\([102]\) | MLST/bl, pl/pneumococcal necrotizing pneumonia | <18 years | 12 | 14 (75.0 %) | 19A (16.7 %) | None | None |
| | | | | | 3 (8.3 %) | | |
| | Subtotal\(^d\) | | | 75.0 % | | 25.0 % | 0 % | 0 % |
| 2008–2009, Taiwan\([53]\) | Quellung, multiplex PCR/bl, pl/pneumococcal empyema, or pneumococcal parapneumonic pleural effusion | <18 years/empyema | 33 | 14 (12.1 %) | 19A (42.4 %) | Unknown (24.2 %) |
| | | | | | 6B (6.1 %) | 3 (12.0 %) | |
| | | | | | | 1 (3.0 %) | |
| | Subtotal\(^d\) | | | 75.0 % | | 25.0 % | 0 % | 0 % |
| | Parapneumonic pleural effusion | | | 18.2 % | | 57.6 % | n/a | n/a |
| | | | | 6B (5.0 %) | 19A (20.0 %) | 23A (5.0 %) | |
| | | | | 14 (5.0 %) | 3 (5.0 %) | Unknown (60.0 %) | |
| | | | | 10.0 % | | 25.0 % | n/a | n/a |
| | Subtotal\(^d\) | | | 57.6 % | | n/a | n/a | n/a |
| **Last year of surveillance: 2010** | | | | | | | | | |
| 2003–2010, Korea\([54]\) | Multiplex PCR/pneumococcal empyema | 29–124.5 months | 13 | 14 (7.7 %) | 19A (46.2 %) | 34 (7.7 %) | Unknown (30.8 %) |
| | | | | | 1 (7.7 %) | | |
| | Subtotal\(^d\) | | | 7.7 % | | 53.8 % | 0 % | 38.5 % |
| 1998–2010, Taiwan\([48]\) | Quellung/bl, pl/CPP | <18 years | 31 | 14 (32.3 %) | 3 (35.5 %) | 19A (12.9 %) | 38.5 % |
| | | | | 6B (12.9 %) | 19A (12.9 %) | | |
| | | | | | 9V (6.5 %) | | |
| | Subtotal\(^d\) | | | 48.4 % | | 0 % | 0 % | 0 % |
| Years, country/[ref] | Serotype assessment methodology/source/diagnosis | Isolates | Serogroups or serotypes |
|---------------------|-------------------------------------------------|----------|-------------------------|
|                     | Age range/subgroup | Number serotyped | PCV7 serotypes/serogroups (%)<sup>a</sup> | 6 additional<sup>b</sup> serotypes/serogroups in PCV13 (%)<sup>a</sup> | 11 additional<sup>c</sup> serotypes/serogroups in PPV23 (%)<sup>a</sup> | Non-vaccine serotypes/serogroups, or other (%)<sup>a</sup> |
|                     |                    |           | Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F | Serotypes 1, 3, 5, 6A, 7F, and 19A | Serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F |
| Last year of surveillance: 2011 |
| 2007–2011, Taiwan[83] | Latex agglutination/bl, pl/pneumococcal necrotizing pneumonia, pneumococcal empyema | <18 years/necrotizing pneumonia | 13 | n/a | 19A (69.2 %)<sup>e</sup> | n/a | n/a |
|                      |                    |           | Empyema | 31 | n/a | n/a | n/a |
|                      |                    |           | n/a | 19A (71.0 %)<sup>e</sup> | n/a | n/a |
| Subtotal<sup>d</sup> |                    |           | n/a | 83.3 % | n/a | n/a |
| B. Adults | | | | | | |
| North America | | | | | | |
| Last year of surveillance: 2010 |
| 2000–2010, Texas, USA/[40] | Agglutination; Quellung/source not specified/ necrotizing pneumococcal pneumonia | Adults | 16 | 9V (12.5 %) | 3 (31.2 %) | 12F (6.2 %) | 15A (6.2 %) |
|                      |                    |           | 6B (6.2 %) | 19F (6.2 %) | 23F (6.2 %) | 6B (6.2 %) | 9N (6.2 %) |
| Subtotal<sup>d</sup> |                    |           | 31.2 % | 31.2 % | 18.8 % | 18.8 % |
| 2009–2010, Utah, USA/[82] | Not specified/bl, pl/ pneumococcal empyema | ≥18 years | 6 | n/a | 19A (50.0 %)<sup>e</sup> | 7F (33.3 %)<sup>e</sup> | n/a | n/a |
| Subtotal<sup>d</sup> |                    |           | n/a | 83.3 % | n/a | n/a |
| Europe | | | | | | |
| Last year of surveillance: 2007 |
| 2007, France[97] | Latex agglutination; multiplex PCR/pl, hospitalized patients with pneumococcal disease | ≥15 years | 12 | n/a | 19A (33.3 %)<sup>e</sup> | n/a | n/a |
| Subtotal<sup>d</sup> |                    |           | n/a | 33.3 % | n/a | n/a |
| Last year of surveillance: 2009 |
| 1996–2009, Spain[17] | Quellung/bl, pl/ pneumococcal empyema | >18 years/1996–2001 | 61 | 9V (6.6 %) | 3 (24.6 %) | 8 (6.6 %) | Other (11.5 %) |
|                      |                    |           | 14 (6.6 %) | 1 (14.8 %) | 7F (9.8 %) | | |
| Years, country/[ref] | Serotype assessment methodology/source/diagnosis | Isolates | Serogroups or serotypes | Age range/subgroup | Number serotyped | PCV7 serotypes/serogroups (%)<sup>a</sup> | 6 additional<sup>b</sup> serotypes/serogroups in PCV13 (%)<sup>a</sup> | 11 additional<sup>c</sup> serotypes/serogroups in PPV23 (%)<sup>a</sup> | Non-vaccine serotypes/serogroups, or other (%)<sup>a</sup> |
|---------------------|--------------------------------------------------|----------|-------------------------|--------------------|----------------|------------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|
|                     |                                                 |          |                         |                    |                | Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F | 19F (1.6 %) | 6A (8.2 %) | 11.5 % |                                           |
|                     |                                                 |          |                         |                    |                |                          Other PCV7 serotypes (8.2 %) | 5 (3.3 %) | 19A (3.3 %) |                                           |
|                     |                                                 |          |                         |                    |                | Subtotal<sup>d</sup> 24.6 % | 57.4 % | 6.6 % |                                           |
|                     |                                                 |          |                         |                    |                | 14 (5.0 %) | 1 (43.3 %)<sup>b</sup> | 8 (1.7 %) | Other (10.0 %) |
|                     |                                                 |          |                         |                    |                | 4 (3.3 %) | 3 (13.3 %) |                                           |
|                     |                                                 |          |                         |                    |                | 19F (3.3 %) | 7F (6.7 %) |                                           |
|                     |                                                 |          |                         |                    |                | 9V (1.7 %) | 6A (5 %) |                                           |
|                     |                                                 | 2005–2009 | 60 |                     |                |                          Other PCV7 serotypes not listed (1.7 %) | 5 (3.3 %) |                                           |
|                     |                                                 |          |                         |                    |                | Subtotal<sup>d</sup> 15.0 % | 73.3 % | 1.7 % | 10.0 % |
|                     |                                                 |          |                         | 2006–2009, Spain/[39] | Multiplex real-time PCR/bl, pl, sp/CPP | Adults | 52 | 14 (7.7 %) | 1 (32.7 %) | 9A (1.9 %) |                                           |
|                     |                                                 |          |                         |                    |                | 4 (3.8 %) | 19A (21.2 %) | 10A (1.9 %) | 31 (1.9 %) |
|                     |                                                 |          |                         |                    |                | 9V (3.8 %) | 3 (9.6 %) | 5 (5.8 %) | 6A (1.9 %) |                                           |
|                     |                                                 |          |                         |                    |                | Subtotal<sup>d</sup> 15.4 % | 73.1 % | 7.7 % | 3.8 % |
|                     |                                                 |          |                         | Last year of surveillance: 2010 | Dot blot; Quellung/bl, pl/pneumococcal empyema | 18–64 years | 68 | 19F (4.4 %) | 1 (25.0 %) | 8 (2.9 %) | 23A (2.9 %) |
|                     |                                                 |          |                         |                    |                | 23F (4.4 %) | 3 (11.7 %) | 22 (2.9 %) | Other (16.2 %) |
|                     |                                                 |          |                         |                    |                | 4 (2.9 %) | 7F (5.9 %) |                                           |
|                     |                                                 |          |                         |                    |                | 6B (2.9 %) | 5 (44 %) |                                           |
|                     |                                                 |          |                         |                    |                | 9V (2.9 %) | 19A (4.4 %) |                                           |
|                     |                                                 |          |                         |                    |                | 18C (2.9 %) | 6A (2.9 %) |                                           |
|                     |                                                 |          |                         |                     | n/a<sup>f</sup> |                       | 54.4 % | n/a<sup>f</sup> | 19.1 % |
|                     |                                                 |          |                         | 2006–2010, Spain/[89] | Latex agglutination/bl, pl, br/pneumococcal empyema | Adults (age range not otherwise specified) | 4 | 1 (50.0 %) | 3 (25.0 %) | 19A (25.0 %) |                                           |
|                     |                                                 |          |                         |                    |                | Subtotal<sup>d</sup> 0 % | 100 % | 0 % | 0 % |

<sup>a</sup> Percentage of isolates.

<sup>b</sup> Percentage calculated from the PCV13 serotypes.

<sup>c</sup> Percentage calculated from the PPV23 serotypes.

<sup>d</sup> Subtotal for each year.

<sup>e</sup> Data not available.

<sup>f</sup> Not applicable.
| Years, country/[ref] | Serotype assessment methodology/source/diagnosis | Isolates | Serogroups or serotypes |
|----------------------|-----------------------------------------------|----------|------------------------|
|                      |                                               |          |                        |
|                      |                                               |          | PCV7 serotypes/serogroups (%)<sup>a</sup> | 6 additional<sup>b</sup> serotypes/serogroups in PCV13 (%)<sup>a</sup> | 11 additional<sup>c</sup> serotypes/serogroups in PPV23 (%)<sup>a</sup> | Non-vaccine serotypes/serogroups, or other (%)<sup>a</sup> |
|                      |                                               |          | 0–65 years             | Number serotyped | Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F | Serotypes 1, 3, 5, 6A, 7F, and 19A | Serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F | Other (10.5 %) |
| 1996–2000, India[81] | Co-agglutination/bl, pl/pneumococcal empyema  | 19       | 23 (5.3 %)             | Other (10.5 %)  | 1 (47.4 %)                                  | 5 (10.5 %)                          | 3 (5.3 %)                               | 63.2 %       |
|                      |                                               |          |                        | Other (10.5 %)  |                                           |                                   |                                        |              |
|                      |                                               |          |                        |                  |                                           |                                   |                                        |              |
|                      |                                               |          |                        |                  |                                           |                                   |                                        |              |
|                      |                                               |          |                        |                  |                                           |                                   |                                        |              |
| Subtotal<sup>f</sup> |                                               | 5.3 %    | 63.2 %                 | n/a             | n/a                                        | n/a                                | n/a                                    |              |

bl, blood; br, bronchoscopy; CPP, complicated pneumococcal pneumonia; CSF, cerebrospinal fluid; lt, lung tissue; MLST, multilocus sequence typing; n/a, not applicable; NG, no growth during serotyping; NT, non-typeable; PAD, pneumococcal antigen detection via immunochromatography; PCR, polymerase chain reaction; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; pl, pleural fluid; PPV23, 23-valent pneumococcal polysaccharide vaccine; RT-PCR, reverse transcriptase PCR; sp, sputum

<sup>a</sup> %=number of samples with a given serotype, divided by the number of samples serotyped, among patients with a given diagnosis

<sup>b</sup>Serotypes in addition to those in PCV7

<sup>c</sup>Serotypes in addition to those in PCV7 and serotypes 1 and 3, which are in PCV13

<sup>d</sup>Subtotal percentages were calculated based on the number of cases for a given serotype category divided by the number serotyped. Due to rounding, subtotals may not equal the sum of the percentages, and the subtotals in each row may not add up to 100

<sup>e</sup>Other serotypes not reported

<sup>f</sup>Insufficient pleural fluid available for testing

<sup>g</sup>One specimen had two serotypes (4 and 23F)

<sup>h</sup>Vaccinated with PCV7

<sup>i</sup>Includes both pneumonia and empyema

<sup>j</sup>Three specimens had two serotypes each (19A and 3, 19A and 1, 6C and 15F)

<sup>k</sup>p<0.001 for increase
2006), serotype 3 was the most frequent cause of pneumococcal necrotizing pneumonia (28.9 %; 11/38 cases), whereas serotype 1 (22.6 %; 28/124 cases) was predominant in uncomplicated pneumococcal pneumonia [35]. Conversely, among children with community-acquired invasive pneumococcal pneumonia (IPP) (i.e., pneumonia with S. pneumoniae isolated from blood or pleural fluid) in Italy (2007–2009), serotype 1 caused a significantly higher percentage of CPP than uncomplicated pneumonia (50 % vs. 18.2 %; p=0.005) [32]. In children aged <18 years in Taiwan (1998–2010), the proportions of cases of CPP caused by PCV7 and non-PCV7 serotypes were similar (51.6 % and 48.4 %, respectively), and serotypes 14 and 3 were the most common serotypes (32.3 % and 35.5 % of cases, respectively). Serotype 3 was the most common serotype causing CPP compared with uncomplicated lobar pneumonia (OR, 0.114; 95 % confidence interval [CI], 0.013–0.973) [48].

In children with any-cause empyema in the UK (2002–2009), S. pneumoniae was the most frequently isolated organism, found in 44 of 70 children (62.9 %) from whom an organism was identified [62]. Serotype 3 was significantly more common in pneumococcal bronchopleural fistula (10/13 cases) compared with no fistula (1/15 cases) (p<0.0001), whereas serotype 1 was the most common serotype among cases without fistula (7/15 cases) and was not found among those with fistula [62]. In children in England with cavitory disease complicating PnEmp or pneumococcal parapneumonic effusion, the most common serotypes were 1 (4/11 cases, 36.4 %) and 3 (3/11 cases, 27.3 %) [55].

Among Spanish adults (2006–2009), serotype 1 was the most frequent cause of CPP (32.7 %) and uncomplicated pneumococcal pneumonia (31.2 %); the other frequent causes of complicated pneumonia, in descending order of frequency, were serotypes 19A, 3, 14, 5, and 12F (Table 3) [39]. In adults in the USA with pneumococcal pneumonia (n=351), serotype 3, the most common cause of pneumonia overall, was isolated in 5 of 16 specimens (31.2 %) from patients with pneumococcal necrosis; 10 other serotypes caused the remaining 11 cases (Table 3) [40].

Serotype 1 undergoes periodic outbreaks, so it is possible that increases in serotype 1 PnEmp may be associated with a cyclic pattern [87]. Serotype 1 clones were analyzed in PnEmp among children [31, 87, 101] and adults [47]. Multilocus sequence typing (MLST) analysis of pediatric PnEmp cases in Utah (USA) suggested that replacement sequence types (STs) contributed to the increase in incidence of pediatric PnEmp post-PCV7 [31]. Before 2001, only ST227 (serotype 1) was identified; by 2003, six additional STs were associated with serotype 1, including a single-locus variant of ST227. In contrast, among serotype 1 isolates causing pediatric PnEmp in Spain (2004–2006), three clones were identified (ST228, ST306, and ST304); these were historically well-established clones [101]. A more recent study of pediatric PnEmp in Spain (2003–2006) identified the same three serotype 1 clones in pleural fluid [87]. MLST types associated with the increased incidence of pediatric PnEmp had been present previously in Spain and elsewhere in Europe, and, therefore, the increase in proportions of PnEmp (predominantly serotype 1) was probably not associated with the emergence of new clones or of capsular switching [87, 101]. For adults in Spain (1996–2010), an increase in PnEmp incidence in otherwise healthy adults with pneumonia was associated predominantly with serotype 1, in particular, ST306 [47].

Antibiotic resistance

Antibiotic sensitivity data are available from CPP isolates, which are predominately the serotypes 14, 1, and 19A; among these three predominant PCV13 serotypes, only 19A tends to be associated with antibiotic resistance (probably due to its relationship with nasopharyngeal carriage).

Among children in Utah (USA) (1993–1999), PnEmp was less likely than uncomplicated pneumococcal pneumonia to be caused by penicillin-resistant pneumococci (16 % vs. 48 %; p=0.0021); all serotype 1 isolates were penicillin-susceptible [30]. For pediatric CPP in Tennessee (USA) (1996–2001), all serotype 1 isolates (n=5) were susceptible to penicillin, whereas 5 of 7 serotype 14 isolates (the most frequently identified isolate in this sample) were penicillin-resistant [7]. (By contrast, in eight children’s hospitals in the USA (1993–2000), the antibiotic resistance rates were similar among isolates from CPP and uncomplicated pneumococcal pneumonias [34].)

Serotype 19A is associated with reduced sensitivity to antibiotics [15, 53, 83, 90]. In Spain, 11 % of cases of pediatric PnEmp were caused by serotype 19A; all three culture-positive serotype 19A isolates were non-susceptible to cefotaxime, and two were also non-susceptible to parenteral penicillin [90]. Other serotypes isolated in this study (1, 5, and 7F) were susceptible to parenteral beta-lactams and showed low rates of resistance to oral penicillin and erythromycin. In another Spanish study (2003–2006), 8 of 27 pneumococcal isolates from pediatric PnEmp showed reduced susceptibility to penicillin; two serotype 19A isolates and one each of serotypes 14 and 3 showed resistance to multiple antibiotics [15]. Similarly, in Taiwan (2007–2011), serotype 19A isolates from pediatric PnEmp had lower levels of susceptibility to cefotaxime than non-19A isolates, although the 19A and non-19A isolates had similar susceptibility to other antibiotics [83]. In Taiwanese children with empyema (2008–2009), 4 of 8 pneumococcal isolates were penicillin-resistant (i.e., serotypes 19A [n=3] and 14 [n=1]) [53].

Several studies evaluated the association of pneumococcal conjugate vaccine introduction with antibiotic resistance among pneumococcal serotypes associated with CPP or PnEmp. In Israel (1990–2002), no penicillin-resistant pneumococci were
isolated from pediatric CPP [14], whereas in Taiwan (1995–2003), more pneumococcal isolates from pediatric CPP than from lobar pneumonia were immediately susceptible or resistant to penicillin [9]. In a subsequent study (1996–2005), the penicillin resistance rates in PnEmp declined from 21 % to 12 % (p=0.3) following PCV7 introduction [73]. Similarly, in Spain (2005–2009), all pneumococcal isolates (n=34) from pediatric PnEmp were susceptible to penicillin [88].

In Spanish adults (2001–2009), significantly higher proportions of penicillin-susceptible isolates (p=0.013) were identified from CPP compared with uncomplicated pneumococcal pneumonia, which was associated with a higher rate of erythromycin resistance (p=0.033) [74]. Among adults in Spain with IPP, antibiotic resistance decreased and antibiotic susceptibility increased between 1996–2001 and 2005–2009, significantly so for penicillin (p=0.01) [63]. Likewise, among adults with IPP in Spain (1996–2009), the proportion of cases caused by penicillin-susceptible pneumococcal strains increased from 71.7 % to 80.3 % (p=0.012), and susceptibility to other antibiotics also trended upward [17].

Effect of age on serotype epidemiology

Age-based differences were observed in pneumococcal serotype proportions. In France (2007), both serotypes 1 (5/10 isolates) and 19A (5/10 isolates) were uniquely isolated from pleural fluid in children with IPD, whereas from pleural fluid in adults, the most frequent was serotype 19A (4/12 isolates) [97]. In Spanish studies, serotype 1 was associated with IPD in older children, whereas serotype 19A predominated in younger children [44, 49, 87, 90]. In Spain (2007–2009), among children aged 3–59 months with IPD, serotype 1 was the most frequent cause of PnEmp (24.9 % of all cases), and serotype 1 IPD was significantly more common in children aged 24–59 months than those aged 3–23 months (adjusted OR, 7.70; 95 % CI, 2.12–10.38) [44]. Serotype 19A-related IPD was noted to be more common among children aged <24 months, although the proportion of cases with PnEmp in this age group was not specified, and serotype 19A was also associated with PnEmp (14.3 % of all cases). In another Spanish study (2003–2006), serotypes 1, 5, 7F, and 14 (i.e., serotypes with higher invasive disease potential) were more frequent causes of PnEmp in older children (median ages 56 months vs. 24 months; p=0.0001) compared with serotypes 6A, 9V, 19A, and 23F (i.e., serotypes with low invasive disease potential) [87]. This pattern was also evident in pediatric pneumonia in Italy (2007–2009): serotype 1 was only detected in children aged >2 years and was the predominant serotype associated with CPP (50 % of cases), whereas serotype 19A was significantly associated with younger age [32]. In Spanish children with PnEmp (2007–2009), serotype 1 was more common in children aged >36 months, serotype 3 was more common in children aged 24–36 months, and serotype 19A was more common in children aged <24 months [90]. More recently, in a Spanish study of children aged <15 years with PnEmp (2007–2012), the median overall age (52.0 vs. 44.0 months; p=0.028) and the age of children with serotype 1 disease (74.0 vs. 49.5 months; p=0.002) was significantly higher one year after the introduction of PCV13 (2011–2012) compared with 2007–2010 [49].

Discussion

The reported proportion of cases of CPP and PnEmp has increased over the past several decades. For example, among children aged <18 years with IPD in Utah (USA), the most common form of IPD had been bacteremia without focus (37 %) during 1997–2000, whereas by 2001–2010, CPP became the most common form of IPD (33 %); the proportion of CPP increased from 17 % (22/128 cases) to 33 % (127/385 cases) (p<0.001) [18]. Among hospitalized children with IPD in Barcelona (Spain), the mean number of cases of PnEmp increased significantly from 1998–2001 to 2002–2005 (15 vs. 43, respectively; p<0.02) [101].

Serotypes 1, 19A, 3, 14, and 7F predominated as causes of CPP and empyema. For example, in the USA (1993–2000), the most frequent serotypes causing pediatric CPP were serotypes 14 (29.1 %) and 1 (24.4 %) [34]. In another study in the USA (1996–2001), serotypes 14 (35.0 %), 1 (25.0 %), and 19A (15.0 %) were the most frequent causes of CPP [7]. In a study in Italy among children with CPP (n=35), serotypes 1 (50.0 %), 3 (13.9 %), and 19A (11.1 %) predominated [32].

After the introduction of PCV7 into pediatric immunization programs, several studies reported increases in the proportion of CPP caused by non-PCV7 serotypes, particularly serotypes 1, 3, 7F, and 19A [17, 18, 31, 35, 50, 52]. In Barcelona (Spain), the proportion of serotype 19A pediatric PE increased from none (0/7) in 1997–2001, to 1/13 cases (8 %) during 2002–2004, to 6/34 cases (18 %) during 2005–2007; these data also reflect an increase in the overall number of pediatric PnEmp cases [86]. PCV7 serotypes and non-PCV7 serotypes caused similar proportions of cases of CPP (51.6 % and 48.4 %, respectively) in children in Taiwan during a period (1998–2010) when PCV7 immunization rates were low (i.e., in 2007, 15.9 % of children aged <5 years had received ≥1 dose), although serotype 3 was significantly more likely to cause CPP compared with lobar pneumonia [48]. While fewer data are available for PnEmp in adults, a Spanish study reported significant increases from 1996–2001 to 2005–2009 in the PnEmp incidence (0.5 to 1.6 cases/100,000 population; p<0.001) and the serotype 1 PnEmp incidence (0.1 to 0.8 cases per 100,000 population; p<0.001) in adults aged 18–50 years [17]. In England, the serotype 19A incidence for pediatric CPP increased significantly from 0.48 to 2.02 per
1,000,000 children from 2006–2007 to 2010–2011 (incidence rate ratio, 4.17; 95 % CI, 1.53–14.2) [94].

Although in some studies the emergence of serotypes 1, 19A, 3, and 14 in CPP and PnEmp has corresponded to the years following the introduction of PCV7 [17, 18, 31, 35, 50, 52, 86], a few studies demonstrated that their increasing role in CPP and PnEmp began prior to the introduction of PCV7 [28, 29, 68]. For example, in a study of IPD in Spain (1989–2008), the proportion of cases of IPD caused by serotype 1 was increasing prior to the introduction of PCV7, and this trend continued after the introduction of PCV7 (2 %, 8.6 %, 14.9 %, and 23.8 % of cases in 1989–1993, 1994–1998, 1993–2003, and 2004–2008, respectively [p<0.001]) [68]. This suggests that emergence involves more than simply serotype replacement following PCV7 introduction; characteristics particular to certain serotypes, such as differences in antibiotic sensitivity or their propensity to cause pleural infection, may be responsible for these increases. In addition, several studies established a relationship between the proportion of CPP and age that contrasts with the age-specific incidence of IPD [32, 40, 44, 49, 87, 90, 97], which may suggest an interaction between the propensity of given serotypes to infect and the age-dependent susceptibility of patients to infection by these same serotypes.

Recent data suggest that PCV13 may impact on pediatric PnEmp caused by serotypes associated with CPP, such as 1 and 19A. In Spain, where PCV13 was introduced in 2010, the incidence of pediatric PnEmp caused by serotypes targeted by PCV13 declined significantly from 2009–2010 to 2010–2011 (5.52 vs. 3.55 per 100,000 population; p=0.049), mainly due to reductions in serotypes 1 (2.81 vs. 2.07 per 100,000 population) and 19A (1.51 vs. 0.69 per 100,000 population) [46]. More recently, in children aged <15 years in Spain, the PnEmp incidence declined significantly (p=0.0019) from 5.72 to 3.12 per 100,000 population in, respectively, 2007–2010 and 2011–2012, while the median age of children with PnEmp was greater in 2011–2012 (i.e., following PCV13 introduction) than 2007–2010 (47.0 vs. 42.0 months; p=0.032) [49].

Although this review has recapitulated the basic epidemiology of CPP (including PnEmp) over the past several decades, the increased use of more specific diagnostic imaging (e.g., CT and ultrasound) in recent years may affect the reported rate of PE and empyema because of the more accurate identification. Improved diagnostic methodologies, clinical (ultrasound or CT vs. physical examination or chest X-ray) and microbiological (e.g., PCR vs. culture), as well as increased awareness of and vigilance for PE and empyema may have resulted in an apparent increase in the proportion of CPP over the time period included in this analysis, which, given the limitations of the retrospective nature of this analysis, may be a confounding factor in the determination of any true increase in the proportion of CPP.

This review is also limited by the fact that many of the studies used culture to identify pathogens. Culture may be less than ideally sensitive to the presence of specific pathogens because of factors such as prior antibiotic use or other difficulties in culturing pathogens. In recent years, PCR has been applied to identify the pneumococci causing CPP and to identify serotypes in culture-negative specimens [32, 59, 64, 84, 87, 93]. As antibiotic treatment may reduce the likelihood of detecting bacteria via culture, PCR is useful in detecting pneumococci in culture-negative samples from patients previously treated with antibiotics. For example, in a Spanish study of culture-negative pleural fluid specimens from children with empyema, PCR typing identified eight different serotypes (i.e., serotypes 1, 3, 5, 7F/7A, 8, 14, 19A, and 19F/B/C) in 52 of 67 culture-negative pleural fluid samples from children with PnEmp, with a sensitivity of 96.0 % and a specificity of 98.6 % [93]. Spanish pediatric empyema patients with S. pneumoniae culture-negative/PCR-positive samples were found to be significantly more likely to have received antibiotics than those with culture-positive samples (92 % vs. 53 %, respectively; p<0.0001) [87]. Rapid pneumococcal antigen detection by means of immunochromatography has also been used to detect pneumococci in isolates from patients with empyema [51]. In hospitalized children with parapneumonic effusion, conventional microbiologic culture of pleural fluid samples detected pneumococci in 15 of 55 isolates, real-time PCR detected pneumococci in 13 of 16 culture-negative isolates (81.2 %), and immunochromatographic testing detected pneumococci in 24 of 27 culture-negative isolates (88.9 %) [51]. Such molecular methods may complete the information available on changes in the IPD and CPP serotype epidemiology over time.

Finally, most of the studies reviewed here used retrospective database analyses to identify cases of CPP and PnEmp. The specificity of information in these databases could vary, as cases may have been missed due to misclassification. In recent years, increased awareness of CPP and PnEmp has led to prospective surveillance studies, which may enhance disease identification. In addition, studies used different breakpoints to determine penicillin sensitivity, making it difficult to compare antibiotic resistance results.

In conclusion, the reported proportion of cases of CPP and PnEmp due to non-PCV7 serotypes has increased over the past several decades in countries that introduced PCV7 into the pediatric immunization program. Whether this increase reflects the advent and wider use of more specific diagnostic methods and increased awareness due to research initiatives, or if it, indeed, represents a true increase in disease incidence, is unclear. Several factors may account for these greater proportions, including enhanced disease detection due to a higher index of suspicion and more sophisticated diagnostic assays, as well as the prevalence of certain non-PCV7 serotypes that are capable of invading the pleural space.

It is established that reductions in the proportion of PCV7 serotype CPP have been observed in countries using PCV7.
Most serotypes associated with CPP and PnEmp—particularly serotypes 1, 19A, 3, and 7F—are targeted by PCV13, which was registered for pediatric vaccination from 2009 and for adult vaccination from 2011. Early reports suggest declines in the incidence and proportion of cases of vaccine serotype CPP post-PCV7 introduction, and then further with PCV13, although studies are ongoing.

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