Pneumonia is an inflammatory disease of the lung, responsible for high morbidity and mortality worldwide. It is caused by bacteria, viruses, fungi, or other microorganisms. *Streptococcus pneumoniae*, a gram-positive bacterium with over 90 serotypes, is the most common causative agent. Moreover, comorbid factors including heart failure, renal disease, and pulmonary disease could increase the risk of pneumococcal pneumonia. Since the advent of the pneumococcal vaccine in the 1980s, the incidence of pneumonia has decreased significantly. However, current vaccines confer only limited protection against serotypes included in the vaccine. Thus, to overcome this limitation, new types of pneumococcal vaccines have been sought and under clinical trials. In this review, we discuss pneumonia and summarize the various types of pneumococcal vaccines in progress.

**Keywords** Pneumonia · *Streptococcus pneumoniae* · Pneumococcal vaccine

**Introduction**

In 2015, a World Health Organization (WHO) report showed that respiratory diseases including lower respiratory infections, chronic obstructive pulmonary disease (COPD), trachea/bronchus/lung cancers, and tuberculosis, comprised 4 of the top 10 causes of death in the world. In addition, lower respiratory infections, which are the deadliest communicable diseases, are the leading cause of death in low-income economies (WHO 2017a). According to the WHO and Europe Detailed Mortality Databases, respiratory diseases were responsible for 15% of deaths in the European Union (EU), with pneumonia being the leading cause.

Pneumonia is one of the leading causes of death (Jackson et al. 2004), and a common cause of sepsis, responsible for 50% of all episodes. Most people recover from pneumonia or do not exhibit the symptoms anymore. However, it can be a life-threatening for those with weak or compromised immune systems including infants, young children, the elderly, and people suffering from other chronic diseases (Lynch and Zhanel 2009). For example, hospital-acquired pneumonia has a particularly high mortality rate (ERS 2017). Moreover, most deaths during the post-neonatal stage (1–59 months) occur because of pneumonia (WHO 2017b). To reduce mortality rates worldwide, vaccination with the pneumococcal vaccine is highly recommended because *S. pneumoniae* is the most common causative agent of pneumonia (Musher and Thorner 2014). Thus, many types of pneumococcal vaccines have been developed and are undergoing clinical trials. However, no studies have examined pneumococcal vaccines that have been studied or investigated at the clinical trial stage. In this review, we summarize information regarding pneumonia, its causative agent, and the preventive pneumococcal vaccine.

**Pneumonia**

Pneumonia is a respiratory infection that accounts for high morbidity in young and old individuals with weakened immune systems (Fry et al. 2005). In addition, the presence of chronic underlying conditions contribute to a marked
increase in pneumonia risk with age (Jackson et al. 2004; Fry et al. 2005).

The most common pneumonia is community acquired pneumonia (CAP) (Musher and Thorner 2014), which is caused by bacteria, viruses, and less commonly by fungi or other microorganisms (MayoClinic 2017). Unlike hospital-acquired pneumonia, which is acquired during or after hospitalization for other diseases, CAP can also be acquired by non-hospitalized individuals. *S. pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, influenza virus, and pulmonary diseases including lung cancer are the main causative agents of pneumonia. *Pseudomonas aeruginosa*, *Pneumocystis jirovecii*, *Moraxella catarrhalis*, and other gram-negative bacteria are less common causative agents (Musher and Thorner 2014). Prior to the use of antibiotics, more than 75% of pneumonia cases were caused by *S. pneumoniae* (Musher and Thorner 2014). However, recent studies have revealed that only 5 to 15% of pneumonia cases in the United States (US) are caused by *S. pneumoniae* (Restrepo et al. 2008; Jain et al. 2015), whereas, in some other countries, *S. pneumoniae* is responsible for a higher proportion of cases (Musher and Thorner 2014; Gadsby et al. 2016).

Pneumonia shows a high incidence rate in hospitalized patients, older outpatients, and men of all ages (Jackson et al. 2004). In addition, there are various risk factors for pneumonia, including smoking, diabetes, heart failure, lung cancer, renal disease, COPD, and viral infection. For example, CAP incidence rates have coincided with influenza virus epidemics (Carvalho et al. 2009; Sheng et al. 2011). National statistical data also shows that the CAP pattern closely reflected the temporal pattern of death percentages attributed to pneumonia and influenza in the US (Jackson et al. 2004).

There are many pneumonia treatments available, such as antibiotics, breathing treatments, and oxygen therapy (Korsgaard et al. 2005; van der Poll and Opal 2009). However, people with weak immune systems are likely to have complications such as respiratory failure, uncontrolled inflammation (i.e., sepsis), and lung abscesses (CDC 2017). In addition, the emergence of antibiotic resistant strains is considered a serious problem (Kaplan and Mason 1998; Picazo 2009). Thus, preventing pneumonia occurrence through vaccination is important. Indeed, the pneumococcal vaccine and seasonal flu vaccine are recommended for all children and adults (KSID 2014).

The pneumococcal vaccine has been commercially available since 1983, and its use has reduced the burden of pneumococcal disease among children and the elderly. Moreover, the decline of CAP caused by pneumococcus in the US was due to universal pneumococcal vaccination in adults and children (Musher 2016). Thus, the Advisory Committee on Immunization Practices (ACIP) recommends pneumococcal vaccination for immunocompromised adults (Kim et al. 2017; Robinson et al. 2017) as for prevention of pneumonia.

### S. pneumoniae

*S. pneumoniae* is a gram positive bacterium with over 90 serotypes (Kalin 1998). Until recently, 92 serotypes were identified (Kapatai et al. 2016). *S. pneumoniae* have been known as the most common cause of CAP (Steel et al. 2013; Bewick et al. 2012) and causative agent of pneumococcal diseases such as otitis media, meningitis, and bacteremia (Bogaert et al. 2004). *S. pneumoniae* can colonize the nasopharynx asymptomatically, but is one of the leading causes of high mortality and morbidity in infants, the elderly, and immunocompromised people (Black et al. 2010; Wunderink and Waterer 2014).

Specific serotypes may colonize the nasopharynx and become prevalent, depending on their invasiveness, indirectly reflecting epidemiologic changes (Flasche et al. 2011). In *S. pneumoniae*, many virulence factors could contribute to colonization and development of pneumococcal diseases (Kadioglu et al. 2008). Bacterial and host factors contributing to colonization have been defined in animal models (Kadioglu et al. 2008). In a mouse acute pneumonia model, pneumolysin (Ply) was an essential factor for bacterial survival in the respiratory tract (Kadioglu et al. 2008). Other virulence factors such as PspA, LytA, PsaA, PiaA, and NanA also play a leading role in respiratory tract infection and pneumonia (Kadioglu et al. 2008).

Pneumolysin, a cytolytic toxin, is a well-known virulence factor of *S. pneumoniae*. It functions as a Toll-like receptor ligand, activates the complement pathway, and stimulates various inflammatory cytokines (Hirst et al. 2004). LytA, also known as autolysin, digests the cell wall and releases pneumolysin and other cellular contents (van der Poll and Opal 2009). Moreover, it inhibits C3 convertase formation (Andre et al. 2017). PsaA, pneumococcal surface antigen A, is involved in metal ion uptake, which leads to protection from oxidative stress (Kadioglu et al. 2008). PiaA, pneumococcal iron acquisition A, is another component of the ATP-binding cassette transport system and is involved in the acquisition of iron for bacterial growth (van der Poll and Opal 2009). Finally, NanA, a neuraminidase that is also known as sialidase, cleaves the terminal sialic acid, which promotes adhesion and colonization (Kadioglu et al. 2008). This molecule also deglycosylates complement components to evade the host complement pathway (Andre et al. 2017).
Factors increasing pneumonia risk in pneumococcal infections

Influenza virus, respiratory syncytial virus, parainfluenza virus, adenovirus, and coronavirus are commonly detected in patients with CAP, but it may be unclear to what extent any of these organisms are causing the disease or have predisposed the patient to secondary bacterial infection (Johnstone et al. 2008; Pavia 2013).

When influenza A virus is serially infected with bacteria, its lethality is increased (Mina and Klugman 2013). For example, pneumococcal coinfection was responsible for high mortality during the 2009 H1N1 pandemic (Monsalvo et al. 2011). Moreover, it has been reported that influenza virus coinfection comprises 22% of CAP cases (Michelow et al. 2004).

Although influenza virus and pneumococcus coinfection is responsible for higher mortality and morbidity, the current pneumococcal conjugate vaccine does not provide sufficient protection in the serial coinfection model (Metzger et al. 2015). Therefore, the development of a new type of vaccine, which can protect against influenza virus and pneumococcus coinfection, is required.

Pneumococcal vaccine

The pneumococcal vaccine is divided into whole cell vaccine and subunit. Whole cell vaccine included live attenuated vaccine and inactivated vaccine, and subunit vaccine included polysaccharide vaccine, conjugate vaccine and protein based vaccine. Commercially available pneumococcal vaccines are belonging in subunit vaccine. PPV23 and PCV13 is available pneumococcal vaccine in the marker in recent. Pediatric pneumococcal disease incidence was already successfully reduced after the introduction of the conjugate pneumococcal vaccine (Vila-Corcoles and Ochoa-Gondar 2013). However, current pneumococcal vaccine usage increases prevalence of pneumococcal diseases induced by serotypes not included in the vaccine (Flannery et al. 2006; Croucher et al. 2013). In addition, pneumococcal disease in the elderly remained a considerable burden, despite PPV23 vaccination. Thus, immunization with both the PCV13 and PPV23 vaccines is recommended in the elderly (Hayward et al. 2016) to overcome the disadvantages of each vaccine (Table 1). Indeed, combination of current pneumococcal vaccines produces a superior immune response than PPV23 alone. For this reason, the ACIP has recommended serial vaccination of the elderly with PCV13 and PPV23 since 2014 (Kobayashi et al. 2015). Therefore, new potential vaccines that effectively protect against pneumonia have been investigated (Table 2) and are undergoing clinical trials (Table 3).

### Whole cell vaccine

**Live attenuated vaccine**

An attenuated or weakened form of the pathogen is used as a vaccine. Currently available live vaccines are the most cost effective (Minor 2015). In rare cases, the live attenuated vaccine strain can revert to its virulent wild type, causing severe disease (Pliaka et al. 2012). However, whole cell vaccines are superior to provide protection against various pneumococcal serotypes, as demonstrated by live attenuated mucosal vaccine (Wu et al. 2014; Roche et al. 2007; Kim et al. 2016).

**Inactivated vaccine**

The inactivated vaccine is made by treating pathogens with chemicals or physical processes. Compared to live attenuated vaccines, inactivated vaccines are safer (McConnell and Pachon 2010). Inactivated whole cell vaccine could confer effective protection against lethal pneumococcal challenge demonstrated by reduced colonization or higher survival rate (Choi et al. 2013; Moffitt et al. 2012; Hvalbye et al. 1999).

| Table 1 | Comparison of PPV23 and PCV13 |
|---------|-------------------------------|
| Efficacy | Limitation                     |
| **PPV23 (polysaccharide vaccine)** | Coverage of 23 serotypes       |
|         | Effectiveness against invasive pneumococcal diseases (IPD) | Poor immunogenicity |
|         | Minimizing the severity of Pneumonia | Poor Effectiveness against pneumococcal pneumonia prevention |
| **PCV13 (conjugate vaccine)** | Higher immunogenicity than PPV23 |
|         | Effectiveness against pneumonia | Coverage of 13 serotypes only |
|         | Effectiveness against invasive pneumococcal diseases (IPD) | High cost |

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| Vaccine                                              | Vaccine type                      | Protection                                                                 | Reference                                      |
|------------------------------------------------------|-----------------------------------|---------------------------------------------------------------------------|-----------------------------------------------|
| Whole cell vaccine                                   | Live attenuated vaccine           | IgA/IgG/colonization/survival/serotype independent                        | Roche et al. (2007)                           |
|                                                      |                                    | Immunization route; intranasal                                             |                                               |
|                                                      |                                    | IgA/IgG/colonization/survival/serotype independent cellular immune response | Kim et al. (2016, 2012)                       |
|                                                      |                                    | Immunization route; intranasal                                             |                                               |
|                                                      |                                    | IgG/colonization/survival/serotype independent cellular immune response   | Wu et al. (2014)                              |
|                                                      |                                    | Immunization route; Intranasal/adjuvant                                   |                                               |
|                                                      | Inactivated vaccine                | IgA/IgG/colonization/survival/serotype independent                        | Hvalbye et al. (1999)                         |
|                                                      |                                    | Immunization route; Intranasal/adjuvant & no adjuvant                     |                                               |
|                                                      |                                    | IgG/colonization/serotype Independent/Th17 response                      | Moffitt et al. (2012) and Lu et al. (2010)    |
|                                                      |                                    | Immunization route; subcutaneously/adjuvant                               |                                               |
|                                                      |                                    | Colonization/survival                                                     | Choi et al. (2013)                            |
|                                                      |                                    | Immunization route; Intranasal/adjuvant                                   |                                               |
| Trivalent conjugate of fusion protein (PsaA, Ply) with cell wall polysaccharide | Conjugate vaccine                | IgG/colonization/IL-17 response/survival/serotype Independent            | Lu et al. (2009)                              |
|                                                      |                                    | Immunization route; Intranasal/adjuvant                                   |                                               |
| Pneumococcal surface protein (PspA)                  | Recombinant protein vaccine        | IgA, IgG/survival/serotype independent/clinical trials (Phase I)         | Briles et al. (2000, 1996)                    |
|                                                      |                                    | Immunization route; subcutaneously/adjuvant                               |                                               |
|                                                      |                                    | Colonization/survival/serotype independent                                | Glover et al. (2008)                          |
|                                                      |                                    | Immunization route; subcutaneously/adjuvant                               |                                               |
|                                                      |                                    | Survival/serotype independent                                             | Daniels et al. (2010)                         |
| Trivalent protein antigen (PcsB, StkP)               | Recombinant protein vaccine        | IgA, IgG/survival/serotype independent/clinical trials (Phase I)         | Giefing et al. (2008)                         |
|                                                      |                                    | Immunization route; subcutaneously/adjuvant                               |                                               |
| Trivalent protein antigen (PcsB, StkP, PsaA, PspA)   |                                    | IgA, IgG/colonization                                                     | Olafsdottir et al. (2012)                     |
|                                                      |                                    | Immunization route; subcutaneously/adjuvant                               |                                               |
| Trivalent protein antigen (PcpA,PhpD, PlyD1)         |                                    | IgG/survival/colonization/serotype independent                           | Verhoeven et al. (2014)                       |
|                                                      |                                    | Immunization route; intramuscular/adjuvant                                |                                               |
| Pneumolysin (Ply)                                    | Recombinant protein vaccine        | IgG/survival/colonization/survival/serotype independent                   | Ogunniyi et al. (2001)                        |
|                                                      |                                    | Immunization route; intraperitoneal/adjuvant                              |                                               |
|                                                      |                                    | IgG/survival/colonization/survival/serotype independent                   | Briles et al. (2003)                          |
### Table 3 Pneumococcal vaccine in clinical trials (As of 2017, April)

| Name                  | Composition                                                                 | Institute                                      | Status         | ClinicalTrials.gov Identifier |
|-----------------------|-----------------------------------------------------------------------------|-----------------------------------------------|----------------|------------------------------|
| V114                  | 15-valent polysaccharides conjugate vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F + CRM197 protein) | Merck Sharp & Dohme Corp.                     | Phase 2 complete | NCT01513551                  |
| V114 w/Alum           | 15-valent polysaccharides conjugate vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F + CRM197 protein) | Merck Sharp & Dohme Corp.                     | Phase 2 complete | NCT01215188                  |
| Whole cell vaccine (SPWCV) w/Alum | Killed, nonencapsulated S. pneumoniae                                   | PATH                                          | Phase 1 complete | NCT01537185                  |
| dPly/PhdD w/PHID-CV   | Protein vaccine with Infanrix hexa                                         | GSK                                           | Phase 2 complete | NCT01204658                  |
| PHID-CV               | 10-valent pneumococcal conjugate vaccine (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F + non-typeable H. influenzae protein D conjugate vaccine) | GSK                                           | Phase 3 complete | NCT02447432                  |
| IC47                  | Recombinant/purified protein vaccine (PcsB, StkP, PsaA)                    | Valneva Austria GmbH, PATH                     | Phase 1 complete | NCT00873431                  |
| 09-RASV-Sp-01         | Attenuated, avirulent Salmonella Typhi strains expressing PspA              | Arizona State University                      | Phase 1 complete | NCT01033409                  |
| PHID-CV w/PPV 23      | 10-valent pneumococcal conjugate vaccine (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F + non-typeable H. influenzae protein D conjugate vaccine) | GSK                                           | Phase 3 complete | NCT00907777                  |
| PcpA/PhdT/PhyD1       | Protein vaccine                                                            | International Centre for Diarrhoeal Disease Research, Bangladesh/Sanofo Pasteur | Phase 1 complete | NCT01764126                  |

The abbreviation of each pneumococcal protein is followed by PcsB protein required for cell wall separation of group B streptococcus, StkP serine/threonine protein kinase, PcpA choline binding protein A, PhdT pneumococcal histidine triad D, PlyD1 genetically detoxified pneumolysin.

**Subunit vaccine**

*Polysaccharide vaccine*

The polysaccharide capsule from encapsulated bacteria is a major virulence factor and can be used as an antigen. However, the polysaccharide antigen interacts with B cells and directly induces antibody production without a T cell response (Goldblatt 2000; Song et al. 2013). Infants have a particularly immature B cell response, and so vaccines that do not also induce a T cell response cannot provide adequate protection against pneumococcal infection (Simon et al. 2015). The pneumococcal polysaccharide vaccine (PPV23; Pneumovax 23) comprises polysaccharide from 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F), which are responsible for 85-90% of invasive pneumococcal infections in the world (WHO 2017c). PPV23 is effective against invasive pneumococcal disease (IPD), and is recommended to individuals aged ≥50 and children aged ≥2 (Fedson and Guppy 2013). However, PPV23 does not prevent the incidence of pneumonia or morbidity (Huss et al. 2009), since it elicits serum IgG but not secretory IgA in the nasopharynx. Although no strong evidence on PPV23-induced CAP prevention is available, PPV23 seems to alleviate CAP severity (Kraicer-Melamed et al. 2016; Johnstone et al. 2007).

*Conjugate vaccine*

This vaccine uses polysaccharide antigens conjugated with carrier proteins (Goldblatt 2000). In contrast to polysaccharide vaccines, the conjugate vaccine can elicit T cell response, resulting in superior immunogenicity (Song et al. 2013) and immunity that lasts longer (Goldblatt 2000). Pneumococcal conjugate vaccine with 7 valent capsular polysaccharides (PCV7; Prevnar®) includes serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, and PCV10 (Synflorix®) comprises serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Serotypes 3, 6A, and 19A were added to PCV13 (Prevnar 13®). PCV7 has been shown to induce protective effects against IPD, pneumonia, and otitis media (Lee et al. 2014; Pilishvili et al. 2010). Moreover, PCV7 could protect HIV-infected adults from pneumococcal infection (French et al. 2009).
et al. 2016). PCV13 markedly decreased pneumococcal pneumonia incidence in children because pneumococcal serotypes 19A and 3 are responsible for half of childhood pneumococcal pneumonia cases (Olarte et al. 2017). PCV13 vaccination is recommended for infants, children, and adults.

Protein based vaccine (Recombinant protein vaccine)

These vaccines consist of purified protein antigens that have been produced in bacteria (Nascimento and Leite 2012). The protein antigen elicits antibodies in a vaccinated person, thus protecting them from disease. Various recombinant protein vaccine was developed to elicit a sufficient protective immune response (Table 2).

Pneumococcal vaccine studies in the future

Respiratory pathogens initiate colonization in the mucosal surface to cause disease. Therefore, the mucosal immune system plays an important role as a primary physical barrier in protection against respiratory diseases (Neutra and Kozlowski 2006; Holmgren and Czerkinsky 2005). In the mucosal immune system, secretory IgA, a key factor in mucosal immunity, is induced by vaccination to entrap microbes or block microbial adherence and invasion (Lamm 1997; Hutchings et al. 2004). Local IgG is also induced (Kozlowski et al. 2002). Thus, mucosal vaccination induces both mucosal and systemic immune responses to provide effective protection against respiratory diseases such as pneumonia. Compared with mucosal vaccines, injectable vaccines are less effective at generating mucosal immune responses (Lamm 1997), and could transmit infection via the blood through contaminated needles (Levine and Dougan 1998). Despite the mucosal vaccine’s advantages, and their use against diseases such as cholera, polio and influenza, few of these vaccines are available (Holmgren and Czerkinsky 2005). This is because the mucosal immune system reacts to mucosal vaccines as they do for microorganisms, making their implementation difficult; i.e., the mucosal vaccine adheres to the mucosal surface and is subject to degradation by proteases and nuclease, triggering the same immune response as the real pathogen. Thus, to be feasible, mucosal vaccines must overcome this hurdle, and evoke secretory immune responses, such as secretory IgA.

Conclusion

The most common pneumonia, CAP, is mainly caused by S. pneumoniae. Although antibiotics have been used to treat pneumonia, the incidence of antibiotic resistance has increased and the risk of pneumonia in children and the elderly with weak immune responses is high. Thus, to prevent pneumonia or IPD, including sepsis, the WHO and ACIP recommend vaccination. Moreover, influenza virus, a critical factor in increased pneumococcal pneumonia risk, has been linked to higher mortality. After the introduction of PCV vaccination, the incidence of pneumonia and IPD greatly decreased. However, the current vaccine cannot prevent emergence of pneumococcal diseases caused by serotypes not included in the vaccine. Thus, development of new mucosal vaccine types is needed to protect against a broader range of serotypes.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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