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# Outbreaks of severe pneumococcal disease in closed settings in the conjugate vaccines era, 2010–2018: A systematic review to inform national guidance in the UK

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SUMMARY

*Introduction:* Pneumococcal outbreaks are rare but they still occur, particularly in closed settings usually involving vulnerable groups. We undertook a systematic review to identify strategies for controlling pneumococcal outbreaks since the licensure of higher-valent pneumococcal conjugate vaccines (PCVs).
*Methods:* A systematic literature search was performed for pneumococcal outbreaks published since 2010. A cluster was defined as two or more cases of severe pneumococcal disease in a closed setting within 14 days.
*Results:* Eleven reports were identified, including seven caused by serotypes in both the 13-valent PCV (PCV13) and the 23-valent polysaccharide vaccine (PPV23); two were due to a PCV13-only serotype (6A) and one each by a PCV13-related serotype (6C) and a non-vaccine serotype (15A). Eight reported infection control measures, including reinforcing hand washing, respiratory hygiene and patient cohorting. PPV23 was used in five outbreaks, while PCV13 and both vaccines were used in one outbreak each. Different antibiotics were used for chemoprophylaxis in eight outbreaks.
*Conclusions:* Most pneumococcal outbreaks are currently caused by vaccine-preventable serotypes, and PPV23 is the preferred vaccine in more than half the outbreaks. Early implementation of infection control measures is important, and antibiotic chemoprophylaxis should be considered for high-risk individuals.


## Introduction

Outbreaks of severe pneumococcal disease occur sporadically and can affect large numbers of individuals, although they are less frequent compared to the pre-antibiotic era.[1] The responsible pathogen, *Streptococcus pneumoniae*, is a Gram-positive bacterium that commonly colonises the nasopharyngeal tract, especially in young children. Occasionally, however, it can invade locally to cause mucosal infections including sinusitis, otitis media or pneumonia. Rarely, invasion of the bloodstream can lead to more serious infections, including septicaemia and meningitis. The incidence of invasive pneumococcal disease (IPD) is highest in young children (<2 years), older adults (≥65 years) and in those with particular underlying comorbidities that increase their risk of IPD.[2] Outbreaks of serious pneumococcal infections have previously been reported in closed and/or institutionalised settings such as chronic care facilities,[3] the military,[4] prisons,[5] and shelters[6]. There are currently almost 100 pneumococcal serotypes identified, each with their own characteristic polysaccharide capsule.

A polysaccharide vaccine that aims to protect against 23 of the most prevalent pneumococcal serotypes causing IPD (PPV23) has been available for more than three decades. Polysaccharide vaccines, however, are not immunogenic in young children and offer only limited short-term protection in adults. A polysaccharide-conjugate vaccine that offers protection against the seven most common serotypes causing IPD in young children (PCV7) was licensed in 2000 and has been replaced with a 10-valent (PCV10) and a 13-valent vaccine (PCV13). Unlike the polysaccharide vaccine, conjugate vaccines are immunogenic from birth up to older adults, induce immunological memory with boosting of antibody responses following each additional dose and prevent nasopharyngeal carriage acquisition in vaccinated children, thereby inducing population (indirect, herd) protection by interrupting transmission to susceptible, unvaccinated older children and adults. The implementation of PCVs into national immunisation programmes has led to rapid, large and sustained reductions in pneumococcal disease

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EMBASE: exp *pneumococcal infection OR "Streptococcus pneumoniae".tw OR (pneumococcal adj (infection* or pneumonia or meningitis or disease)).tw AND epidemic OR (epidemic or outbreak* or cluster*).tw.

Medline: exp *Pneumococcal Infections OR *Streptococcus pneumoniae OR "Streptococcus pneumoniae".tw OR (pneumococcal adj (infection* or pneumonia or meningitis or disease)).tw AND exp Disease Outbreaks/ (epidemic or outbreak* or cluster*).tw.

**Fig. 1.** Search strategy for identifying relevant publications for pneumococcal outbreaks.

caused by the respective vaccine serotypes.[7] A small increase in replacement disease due to non-vaccine serotypes has been reported but the overall reduction in pneumococcal disease burden has been very positive.[7]

Our previous review summarised outbreaks of serious pneumococcal disease in closed settings from 1980 to 2010, when neither PCV10 nor PCV13 was routinely available.[8] Implementation of these vaccines into national immunisation programmes has changed the epidemiology of pneumococcal disease such that most infections are now due to non-PCV serotypes. Another study reviewed outbreaks caused by *S. pneumoniae* over the past century but this was not limited to serious pneumococcal disease or closed settings.[9] The purpose of this systematic review is to extend our previous review during an eight-year period when PCV10 and PCV13 were routinely used in national immunisation programmes in order to inform national guidelines for the management and control of pneumococcal disease clusters and outbreaks in the UK, in terms of both antibiotic chemoprophylaxis and the choice of pneumococcal vaccination.

## Methods

### *Search strategy*

A systematic literature search for pneumococcal outbreaks was performed using the EMBASE, Medline and Scopus databases. The Cochrane database was also searched for published systematic reviews. The search strategy was supplemented by reviewing reference lists within publications included in the initial search. The final search was undertaken on 6 September 2019 and included all publications after 01/01/2010, without any restrictions to language. Studies included in the analysis were reports of clusters or outbreaks in which two or more individuals had experienced an episode of severe pneumococcal disease in a closed setting. A closed setting was defined as a place where people were able to come and go (e.g. schools, nurseries and homeless shelters) and also places where people resided for longer periods of time such as hospitals, prisons, care homes and military barracks. A cluster was defined as two or more cases of severe pneumococcal disease occurring in a closed setting within a 14-day period; where the same pneumococcal strain was identified, this was considered an outbreak. Severe pneumococcal disease included pneumococcal pneumonia, meningitis and bacteraemia. Pneumococcal pneumonia was defined as a clinical diagnosis of chest infection with an *S. pneumoniae* culture-positive sample of sputum or pleural fluid or urine-positive for pneumococcal antigen. IPD was defined as isolation of *S. pneumoniae* from blood or any other sterile site.

### *Selection criteria*

Study inclusion criteria were developed to identify interventions used in outbreak management and effect of antibiotics on pneumococcal carriage. We included outbreaks or clusters of severe pneumococcal disease in closed settings, where at least two clinical cases of severe pneumococcal disease were reported with appropriate microbiological investigation and laboratory confirmation for at least one of the cases. Surveillance studies that did not report any clinical or epidemiological data in addition to microbiological results were excluded. A detailed search strategy was formulated using Medical Subject Heading (MeSH) and thesaural terms for 'pneumococcal disease' and 'outbreak'. Ovid was used to search both the EMBASE and Medline databases (Fig. 1).

### *Data extraction*

Results of the search strategy were imported into the reference management software EndNote where they were de-duplicated before transferring to the EPPI-Reviewer 4 software where they were further de-duplicated. Two authors (ZA and NI) independently examined each title with the abstract to exclude any publications that did not meet the selection criteria. The remaining full text articles were then reviewed by the same authors. Any differences in discrepancies were adjudicated through discussion with a third investigator (SNL).

### *Data synthesis and analysis*

Reports of severe pneumococcal disease outbreaks in closed settings were summarised and tabulated. Data were described based on summary characteristics, prophylactic vaccine and antibiotic usage, and infection control measures used.

## Results

Eleven reports describing outbreaks and/or clusters of severe pneumococcal disease in closed settings met the inclusion criteria; the outbreaks occurred during 2010–2015 and were published between 2010 and 2018 (Fig. 2). Reference lists of included studies were reviewed but no additional articles were identified (Table 1). One publication by Patterson *et al.*[10] was excluded because the same outbreak was published in more detail elsewhere.[11] Four of the eleven outbreaks occurred in hospital wards, two in military units, two in psychiatric units, one in a care home, one at an oil rig and one in a prison. Outbreaks were mainly reported in the UK ($n=4$) and the US ($n=3$). Serotype 3 was responsible for three outbreaks, in two outbreaks serotype 4 and 11A/E were also implicated; the other serotypes included 5, 15A, 9 V, 6A, 6C, 14, and 8. Seven outbreaks were caused by serotypes that are included in both PCV13 and PPV; two by a PCV13-only serotype (6A) and one each by a PCV13-related serotype (6C) and a non-vaccine serotype 15A.

### *Pneumococcal vaccination*

Pneumococcal vaccination was used in six of the 11 outbreaks (Table 2). PPV was used in five outbreaks (including one that also

**Table 1**
Summary of characteristics of outbreaks of severe pneumococcal disease published between 2010 and 2018.

| First Author | Year of cluster | No of confirmed cases | No of probable cases | Type of pneumococcal disease | Setting | Type of confirmation | Country | Age range (median) | Serotype | Interval between onset in first and last case | Confirmed case attack rate | Case fatality rate |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Balicer et al., 2010[17] | 2005–06 | 4 | 11 | Pneumococcal pneumonia | Military training unit | Blood/endotracheal culture | Israel | 18–20[b] | 5 | 30 days | 0.7% (4/596) | 0 |
| Bamberg et al., 2013[18] | 2012 | 2 | 5 (1 staff) | Invasive pneumococcal disease | Assisted-living facility | Culture | USA | 39–97 (80)[c] | 3 | 19 days | 16.7% (2/12) | 33.3% (2/6) |
| Dawood et al., 2011[20] | 2009 | 2 | 72 | Pneumococcal meningitis/ pneumonia | Military training unit | CSF culture | USA | Unknown | 7F | 20 days | 0.7% (2/303) | 2.8% (2/74) |
| Ewing et al., 2017[24] | 2015 | 4 | 5 | Pneumococcal pneumonia | Oil rig | Blood culture (4) Urinary antigen (1) | UK | 20–60 (43)[c] | 3, 4 | 24 days | 0.6% (4/680) | 0 |
| Fleming-Dutra et al., 2012[16] | 2010–11 | 3 (1 staff) | 8[a] (2 staff) | Invasive pneumococcal disease | Paediatric psychiatric unit | PCR | USA | 4–24 (13)[b] | 15A/non-typeable | 91 days | 15.0% (3/20) | 0 |
| Jauneikaite et al., 2017[25] | 2015 | 3 | - | Pneumococcal bacteraemia/ pneumonia | Adult respiratory medicine ward | Blood/sputum culture | UK | 59–76 (70) | 9V | 6 days | – | 0 |
| Prebil et al., 2016[12] | 2013 | 5 | – | Pneumococcal pneumonia | Geropsychiatric unit | Sputum culture | Slovenia | 66–95 (80) | 6A | 9 days | – | 0 |
| Sheppard et al., 2016[15] | 2013 | 5 | – | Pneumococcal pneumonia/ bacteraemia | Elderly care ward | Blood culture (2) Urinary antigen (4) | UK | Unknown | 6C | 11 days | 17.9% (5/28) | 60% (3/5) |
| Skoczynska et al., 2012[13] | 2009 | 4 | – | Pneumococcal pneumonia | Respiratory ward | Sputum culture | Poland | 56–73 (65) | 14 | 9 days | – | 0 |
| Thomas et al., 2015[19] | 2012 | 11 | 4 | Pneumococcal pneumonia | Care home | Blood culture (1) Urinary antigen (10) | UK | 75–94 (90)[b] | 8 | 14 days | 47.8% (11/23) | 6.7% (1/15) |
| Yamazaki et al., 2017[14] | 2015 | 7 | – | Pneumococcal pneumonia | Mental health facility | Sputum culture | Japan | 61–77 | 3, 11A/E | 10 days | 30.4% (7/23) | – |

[a] 6 confirmed pneumonia, 2 suspected pneumonia.
[b] Age range of resident patients during the outbreak.
[c] Including cases with probable pneumococcal disease.

**Table 2**
Vaccination and antimicrobial chemoprophylaxis regimens used in outbreak control.

| First Author | Serotype (vaccine-type) | Antibiotic susceptibility | Antibiotic non-susceptible | Antibiotic used for contacts | Name of antibiotic | Dose for contacts | Duration | Time administered | Vaccine for contacts |
|---|---|---|---|---|---|---|---|---|---|
| Balicer et al., 2010[17] | 5 (both) | Penicillin, erythromycin, clindamycin, tetracycline and chloramphenicol | TMP/SMX | Yes | Azithromycin | 2 doses of 500mg | 2 doses one week apart | Outbreak day 23 and day 30 | PPV |
| Bamberg et al., 2013[18] | 3 (both) | Not stated | Not stated | Yes | Not stated | Not stated | Not stated | Not stated | PCV13 |
| Dawood et al., 2011[20] | 7F (both) | Penicillin | | Yes | Benzathine penicillin G/azithromycin | 1.2 million units/1 mg | Not stated | 13–21 days after first case | PPV |
| Ewing et al., 2017[24] | 3, 4 (both, both) | Not stated | Not stated | Yes | Azithromycin | 500 mg once daily | 3 days | 2 weeks after first case | PPV |
| Fleming-Dutra et al., 2012[16] | 15A/non-typeable (neither) | Not stated | Not stated | Yes | Amoxicillin | 90 mg/kg/day divided in 2 doses, max of 1000 mg | 5 days | 5 weeks after first case | No |
| Jauneikaite et al., 2017[25] | 9V (both) | Penicillin | Macrolides, tetracycline | Yes | Levofloxacin | Not stated | 3 days | Within 14 days | PPV & PCV13 |
| Prebil et al., 2016[12] | 6A (1 unknown) (PCV13 only) | N/A | N/A | No | N/A | N/A | N/A | N/A | No |
| Sheppard et al., 2016[15] | 6C (PCV13-related) | Not stated | Not stated | Yes | Amoxicillin, penicillin | Not stated | 5 days | 1 day after first case | No |
| Skoczynska et al., 2012[13] | 14 (both) | N/A | N/A | No | N/A | N/A | N/A | N/A | No |
| Thomas et al., 2015[19] | 8 (PPV only) | Penicillin, erythromycin and tetracycline | N/A | Yes | Amoxicillin | 2 doses of 500 mg | 7 days | 3 days after first case | PPV |
| Yamazaki et al., 2017[14] | 3, 11A/E (both, PPV only/neither) | N/A | N/A | No | N/A | N/A | N/A | N/A | No |

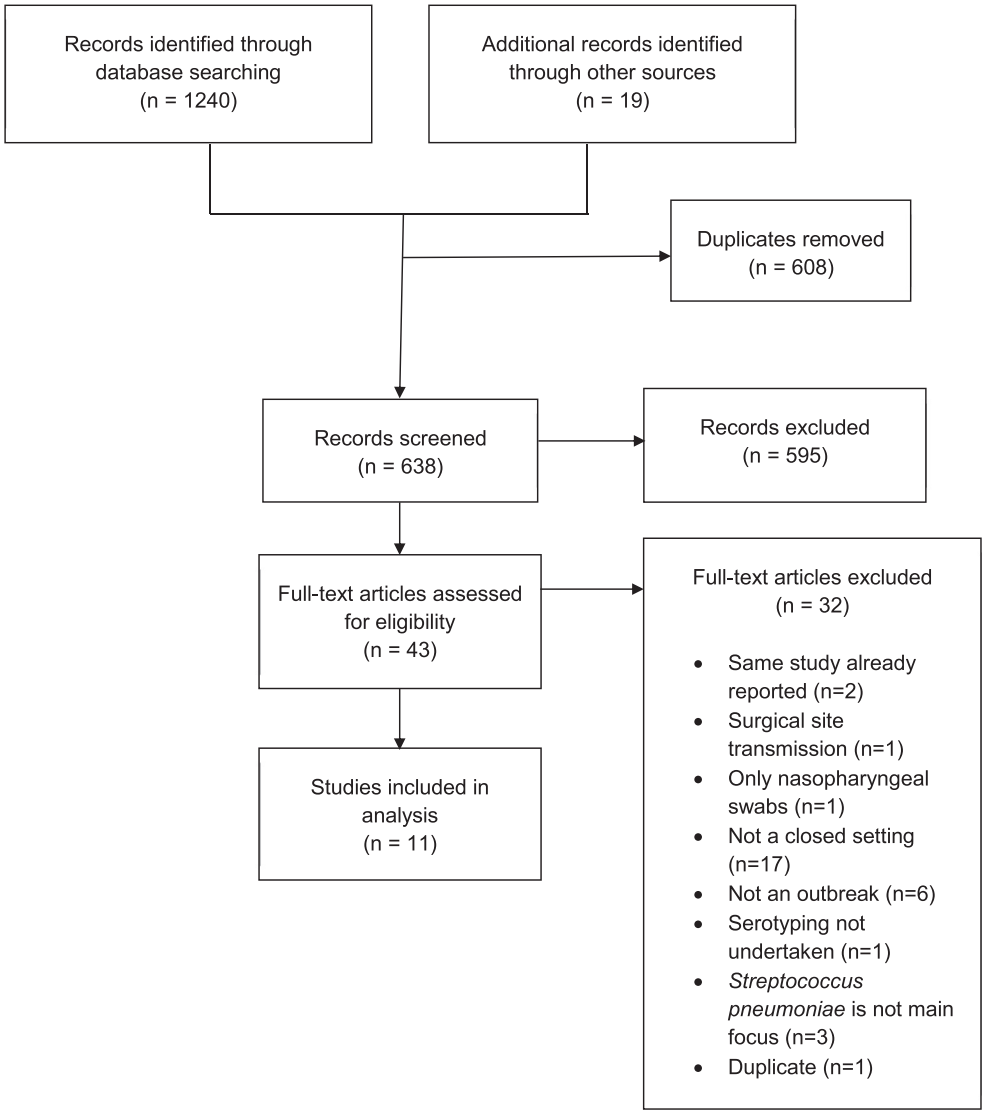


**Fig. 2.** Selection process for inclusion of articles.

included PCV13) and PCV13 in one outbreak due to serotype 3; four other outbreaks occurred in a hospital setting and were controlled by rapid institution of infection control practices, including isolation and antibiotic treatment of the infected patients,[12-14] with antibiotic prophylaxis for contacts in one of the outbreaks[15] and treatment of an underlying influenza outbreak in another.[14] One other outbreak was due to a non-vaccine strain.[16]

*Antimicrobial prophylaxis*

Antibiotic chemoprophylaxis was offered in eight of the 11 outbreaks; in the remaining three outbreaks which occurred in psychiatric ($n=2$) or respiratory ($n=1$) units, outbreak control measures were sufficient to prevent further cases, [12-14] even though in one of the outbreaks, four of 18 otherwise well patients – who were hospitalised in the same unit at the same time as the cases – had the outbreak pneumococcal serotype identified in their nasopharyngeal specimens.[12] A number of different antibiotics were used for chemoprophylaxis of close contacts (Table 2).

*Other infection control measures*

Infection control measures other than chemoprophylaxis and vaccination are summarised in Table 3. Reinforcing hand and respiratory hygiene was reported in four of the eight outbreaks that reported infection control measures. Isolation was reported in two outbreaks and some form of patient cohorting was also reported in two additional outbreaks. Four outbreaks did not report on infection control.

*Infection in staff members*

Information about staff members being affected in the outbreak was reported in six studies.[14-19] In a paediatric psychiatric unit outbreak, one of three confirmed pneumococcal cases and two of eight probable pneumococcal cases occurred in staff members.[16] In that outbreak, the attack rate was 25% for patients (5/20) but <3% in staff members. In another pneumococcal outbreak in an assisted-living facility, one staff member with underlying asthma was diagnosed with probable pneumococcal disease.[18] Two studies reported that none of the staff was symptomatic developed pneumococcal disease,[15, 19] including one that reported no carriage among staff members.[15] On the other hand, none of the staff members in a military training was symptomatic but 3/18 (17%) staff members and 55/124 (44%) military recruits were identified as pneumococcal nasopharyngeal carriers.[17] Finally, during a pneumococcal outbreak in a mental health facility, ten staff members

**Table 3**
Other infection control measures used to control outbreak.

| First Author | Infection control measure(s) in addition to vaccination/chemoprophylaxis | Infection control measure(s) | Setting |
|---|---|---|---|
| Balicer et al., 2010[17] | All trainees sent home on outbreak day 19 | Removed from exposure | Military training unit |
| Bamberg et al., 2013[18] | Not stated | Not stated | Assisted-living facility |
| Dawood et al., 2011[20] | Hand hygiene/cough etiquette reviewed with all trainees and staff | Hand/respiratory hygiene practice | Military trainee company |
| Ewing et al., 2017[24] | Information and advice regarding pneumococcal disease and symptom awareness, respiratory protective equipment (RPE) provided to employees | Information and advice, respiratory protective equipment (RPE) | Oil rig |
| Fleming-Dutra et al., 2012[16] | Hand and respiratory hygiene compliance sessions for patients every 2–3 h, infection control training sessions | Hand/respiratory hygiene practice | Psychiatric unit |
| Jauneikaite et al., 2017[25] | Not stated | Not stated | Adult respiratory medicine ward |
| Prebil et al., 2016[12] | Contact isolation | Isolation | Geropsychiatric unit |
| Sheppard et al., 2016[15] | Information disseminated to patients, staff, visitors, cleaning, unspecified infection control measures | Hand/respiratory hygiene practice | Elderly care ward |
| Skoczynska et al., 2012[13] | Isolation of cases, reinforced sanitary regimen (masks and coats for patients and personnel, bactericidal lamps, instruction on hand washing and disinfection, limiting visitors to ward | Isolation, hand/respiratory hygiene practice, RPE, bactericidal lamps | Respiratory ward |
| Thomas et al., 2015[19] | Isolation and cohorting of symptomatic residents, use of personal protective equipment, enhanced cleaning | Isolation, cohorting, PPE, enhanced cleaning | Residential care home |

**Table 4**
Pneumococcal carriage rates before and after antibiotic treatment in outbreaks.

| First Author | Antibiotic regimen | Time to sampling (days) | Number of carriers before antibiotics | Number of carriers after antibiotics | Percentage reduction |
|---|---|---|---|---|---|
| Balicer et al., 2010[17] | 2 × 500 mg azithromycin for 5 days | 24 and 45 days after first dose | 55/124 (29/116) | 1/144 and 1/105 positive for *Spn* (none were ST5) | 63.9%/46.6% |
| Bamberg et al., 2013[18] | Not stated | Not stated | Not stated | Not stated | Not stated |
| Dawood et al., 2011[20] | 1.2 million units benzathine penicillin G (or 1 g azithromycin for those with penicillin allergy) | 4–25 days prior to first dose | 45/299 | Not undertaken | – |
| Ewing et al., 2017[24] | 1 × 500 mg of azithromycin for 3 days | Not stated | Not stated | Not undertaken | Not stated |
| Fleming-Dutra et al., 2012[16] | 2 × 45 mg/kg/day amoxicillin for 5 days | 9 days prior to first dose | 6/20 | Not undertaken | – |
| Jauneikaite et al., 2017[25] | Levofloxacin for 3 days | Not undertaken | Not undertaken | Not undertaken | – |
| Prebil et al., 2016[12] | Not given | N/A | N/A | N/A | N/A |
| Sheppard et al., 2016[15] | Amoxicillin or penicillin for 5 days | Not stated | Not undertaken | All of the screening swabs collected from staff were culture negative | – |
| Skoczynska et al., 2012[13] | Not given | N/A | N/A | N/A | N/A |
| Thomas et al., 2015[19] | 2 × 500 mg amoxicillin for 7 days | Not undertaken | Not undertaken | Not undertaken | – |
| Yamazaki et al., 2017[14] | Not given | N/A | N/A | N/A | N/A |

were diagnosed with influenza B infection although none went on to develop pneumococcal disease.[14]

*Effect of antimicrobials on pneumococcal carriage*

Pneumococcal carriage surveys were undertaken in four of the eleven outbreaks, although only one included a before and after survey allowing calculation of percentage reduction in carriage (Table 4). In another survey, *S. pneumoniae* was isolated from nasopharyngeal and oropharyngeal swabs taken from 55/124 (44.4%) of patients and 60% of isolates from patients and staff were serotype 5.[17] Six weeks after the first dose of antibiotics, only 1/144 and 1/105 patients tested positive for *S. pneumoniae*; none were infected with serotype 5.

In a military training unit outbreak, *S. pneumoniae* was isolated from nasal and throat swabs from 45 of 299 trainees and the most common serotypes identified were serotypes 7F (14, 30%), 3 (14, 30%) and 23A (5, 11%);[20] no carriage study was performed after offering penicillin and azithromycin prophylaxis. In a psychiatric unit outbreak, a carriage study undertaken prior to antibiotic prophylaxis identified 6 of 20 residents as carriers of the outbreak serotype 15A.[16] Amoxicillin prophylaxis twice daily for 5 days was offered to all residents and, although no carriage survey was undertaken post antibiotic prophylaxis, an additional case of pneumonia was confirmed in a patient's parent two weeks later. Finally, in an elderly care ward outbreak, all the screening swabs taken after penicillin and amoxicillin prophylaxis were negative for *S. pneumoniae*; no swabs were taken prior to treatment.

## Discussion

There is currently a lack of consensus on the management of clusters and outbreaks of pneumococcal disease in closed settings. It is important to have up-to-date and readily accessible guidelines based on the best available evidence so that public health mea-

sures can be implemented quickly to prevent additional cases and deaths.

Respiratory infections can spread rapidly within closed settings, resulting in high attack rates because of prolonged close contact between residents and patients and their carers. Several outbreaks included secondary pneumococcal cases within 72 h of the index case, highlighting the need for rapid implementation of infection control and other preventive measures. This is particularly important in settings with vulnerable patients, where the morbidity and mortality associated with pneumococcal disease is likely to be high.[3,4,5,6,7]

*Transmission*

In closed settings, pneumococcal transmission can occur through multiple modalities, including transmission from asymptomatic carriers who may be residents or members of staff, unwell individuals with pneumococcal disease or with viral/pneumococcal co-infection, as well as via fomites. Rapid implementation of infection control as well as raising awareness among residents and staff in order to identify and treat cases quickly are critical early steps in the management of any suspected cluster. This is particularly the case for clusters propagated through viral infections, especially due to influenza and respiratory syncytial virus (RSV), leading to secondary pneumococcal pneumonia[17], where infection control is likely to play a crucial role. Such clusters are more likely to be seasonal and peak during the winter months, although sporadic outbreaks can occur throughout the year. Guidelines on the management of outbreaks of influenza-like illness in care homes in the UK are published,[17] with detailed recommendations for infection control among residents, staff and visitors, as well as antiviral use for treatment and post-exposure prophylaxis in outbreaks where influenza is confirmed in at least one case. Seasonal influenza vaccination is also recommended for unvaccinated staff and residents who are in the at-risk group, although its benefit as an infection control measure in a cluster setting is likely to be limited because it takes more than a week for a protective immune response to develop after vaccination. Unlike the previous interim UK guidance[21] which identified no secondary transmission leading to severe pneumococcal disease in staff during any of the reported outbreaks, we identified one confirmed IPD and three probable cases of pneumococcal disease. The attack rate for pneumococcal disease in one of the reports was <3% for staff compared to 25% among patients,[16] suggesting that the risk to staff members, especially those with no underling comorbidities, is likely to be very low. On the other hand, staff members may develop influenza infection during outbreaks,[14] highlighting the importance of reinforcing annual influenza vaccination for staff members working closely with at-risk patients.

*Responsible serotypes*

In our systematic review, nearly all clusters and outbreaks of severe pneumococcal disease reported during the past decade have been due to vaccine-preventable serotypes. Many of these serotypes are associated with severe clinical manifestations and complications, including empyema/parapneumonic effusion (serotype 1),[22] meningitis (serotypes 12, 23F),[23] and a high case fatality rate (serotypes 14, 23F).[7,9]

*Antibiotic prophylaxis*

The aim of antibiotic chemoprophylaxis is to eliminate pneumococcal carriage and, consequently, onward transmission to susceptible individuals within the closed setting. Antibiotic chemoprophylaxis may also provide direct protection to individuals early in the incubation phase of the disease. The published reports indicate that antibiotic chemoprophylaxis is an effective control measure for clusters and outbreaks, and a longer course of antibiotics may be associated with a more sustained effect. The choice and duration of antibiotics has varied among the reported clusters. For sensitive pneumococci, penicillin (7–10 days), amoxycillin (6 days), rifampicin (2–4 days) and azithromycin (1–5 days) have all been used effectively. Penicillin and amoxycillin were effective in reducing both carriage and additional cases in cluster settings. However, additional cases were observed in outbreaks utilising azithromycin and, for rifampicin, there are limited data on the effect on carriage.[8] In a recent systematic review, the responsible pneumococcal strain was non-susceptible to at least one antibiotic in most outbreaks (73.1%), with nonsusceptibility to penicillin (56.0%) and erythromycin (52.6%) being particularly common, although this could be due to reporting bias because outbreaks associated with antibiotic-resistant pneumococci are more likely to be published. Development of antibiotic resistance during outbreaks has been also reported.[9] The choice of antibiotic chemoprophylaxis in such situations will depend on the antibiotic susceptibility of the infecting strain.

*Vaccines*

Antibiotics, however, will offer only short-term individual protection and this will wane within days of completing the antibiotic course. In clusters involving a vaccine-preventable pneumococcal serotype, therefore, vaccination is recommended to provide longer-term individual protection. The choice of pneumococcal vaccine will depend on the responsible serotype. PCVs have several advantages over PPV in that they are immunogenic at any age, with higher antibody concentrations and longer duration of protection, as well as reducing carriage and transmission to susceptible close contacts, but they are expensive. Polysaccharide vaccines, on the other hand, are cheaper and provide individual protection against more pneumococcal serotypes, which may be particularly important in clusters where the infecting pneumococcal serotype is not known. In our systematic review, PPV23 alone was used effectively in four outbreaks even when higher-valent PCVs were licensed and readily available. However, PCV13 would be recommended for clusters involving young children, especially <2-year-olds, because polysaccharide vaccines are ineffective in this age-group, and in clusters and outbreaks due to serotype 6C which is not included in PPV23. An outbreak response provides healthcare professionals an opportunity to assess the immunisation history of the cases and contacts, and ensure that they have been appropriately immunised according to national recommendations.

*Strengths and limitations*

This review updates the previous systematic review that covered the period up to the introduction of PCV7 into the UK childhood immunisation programme. This updated review summarises more recent outbreaks, focussing particularly on the responsible serotypes in the era of higher-valent PCV use, the antimicrobial susceptibility profile of the responsible pneumococcal strains and the choice of vaccination used in the reported outbreaks. As with other systematic reviews, a limitation is publication bias towards atypical clusters and outbreaks, such as those due to antibiotic-resistant pneumococci or associated with more severe clinical manifestations or outcomes. Methods of microbiological testing in the different outbreaks were variable and included different combinations of culture and antigen testing of sputum and sterile site specimens. Additionally, the outbreak settings and the population affected were very variable but combining the information into a

single review has provided invaluable insight into their management and control of the outbreak.

## Conclusions

Despite these limitations, this systematic review summarises the current evidence and lessons learn from recent pneumococcal outbreaks during a period when higher-valent PCVs are available and mainly in countries where such vaccines are well-established in the respective national immunisation programmes. The findings of this systematic review were used to develop national UK guidelines for the public health management of clusters of severe pneumococcal disease in closed settings. These guidelines are available online at: https://www.gov.uk/government/publications/managing-clusters-of-pneumococcal-disease-in-closed-settings.

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None.

## Declaration of Competing Interest

The Immunisation Department has provided vaccine manufacturers with post-marketing surveillance reports on pneumococcal and meningococcal infection which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports. SNL performs contract research on behalf of St. George's University of London (SGUL) and Public Health England (PHE) for pharmaceutical companies but receives no personal remuneration.

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