

An explosive outbreak of *Streptococcus pneumoniae* serotype-8 infection in a highly vaccinated residential care home, England, summer 2012

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SUMMARY

In August 2012, an explosive outbreak of severe lower respiratory tract infection (LRTI) due to *Streptococcus pneumoniae* serotype-8 occurred in a highly vaccinated elderly institutionalized population in England. Fifteen of 23 residents developed LRTI over 4 days (attack rate 65%); 11 had confirmed *S. pneumoniae* serotype-8 disease, and two died. Following amoxicillin chemoprophylaxis and pneumococcal polysaccharide vaccine (PPV) re-vaccination no further cases occurred in the following 2 months. No association was found between being an outbreak-associated case and age ($P = 0.36$), underlying comorbidities [relative risk (RR) 0.84 95% confidence interval (CI) 0.34–2.09], or prior receipt of PPV (RR 1.4, 95% CI 0.60–3.33). However, the median number of years since PPV was significantly higher for cases ($n = 15$, 10.2 years, range 7.3–17.9 years) than non-cases ($n = 8$, 7.2 years, range 6.8–12.8 years) ($P = 0.045$), provided evidence of waning immunity. Alternative vaccination strategies should be considered to prevent future *S. pneumoniae* outbreaks in institutionalized elderly populations.

Key words: Disease outbreaks, pneumococcal infections, pneumococcal polysaccharide vaccine.

INTRODUCTION

Streptococcus pneumoniae is a major cause of morbidity and mortality, with the burden of invasive pneumococcal disease (IPD) and pneumococcal pneumonia falling disproportionately on the elderly [1]. Although *S. pneumoniae* usually causes sporadic infections, outbreaks of severe pneumococcal disease caused by a single serotype are occasionally

recognized, particularly in institutionalized settings. A systematic review of outbreaks of serious pneumococcal disease in closed settings [2] identified only 11 published outbreaks in elderly care residential settings over four decades [3–12], with clinical attack rates ranging from 3.5–15%. These outbreaks all occurred in settings with a low uptake of pneumococcal polysaccharide vaccine (PPV), and increasing PPV uptake was recommended to prevent future outbreaks.

Current vaccination strategies both in the USA [13] and the UK [14] recommend a single dose of the 23-valent PPV to those aged ≥ 65 years. We report an explosive outbreak of severe lower respiratory tract infection (LRTI) due to *S. pneumoniae* serotype-8

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in a residential care home for the elderly in England in August 2012. Unlike previous reported outbreaks, the population had a high uptake of the PPV, which contains the serotype-8 outbreak strain.

Background and outbreak setting

On 9 August 2012, staff of a residential home in England notified the Health Protection Agency (HPA) of an outbreak of acute respiratory tract infection among elderly residents. The residential home was a three-floor building housing 23 long-stay elderly residents, cared for by 22 staff. The residents each had their own individual rooms, apart from two couples, but mixed freely in social and dining areas.

Seven of the 23 residents had developed symptoms of cough and breathlessness since 8 August. One resident had been admitted to hospital; a chest radiograph showed right basal consolidation and *S. pneumoniae* was grown from blood culture. An outbreak of *S. pneumoniae* disease was suspected, and urine samples and sputum, when available, were collected from all symptomatic residents.

Control measures

On 9 August, the home was closed to new admissions and enhanced infection control measures were introduced, including isolation and cohorting of symptomatic residents, use of personal protective equipment, and enhanced cleaning.

By 11 August, three cases had been diagnosed with disease caused by *S. pneumoniae* (one bacteraemia, two urine antigen positive), establishing that an outbreak of pneumococcal disease had occurred. The outbreak-associated cases were treated with either amoxicillin or erythromycin as appropriate. Chemoprophylaxis (500 mg amoxicillin twice daily for 7 days) was given to all asymptomatic residents. On 21 August, PPV vaccination was given to all 13 residents who had not been vaccinated within the previous 10 years. Active follow-up for further cases continued for 2 months.

METHODS

Outbreak investigation

The study population was defined as all residents of the residential home during the period from 8 to 22 August 2012.

The following case definitions were used:

Probable case. Resident with a clinical diagnosis of LRTI with onset from 8 to 22 August 2012.

Confirmed case. Probable case with *S. pneumoniae* serotype-8 identified in a blood culture or by urine antigen testing.

Outbreak-associated case. A confirmed or probable case.

Microbiological methods

Sputum was collected from symptomatic residents with productive cough and cultured on blood agar (with optochin disc), chocolate and CLED agar plates following homogenization of the sample using Sputasol (Oxoid, UK). Plates were incubated at 37 °C in CO₂ and examined for characteristic colonies after 18–24 h incubation. Any colonies on blood agar with typical morphology were confirmed as *S. pneumoniae* if they were susceptible to optochin. The *S. pneumoniae* isolated from the hospitalized resident's blood culture was confirmed using the above methods, and in addition was serotyped.

Nasopharyngeal swabs were collected from the symptomatic residents and tested against a PCR respiratory virus panel including influenza A and B, parainfluenza virus, Adenovirus, Rhinovirus, respiratory syncytial virus (RSV) and human metapneumovirus. Urine samples were collected from symptomatic residents and tested using the BinaxNOW pneumococcal urinary antigen test (Binax, USA) and the Bio-Plex pneumococcal serotype assay (Bio-Rad, USA) to determine serotype [15]. In the case of one of the patients who died, and for whom a urine sample was not available, a nasopharyngeal swab was tested using the Binax NOW and Bio-Plex assays.

Analytical epidemiological study

We conducted a retrospective cohort study to investigate factors associated with being an outbreak-associated case during the outbreak period. The cohort included all residents of the home during the outbreak period.

Demographic data and information about symptoms were collected from the residential home manager. Further information on symptoms, and details of comorbidities and previous vaccination with PPV were obtained from the residents' general practitioners.

Data were analysed using Stata v. 12 (StataCorp., USA). Attack rates and relative risks were calculated for all binary variables; Fisher's exact *P* values were

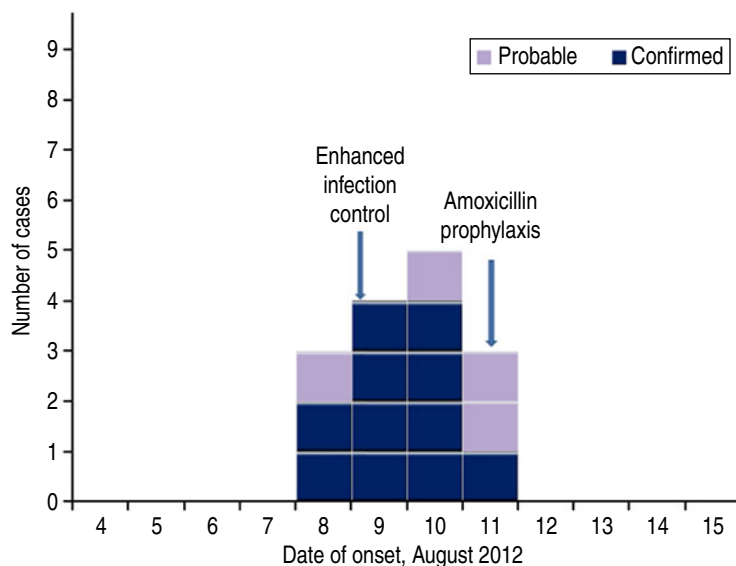


Fig. 1. Distribution of cases of lower respiratory tract infection by date of onset, residential home, England, August 2012.

calculated due to small sample size. The distribution of continuous variables was compared using the Mann–Whitney rank sum test.

RESULTS

Descriptive epidemiology

The median age of the 23 residents was 90 years (range 75–94 years) and 15/23 were female. All but three had underlying comorbidities.

There were 15 outbreak-associated cases. All 15 had symptoms of cough; in addition, five reported anorexia, three had wheeze and two had shortness of breath. Only one case was febrile, and a blood sample for culture was collected for this patient. Eleven cases were microbiologically confirmed, one by positive blood culture and the remaining ten cases by urinary antigen testing. This gave a confirmed-case attack rate of 48%. An additional four probable cases also occurred during the outbreak period (outbreak-associated case attack rate 65%). Two of the outbreak-associated cases died (case-fatality ratio 13%).

Eight (73%) of the 11 confirmed cases had previously been vaccinated with PPV, a median of 12 years prior to the outbreak (range 8–18 years). Twelve (80%) of the 15 outbreak-associated cases had previously been vaccinated with PPV, a median of 10 years prior to the outbreak (range 7–18 years).

None of the residents had had symptoms typical of a viral respiratory infection prior to the outbreak. No staff were symptomatic during the outbreak period.

The distribution of cases by date of onset is shown in Figure 1. All cases clustered over the 4 days from 8 to 11 August, with no new cases occurring in the subsequent 2 months' follow-up.

Microbiological findings

No pathogenic bacteria were isolated from sputum of the three residents who had a productive cough. The *S. pneumoniae* isolated from the blood culture was found to be serotype-8, MLST sequence type 53, and susceptible to penicillin, erythromycin and tetracycline.

The microbiological results for the 15 outbreak-associated cases are presented in Table 1.

Analytical epidemiology

The clinical attack rates by key epidemiological characteristics are presented in Table 2. The attack rate was very similar in males and females [relative risk (RR) 0.94, 95% confidence interval (CI) 0.49–1.79]. The median age of the outbreak-associated cases (89 years, range 77–93 years) was very similar to the median age of the non-cases (91 years, range 75–94 years, $P = 0.36$). There was no significant association between being an outbreak-associated case and the presence of any underlying comorbidities ($P = 1.0$).

There was no association between prior receipt of PPV and being an outbreak-associated case (RR 1.4, 95% CI 0.60–3.33, $P = 1.0$). However, the median

Table 1. Laboratory results of outbreak-associated cases of lower respiratory tract infection in a residential home, England, 2012

Case	Blood culture	Nasal swab PCR respiratory virus panel	Binax assay on urine (U) or nasal swab (N)	Bio-plex assay on urine (U) or nasal swab (N)	Clinical outcome
1	<i>S. pneumoniae</i> serotype-8				Died
2		Negative			Survived
3		Negative	Negative (U)	<i>S. pneumoniae</i> serotype 8 (U)	Survived
4		Negative	Negative (U)	<i>S. pneumoniae</i> serotype 8 (U)	Survived
5		Negative	Negative (U)	<i>S. pneumoniae</i> serotype 8 (U)	Survived
6		Negative	Negative (U)	<i>S. pneumoniae</i> serotype 8 (U)	Survived
7		Rhinovirus	Positive (N)	<i>S. pneumoniae</i> serotype 8 (N)	Died
8		Negative	Positive (U)	<i>S. pneumoniae</i> serotype 8 (U)	Survived
9			Positive (U)	<i>S. pneumoniae</i> serotype 8 (U)	Survived
10			Positive (U)	<i>S. pneumoniae</i> serotype 6A/C (U)	Survived
11			Negative (U)	<i>S. pneumoniae</i> serotype 8 (U)	Survived
12			Negative (U)	<i>S. pneumoniae</i> serotype 8 (U)	Survived
13			Negative (U)	Not detected	Survived
14			Negative (U)	Not detected	Survived
15			Negative (U)	<i>S. pneumoniae</i> serotype 8 (U)	Survived

number of years since receipt of PPV was significantly higher for outbreak-associated cases (10.2 years, range 7.3–17.9 years) compared to non-cases (7.2 years, range 6.8–12.8 years), Wilcoxon rank sum $P = 0.045$.

A sensitivity analysis was conducted restricting the analysis to the confirmed cases ($n = 11$) and non-cases ($n = 8$). The results obtained were very similar. Again, there was no association between being a case and prior receipt of PPV (RR 1.23, 95% CI 0.50–3.05, $P = 1.0$), and the median number of years since receipt of PPV was significantly higher for the cases (11.7 years, range 8.0–17.9 years) compared to the non-cases (7.2 years, range 6.8–12.8 years, $P = 0.040$).

DISCUSSION

This was an unusual outbreak of LRTI due to *S. pneumoniae* serotype-8 with an exceptionally high attack rate during summertime.

Prompt reporting of the outbreak led to rapid identification of the causative agent and implementation of control measures. No new outbreak-associated cases developed over the 2-month period since antibiotic chemoprophylaxis of asymptomatic residents and re-vaccination.

The exceptionally high attack rate in a population with a high uptake of PPV-23, which includes the serotype-8 antigen, is of particular concern. Previously published outbreaks of *S. pneumoniae* in residential

facilities for the elderly have all reported low levels of PPV vaccination. In this outbreak, 80% of outbreak-associated cases had documented evidence of PPV vaccination. The finding that all the vaccinated cases had received PPV more than 7 years prior to the outbreak, and that cases had received vaccine significantly longer ago than non-cases, suggests that the low level of PPV protection may in part reflect waning immunity.

A small number of published observational studies have found a low level of PPV vaccine effectiveness against IPD in the elderly, and a decrease in effectiveness after 5 years [16, 17]. However, although there is evidence that vaccine effectiveness varies by serotype [18], these studies have not had the power to estimate serotype-specific vaccine effectiveness by time since vaccination. Evidence of the effectiveness of PPV against pneumonia in the elderly is even sparser, with the few published studies to date providing contradictory findings [19, 20]. This could in part be explained by lack of consideration of time since vaccination as an important effect modifier. Waning vaccine effectiveness is consistent with what is known about the immune response to PPV, as PPV-induced capsular-specific antibody levels have been shown to decrease over time [21]. Our findings provide evidence of waning immunity of PPV in the prevention of severe LRTI due to serotype-8 disease in an elderly population. Current vaccination strategies both in the USA [13] and the UK [14] recommend only a

Table 2. Attack rates and relative risks for outbreak-associated cases (probable and confirmed cases) ($n = 15$) in residents of a residential home, England, 2012 by potential risk factors ($N = 23$)

Characteristics	Attack rate among exposed			RR	95% CI	Fisher's exact P value	
	No.	Total	%				
Sex	Female	5	8	62.5	0.94	0.49–1.79	1.0
	Male	10	15	66.7			
Age	<90 years	8	11	50	0.8	0.44–1.46	0.8
	≥ 90 years	7	12	58.3			
Floor	2	2	5	40	Ref.	0.5–5.09	0.33
	1	7	11	63.6			
	G	6	7	85.7			
Comorbidities	Chronic heart disease: Yes	6	7	85.7	1.52	0.9–2.58	0.35
	Chronic heart disease: No	9	16	56.3			
	Chronic resp. disease: Yes	2	2	100	1.62	1.15–2.26	0.53
	Chronic resp. disease: No	13	21	61.9			
	Diabetes: Yes	2	4	50	0.73	0.26–2.04	0.59
	Diabetes: No	13	19	68.4			
	Chronic renal disease: Yes	6	9	66.7	1.04	0.57–1.9	1.0
	Chronic renal disease: No	9	14	64.3			
	Cardiovascular disease: Yes	2	5	40	0.55	0.18–1.68	0.3
	Cardiovascular disease: No	13	18	72			
	Hypothyroidism: Yes	2	3	66.7	1.03	0.43–2.43	1.0
	Hypothyroidism: No	13	20	65			
	Dementia: Yes	2	3	66.7	1.03	0.43–2.43	1.0
	Dementia: No	13	20	65			
	Any comorbidities: Yes	9	16	56.3	0.84	0.34–2.09	1.0
Any comorbidities: No	2	3	66.7				
PPV	Yes	12	17	70.6	1.41	0.60–3.33	1.0
	No	3	6	50			
Among those vaccinated, years since PPV	≤ 5	0	0	0	n.a.		0.61
	6–10	6	10	60	Ref.		
	11–15	4	5	80	1.3	0.68–2.60	
	15–20 years	2	2	100	1.7	1.05–2.89	

RR, Relative risk; CI, confidence interval; n.a., not applicable; PPV, pneumococcal polysaccharide vaccine.

single dose of PPV to those aged ≥ 65 years. If this is given at around the age of 70, more than 10 years will have elapsed by the time such individuals are in their 80s and 90s and at greatest risk of requiring institutionalized care.

The fact that this particularly aggressive outbreak was caused by *S. pneumoniae* serotype-8, a highly invasive strain with a very high case-to-carrier ratio [22], is of concern. To date serotype-8 has not been one of the main causes of IPD in the UK [23], and there has only been one previously reported small institutional outbreak due to this serotype [24]. However, the number of reports of IPD due to serotype-8 in those aged ≥ 65 years has increased by 15% from 2003–2006 to 2009–2011 (PHE, unpublished data). This could reflect natural secular fluctuations in serotype-8 disease [25]. Alternatively, this trend could be a response

to the introduction of the pneumococcal conjugate vaccines PCV-7 and PCV-13, which do not contain serotype-8, into the childhood vaccination programme in the UK in 2007 and 2010, respectively. While there is clear evidence of serotype replacement following the introduction of both PCV-7 and PCV-13 in the UK, it is not yet clear whether this is leading to an overall increase in carriage of serotypes with a high case-to-carrier ratio such as serotype-8 and 22 F, which are more virulent and could lead to more frequent outbreaks of highly invasive strains [26]. Further studies of population carriage of different *S. pneumoniae* serotypes since the introduction of PCV-13 are required.

The detection of this outbreak was possible due to Binax testing in the local laboratory to identify cases of pneumococcal disease, followed by the use of a

specialist serotype-specific Bio-Plex multiplex antigen detection assay. This assay has been shown to be 79.3% sensitive and 99.3% specific in validation experiments on clinical urine specimens from patients with matching blood culture of either pneumococcus or other organisms [15]. However, in this outbreak several urine specimens that were negative in the BinaxNOW test, were positive for serotype-specific pneumococcal antigen. This is in line with a recent large study on community-acquired pneumonia, in which 144 patients with BinaxNOW-negative results gave a serotype in the Bio-plex assay [27]. This data, and analytical data from samples spiked with antigens (C. Sheppard, unpublished data), suggest that the multiplex assay is capable of detecting antigen at a much lower level than the Binax assay. Greater use of the Bio-plex assay in cases of suspected pneumococcal disease would appear to be warranted to increase sensitivity and identify the relevant serotype.

The presence of a single clinical case positive for *S. pneumoniae* serotype 6A/C in an outbreak of serotype-8 is interesting. While this case could represent a coincidental case of infection with a non-outbreak serotype, a non-specific cross-reaction between serotypes cannot be ruled out, although the Bio-plex assay has previously been shown to have high serotype specificity (99.3%) [15]. Another alternative explanation is that this represents the detection of antigen from carriage in an elderly patient, as specific data on serotype carriage and associated multiplex urine specimen tests on elderly patients do not exist. However, this patient had clinical symptoms compatible with *S. pneumoniae* infection, and was also BinaxNOW positive, suggesting that this result was not obtained purely by the enhanced sensitivity of the Bio-Plex assay.

Another unusual aspect of this outbreak was that it occurred in the summer, and there was no evidence of any preceding viral respiratory infections in residents.

This study has a number of limitations. In this very rapidly evolving outbreak, the need to take public health action took precedence over the analytical study, so it was not possible to take pre- and post-chemoprophylaxis nasopharyngeal swabs on asymptomatic residents or staff. It was therefore not possible to describe the extent of asymptomatic carriage of the outbreak strain in the population of the residential home, or to evaluate the impact of amoxicillin chemoprophylaxis on carriage. We were therefore not able to disentangle the possible impact of exhaustion of susceptibles, chemoprophylaxis, infection control measures and PPV in halting the progression of the outbreak, although the

latter would have taken 10–14 days to have an effect. No data were collected on the smoking status of residents, so it was not possible to analyse whether smoking was a risk factor or confounder in this outbreak. In the UK, PPV vaccination is not recommended for residential or nursing staff without individual clinical risk factors warranting vaccination, so details of PPV vaccination status of staff were not collected.

This outbreak highlights the importance of early reporting and investigation of clusters of severe respiratory illness in care homes for the elderly all year round, using both culture- and non-culture-based techniques, to enable prompt initiation of control measures. The very high attack rate despite a high level of previous PPV vaccination, and the fact that cases had a longer time since vaccination than non-cases, adds to the small body of evidence that PPV is of only limited effectiveness in preventing pneumococcal pneumonia in the elderly, and that effectiveness wanes over time. This highlights the importance of considering the diagnosis of pneumococcal pneumonia/IPD even in a highly vaccinated population. Furthermore, this outbreak reinforces the need to improve the evidence base on alternative vaccination strategies, including studies on the efficacy of pneumococcal conjugate vaccines in the elderly, although none of the current conjugate vaccines protect against serotype-8 and so would not have provided protection in this particular outbreak. Finally, further work is required on the indirect impact of the universal childhood PCV-13 vaccination programme, including serotype replacement, on serotype-specific pneumococcal pneumonia and IPD in this high-risk population.

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DECLARATION OF INTEREST

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