

# 1 **13-valent vaccine serotype pneumococcal community acquired** 2 **pneumonia in adults in high clinical risk groups**

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28

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39

40 **Abstract**

41 There is debate regarding the value of vaccinating adults with the 13-valent pneumococcal  
42 conjugate vaccine (PCV-13). This analysis was conducted to investigate the risk of PCV-13  
43 serotype community acquired pneumonia (CAP) in hospitalised adults with co-morbid disease  
44 and risk factors for pneumococcal disease in the UK.

45

46 Consecutive adults hospitalised (2008 - 2013) with a primary diagnosis of CAP, were recruited.  
47 Pneumococcal aetiology disease was identified by use of pneumococcal urinary antigen  
48 detection and serotype identification using a validated multiplex immunoassay or serum latex  
49 agglutination. Adults with PCV-13 serotype CAP were compared to those with non-PCV-13  
50 serotype CAP.

51

52 Of 2224 patients, PCV-13 serotype CAP was identified in 337 (15.2%) and non-PCV-13 serotype  
53 CAP in 250 (11.2%) individuals. Adults aged  $\geq 65$  years with one or more clinical risk factors had a  
54 significantly lower risk of PCV-13 serotype CAP compared to those aged 16-64 years without  
55 clinical risk factors (aOR 0.61, 95%CI 0.41-0.92,  $p=0.018$ ). In a stacked-risk analysis, the presence  
56 of incremental clinical risk factors was associated with lower odds of PCV-13 disease ( $p$  for trend

57 = 0.029) Adults with underlying chronic respiratory disease (aOR) 0.56, 95% CI 0.36-0.85,  
58 p=0.007) and chronic kidney disease (aOR 0.48, 95% CI 0.25-0.92, p=0.028) had significantly lower  
59 adjusted odds of PCV-13 compared to non-PCV-13 serotype CAP.

60

61 This analysis suggests that in the UK, the burden of PCV13 disease is greater in adults outside the  
62 traditional 'at-risk' groups compared to adults in 'at-risk' groups.

63

## 64 **Introduction**

65 Increasing age and the presence of co-morbid diseases are recognised risk factors for  
66 pneumococcal disease.<sup>1-4</sup> In addition, pneumococcal attributable mortality is higher in these  
67 clinical risk groups.<sup>5 6</sup> Therefore, implementation of appropriate vaccination strategies is  
68 important for these individuals. The current UK vaccination policy recommends 23-valent  
69 polysaccharide pneumococcal vaccination (PPV-23) in adults at high risk of pneumococcal  
70 disease, comprising (a) adults aged between 16-64 years with certain co-morbid diseases, and (b)  
71 adults aged 65 years and over.<sup>7</sup> However, polysaccharide vaccine effectiveness in these risk  
72 groups is debated.<sup>8-12</sup> Immunogenicity studies have shown higher antibody concentrations and  
73 functional antibody responses to pneumococcal conjugate compared with polysaccharide  
74 vaccination in adults at higher risk of pneumococcal disease including those with human  
75 immunodeficiency virus (HIV), chronic obstructive pulmonary disease and older adults.<sup>13-15</sup>  
76 Therefore, such patients may benefit from the administration of pneumococcal conjugate  
77 vaccination (PCV) in addition to, or in place of the current polysaccharide vaccine. In randomised  
78 controlled trials in Malawi and the Netherlands, administration of the pneumococcal conjugate  
79 vaccine reduced vaccine-type (VT) invasive pneumococcal disease (IPD) and community acquired  
80 pneumonia (CAP) in risk groups of immunocompromised adults with HIV and those over the age  
81 of 65 years, respectively.<sup>16 17</sup> However, any assessment of the benefits of vaccinating adults with  
82 the conjugate vaccine needs to take into account the burden of VT disease in the target group.  
83 In the UK, there has been a substantial decrease in adult pneumococcal VT disease as a  
84 consequence of herd protection following the introduction of the infant pneumococcal  
85 vaccination programme; this decrease is apparent for both invasive and non-invasive

86 pneumococcal disease.<sup>18-21</sup> In patients with IPD, these herd effects appear similar among patients  
87 with and without clinical risk factors for pneumococcal disease.<sup>3</sup> There are no such relevant data  
88 in adults with non-invasive pneumococcal pneumonia.

89

90 In this study, we sought to determine whether hospitalised individuals at high risk of  
91 pneumococcal disease are more likely to have PCV-13 serotype CAP compared to non-PCV-13  
92 serotype CAP.

## 93 **Methods**

### 94 **Study design**

95 We conducted a prospective cohort study of consecutive adult patients admitted, with a primary  
96 diagnosis of community acquired pneumonia, to two large university hospitals in Nottingham,  
97 between September 2008 and 2013. Combined, these two hospitals cover the catchment area  
98 for acute and emergency admissions in the Greater Nottingham area. All patients admitted to  
99 medical admissions units were screened every weekday, using radiological and clinical records,  
100 to assess for study eligibility. Study eligible patients were aged 16 years or over, presenting with  
101 symptoms of a lower respiratory tract infection (at least one of: cough, increasing breathlessness,  
102 sputum production and fever), who had radiographic infiltrates consistent with respiratory  
103 infection, and who were treated by their clinical team for a diagnosis of CAP. Adults hospitalised  
104 in the 10 days preceding the index admission or who had a diagnosis of tuberculosis or post-  
105 obstructive pneumonia were excluded. Informed consent was obtained from all study patients;  
106 in the event that patients lacked capacity, patient personal consultees were approached for proxy  
107 consent. Patient demographics and clinical details were collected from patient records. All study  
108 procedures were approved by Nottingham Research Ethics Committee.

109

### 110 **Study population**

111 Routine microbiological investigations were performed at the discretion of the clinical team. In  
112 addition, urine samples were taken on admission from each individual for pneumococcal specific  
113 microbiological analysis; Binax-NOW<sup>®</sup> assays were performed for pneumococcal C-

114 polysaccharide urinary antigen detection (UAD) at the local microbiological laboratories whilst  
115 the remaining volume of urine was frozen and batch transported to Public Health England (PHE)'s  
116 Respiratory and Vaccine Preventable Bacteria Reference Unit in Colindale for serotyping of  
117 pneumococcal strains by a multiplex immunoassay (Bio-plex). The Bio-plex assay was validated  
118 for detection of pneumococcal serotypes 1, 3, 4, 5, 6A/C, 6B, 7F/A, 8, 9V, 14, 18, 19A, 19F and  
119 23F.<sup>22</sup> The sensitivity and specificity for pneumococcal detection using the Binax-NOW<sup>®</sup> method,  
120 is 74% and 97%, respectively and for the Bio-plex method, is 79% and 99%, respectively.<sup>22 23</sup>  
121 Bacteraemic cases of CAP due to *Streptococcus pneumoniae* were identified and serotyped by  
122 serum latex agglutination at PHE's reference laboratory. Patients were considered to have  
123 pneumococcal CAP if any of the following criteria were met: (a) a positive pneumococcal UAD, or  
124 (b) a positive blood culture for *S pneumoniae*, or (c) pneumococcal serotype detection by the Bio-  
125 plex assay.

126

## 127 **Statistical considerations**

128 Statistical analyses were performed using Stata/IC 13.1 (©StataCorp., 2013). Serotypes were  
129 grouped into PCV-7 types (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F), 'additional' PCV-13 types  
130 not present in PCV-7 (serotypes 1, 3, 5, 6A/C, 7F/A, 19A) and 'other' non-PCV-13 serotypes. PCV-  
131 13 disease was defined as the identification of one or more of serotypes in either the PCV-7 or  
132 'additional' PCV-13 groups. Non-PCV-13 disease was defined as the isolation of any other  
133 pneumococcal serotype or the presence of 'untyped' non-invasive pneumococcal CAP (based on  
134 a positive UAD). Baseline characteristics and putative co-morbid disease risk factors for PCV-13  
135 disease were compared using Pearson's chi-square or Fisher's tests for categorical variables, and



136 the Mann Whitney U-test for non-parametric continuous variables. The independent association  
137 between baseline co-morbidity and PCV-13 disease compared to non-PCV-13 disease was  
138 examined using a multivariable logistical regression model; those co-morbid diseases with a p  
139 value of < 0.2 on univariate analysis were included in the multivariable model. Likelihood ratio  
140 tests were used to determine the best model fit for continuous variables. Secondary analysis  
141 were conducted examining the odds of PCV-13 disease in (a) all 'at-risk' individuals (defined as  
142 those aged 16-64 with a clinical risk factor for pneumococcal disease *or* those  $\geq$  65 years), (b)  
143 individuals stratified according to age (dichotomised at 65 years) and the presence of a clinical  
144 risk factor for pneumococcal disease: (1) aged 16-64 years without a clinical risk factor, (2) aged  
145 16-64 years with one or more clinical risk factors, (3) aged  $\geq$ 65 years without a clinical risk factor,  
146 (4) aged  $\geq$ 65 years with one or more clinical risk factors and (c) individuals with increasing  
147 numbers of clinical risk factors; gender was included *a priori* in these models. Clinical risk factors  
148 for pneumococcal disease were defined as those eligible for pneumococcal vaccination in the UK  
149 as described in PHE's 'Immunisation against Infectious Diseases'; in brief, risk factors included  
150 chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease,  
151 immunosuppression, diabetes, splenic dysfunction and individuals with cerebrospinal fluid (CSF)  
152 leaks or cochlear implants.<sup>7</sup> Immunosuppression was defined as the presence of splenic  
153 dysfunction, haematological disease including malignancy, solid organ or bone marrow  
154 transplant, immunodeficiency, treatment with immunosuppressive medication (not including  
155 steroids) or HIV; all other case definitions were derived from a previous study examining clinical  
156 risk groups in pneumococcal disease.<sup>24</sup>

157

158 Incidence data for pneumococcal CAP in the Greater Nottingham area were calculated using data  
159 on population demographics collected from (a) the National Infection Service, PHE, for adults  
160 aged 16-64 with clinical risk factors, and (b) the UK census (2011) for adults aged  $\geq 65$  years.<sup>25</sup>  
161 As there is no national registry of risk groups for pneumococcal disease, population demographic  
162 data for influenza risk groups were taken as a surrogate measure for incidence calculations.<sup>26</sup>  
163

164 **Results**

165 **Study population**

166 Over the 5 year study period, 2702 patients were eligible for study inclusion. Of these, 284  
167 (10.5%) were subsequently found to have an alternative diagnosis to CAP and in a further 194  
168 patients, study consent was not obtained. The final study cohort consisted of 2224 adults.  
169 Patients in whom consent was not obtained were older (median age: 82 years, IQR 73-89 years  
170 versus 71 years, IQR 56-80 years,  $p<0.001$ ) and were more likely to have chronic kidney disease  
171 (13.4% versus 7.6%,  $p=0.004$ ), cerebrovascular disease (21.8% versus 9.1%,  $p<0.001$ ) and  
172 dementia (33.5% versus 2.0%,  $p<0.001$ ) compared to patients in the study cohort. They were also  
173 less likely to have chronic respiratory disease (14.4% versus 25.7%,  $p<0.001$ ). No other biases in  
174 co-morbid diseases were observed.

175 Pneumococcal CAP was diagnosed in 643 of 2224 (28.9%) individuals. Urine was unavailable for  
176 serotype analysis in 56 (8.7%) of 643 cases. One or more serotypes were identified in 429 (66.7%)  
177 of 643 cases of pneumococcal CAP; the remainder represent untyped cases of pneumococcal  
178 CAP. Cases where urine was unavailable for serotyping were excluded from analysis of the  
179 association of clinical risk group and PCV-13 disease.

180

181 **Baseline characteristics**

182 Of 643 patients with pneumococcal CAP, 294 (45.7%) had one or more clinical risk factors for  
183 pneumococcal disease; of these, chronic respiratory disease ( $n=130$ , 44.2%) and chronic heart  
184 disease ( $n=124$ , 42.2%) represented the majority of cases. There were 68 patients (10.6%) aged

185 16-64 years with a clinical risk factor and 377 (58.6%) patients were aged  $\geq$  65 years. Three  
186 hundred and forty nine (54.3%) patients with pneumococcal disease had no underlying clinical  
187 risk factor for pneumococcal disease; one clinical risk factor was present in 205 (31.9%) patients,  
188 two clinical risk factors were present in 62 (9.6%) patients and three or more clinical risk factors  
189 were present in 27 (4.2%). Diabetes (9.8%) and chronic respiratory disease (8.7%) represented  
190 the most common co-morbid diseases amongst patients aged 16-64 years, whilst chronic heart  
191 disease (29.2%) and chronic respiratory disease (28.4%) were the most common co-morbid  
192 diseases amongst those aged  $\geq$  65 years (**Table 1**). There were no patients with cochlear implants  
193 or CSF fluid leaks.

194

#### 195 **Clinical risk groups and PCV-13 disease**

196 Of 587 pneumococcal CAP cases where a urine was available for serotype identification, PCV-13  
197 and non-PCV-13 disease comprised 337 (57.4%) and 250 (42.6%) cases respectively. Baseline  
198 characteristics of patients with PCV-13 and non-PCV-13 serotype CAP are shown in (**Table 2**).  
199 Patients with underlying chronic respiratory disease and chronic kidney disease had significantly  
200 lower odds of PCV-13 disease compared to non-PCV-13 disease (adjusted Odds Ratio (aOR) 0.56,  
201 95% CI 0.36-0.85,  $p=0.007$ , and aOR 0.48, 95%CI 0.25-0.92,  $p=0.028$ , respectively). Conversely,  
202 those with dementia had significantly higher odds of PCV-13 disease (aOR 3.91, 95%CI 1.10-  
203 13.91,  $p=0.036$ ).

204

205 Of patients with pneumococcal CAP, 184 (31.4%) were aged 16-64 years with no clinical risk  
206 factors, 57 (9.7%) were aged 16-64 years with one or more clinical risk factors, 133 (22.7%) were

207 aged  $\geq 65$  years with no clinical risk factors and 213 (36.3%) were aged  $\geq 65$  years with one or  
208 more clinical risk factors. In the gender-adjusted model, patients aged  $\geq 65$  years with one or  
209 more clinical risk factors had a significantly lower risk of PCV-13 serotype CAP compared to those  
210 aged 16-64 years without clinical risk factors (aOR 0.61, 95%CI 0.41-0.92,  $p=0.018$ ) (**Table 3**). In a  
211 stacked-risk analysis adjusted for gender and age, the presence of incremental clinical risk factors  
212 was associated with lower odds of PCV-13 disease (**Figure 1**). The gender-adjusted odds of PCV-  
213 13 disease was lower in patients that comprised the total 'at-risk' group (those aged 16-64 years  
214 with clinical risk factors or those aged  $\geq 65$  years): aOR 0.71, 95%CI 0.49-1.02,  $p=0.062$ .

215

#### 216 **Serotype distribution of pneumococcal CAP by risk group**

217 **Table 4** shows the distribution of single serotypes with  $>10$  isolates. Serotypes 7F/A and 8 were  
218 the most common, both being isolated in 69 patients. Using serotype 8 as reference, serotypes  
219 3, 5 and 14 were significantly associated with causing disease in 'at-risk' patients compared to  
220 those not at-risk whilst serotype 7F/A was associated with lower odds of disease in 'at-risk'  
221 patients.

222

#### 223 **Incidence of pneumococcal CAP in clinical risk groups**

224 The overall incidence of pneumococcal CAP was 20.7 per 100,000 persons whilst that of PCV-13  
225 CAP was 10.8 per 100,000 and non-PCV-13 CAP was 8.0 per 100,000. The highest overall  
226 incidence of pneumococcal CAP was observed in those over 65 years (64.3 per 100,00); in these  
227 patients the incidence of PCV-13 serotype CAP was 32.9 per 100,000 persons, and that of non-

228 PCV-13 serotype CAP was 26.1 per 100,000 persons. The incidence of PCV-13 and non-PCV-13  
229 pneumococcal CAP by clinical risk group is shown in **Figure 2**. Incidence rates of non-PCV-13  
230 serotype CAP was two to three fold that of PCV-13 serotype CAP in patients aged 16-64 years  
231 with chronic liver disease and those who were immunocompromised. Conversely, patients aged  
232 16-64 years with diabetes had a higher incidence of PCV-13 compared to non-PCV-13 serotype  
233 CAP (16.7 versus 5.6, per 100,000 persons).

234

### 235 **Mortality**

236 Overall, 30-day mortality in patients with pneumococcal CAP was 7.5%. Of those individuals 'at-  
237 risk' of pneumococcal disease, 30-day pneumococcal CAP mortality was 10.3% compared to 1.0%  
238 in those under 65 years considered not at risk. The highest pneumococcal CAP mortality was  
239 observed in individuals  $\geq 65$  years with a clinical risk factor (14.2%), followed by those  $\geq 65$  years  
240 without a clinical risk factor (8.6%). For those under 65 years with a clinical risk factor, 30-day  
241 mortality was 1.5%. There was no significant difference in 30-day mortality in all individuals with  
242 PCV-13 compared to non-PCV-13 serotype CAP (8.3% vs 7.6%; OR 1.10, 95% CI 0.60-2.02,  
243  $p=0.755$ ), nor in those individuals classified as 'at-risk' (11.7% vs 10.5%; OR 1.13, 95% CI 0.60-  
244 2.12,  $p=0.701$ ).

245

246 **Discussion**

247 In adults hospitalised with pneumococcal CAP, we found that PCV-13 serotype CAP was 44% less  
248 likely in patients with chronic respiratory disease and 52% less likely in chronic kidney disease  
249 compared to non-PCV-13 serotype CAP. The odds of PCV-13 serotype CAP were significantly  
250 lower with increasing numbers of clinical risk factors for pneumococcal infection.

251

252 These results are consistent with findings observed from studies in adult IPD, where PCV-13  
253 serotypes have been shown to be less frequently associated with the presence of underlying co-  
254 morbid disease, compared to non-PCV-13 serotypes.<sup>5 27 28</sup> Similarly, a 16-year cohort study  
255 demonstrated that individuals with chronic respiratory disease and chronic kidney disease were  
256 more likely to have non-vaccine type (NVT) (non-PCV-13 and non-PPV-23) IPD compared to PCV-  
257 13 disease.<sup>28</sup> However, in contrast to analyses in IPD cohorts which have shown an association  
258 with younger age and PCV-13 serotype disease, we observed no association between PCV-13  
259 serotype disease and age.<sup>5 28</sup>

260

261 In the UK, introduction of the infant vaccination programme has been highly successful in  
262 reducing VT serotype IPD as a consequence of herd protection.<sup>18 29 30</sup> Whether these reductions  
263 in VT disease equally apply to adults at clinical risk of pneumococcal disease as to other adults is  
264 less well defined.<sup>3 31 32 33</sup> In addition, despite overall decreases in VT pneumococcal disease,  
265 increases in NVT IPD have been observed in at risk populations including the  
266 immunocompromised and those over 65 years.<sup>20 28 34</sup> Our findings, involving mainly adults with

267 non-invasive CAP, adds to the evidence base that older adults with clinical risk factors are more  
268 likely to have non-PCV-13 serotype CAP compared to PCV-13 serotype CAP. Differences in the  
269 invasive potential of pneumococcal serotypes may provide a possible explanation for these  
270 observations; non-PCV-13 serotypes are generally less invasive compared to PCV-13 serotypes.<sup>27</sup>  
271 Consequently, non-PCV-13 serotypes may be more likely to act as opportunistic pathogens in  
272 older patients with co-morbid diseases.<sup>35-38</sup>

273

274 Our finding that patients with dementia were much more likely to be hospitalised with CAP due  
275 to PCV-13 serotypes was dominated by patients with dementia who had PCV-7 serotype disease  
276 (11 of 19 patients) identified in the first 2 years of the study. Whilst social isolation and lack of  
277 child contact in patients with dementia might explain this finding, confirmation of this association  
278 in a different patient cohort is necessary.<sup>39</sup>

279

280 In adults under 65 years, the presence of chronic liver disease or immunocompromise were  
281 associated with the highest incidence of pneumococcal CAP. Van Hoek *et al* linked UK IPD cases  
282 to Hospital Episode Statistics (HES) data to estimate incidence rates for clinical risk groups; they  
283 too demonstrated that the highest incidence of pneumococcal disease in this age group occurred  
284 in these conditions.<sup>3</sup> The absolute incidence rates for each clinical risk factor were considerably  
285 lower in our study compared to that of Van Hoek *et al* and two similar population based IPD  
286 studies conducted in Finland and the Netherlands.<sup>3626</sup> Possible reasons for this difference include  
287 (a) the inclusion of infants and children in previous IPD studies and (b) incomplete recruitment  
288 of adults in certain high risk groups, to the current study.



289

290 **Strengths and limitations of this analysis**

291 To our knowledge this is the first report to describe the relationship between clinical risk factors  
292 for pneumococcal disease and PCV-13 serotype CAP in adults. A key strength of this study is the  
293 identification of pneumococcal serotypes in non-bacteraemic cases of CAP. The main limitation  
294 of the study was the inability to detect non-PCV-13 serotypes other than serotype 8 in patients  
295 with non-bacteraemic CAP. For the comparative analysis, patients with untyped pneumococcal  
296 CAP were considered to have non-PCV-13 serotype CAP. Although the Bio-plex assay has a high  
297 sensitivity for the detection of 14 serotypes, some patients with untyped pneumococcal CAP may  
298 have had PCV-13 serotype CAP; thus any differences identified between groups are likely to be  
299 conservative for the association with PCV-13 serotype disease. The overall proportion of study  
300 patients with dementia as a co-morbid illness was low in this study. Whilst this may be a true  
301 finding, we are unable to exclude temporal selection bias given the high prevalence of PCV-7  
302 serotypes and contemporaneous national data from the British Thoracic Society CAP audit which  
303 demonstrated an increase in the proportions of patients with dementia over the study period  
304 (the inverse of which was seen in the present study).<sup>40</sup>

305

306 For incidence calculations, population level data on influenza risk groups from 2015/16 were used  
307 in place of pneumococcal clinical risk groups as a national registry of the latter is lacking.  
308 Influenza risk groups overlap with pneumococcal clinical risk groups, with the exception of  
309 cochlear implants and CSF leaks, the latter two of which had no study patients. The impact of this  
310 limitation on study results is likely to be small. Completeness of case ascertainment and

311 microbiological testing would also be expected to influence incidence calculations. A small  
312 proportion of patients admitted over weekends and with very short lengths of stay may not have  
313 been recruited to the study; urine samples were also not available for serotype analysis in 56  
314 (8.7%) patients with pneumococcal CAP. Therefore, incidence rate estimates are likely to be  
315 conservative.

### 316 **Implications of results**

317 Whilst PCV-13 vaccine efficacy against VT serotype pneumococcal pneumonia has been  
318 demonstrated in older adults, the effect of conjugate vaccine administration across other clinical  
319 risk groups remains uncertain.<sup>17</sup> An important question for pneumococcal vaccine policy is  
320 whether there are identifiable groups of adults at risk of VT disease despite herd protection  
321 effects arising from pneumococcal vaccination programmes. We found that in the presence of a  
322 strong infant pneumococcal vaccination programme, the burden of PCV13 disease is greater in  
323 adults outside the traditional 'at-risk' groups compared to adults in 'at-risk' groups. Adults in the  
324 traditional 'at-risk' groups were more likely to be hospitalised with non-PCV-13 serotype CAP  
325 than PCV-13 serotype CAP. Offering PCV-13 vaccination to adults in clinical risk groups may  
326 therefore be of limited benefit in this setting.

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## **Author contributions**

Study conception and design: PD, CT and WSL

Acquisition of data: CR, TB, SG and CS

Analysis and interpretation of data: PD, CT, TM and WSL

Drafting of manuscript: PD and WSL

Critical revision: all authors

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## **Conflicts of interest**

PD - received salaries derived from an investigator initiated unrestricted grant from Pfizer

CR - received salaries part funded by an NIHR grant and an investigator initiated unrestricted grant from Pfizer during his research

TB – received salaries derived from an investigator initiated unrestricted grant from Pfizer during his research

SG – received salaries derived from an unrestricted grant from Pfizer

TMM - nil

CS - nil

CT – received consulting payment from GSK in 2013 and an honorarium from Sanofi Pasteur in 2015

WSL – received grants from the National Institute of Health Research and an investigator initiated unrestricted grant from Pfizer.

## **Table and figures**

**Table 1 – Distribution of co-morbid diseases in adults with pneumococcal CAP**

	<b><i>16-64 years</i></b> <i>n=266</i>	<b><i>≥65 years</i></b> <i>n=377</i>
Chronic heart disease	14 (5.3)	110 (29.2)
Chronic respiratory disease	23 (8.7)	107 (28.4)
Diabetes	26 (9.8)	56 (14.9)
Chronic kidney disease	4 (1.5)	44 (11.7)
Chronic liver disease	6 (2.3)	4 (1.1)
Immunosuppressed	8 (3.0)	10 (2.7)
Cancer	12 (4.5)	26 (6.9)
Dementia	0 (0.0)	19 (5.0)
Cerebrovascular disease	5 (1.9)	62 (16.5)

All values given as n (%)

Table 2 - Clinical features of adults admitted with CAP and comparative analysis of those with PCV-13 versus non-PCV-13 serotype CAP

	<i>All cause CAP</i>	<i>Pneumococcal CAP</i>		<i>OR (95%CI)</i>	<i>p value</i>
	(n=2224)	PCV-13 disease (n=337)	Non-PCV-13 disease (n=250)		
<b>Age</b>					
16-49 years	431 (19.4)	86 (25.5)	58 (23.2)	Reference	0.216 <sup>†</sup>
50-64 years	424 (19.1)	58 (17.2)	39 (15.6)	1.00 (0.59-1.70)	
65-74 years	468 (21.0)	75 (22.3)	44 (17.6)	1.15 (0.70-1.90)	
75-84 years	577 (25.9)	67 (19.9)	72 (28.8)	0.63 (0.39-1.01)	
≥85 years	324 (14.6)	51 (15.1)	37 (14.8)	0.93 (0.54-1.59)	
<b>Male</b>	1225 (55.1)	180 (53.4)	115 (46.0)	1.35 (0.97-1.87)	0.076
<b>Care home resident<sup>‡</sup></b>	92 (4.2)	15 (4.5)	13 (5.2)	0.86 (0.40-1.85)	0.702
<b>PPV23 vaccination<sup>‡</sup></b>	931 (47.3)	123 (41.6)	108 (50.2)	0.70 (0.49-1.00)	0.052
<b>Smoking status<sup>‡</sup></b>					
Never	612 (29.1)	82 (25.8)	64 (27.2)	Reference	0.864 <sup>†</sup>
Ex	989 (46.9)	144 (45.3)	97 (41.3)	1.16 (0.76-1.76)	
Current	506 (24.0)	92 (28.9)	74 (31.5)	0.97 (0.62-1.52)	
<b>Alcohol excess</b>	47 (2.1)	9 (2.7)	7 (2.8)	0.95 (0.35-2.60)	0.924
<b>Chronic respiratory disease</b>	572 (25.7)	52 (15.4)	66 (26.4)	0.51 (0.34-0.77)	<b>0.001</b>
Asthma	267 (12.0)	40 (11.9)	39 (15.6)	0.73 (0.45-1.17)	0.191
COPD	509 (22.9)	46 (13.7)	60 (24.0)	0.50 (0.33-0.77)	<b>0.001</b>
<b>Chronic heart disease</b>	500 (22.5)	63 (18.7)	53 (21.2)	0.85 (0.57-1.29)	0.451
CCF	146 (6.6)	19 (5.6)	15 (6.0)	0.94 (0.47-1.88)	0.853
IHD	249 (11.2)	28 (8.3)	27 (10.8)	0.75 (0.43-1.31)	0.306
<b>Diabetes</b>	305 (13.7)	48 (14.2)	26 (10.4)	1.43 (0.86-2.38)	0.166
<b>Chronic liver disease</b>	24 (1.1)	5 (1.5)	5 (2.0)	0.74 (0.21-2.58)	0.751
<b>Chronic kidney disease</b>	169 (7.6)	17 (5.0)	27 (10.8)	0.44 (0.23-0.83)	<b>0.009</b>
<b>Immunocompromised</b>	82 (3.7)	6 (1.8)	8 (3.2)	0.55 (0.19-1.60)	0.265

<b>Severely immunocompromised*</b>	22 (1.0)	0 (0.0)	5 (2.0)	-	-
<b>Active malignancy</b>	169 (7.6)	21 (6.2)	13 (5.2)	1.21 (0.59-2.47)	0.597
<b>Dementia</b>	45 (2.0)	16 (4.8)	3 (1.2)	4.10 (1.17-14.34)	<b>0.016</b>
<b>Cerebrovascular disease</b>	202 (9.1)	42 (12.5)	23 (9.2)	1.41 (0.82-2.41)	0.213
<b>Number of clinical risk factors:</b>					
<b>0</b>	1078 (48.5)	198 (58.8)	119 (47.6)	Reference	<b>0.016<sup>†</sup></b>
<b>1</b>	751 (33.8)	98 (29.1)	92 (36.8)	0.64 (0.44-0.92)	
<b>2</b>	289 (13.0)	30 (8.9)	26 (10.4)	0.69 (0.39-1.23)	
<b>≥3</b>	106 (4.8)	11 (3.3)	13 (5.2)	0.51 (0.22-1.18)	
<b>Low severity (CURB65≤1)</b>	1029 (46.3)	134 (39.8)	100 (40.0)	Reference	0.732 <sup>†</sup>
<b>Moderate severity (CURB65=2)</b>	684 (30.8)	107 (31.8)	84 (33.6)	0.95 (0.65-1.40)	
<b>High severity (CURB65≥3)</b>	511 (23.0)	96 (28.5)	66 (26.4)	1.09 (0.72-1.63)	
<b>30-day mortality</b>	230 (10.3)	28 (8.3)	19 (7.6)	1.10 (0.60-2.02)	0.755

All values expressed as n (%); †- p for trend; ¥- care home and smoking status unavailable for 26 and 117 patients, respectively.

PPV23 – 23-valent pneumococcal polysaccharide vaccine (¥ data unavailable for 254 patients), COPD – chronic obstructive pulmonary disease, CCF – congestive cardiac failure, IHD – ischaemic heart disease. \* - severely immunocompromised group consists of bone marrow transplant patients, patients with acute and chronic leukaemia, multiple myeloma or those with genetic disorders affecting the immune system

OR and p values compare PCV-13 serotype disease to non-PCV-13 disease.



**Table 3 – Association between clinical risk group and PCV-13 disease**

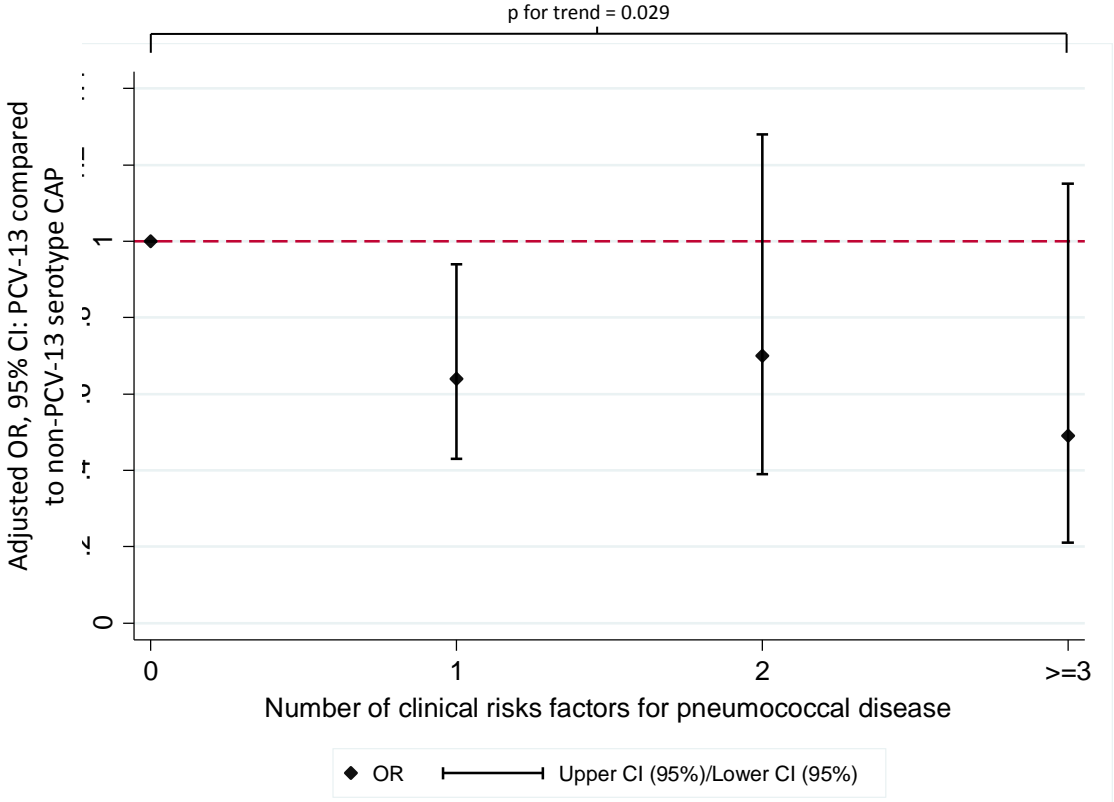
	<i>aOR (95% CI)</i>	<i>p value</i>
<b>16-64 yrs with no clinical risk factor</b>	Reference	-
<b>16-64 yrs with clinical risk factor(s)</b>	0.58 (0.32-1.06)	0.077
<b>≥65 yrs with no clinical risk factor</b>	0.98 (0.61-1.55)	0.915
<b>≥65 yrs with clinical risk factor(s)</b>	0.61 (0.41-0.92)	<b>0.018</b>
<b>Male gender</b>	1.43 (1.02-1.99)	<b>0.037</b>

**Table 4 – Association between pneumococcal serotypes and individuals at risk of pneumococcal disease**

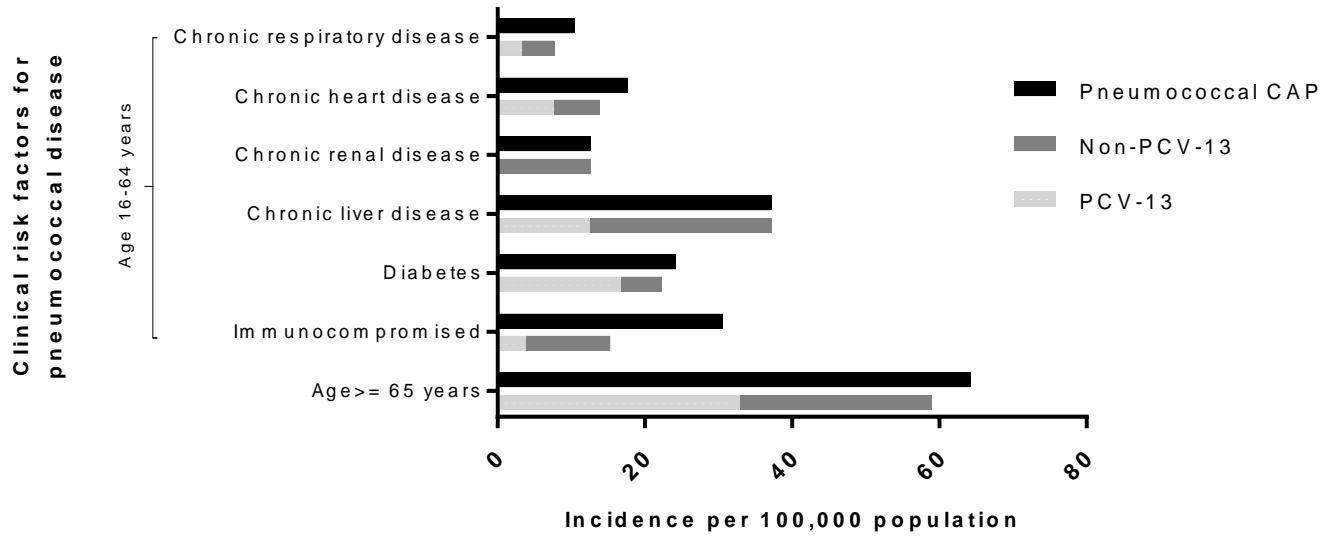
<i>Serotype</i>	<i>'At-risk' group (n=403)</i>	<i>No risk group (n=184)</i>	<i>OR (95%CI)</i>	<i>P value</i>
1	34	28	0.78 (0.39-1.57)	0.485
3	21	3	4.50 (1.22-16.56)	<b>0.024</b>
4	9	7	0.83 (0.28-2.48)	0.734
5	20	4	3.21 (0.99-10.43)	<b>0.052</b>
6A/C	19	4	3.05 (0.94-9.95)	0.064
7F/A	25	44	0.37 (0.18-0.73)	<b>0.004</b>
8	42	27	Reference	
14	41	9	2.93 (1.23-6.98)	<b>0.015</b>
19A	27	11	1.58 (0.67-3.70)	0.294

All values given as n; 'At-risk' group defined as those aged 16-64 years with clinical risk factors for pneumococcal disease or those aged ≥65 years

Figure 1 – Gender and age adjusted odds of PCV-13 serotype CAP with increasing numbers of clinical risk factors for pneumococcal infection



**Figure 2 - Incidence of PCV-13 and non-PCV-13 pneumococcal CAP by age and clinical risk group**



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