

**Interim JCVI statement on adult pneumococcal vaccination in the UK****November 2015****Summary**

1. There has been a significant reduction in pneumococcal disease due to conjugate vaccine serotypes in the UK, in all ages, resulting from the direct and indirect impact of the very successful UK childhood pneumococcal conjugate vaccination (PCV) programmes.<sup>1 2</sup> The vaccine first used in the childhood programme, PCV7, has within seven years led to a near elimination of PCV7 vaccine-type invasive pneumococcal disease (IPD) in the UK. Since moving to use of the PCV13 vaccine in 2010, there has also been a significant reduction in disease caused by the six additional serotypes in PCV13. JCVI believes that it is likely this trend will continue, and there will be a near elimination of PCV13 vaccine-type IPD in all ages within the next three years.
2. Evidence indicates that the indirect impact of the childhood vaccination programme in the UK is leading to a reduction in both vaccine-type IPD and vaccine-type community acquired pneumonia (CAP).<sup>3</sup> Reductions in IPD in sentinel risk-groups, such as HIV-positive individuals, indicate that the indirect effects of the childhood programme are also being seen in those individuals in clinical risk-groups in the UK.<sup>4 5</sup>
3. While evidence indicates that the vaccination of immunocompetent individuals aged 65 years and over with PCV13 is efficacious in preventing vaccine type IPD and CAP, evidence does not indicate any impact of vaccination on all-cause mortality in this group<sup>6</sup>. Evidence is still lacking regarding the efficacy of PCV13 vaccine in many individual clinical risk groups, although data does indicate a lack of efficacy in adults aged 65 years and over who are immunocompromised.<sup>6</sup> It has therefore been important for JCVI to consider whether the reducing incidence of PCV13 vaccine-type disease in all ages in

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<sup>1</sup> <https://www.gov.uk/government/collections/pneumococcal-disease-guidance-data-and-analysis>

<sup>2</sup> Waight *et al* (2015) Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. *Lancet Infect Dis* 15: 535-43

<sup>3</sup> Rodrigo *et al* (2015) Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. *Eur Respir J* 45(6):1632-41.

<sup>4</sup> van Hoek AJ *et al* (2012) The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. *J Infect* 65(1):17-24.

<sup>5</sup> Yin Z *et al*, (2012) Invasive pneumococcal disease among HIV-positive individuals, 2000-2009. *AIDS* 26(1):87-94.

<sup>6</sup> Bonten MJ, Huijts SM, Bolkenbaas M, et al (2015) Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med* 372(12):1114-25.

the UK makes the benefits of vaccinating additional groups so limited as to not be cost-effective.

4. JCVI therefore considered evidence on the cost-effectiveness of PCV13 vaccination of adults aged 65 years and over.<sup>7</sup> The findings of this analysis agree with the qualitative assessment of the Committee, and indicate that it is highly unlikely that a programme to vaccinate those aged 65 years and over in the UK with PCV13 would be cost-effective at this time. It is also likely that any programme would become less cost-effective in future, as the indirect impact of the childhood PCV13 vaccination programme continues to accumulate.
5. Evidence on the efficacy of pneumococcal polysaccharide vaccine (PPV) in those aged 65 years and over and in clinical risk groups, while limited, does indicate that PPV23 may provide some short-lived protection against IPD.<sup>8</sup> Taken as a whole, the evidence does not demonstrate an impact against CAP and there is no direct evidence of efficacy against death. As the PPV23 vaccine includes eleven pneumococcal serotypes not found in the PCV13 vaccine, the Committee considered that continuation of a PPV23 vaccine programme to vaccinate those aged 65 years and over and those in clinical risk groups continues to be clinically justified at this time.
6. A qualitative analysis<sup>9</sup> of the data also indicates that use of PPV23 is likely to remain cost-effective at this time. However, as the incidence of pneumococcal disease caused by the twelve serotypes common to PCV13 and PPV23 continues to decline in all age groups, use of PPV23 vaccine may cease to be cost-effective in the medium term, and JCVI will keep this under review. JCVI noted considerable uncertainty in the parameterisation of the PPV23 cost-effectiveness analysis, and has asked the Cost-Effectiveness Methodology for Immunisation Programmes and Procurements (CEMIPP) to consider providing advice on how uncertainty should be considered with regards to discontinuation of vaccination programmes.
7. Overall JCVI concluded that there should be no changes to the advice on adult pneumococcal vaccination in the UK at this time. PPV23 should continue to be offered to those aged 65 years and over and the indicated risk groups. PCV13 should continue to be offered to those risk groups previously identified as being

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7 van Hoek and Miller (unpublished) Cost-effectiveness of vaccinating immunocompetent elderly with the 13-valent pneumococcal conjugate vaccine in England.

<sup>8</sup> Andrews *et al* (2012) Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. *Vaccine* 30(48):6802-8.

<sup>9</sup> PHE (unpublished), Qualitative analysis of Melegaro A and Edmunds WJ (2004) The 23-valent pneumococcal polysaccharide vaccine. Part II. A cost-effectiveness analysis for invasive disease in the elderly in England and Wales. *Eur J Epidemiol* 19(4):365-75.

at particularly high risk of, and high mortality from, IPD, but should not be offered more widely to other risk-groups or older adults.

8. The epidemiology of pneumococcal disease is still evolving following the introduction of PCV13 into the childhood programme, and as such JCVI will keep the adult pneumococcal programme under review. It has been agreed that JCVI will consider the use of PPV23 again in three years, when it is anticipated that pneumococcal epidemiology in the UK may have achieved a steady state.

## Background

9. Prior to introduction of the routine childhood pneumococcal vaccination programme, there was a significant burden of pneumococcal disease in the UK, particularly affecting the very young, the elderly and those in clinical risk groups.
10. In 1992 pneumococcal polysaccharide immunisation was recommended for all those with medical conditions for whom pneumococcal infection was likely to be more serious. In 2003 this recommendation was extended to include all those aged 65 years and over, based on cost-effectiveness analyses<sup>10 11</sup> considered by JCVI.
11. In 2002, pneumococcal conjugate vaccine containing polysaccharide from seven common capsular types (PCV7) was recommended for all those in clinical risk groups less than two years of age, and in 2004 this was extended to all those in clinical risk groups less than five years of age. In 2006, PCV7 was added into the routine childhood vaccination programme for all children. In April 2010 PCV7 was replaced by the PCV13 vaccine.
12. In 2013 JCVI advised against the routine use of the PCV13 vaccine in older adults and clinical risk groups because of accumulating indirect protection being seen in all age groups as a result of the childhood PCV7 and PCV13 programmes.<sup>12</sup> However, JCVI advised that some clinical risk groups with a particularly elevated risk of, and high mortality from, IPD would benefit from immunisation with PCV13 in the short-term while PCV13 vaccine serotypes continued to circulate.<sup>11</sup>

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<sup>10</sup> Melegaro A and Edmunds WJ (2004) The 23-valent pneumococcal polysaccharide vaccine. Part I. Efficacy of PPV in the elderly: a comparison of meta-analyses. *Eur J Epidemiol* 19(4):353-63;

<sup>11</sup> Melegaro A and Edmunds WJ (2004) The 23-valent pneumococcal polysaccharide vaccine. Part II. A cost-effectiveness analysis for invasive disease in the elderly in England and Wales. *Eur J Epidemiol* 19(4):365-75.

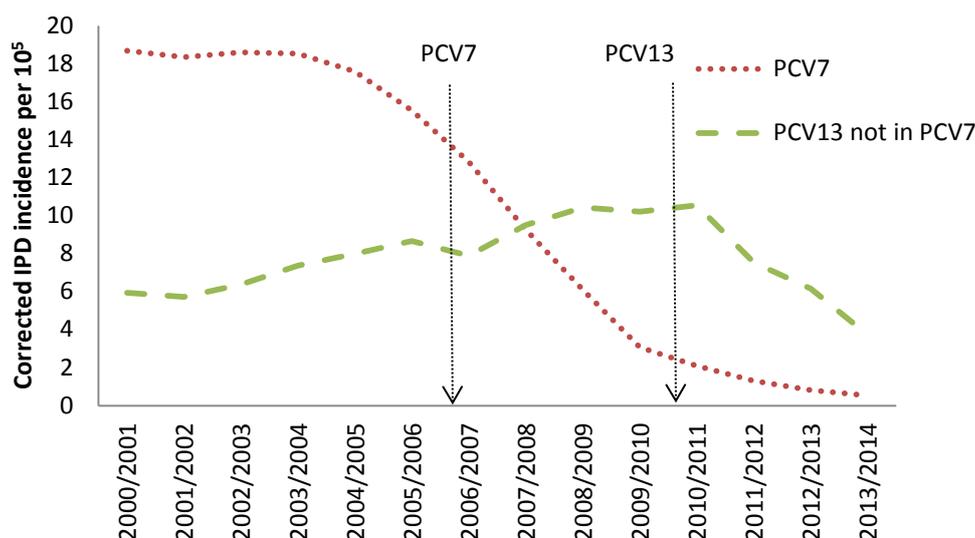
<sup>12</sup> JCVI statement on the wider use of pneumococcal conjugate vaccines in the UK (July 2013)

<https://www.gov.uk/government/publications/jcvi-statement-on-the-wider-use-of-pneumococcal-conjugate-vaccines>

Epidemiology

13. The impact of the childhood PCV7 and PCV13 immunisation programmes on the incidence of IPD and CAP in adults has been substantial. PCV7 vaccine-type IPD has been nearly eliminated in all age groups including those aged 65 years and over (Figure 1). PCV13 vaccine type invasive disease has also significantly reduced in all age groups including those aged 65 years and over (Figure 1), and will also likely diminish to very low levels within the next three years.

Figure 1 – PCV7 and PCV13 Vaccine-type invasive pneumococcal disease in adults aged 65 years and over 2000-2014



14. Similarities in the rates of decline in PCV13 vaccine-type IPD and PCV13 vaccine type CAP over the last five years indicate that the indirect effect of the childhood immunisation programme is of a similar magnitude for both IPD and CAP.<sup>13 14</sup> JCVI considers this biologically plausible, as the indirect effect acts principally to reduce transmission and transmission is required for either IPD or pneumococcal CAP.

<sup>13</sup> Rodrigo *et al* (2015) Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. *Eur Respir J* 45(6):1632-41.

<sup>14</sup> PHE (unpublished) re-analysis of Rodrigo *et al* (2015)

15. There is evidence that the indirect impact of the childhood programme on IPD in healthy adults is also being seen in clinical groups at increased risk of pneumococcal disease, including HIV-positive individuals.<sup>15 16</sup> While there are currently limited data to demonstrate the indirect effects of the PCV13 childhood immunisation programme on vaccine-type CAP in clinical risk groups JCVI agreed that there was currently no compelling evidence to suggest that vaccine-type CAP in risk groups would decline in a different manner to vaccine-type IPD in these groups.

### Vaccine efficacy

#### *Pneumococcal Polysaccharide Vaccine (PPV23)*

16. There are a limited number of trials on the efficacy of PPV23 in those aged 65 years and over without risk-factors. After examining data from observational and intervention studies, and incorporating the literature on efficacy in adults in general, JCVI considered it likely that PPV23 provides some short-lived protection against vaccine-type IPD<sup>17</sup>, but there was unlikely to be any protection against vaccine-type CAP<sup>18</sup>. Evidence regarding efficacy in clinical risk groups is conflicting, and where efficacy was seen duration of protection appeared to be short-lived. One ecological study indicated 63% vaccine effectiveness in immunocompetent clinical risk groups, and 43% vaccine effectiveness in those who were immunocompromised in the first two years following vaccination.<sup>19</sup>
17. Concerns have sometimes been raised around repeat vaccination with PPV giving rise to hypo-responsiveness; however JCVI considered there to be no evidence that this occurred when doses of PPV23 were given five or more years apart, although data are limited.

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<sup>15</sup> van Hoek AJ *et al* (2012) The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. *J Infect* 65(1):17-24.

<sup>16</sup> Yin Z *et al*, (2012) Invasive pneumococcal disease among HIV-positive individuals, 2000-2009. *AIDS* 26(1):87-94.

<sup>17</sup> Andrews *et al* (2012) Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. *Vaccine* 30(48):6802-8.

<sup>18</sup> Moberley S, Holden J, Tatham DP and Andrews RM (2013) Vaccines for preventing pneumococcal infection in adults. *Cochrane Database Syst Rev* 1:CD000422.

<sup>19</sup> Andrews *et al* (2012) Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. *Vaccine* 30(48):6802-8.

*Pneumococcal Conjugate Vaccine (PCV13)*

18. When JCVI last considered use of PCV13 vaccine in older adults and risk groups, there was a lack of evidence regarding efficacy of PCV13 on CAP in adults and individual clinical risk groups<sup>20</sup>. Since that time studies have been undertaken to examine the efficacy of PCV13 on CAP in those aged 65 years and over who are immunocompetent,<sup>21</sup> but there remains little evidence regarding the efficacy of PCV13 in individual clinical risk groups.
19. JCVI reviewed a recently published study to assess the impact of PCV13 vaccination in adults, the Community Acquired Pneumonia Immunisation Trial in Adults (CAPiTA)<sup>21</sup>. JCVI considers this a well conducted study which provides key evidence on the efficacy of PCV13 vaccine on IPD and CAP in immunocompetent older adults.
20. Exclusion of immunocompromised individuals from the study means that a substantial proportion of those aged 65 years and older who are at risk of pneumococcal disease were excluded from the analysis, although evidence from CAPiTA did not suggest efficacy in those who developed immunodeficiency after the start of the trial. A high percentage of individuals enrolled in the CAPiTA study who developed CAP had co-morbidities, but vaccine efficacy estimates in clinical risk groups were not available. One exception with regards to the efficacy of PCV13 in clinical risk groups is in HIV-positive individuals<sup>22</sup>.
21. While the number of deaths in study participants was low, it was notable that the CAPiTA study showed no difference in mortality in those vaccinated versus those who received placebo. Mathematical modelling exercises to estimate cost-effectiveness predict a reduction in mortality based on the product of the vaccine efficacy against pneumococcal pneumonia and the case-fatality ratio of pneumococcal pneumonia and this is an important assumed benefit that was not observed in the trial.

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<sup>20</sup> JCVI statement on the wider use of pneumococcal conjugate vaccines in the UK (July 2013)  
<https://www.gov.uk/government/publications/jcvi-statement-on-the-wider-use-of-pneumococcal-conjugate-vaccines>

<sup>21</sup> Bonten *et al* (2015) Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med* 372(12):1114-25.

<sup>22</sup> Moberley S, Holden J, Tatham DP and Andrews RM (2013) Vaccines for preventing pneumococcal infection in adults. *Cochrane Database Syst Rev* 1:CD000422.

### Clinical risk-groups

22. A review of the evidence indicates that the pneumococcal risk-groups previously identified (Annex A) remain appropriate<sup>23</sup>, although JCVI has asked Public Health England (PHE) to consider a number of small clarifications.

### Cost-effectiveness

#### *PPV23 in those aged 65 years and over and in clinical risk groups*

23. Considerations by JCVI on use of PPV23 in those aged 65 years and over and those in clinical risk-groups overlapped considerably due to the fact that 45% of those aged 65 years and over are in clinical risk groups.
24. A qualitative analysis<sup>24</sup> was undertaken by PHE to update the findings of the 2004 study previously considered by JCVI in its assessment of the cost-effectiveness of PPV23 vaccination of adults 65 years and over. The qualitative analysis took into account the changing epidemiology of pneumococcal disease in the UK, and changes to population demographics.
25. The findings of this work indicate that the PPV23 serotype incidence reduction in 65-69 year olds was about 30% (which is less than the 50% seen in all over 65 year olds) and that this level of reduction would not be sufficient to substantially change the original cost-effectiveness analysis.
26. While there remains considerable uncertainty regarding PPV23 efficacy for IPD in risk groups, JCVI agreed that the evidence indicates the vaccine may provide some short-lived protection against IPD in risk groups, and should therefore provide some protection against the 11 serotypes to which no indirect protection was being afforded by the childhood PCV13 vaccination programme. Given this JCVI agreed that the PPV23 immunisation programme in risk-groups should continue at the current time.

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<sup>23</sup> PHE literature review for JCVI on 'Evidence for clinical groups at increased risk of pneumococcal Disease' (unpublished)

<sup>24</sup> Qualitative analysis of Melegaro A and Edmunds WJ (2004), PHE (unpublished)

27. The falling incidence of PPV23 vaccine-type IPD resulting from indirect protection afforded by the PCV13 childhood programme against the twelve serotypes common to both vaccines means the cost-effectiveness of the PPV23 programme may continue to reduce over time. However, this depends on the extent to which the reduction in PCV13 serotype disease is offset by increases in non-PCV13 serotype disease. As such, JCVI has asked PHE to define an incidence threshold of PPV23 vaccine-type IPD below which the PPV23 programme would no longer be cost-effective

*PCV13 vaccination for those aged 65 years and over*

28. A pre-publication paper from PHE and the London School of Hygiene and Tropical Medicine on the cost-effectiveness of vaccinating immunocompetent older adults with PCV13 was provided to JCVI.<sup>25</sup> The study used a static cohort model, and assumed the continuation of the routine PPV23 immunisation programme for individuals aged 65 years and over.
29. In the base case analysis the cost per quality adjusted life year (QALY) gained is substantially higher than the accepted threshold of £20,000 and the maximum price per dose of vaccine using a threshold of £20,000/QALY is negative when administration costs are taken into account. Sensitivity analyses undertaken indicate that cost-effectiveness is particularly sensitive to the case fatality rate, waning of protection and the projected future incidence of IPD. However these analyses still indicate that the cost per QALY is likely to be markedly higher than the £20,000/QALY threshold.
30. Even if it is assumed that the incidence of PCV13 vaccine-type IPD and CAP does not reduce any further (due to the indirect effects of the childhood immunisation programme) after 2015/16, the maximum price per dose to achieve an ICER of £20,000 is below a practical value, as indicated by the Department of Health.

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<sup>25</sup> Van Hoek and Miller (Unpublished). Cost-effectiveness of vaccinating immunocompetent elderly with the 13-valent pneumococcal conjugate vaccine in England.

*PCV13 vaccination for clinical risk groups*

31. Previous considerations on the use PCV13 in clinical risk groups was informed by a cost-effectiveness study conducted by the Health Protection Agency (HPA) and LSHTM. This analysis concluded that it was unlikely a PCV13 vaccination programme for all risk-groups would be cost-effective.<sup>26</sup> Vaccination of most individual risk groups, with the exception of those individuals with chronic liver disease, was also considered unlikely to be cost-effective unless PCV13 effectiveness against CAP in the relevant risk-group was assumed (and on which evidence is still limited – see above). The study also indicated that the cost-effectiveness of vaccinating clinical risk groups with PCV13 would reduce over time given the accumulating indirect protection against PCV13 vaccine-type disease resulting from the childhood PCV13 vaccination programme.
32. After consideration of relevant studies and the cost-effectiveness analysis, it was concluded that routine vaccination of all risk groups and vaccination of most individual groups in the UK was unlikely to be cost-effective at this time, and given the accumulating indirect protection afforded by the childhood PCV13 programme, vaccination of risk groups with PCV13 vaccine was highly likely to become less cost-effective in future.
33. It remains the view of the committee that use of PCV13 vaccine in risk-groups should remain limited only to those at the very highest risk of, and mortality from, IPD. Such use of the vaccine remains justified while the full impact of the PCV13 programme is yet to be realised.

**Conclusions**

34. The indirect impact of the childhood PCV13 vaccination programme on pneumococcal disease in older adults and those in clinical risk groups means that the additional benefit of the direct protection provided by wider use of PCV13 in older adults and clinical risk-groups in the UK is declining and is likely to diminish further over the next few years.
35. Analyses indicate that it would not be cost-effective to extend the PCV13 vaccination programme to those aged 65 years and over or to additional clinical risk groups, and it is likely to become less cost-effective over time. Use of PPV23 vaccine in those aged 65 years and over is likely to remain cost-

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<sup>26</sup> Rozenbaum MH, *et al* (2012) Vaccination of risk groups in England using the 13 valent pneumococcal conjugate vaccine: economic analysis. *BMJ*; 345: e6879.

effective at this time, although this programme may become less cost-effective over the next few years, and will be kept under review. Evidence suggests that vaccination of clinical risk groups with PPV23 should also continue at this time.

36. JCVI has therefore concluded that there should be no changes to the advice on adult pneumococcal vaccination in the UK at this time. PPV23 should continue to be offered to those aged 65 years and over and the indicated risk-groups. PCV13 should continue to be offered to those risk-groups previously identified as being at particularly high risk of, and high mortality from, IPD, but should not be offered more widely to other risk-groups or older adults.

### **Joint Committee on Vaccination and Immunisation**

**November 2015**

Annex A

**Clinical risk groups who should receive the pneumococcal immunisation as listed in the Green Book: Immunisation against infectious disease (June 2015)**

<b>Clinical risk group</b>	<b>Examples (decision based on clinical judgement)</b>
<b>Asplenia or dysfunction of the spleen</b>	This also includes conditions such as homozygous sickle cell disease and coeliac syndrome that may lead to splenic dysfunction.
<b>Chronic respiratory disease</b>	This includes chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema; and such conditions as bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD). Children with respiratory conditions caused by aspiration, or a neurological disease (e.g. cerebral palsy) with a risk of aspiration. Asthma is not an indication, unless so severe as to require continuous or frequently repeated use of systemic steroids (as defined in Immunosuppression below).
<b>Chronic heart disease</b>	This includes those requiring regular medication and/or follow-up for ischaemic heart disease, congenital heart disease, hypertension with cardiac complications, and chronic heart failure.
<b>Chronic kidney disease</b>	Nephrotic syndrome, chronic kidney disease at stages 4 and 5 and those on kidney dialysis or with kidney transplantation.
<b>Chronic liver disease</b>	This includes cirrhosis, biliary atresia and chronic hepatitis.
<b>Diabetes</b>	Diabetes mellitus requiring insulin or oral hypoglycaemic drugs. This does not include diabetes that is diet controlled.
<b>Immunosuppression</b>	Due to disease or treatment, including patients undergoing chemotherapy leading to immunosuppression, bone marrow transplant, asplenia or splenic dysfunction, HIV infection at all stages, multiple myeloma or genetic disorders affecting the immune system (e.g. IRAK-4, NEMO, complement deficiency) Individuals on or likely to be on systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day (any age), or for children under 20kg, a dose of 1mg or more per kg per day.
<b>Individuals with cochlear implants</b>	<i>It is important that immunisation does not delay the cochlear implantation.</i>
<b>Individuals with</b>	This includes leakage of cerebrospinal fluid such as

<b>cerebrospinal fluid leaks</b>	following trauma or major skull surgery.
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Note: The Green Book currently recommends ‘Severely immunocompromised children aged at least five years and adults – including bone marrow transplant patients, patients with acute and chronic leukaemia, multiple myeloma or genetic disorders affecting the immune system (e.g. IRAK-4, NEMO, complement deficiency) – should be offered a single dose of PCV13 followed by PPV23 at least two months later (irrespective of their routine childhood vaccinations).

For leukaemia patients, PCV13 should be given from six months after completion of chemotherapy, and for bone marrow transplant patients, PCV13 should be offered 9-12 months following transplantation.

Severely immunocompromised patients who have already received PPV23 should be offered PCV13 with an interval of at least six months following the dose of PPV23 to reduce the risk of pneumococcal serotype-specific hypo-responsiveness’.