JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

Pneumococcal sub-committee

Minute of meeting on Wednesday 30 May 2012
Skipton House, Department of Health, 80 London Road
London SE1 6LH

Members

Professor Jon Friedland (Chair)
Dr Syed Ahmed
Mr Nick Andrews
Professor John Edmunds
Dr Alison Palmer-Smith (in place of Dr Jim McMenamin)
Professor Ray Borrow
Mrs Anne McGowan
Professor Liz Miller
Professor Claire-Anne Siegrist
Professor Andy Hall
Dr Punam Mangtani
Professor David Goldblatt

Additional invited experts

Professor Ian Feavers
Dr Peter Arkwright
Dr Donal O'Donoghue
Professor Robert Read
Professor Andy Pollard

Observers

Dr Nicola Steedman (Scottish Government)

DH

Professor David Salisbury
Dr Tom Barlow (minute)
Andy Earnshaw (minute)
Carolyn Heaney
Dr Peter Grove

I. Welcome

1. The chair welcomed all to the meeting. Apologies had been received from members: Drs Syed Ahmed, Derrick Crook, Caroline Trotter and Paul Heath and Ms Anne McGowan and the Devolved Administration observers: Drs Heather Payne, David Vardy and Elizabeth Reaney.

2. The chair explained that as a number of sub-committee members had been involved in the production of key papers the sub-committee was reviewing, additional invited experts had been invited for this meeting and he welcomed Drs, Peter Arkwright and Donal O'Donoghue and Professors Ian Feavers, Robert Read and Andy Pollard to the meeting. Professor Matt Keeling had agreed to participate but had sent apologies shortly before the meeting. Conflicts of interest were considered (Annex A). The chair reminded all that unpublished information had been provided in confidence and

that papers should not be circulated nor the information discussed with others outside of the meeting.

II. Minute of the previous meeting

3. The committee agreed that the minute of the meeting of 5 October 2011 was an accurate record and all the actions had been completed or would be discussed during the meeting.

III. Update on pneumococcal disease epidemiology

4. An overview of analyses of epidemiological data on pneumococcal serotypes and invasive pneumococcal disease (IPD) in England and Wales up to calendar week 14 in 2012 was presented. The sub-committee noted that the data suggest that:
   - following the introduction in April 2010 of the 13-valent pneumococcal conjugate vaccine (PCV13) into the routine childhood immunisation programme in place of the seven-valent pneumococcal conjugate vaccine (PCV7), there had been a decline by around one half in IPD in children aged under five years due to any of the six serotypes in PCV13 but not in PCV7;
   - PCV7 and PCV13 are of similar effectiveness against the common seven serotypes;
   - PCV13 is effective against most of the additional six serotypes in PCV13 but not in PCV7. PCV13 appears ineffective against serotype three. However, there are few cases of invasive disease due to this serotype in children in England and Wales. It was suggested that the high amount of polysaccharide capsule expressed by wild-type serotype 3 may explain the difference in vaccine effectiveness;
   - there had been a rapid and continuing decline by about one third in IPD due to the serotypes in PCV13 in those aged five years and above suggesting rapid accumulation of indirect protection even in the absence of a catch-up campaign when PCV13 was introduced;
   - an increase in IPD from replacement serotypes had not so far been observed in the general population, possibly because non-PCV13 replacement serotypes may be less invasive;
   - however an analysis of serotypes causing IPD in children with co-morbidities suggested that they may be more vulnerable to IPD from replacement serotypes;
   - furthermore, a comparative analysis of non-bacteraemic all cause pneumonia (NBP) in healthy children and those with co-morbidities suggested a protective effect of vaccination on non-bacteraemic pneumococcal pneumonia (NBPP) for healthy children but not for children with co-morbidities, however further analysis with more data would be required to make firm conclusions. It was suggested that this effect may not be because the vaccine did not protect against NBPP but that in those with co-morbidities, NBPP from PCV13 types was substituted quickly by NBPP from non-PCV13 replacement serotypes as those with co-morbidities are more susceptible to these types.

5. The sub-committee agreed that the data suggested that those with co-morbidities may be more susceptible to both IPD and NBPP from non-PCV13 replacement serotypes than the healthy population, although recognised this needed further study. It was

possible that this susceptibility could vary depending on co-morbidity, although currently data are too limited for this to be determined.

IV. Submissions from vaccine manufacturers

6. Submissions from vaccine manufacturers were reviewed. The sub-committee noted there was some evidence of immune hypo-responsiveness with the coinjugate vaccine if a second dose was given within a year although, unlike pneumococcal polysaccharide vaccine (PPV23), this was not evident with a four year interval. Further studies of the effect of the interval between repeat doses of PCV13 would be required to determine the duration of this hypo-responsiveness more precisely. Overall the committee concluded that the data were informative for the further discussions.

V. Impact and cost effectiveness of wider use of pneumococcal conjugate vaccines

7. An overview of a study by the Health Protection Agency and London School of Hygiene and Tropical Medicine (HPA-LSHTM) estimating the cost effectiveness of use of PCV13 in those aged two years and older in clinical risk groups for invasive pneumococcal disease in England was presented. The study followed the methodology and criteria of the National Institute of Health and Clinical Excellence to assess cost effectiveness. It had been peer-reviewed for publication in a journal, although was not yet published. In addition, the study had been separately peer-reviewed by a health economist on behalf of the sub-committee who made a number of comments but regarded the study to be well conducted. The study had been modified to take into account the journal peer-reviewer comments and the separate comments from the health economist.

8. In reviewing the study, the sub-committee noted that:
   - the study took into account the indirect protection arising from use of PCV13 in the routine childhood immunisation programme. It had been assumed that indirect protection from PCV13 would accumulate in a similar manner to that observed for PCV7 but delayed by a year to take into account the lack of a PCV13 catch-up campaign. However, given the rapidly accumulating indirect protection this may be a conservative assumption. In addition it had been assumed that there is little difference in the rate of accumulation of indirect protection by age group and this was considered reasonable;
   - the base-case of the study had assumed that PCV13 would have no impact on NBPP. This was to take into account the observation of a lack of impact of vaccination on NBP in children risk groups (see paragraphs 4 and 5) and uncertainty about the contribution of pneumococcal bacteria to NBP. A sensitivity analysis including an impact on NBPP showed the results were highly sensitive to this assumption;
   - other sensitivity analysis had been included on a range of parameters including vaccine price, vaccine effectiveness, number of doses and indirect protection;
   - as data on the effectiveness and duration of protection of PCV in immuno-competent and immuno-compromised clinical risk groups are limited, assumptions

had been made based on the opinions of an expert elicitation panel made up of members of the sub-committee following accepted methods. It had been assumed that the vaccine was ineffective against serotype 3 in light of the effectiveness data. Although the expert panel did suggest that the vaccine may be effective against NBPP, their estimates were not used in the base-case on the grounds that there is little or no evidence of population-level effectiveness of PCV7 against this endpoint in clinical risk groups (see paragraph 4). Whilst the sub-committee noted that a large study of the effectiveness of PCV13 in older adults against NBPP and IPD was due to conclude in 2013, this would provide no direct data on the effectiveness in clinical risk groups;

- a key data source was a published study produced by HPA[1] that quantified the risk of IPD in different risk groups based on linking data on cases of IPD with corresponding hospitalisation records and data on the prevalence of clinical risk factors. It was suggested that use of PPV23 in older age groups or PCV7 in children in some clinical risk groups may have reduced the relative risk value for those groups. The incidence of pneumonia had been estimated from Hospital Episode Statistics.

9. The sub-committee noted that the study suggested that due to the increasing indirect protection arising from the use of PCV13 in the routine childhood immunisation programme, the burden of disease that could be reduced from additionally targeting those in clinical risk groups would decrease rapidly over time. The study suggested that even if a vaccination programme were to be introduced in 2012/13, it would be unlikely to be cost effective to vaccinate those in clinical risk groups (>£30,000/QALY), except those with chronic liver disease but this was borderline (>£20,000/QALY) if it was assumed the vaccine was not protective against NBPP. If it was assumed that the vaccine was protective against NBPP, vaccinating most clinical risk groups was likely to be cost effective (<£20,000/QALY) if a programme was introduced in 2012/13. However, the sub-committee considered (based on an extrapolation of the results presented in the study) that due to the impact of increasing indirect protection from the routine childhood programme, the risk group programme was likely to become not cost effective quickly within a small number of years even if it was assumed that the vaccine was protective against NBPP. It was suggested that a programme to vaccinate the very large number of people in clinical risk groups could not be implemented quickly.

10. The sub-committee considered an unpublished cost effectiveness study produced by the manufacturer of PCV13 and noted that:
    - the study used similar methodology and cost effectiveness criteria to the HPA-LSHTM study, used similar data and parameters and had made similar assumptions about increasing indirect protection. However, it only considered adult vaccination;
    - vaccine effectiveness estimates were also based on the opinions of an expert elicitation panel that had been convened by the American Committee on

[1]Van Hoek *et al* (2012) The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England *J. Infection.* In press.

Immunization Practices. Estimates were generally higher than those of the expert panel of sub-committee members, although there was large overlap in the ranges of estimates made by the panels;

- the definition of pneumonia included bacteraemic pneumonia and therefore there would be some double counting of cases of NBPP and IPD;
- the authors suggested that the proportion of NBPP caused by PCV13 serotypes may be underestimated in their study based on another study by Berwick *et al*[2] that estimated the proportion of NBPP likely to be caused by PCV13 serotypes. However, this study was biased as the Bioplex assay (which was the only method of confirmation of a pneumococcal aetiology in 144 of the 366 patients with laboratory evidence of pneumococcal attributable community acquired pneumonia) could only identify PCV13 serotypes and serotype 8;
- the study assumed no vaccine administration costs but costs were likely;
- critically the study assumed PCV13 would be effective against NBPP;
- the study suggested that a single dose of PCV13 for adults in clinical risk groups would be cost effective within established cost effectiveness thresholds used in the UK.

11. The sub-committee concluded that the results of both studies are uncertain given the lack of clear evidence on the effectiveness of PCV13 against NBPP, although there is some emerging evidence from the incidence of NBP in vaccinated children in clinical risk groups that it may not be. Whilst a large study of the effectiveness of PCV13 in older adults against NBPP and IPD was due to conclude in 2013, this would provide no data specifically on the effectiveness in clinical risk groups. Given the likely continuing uncertainty about the effectiveness of PCV13 against NBPP in those in clinical risk groups, the very high cost of a programme (£100s millions), the strong evidence of rapidly increasing indirect protection from the use of PCV13 in the routine childhood immunisation programme, and the time it would take to implement what would be a very large vaccination programme, the sub-committee advised against the use of PCV13 in clinical risk groups or in older adults. This is because neither the vaccination of clinical risk groups nor of older adults are likely to be cost effective and the programmes would rapidly become even less effective and cost effective with time and indeed not effective following the disappearance of the PCV13 serotypes as a result of the routine childhood immunisation programme.

12. The sub-committee agreed that in the short-term, based on an extensive review of the clinical trials data considered by the sub-committee previously, PCV13 may be of individual benefit to some small groups of severely immunocompromised individuals with a high mortality from IPD such as bone marrow transplant patients and those with multiple myeloma, chronic lymphocytic leukaemia or rare genetic disorders effecting the immune system (e.g. IRAK-4, DiGeorge syndrome). In these circumstances, PCV13 should be considered by the supervising clinician in secondary care. It was suggested that a dosage schedule suggested by the sub-committee at its December

[2] Berwick *et al.* (2012) Serotype prevalence in adults hospitalised with pneumococcal non-invasive community-acquired pneumonia *Thorax.*

2010 meeting could be applied in such cases[3]. However, this advice should not include all those with splenic dysfunction, asplenia, HIV infection, or that are immunocompromised for other reasons as whole groups as vaccination of these groups was suggested not to be cost effective by the HPA-LSHTM study assuming that the vaccine offers no protection against NBPP. It was agreed that this advice should be reviewed in the future in light of data on the changing prevalence of PCV13 serotypes.

VI. Review of pneumococcal clinical risk groups

13. The sub-committee considered studies on the increased risk of IPD from various clinical conditions and concluded that no changes should be made to the defined clinical risk groups with the exception of the definition of chronic kidney disease. It was considered that vaccination with PPV23 should only be indicated for those with nephrotic syndrome, chronic kidney disease at stages 4 and 5 and those on kidney dialysis or with kidney transplantation. Individuals in these groups were generally immunosuppressed, had a high infection risk and mortality. Individuals at chronic kidney disease stages 1 to 3 were generally asymptomatic and would benefit from pneumococcal vaccination only if their condition worsened such that they entered the groups defined above.

14. One member agreed to consult the lead author of a study[4] that suggested a possible association between IPD and highly invasive surgery to determine whether surgery itself may be a risk factor for IPD.

VII. Use of PPV in young children in clinical risk groups

15. The findings of a review of evidence[5] on the use of PPV in children was presented. The sub-committee noted that:
    - there are limitations to the data in terms of amount and quality;
    - healthy children can respond to certain serotypes present in PPV from 12 months of age but effectiveness has not been consistently demonstrated. However, there are few data on the effectiveness in immunosuppressed children;
    - repeated doses of PPV at short intervals result in immune unresponsiveness for some serotypes, although the clinical relevance of this finding is unclear;
    - prior PPV vaccination may blunt the immune response to subsequent PCV vaccination;
    - PPV vaccination following earlier PCV vaccination significantly increases antibodies to those serotypes present in the PCV vaccine, but reduces the response to further doses of PPV when given after a short interval;

[3] PCV13 given first with two months between doses and then PPV23 given six months later. Patients that had already received PPV23 (but not PCV13 nor PCV7) should start the new schedule but with an interval of at least six months following the PPV23 vaccination that they had already received.

[4] Hjuler *et al* (2008) Risks of invasive pneumococcal disease in children with underlying chronic diseases. *Pediatrics*. **122**(1):e26-32,

[5] Borrow, Heath & Siegrist (2012) Use of pneumococcal polysaccharide vaccine in children: what is the evidence? *Curr. Opin. Infect. Dis.* 25, 292-303.

- PPV, unlike PCV has no effect on nasopharyngeal carriage;
- the role of repeated PPV vaccinations in at-risk groups remains unclear.

16. The committee agreed that based on the review, there was little compelling evidence to support a change to current Green Book guidance on PPV vaccination of children who are at increased risk of invasive pneumococcal disease. Even with a reduction in circulating PCV13 serotypes, PPV23 may provide protection against replacement serotypes to which those in clinical risk groups may be vulnerable.

17. The sub-committee considered the use of PPV more generally in both children and adults. Noting that there continue to be uncertainties around the effectiveness of PPV23 in adults in clinical risk groups due to limited evidence and that data reviewed by the sub-committee and JCVI in 2011 suggested PPV23 provided only some protection and only for a few years depending on age and co-morbidities and that IPD epidemiology is changing rapidly, it would be important to review the use of PPV23 in adults and children within two years. The review should assess the effectiveness and cost effectiveness of both the clinical risk group- and age group-based programmes and to consider whether these programmes should continue. It was noted that the HPA was following up cases of IPD in children aged five to 18 years to document the proportion with co-morbidities, the coverage of PPV23 in high risk children and, if there was sufficient power, to estimate PPV23 effectiveness using the Broome method.

VIII. Any other business

18. The chair thanked all those for attending in particular those that presented data and the additional invited experts for their input and closed the meeting.

Annex A – conflicts of interest

The following members declared interests in companies that manufacture pneumococcal vaccines (Pfizer, GSK, Sanofi Pasteur MSD (Merck)).

Member	**Interests**	**Action**
Ray Borrow	Non-personal, non-specific Pfizer, Sanofi-Pasteur MSD and GSK	Able to participate in the discussion and vote
Jon Friedland	Non-personal, non-specific Pfizer	Able to participate in the discussion and vote
Anne McGowan (not present)	Non-personal, non-specific GSK, Pfizer, Sanofi-Pasteur MSD	Able to participate in the discussion and vote
Liz Miller	Non-personal, specific Pfizer, and non-personal, non-specific GSK	Able to participate in the discussion but not vote
Nick Andrews	Non-personal, specific Pfizer, and non-personal, non-specific GSK	Able to participate in the discussion but not vote
John Edmunds	Personal, non-specific GSK	Able to participate in the discussion but not vote
Paul Heath (not present)	Non-personal, non-specific GSK and non-personal, specific Pfizer	Able to participate in the discussion but not vote
David Goldblatt	Personal, non-specific Pfizer and GSK and personal, specific Sanofi Pasteur MSD	Able to participate in the discussion but not vote and absent for items on which use of PPV was discussed
Additional experts		
Andy Pollard	Non-personal, non-specific Sanofi Pasteur MSD and non-personal, specific Pfizer and GSK	Able to participate in the discussion but not vote
Ian Feavers	Non-personal, specific GSK, Pfizer and Sanofi Pasteur MSD	Able to participate in the discussion but not to vote
Donal O'Donoghue	Non-personal, specific Pfizer	Able to participate in the discussion but not to vote

Annex B – evidence considered

Agenda item 2:

- Minute of JCVI Pneumococcal sub-committee meeting 15 December 2010

Agenda item 3:

- Presentation given by HPA on pneumococcal disease epidemiology

Agenda item 4:

- GSK, Respose to JCVI Call for Evidence: Use of GSK's Pneumococcal Conjugate Vaccine in Clinical Risk Groups. Sept 2011
- Pfizer, Use of pneumococcal conjugate vaccine in high-risk individuals, Consensus recommendations following a closed scientific discussion. February 2012.
- Pfizer, Pneumococcal Vaccines in Clinical Risk Groups, Response to Department of Health/JCVI request. May 2012.

Agenda item 5:

- Rozenbaum, R et al. Cost effectiveness of vaccinating risk groups in the UK against invasive pneumococcal disease using the 13 valent conjugate pneumococcal vaccine, awaiting publication.
- Health economist review on above paper.
- Pfizer, Cost effectiveness analysis of adult vaccination with the 13-valent Pneumococcal Conjugate Vaccine in the United Kingdom.
- Smith KJ, Wateska AR, Nowalk MP, Raymund M, Nuorti JP, Zimmerman RK. Cost-effectiveness of adult vaccination strategies using pneumococcal conjugate vaccine compared with pneumococcal polysaccharide vaccine. JAMA. 2012 Feb 22;307(8):804-12.

Agenda item 6:

- van Hoek AJ, Andrews N, Waight PA, Stowe J, Gates P, George R, Miller E. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect. 2012 Jul;65(1):17-24.
- van Hoek AJ, Andrews N, Waight PA, Stowe J, Gates P, George R, Miller E. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect. 2012 Jul;65(1):17-24.
- Letter from Diabetes UK
- Paper on "Diabetes as a risk factor for pneumococcal disease" prepared by JCVI secretariat.
- Hjuler T, Wohlfahrt J, Staum Kaltoft M, Koch A, Biggar RJ, Melbye M. Risks of invasive pneumococcal disease in children with underlying chronic diseases. Pediatrics. 2008 Jul;122(1):e26-32.

Agenda item 7:

- Borrow R, Heath PT, Siegrist CA. Use of pneumococcal polysaccharide vaccine in children: what is the evidence? Curr Opin Infect Dis. 2012 Jun;25(3):292-303.