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*The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances*

## JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

**Minute of the meeting on 7 October 2015**

**Skipton House**

**80 London Road, London SE1 6LH**

### **Members**

|                                     |                           |
|-------------------------------------|---------------------------|
| Prof Andrew Pollard (Chair)         | Prof Matt Keeling         |
| Dr Andrew Riordan (Deputy Chair)    | Dr Fiona Van der Klis     |
| Prof Anthony Harnden (Deputy Chair) | Ms Alison Lawrence        |
| Dr Peter Baxter                     | Mrs Anne McGowan          |
| Prof Judith Breuer                  | Prof Anthony Scott        |
| Dr Peter Elton                      | Prof Claire-Anne Siegrist |
| Prof Adam Finn                      | Dr Maggie Wearmouth       |

### **Invited contributors**

Prof Ray Borrow (PHE)

### **Medical advisors**

Prof John Watson (DH)

### **Invited observers from Devolved Administrations and MHRA**

|                                  |                                 |
|----------------------------------|---------------------------------|
| Dr Andrew Riley (Welsh Assembly) | Dr Phil Bryan (MHRA)            |
| David Vardy (Welsh Assembly)     | Nicola Steedman (Scottish Govt) |

### **Observers and presenters**

|                                |                                |
|--------------------------------|--------------------------------|
| Dr Claire Cameron (HPS)        | Dr Gayatri Amirthalingam (PHE) |
| Dr Richard Roberts (HPW)       | Dr Dorian Kennedy              |
| Dr Richard Smithson (PHA)      | Michelle Parkinson (DH)        |
| Dr Sandra Anglin (NHS England) | Dr Peter Grove (DH)            |
| Ms Ruth Howlett-Shiple (MoD)   | Dr Sema Mandal (PHE)           |
| Elaine Burgess (Guernsey)      | Joanne Yarwood (PHE)           |
| Dr Dipti Patel (NathNac)       | Dr Jacqui Dunn (Isle of Man)   |
| Dr Ian Feavers (NIBSC)         | Dr Laura Yates (UKTIS)         |
| Dr Darina O'Flanagan (Eire)    | Dr Linda Diggle (Jersey)       |
| Ms Joanne White (PHE)          | Dr Caroline Trotter (PHE)      |
| Dr Shamez Ladhani (PHE)        | Dr Nick Andrews (PHE)          |
| Dr Albert Jan Van Hoek (LHSTM) | Dr Mark Jit (PHE)              |
| Pauline MacDonald (PHE)        |                                |

### **Secretariat**

|                    |                        |
|--------------------|------------------------|
| Dr Mary Ramsay     | Mr Jonathan Crofts     |
| Mr Andrew Earnshaw | Mrs Emma Burton-Graham |

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## **Welcome**

1. The Chair welcomed all to the meeting. Apologies were received from Chris Liffen, Prof. Rob Read and from Prof. Maarten Postma.
2. The Chair welcomed Julie Yates who has been appointed as a co-opted member for implementation matters for England, and Lorna Willocks for Scotland and Lucy Jessop for Northern Ireland. The Chair noted that Anne McGowan had been asked to take up this appointment for Wales when her term as a main member ends in 2016. The Chair also welcomed members of the Armenian National Immunisation Technical Advisory Group (NITAG), Dr Anna Chobanyan, Dr Nune Baghasaryan and Dr Gayane Sahakyan and Antoine Durupt from the NITAG coordination centre as observers.
3. Members were reminded that papers were provided for the meeting included information which was provided in confidence.
4. Conflicts of interest were checked by the secretariat prior to the meeting and members given the opportunity to provide updates.

## **I. Minute of the February 2015 meeting**

5. The Committee agreed the minute of the February 2015 meeting was an accurate reflection of the discussion and the minute was approved without change

## **II. Matters Arising**

6. The Committee noted that the Secretariat had been asked to approach industry for information regarding Clostridium difficile and group A and B Streptococcal vaccines. Information had been received on Clostridium difficile and Staphylococcus aureus vaccines and the information had been uploaded to SharePoint in the Horizon Scanning section. Members were invited to read the submissions from SharePoint and submit any comments to the Secretariat.
7. The Secretariat had been asked to invite Professor John Cairns to provide an update on the work of the Cost Effectiveness Methodology for Immunisation Programmes and Procurement (CEMIPP) working group to the JCVI and he had been invited to this meeting, but was unable to attend. The Committee noted he would be invited to the February meeting.

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**Action: Secretariat to invite Professor John Cairns to the next meeting of the Committee.**

8. Members had been asked to indicate if they were interested in joining the Norovirus working group and the Secretariat had received nominations from members. It was hoped that the first working group meeting would be held before the end of 2015.
9. The Secretariat had been asked to appoint a designated contact to liaise with the NITAG Resource Centre and to add World Health Organisation (WHO) and the NITAG resource centre to the invitation list for JCVI meetings. The Secretary to JCVI had agreed to take on the role of NITAG liaison, and the WHO and NITAG resource centre now had standing invitations to JCVI main meetings.
10. The Secretariat had agreed to gather information on egg adaptation and how this could impact on the effectiveness of influenza vaccines. Members heard from the Department of Health that there had been considerable national and international discussion on the development of seasonal influenza vaccines to consider how they could be improved. One element of these discussions related to the H3N2 component and the problems of egg adaptation potentially leading to reduced efficacy. The Committee noted that the WHO was taking a leading role on these discussions but the action could not yet be completed. The Department of Health (DH) had agreed to liaise with PHE and the Secretariat to ensure there was broad consideration of the issues in relation to the seasonal flu vaccines.
11. PHE had been asked to consider whether the Committee's views on the use of quadrivalent inactivated influenza vaccine were appropriately conveyed in the wording of the influenza chapter of the Green Book. Members agreed that the revised wording better reflected the position of the committee.
12. The Secretariat provided an update on considerations which had been given to whether the JCVI was subject to the Equalities Act (2010). It was noted that DH had asked for legal advice on the issue, and the discussions highlighted that despite being a committee which provides scientific advice, on balance JCVI undertakes a public function and therefore should demonstrate due regard of issues relating to equality. When making recommendations or providing advice where there is a potential inequality, the committee was advised to ensure such matters were recorded in the minutes and brought to the attention of DH. It was noted that as a scientific advisory committee JCVI was not constituted in such a way as to be able to take a view on whether inequalities arising from their

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advice were objectively justifiable from an equalities perspective, and was not required to comment on such matters.

13. An update was provided to the Committee concerning the availability of Fluenz® for the childhood national immunisation programme and issues over supply. This year it had been intended that, in England, the live attenuated influenza vaccine would be offered to all 2, 3 and 4 year olds and to 5 and 6 year olds via a school programme or through GPs. In 6 pilot areas all primary school children would be offered the vaccine. The Committee noted there has been a delay to the start of the programme in England associated with vaccine supply and that Astra Zeneca UK may make available doses of FluMist®, the US branded version of the same product. The Committee noted that the MHRA was working on the technicalities relating to use of the product in the UK market, and the batches would need to be tested for the European market. The Committee noted that additional contingency plans were being formulated should any batches fail, and an emphasis was currently being placed on stock control.

### **III. Coverage Data**

14. The Committee was informed about the routine childhood vaccination coverage rates for England, Scotland, Wales and Northern Ireland.
15. Coverage data were provided from England for the financial year 2014/15. The data showed a slight decrease in coverage as evaluated at 12 and 24 months of age but small increases as evaluated at 5 years of age. At 12 months of age, just over half of local authorities were achieving the target of 95% uptake and although the total average was just below 95% coverage for most antigens, a lot of areas were achieving high coverage rates. London and the South East had the poorest coverage rates in England. Coverage data for the first quarter of the financial year 2015/16 was provided which showed a slight continuation of the decrease in coverage at 12 months of age. The data for 24 months had improved and stabilised with the data at 5 years which showed just below 95% coverage for two doses of the MMR vaccine.
16. Coverage data in England for Rotavirus vaccine had been collected through Inform, the GP collection system, which showed high coverage for the first and second doses of the vaccine respectively. Public Health England had recently published ethnicity data for the first 12 months of the Rotavirus programme which showed a 13% difference in uptake between the highest achieving ethnicity groups compared to the lowest achieving ethnicity groups.

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17. Data had also been published in July 2015 on the prenatal pertussis programme which covered the period up to the end of May 2015. The coverage data showed that the pattern of uptake closely followed the flu vaccination programme, with higher coverage in the winter period and lower coverage in the summer. Preliminary ethnicity data had been published for the prenatal pertussis programme which showed a 25% difference in coverage between the highest and lowest performing ethnicity groups.
18. Shingles coverage data for England was provided which related to the period up to the end of May 2015 and the routine cohorts had an average coverage which was slightly lower than the coverage achieved at the same point in 2014. PPV coverage in the 65 years only age group showed a small increase in coverage in the financial year 2014/15.
19. Members queried whether it would be possible to collect ethnicity data for HPV vaccination. The Committee noted this would not be possible as the other ethnicity data presented had been collected through GP systems and the HPV vaccination was a schools based programme.
20. Coverage data were provided for Scotland and members were informed that there were no significant other issues to highlight. Coverage data for the shingles vaccination programme were presented.
21. Coverage data was provided for Wales and it was reported that routine immunisation uptake at 12 months of age was over 95% uptake for the second consecutive year. Uptake of the MMR vaccine for the first dose was over 95%. It was noted that vaccinations at 4 years of age were below national targets and that uptake of 3 complete doses of HPV were over 80%. Uptake for both of these programmes was being monitored.
22. Coverage data were provided for Northern Ireland and members heard that coverage rates at 12 months were at 95%, MMR vaccine coverage was over 95% for the first dose, the pre-school booster was just under 95%, and the singles programme at 70 and 78/79 years were over 50%.
23. The maternal pertussis programme was discussed and how the programme was important in preventing infant deaths. Members heard that PHE had undertaken activities to raise awareness of the maternal pertussis programme including working with professionals, such as members of the Royal Colleges of Midwives and GP's and other professional organisations including health visitors, to provide advice on the delivery of the programme. Members were informed that the key issues to overcome were the commissioning arrangements and the delivery of the programme. There was no single system

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for the delivery of antenatal care in England and this created problems. There were also difficulties within primary care in accurately identifying women at 28 weeks gestation and inviting them for pertussis vaccination. In some areas, midwives were delivering the programme however this was dependent upon commissioning arrangements and payments. Caveats around the quality of the data were noted, including that delivery data needed to be recorded on GP systems for the vaccination to be included in the coverage data.

24. Members requested whether the presentation of coverage data across the countries could be standardised to include a template of key indicators which would facilitate comparisons of the data and also allow key messages to be highlighted.

**Action: Secretariat to work with the reporters of coverage data across the devolved administrations to standardise the coverage data and produce a template of key indicators.**

#### **IV. Prophylactic use of paracetamol and vaccination**

25. The Committee were reminded that they had previously advised against the use of prophylactic antipyretics with vaccination, particularly with paediatric vaccinations, due to an association with a reduced response to antigens. However, prior to the introduction of Bexsero®, considerable discussion was held by the committee about the use of prophylactic paracetamol along with the Bexsero® vaccine due to the high rates of some reactions, especially fever, associated with this vaccine. Published studies reviewed by the committee at the time showed very limited impact of prophylactic paracetamol on immunogenicity where Bexsero® was given concomitantly with other vaccines in infancy. Consequently, JCVI advised the prophylactic use of oral paracetamol where Bexsero® was administered concomitantly with other infant vaccines.
26. PHE presented a paper which reviewed the recent literature on antipyretics and post-vaccination fever. A systematic review published in 2014 assessed the effect of prophylactic antipyretic administration on post-vaccination adverse reactions in children and found that paracetamol significantly reduced rates of fever and had additional benefits such as reducing pain of all grades<sup>1</sup>. A key finding was that statistically significant decreases in anti-pneumococcal, anti-PRP, anti-diphtheria, antitetanus, anti-pertactin antibody responses were observed in infants receiving prophylactic paracetamol. However, the authors

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<sup>1</sup> Das RR, Panigrahi I, Naik SS. The Effect of Prophylactic Antipyretic Administration on Post-Vaccination Adverse Reactions and Antibody Response in Children: A Systematic Review. *PLoS One*. 2014;9(9):e106629. doi:10.1371/journal.pone.0106629

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concluded that antibody levels in those receiving prophylactic paracetamol were still well above the seroprotective level (where a correlate of protection had been identified).

27. A subsequent clinical trial published after the systematic review showed no evidence in reduction in vaccine responses for any of the antigens in the vaccine programme<sup>2</sup>. A clinical trial assessing the effect of prophylactic paracetamol in infants specifically after receiving Bexsero® found that the use of prophylactic paracetamol did not affect the immune response to any of the vaccine antigens in the primary immunisation schedule<sup>3</sup>. There was no evidence found that prophylactic ibuprofen has any significant impact on post-vaccination fever rates or any other reaction except improving pain of all grades. The Committee additionally noted a recent WHO position paper on reducing pain at the time of vaccination.
28. Given the available evidence the Committee were invited to consider whether the Green Book should continue to recommend against the use of prophylactic paracetamol, apart from where Bexsero® is administered concomitantly with other infant vaccines. Concerns were raised that the Green Book may cause confusion and unnecessary anxiety on occasions where prophylactic paracetamol was given to infants at the three months vaccination appointment where Bexsero® was not offered. It was noted that pneumococcal vaccination was not currently scheduled for the three month appointment.
29. It was highlighted that the discrepancies in the antibody responses which had been reported in the literature following co-administration of prophylactic paracetamol with childhood vaccination was possibly due to differing levels of reactogenicity of the vaccines used. It was considered possible that while the highly reactogenic vaccines would produce more adverse effects and require the use of prophylactic paracetamol, the fact that these vaccines were highly reactogenic would compensate for any impact of prophylactic paracetamol on vaccine response.
30. The view was put forward that it was very likely that even with Bexsero® there was some biological effect on immunogenicity when giving prophylactic paracetamol at the same time as vaccination. However, there were few data available and it was unknown whether this was biologically important.

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<sup>2</sup> Study Assessing the Effect of Medications to Prevent Fever on Prevenar 13® (ClinicalTrials.gov identifier: NCT01392378).

<sup>3</sup> Prymula R, Esposito S, Zuccotti GV et al. A phase 2 randomized controlled trial of a multicomponent meningococcal serogroup B vaccine (I). *Hum Vaccin Immunother.* 2014;10(7):1993-2004. doi: 10.4161/hv.28666.



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31. It was agreed that the data indicated that prophylactic paracetamol prevented fever when given with immunisations given at the same time as the Bexsero® vaccine and was unlikely to cause harm if given at three months. Therefore it was agreed that the wording in the Green Book should be modified such that it would not explicitly advise against prophylactic use of paracetamol, but also not encourage the use of prophylactic paracetamol except when Bexsero® was administered concomitantly with other infant vaccines. It was agreed it would be important that the wording distinguished between prophylactic use of paracetamol and treatment of fever. It was additionally noted that whilst ibuprofen can also be given to treat post vaccination reactions including fever, the evidence suggested that prophylactic ibuprofen was significantly less effective in preventing post-vaccination fever than paracetamol.

**Action: Secretariat to work with members of the Committee to make changes to the wording in the Green Book about the use of prophylactic paracetamol.**

## **V. Meningococcal disease**

32. Members were informed of the progress of a research proposal regarding the impact of Bexsero® on meningococcal carriage. A proposal had been submitted to the RDD Department in DH and was in the process of being peer reviewed. If the research were to be funded, the researchers expected to be able to report results back to the JCVI within 18 months of the start of the project.

### Latest Epidemiology

33. An update was provided by PHE on the epidemiology of invasive meningococcal disease (IMD) in England up to October 2015. The committee noted that:
- the number of cases of invasive meningococcal B (MenB) disease in England had continued to decrease with the greatest reduction in infants, toddlers and other children but there had been no decline in older age groups;
  - the total number of cases of Invasive Meningococcal Disease (IMD) had increased in 2014/15 compared to the previous year and 100 cases of MenB disease cases were reported in infants and a total of 400 cases of IMD;
  - the number of cases of invasive meningococcal W (MenW) disease had continued to increase with the number of cases doubling year on year, with

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176 confirmed cases of MenW disease reported across all age groups in 2014/15;

- trends in age groups showed the greatest increase in MenW disease to be in those over 65 years of age, however there were also increases in adolescents, those <1 year of age and those 1-4 years of age, with almost 25 cases of MenW disease reported in under 1's in the year 2014/15;
  - data on serum bactericidal activity indicated that Bexsero® vaccine should provide protection against MenW disease. The age distribution of IMD showed that 70% of disease occurred from five months onwards and therefore an impact of the Bexsero® vaccine on MenW disease should be seen in the next 12 to 18 months.
  - 6 out of the 20 cases of MenW disease in the past 2 months had resulted in death.
34. Members heard that there had been a cluster of MenW disease in Scotland amongst a group associated with Scouts returning from a Jamboree in Japan. There had been no reported cases of MenW disease in Wales and no reported cases this year in Northern Ireland, although 3 cases had been reported in the preceding year.

#### Use of MenACWY vaccine in response to the MenW outbreak

35. The Committee noted that in October 2014 the JCVI had advised that the dose of meningitis C conjugate (MenC) vaccine given to adolescents aged around 14 years should be changed to a dose of the combined ACWY conjugate vaccine, if the vaccine could be procured at minimal marginal cost. However, in February 2015, before this advice could be enacted, the Committee had advised the use of MenACWY conjugate vaccine in adolescents aged between 14 and 18 years as an outbreak control measure due to a sustained increase in incidence of MenW disease. As part of the outbreak control the booster dose of MenC vaccine at around 14 years was to be replaced by the MenACWY conjugate vaccine.
36. PHE provided an overview of a rapid assessment of the relative impact of routine vaccination with MenACWY in teenagers to provide continued direct and indirect protection against the hyper-virulent strain belonging to ST-11 clonal complex, using mathematical modelling of hospital admissions data. A transmission dynamic model of carriage and disease, similar to that used to estimate the impact of a MenB vaccine, was used to assess the cases averted over time by replacing the MenC vaccine in teenagers with MenACWY conjugate vaccine. The model looked at additional cases which might be

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averted, over and above those already averted by having the MenC programme in place. The model assumed that the MenACWY vaccine would cover 30% of the total number of IMD cases with a 95% vaccine efficacy against disease and that there would be 60% vaccine efficacy against carriage. The parameters were chosen to look at the relative impact of herd effects and different vaccination strategies.

37. The modelling showed that for programmes, both with and without a one-off catch-up campaign in older adolescents, there was substantial and sustained direct protection against meningococcal A, C, W and Y disease in vaccinated cohorts. In addition, the number of cases averted were considerably higher in the longer term for strategies with herd effects included. The preliminary cost-effectiveness analysis found that the MenACWY vaccine would be cost effective at a relatively small incremental cost and if the incidence of MenW disease continued to increase at the current rate, the vaccine would become increasingly more cost effective.
38. Members heard that the historical pattern for meningococcal disease over the past century had been intermittent periods of high incidence, referred to as hyper-endemic periods, which were usually associated with the introduction of a new clone of meningococcal disease to which there was low immunity in the population. These hyper-endemic periods had typically lasted at least five- to ten years. Assuming that the vaccine would provide protection for 10 years, modelling based on the incidence levels of 2013/14 indicated that the MenACWY vaccine could prevent about 33 cases over the next 10 years and about 3 deaths, through direct effects alone.
39. The question was posed whether the model showed how long the MenACWY vaccine programme would need to be in place before the number of cases of MenW was brought under control. The model did not show when the incidence of disease would stop doubling year on year however it did show that it would take a long time for the disease to be eliminated and that benefits would still be gained after 20 years.
40. Members requested further explanation of the indirect protection effects which appeared large and implied considerable transmission in the age group 16-25 year olds. It was explained that the contact patterns across age groups were obtained from POLYMOD and that modelling had assumed a 60% reduction in carriage, and that the model did show a high level of indirect protection. Whilst the model could be further refined, it was not expected that the qualitative conclusions would change.

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41. The Committee noted that the MenW ST-11 was the same clonal complex which was responsible for outbreaks of MenC disease in the UK during 1999 and the early 2000s. The approach taken to tackling the MenC outbreak was to introduce the MenC vaccine programme which was still in place and had maintained the low incidence of MenC disease seen. Robust information and criteria would be necessary in order to stop a vaccination programme so as to ensure that incidence levels would not start to rise once the programme was halted.
42. The Committee agreed that the modelling indicated it was likely that permanent replacement of the adolescent MenC conjugate vaccine with the MenACWY conjugate vaccine would be cost-effective at a practically attainable additional cost. Modelling indicated that a move from a MenC to MenACWY programme would have a long time horizon for accruing benefits, and a long-term programme would be needed to maximise the potential for herd protection, which could significantly reduce the impact of MenY and MenW disease across the population. The Committee noted that there were a number of uncertainties associated with the analysis and that these would need to be considered further before a final decision could be made. The Committee asked PHE to work with DH to ensure that the analysis was sufficiently robust, and report back to the Committee at a future meeting. Given the information available, and the continuing increase in MenW disease across the population, the Committee advised that use of MenACWY conjugate vaccine in the routine adolescent vaccination programme should continue for at least the next two years as part of the MenW outbreak response. DH and PHE agreed to provide a progress report to the Committee in February 2016.

**Action: PHE and DH to identify and fully assess the uncertainties associated with a permanent extension to the MenACWY programme, and report back progress in February 2016.**

## **VI. Pertussis modelling – an update from PHE**

### Burden

43. PHE provided a presentation to the Committee on modelling of the pertussis resurgence in England and Wales and options for future control. The committee noted that:
  - the study had been undertaken to try and better understand the factors associated with the pertussis resurgence in England and Wales since 2012;

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- prior to the introduction of whole cell pertussis (wP) vaccination programmes in 1957 there had been on-average 100,000 cases of pertussis annually (in some years rising to 170,000 cases);
- following introduction of the whole cell pertussis vaccination programme, the number of notifications dropped significantly, until the late 1970's when notifications rose due to a drop in vaccine coverage associated with reports of a link between wP vaccine and neurological disorders;
- confidence in the vaccine was later regained and a steady state coverage of 92% was reached in 1992;
- in 2001 the preschool booster was introduced and in 2004 the wP vaccine was replaced with an acellular component pertussis (aP) vaccine;
- increased notifications in late 2000 were considered attributable to new testing methods with increased sensitivity which were introduced in 2001, but could not explain increased notifications in 2012 and 2013;
- a transmission dynamic model was developed to explore the likely cause of the resurgence, the possible contribution of the fall in vaccine coverage in the 1970s and 80s to the resurgence, and the potential for the resurgence to continue in the future which would be relevant to the cost effectiveness of the maternal immunisation programme, and the potential impact of additional booster programmes among toddlers or adolescents;
- the model was aged structured with 5,200 weekly age cohorts based on population structures between 1956 and 2030;
- contact patterns between age groups were gained from POLYMOD and classic assortative mixing patterns which were adjusted by annual population structures;
- the model was dynamic and the force of infection changed according to the number of infectious people;
- carriage and transmission of pertussis in aP vaccinated individuals was factored into the study following reports that wP vaccinated baboons cleared infection faster than aP vaccinated baboons, and aP vaccinated baboons could acquire infection and transmit to unvaccinated contacts;
- the model fitted the data very well, indicating a median duration of immunity provided by the wP and aP vaccines to be 25 and 12.5 years respectively, and protection against primary infection provided by the vaccines was 90% and 70% for wP and aP respectively;
- the model indicated there would not have been a resurgence if there hadn't been a switch from the wP primary vaccine to aP vaccine in 2004;

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- if aP had been used for the entire programme there would have been a higher incidence level overall, indicating the resurgence which began in 2012 represented a resetting of the endemic level;
  - there would likely be a continued elevated level of disease in the population, relative to the level of disease seen during periods of high wP vaccine uptake;
  - a continued higher level of disease had implications for the cost effectiveness of the maternal immunisation programme;
  - the modelling indicated the drop in the vaccine coverage in 1970's and 80's was unlikely to be responsible for the resurgence in 2012;
  - adolescent or toddler boosters would have little impact on infant disease but would provide direct protection in those vaccinated;
44. Members queried why the age distribution of those infected during the resurgence of 2012 included adolescents and adults when individuals over 12 years of age would have received the wP vaccine. It was explained that the reason the resurgence was affecting a wide age distribution was due to the force of infection in the population now being greater, and those individuals who were not vaccinated were now contracting the disease due to the higher force of infection. Previously when the wP vaccine was used in the primary series the force of infection was lower, and those individuals who hadn't been vaccinated were less likely to be exposed to infection.
45. Members requested that a critical literature review of other models of pertussis vaccination programmes be undertaken in order to check for discrepancies and for this to be reported back to the committee at a later date.
46. The Committee agreed that the model predicted that the resurgence in pertussis disease would likely continue, and this was supported by real data. Elevated levels of disease in the population had implications for the cost-effectiveness analysis of the maternal immunisation programme, and this should be taken into account when the programme was next considered by the Committee. It was also agreed that other options for control of pertussis should be considered at a future meeting.

## **VII. Adult pneumococcal vaccination**

47. The Chair noted that the Pneumococcal Sub-committee had been reviewing adult pneumococcal vaccination in the UK in light of additional data on the indirect impact of the childhood pneumococcal programme on older adults in the UK, and data on the efficacy of adult pneumococcal conjugate vaccination

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on Community Acquired Pneumonia (CAP). The Committee noted that their considerations were being made with respect to the situation in England and across the UK, where there was a very successful childhood pneumococcal conjugate vaccination programme. The magnitude of the indirect effects of the childhood programme would significantly influence any decision making with regards to adult pneumococcal vaccination for the UK.

## Epidemiology

48. Representatives from PHE and the London School of Hygiene and Tropical Medicine, and the Chair of the Pneumococcal sub-committee provided presentations to the Committee covering the epidemiology of pneumococcal disease. The committee additionally considered a relevant paper<sup>4</sup>, and noted that:

- PCV7 vaccine was introduced into the childhood schedule in the 2006 and replaced by PCV13 in 2010;
- invasive pneumococcal disease (IPD) caused by the serotypes in PCV7 had now been virtually eliminated in all age groups;
- between 2009/10 and 2013/14, IPD caused by the six additional serotypes in PCV13, and not in PCV7, decreased from 40% to 18% of all cases of IPD in adults aged 65 years and over;
- IPD caused by serotypes in the 23-valent vaccine had declined by 50% between 2000/03 and 2013/14 in those aged 65 years and over, primarily due to a decline in PCV13 vaccine-type disease;
- however, in 2013/14, 74% of IPD in the 65-69 years age group was caused by the serotypes in PPV23;
- there had also been a substantial decline in PCV13 vaccine type community acquired pneumonia (CAP) in the five years since 2008/9 which was almost certainly an indirect impact of the childhood PCV immunisation programmes;
- the similarities in the rates of decline in vaccine type IPD and vaccine type CAP suggested that the childhood programme was having an indirect effect on non-bacteraemic vaccine type pneumonia of similar magnitude to the indirect effect on vaccine type bacteraemic disease;
- the decline in IPD due to PCV7 types after introduction was similar in risk groups and the general population;

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<sup>4</sup> Waight PA, Andrews NJ, Ladhani SN, Sheppard CL, Slack MP, Miller E (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.

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- data on serotype-specific IPD in HIV-positive individuals during the period 2006/07 to 2012/13 demonstrated that there was a significant reduction in disease caused by 7-valent serotypes which was similar to the reduction seen in HIV-negative individuals;
  - evidence suggested that IPD caused by the six serotypes in PCV13 but not in PCV7 was also declining in HIV positive individuals;
  - there were currently limited data to demonstrate the indirect effects of the PCV13 childhood immunisation programme on vaccine-type CAP in clinical risk groups;
  - the sub-committee considered 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;
  - the pneumococcal sub-committee had agreed it was reasonable to assume that risk groups in the UK were benefiting from indirect protection from the PCV7/13 vaccination programmes in childhood.
49. The Committee agreed that the impact of the childhood PCV7 and PCV13 immunisation programmes on the incidence of IPD and CAP in adults was substantial, and that PCV13 vaccine type IPD would probably be almost eliminated in the adult population within the next three years. The similarities in the rates of decline in PCV13 vaccine type IPD and PCV13 vaccine type CAP over the last five years suggested that the indirect effect of the childhood immunisation programmes was of a similar magnitude for both vaccine type bacteraemic and non-bacteraemic disease. This was biologically plausible as the indirect effect acts principally to reduce transmission and transmission is required for either IPD or pneumococcal CAP. The Committee further agreed that there was good evidence of an impact of the childhood PCV immunisation programme on the incidence of IPD in clinical groups at increased risk of pneumococcal disease.

### Vaccine efficacy

#### *PPV23*

50. The Committee considered information provided in presentations from PHE and the London School of Hygiene and Tropical Medicine (LSHTM), and the Chair of the pneumococcal sub-committee, noting that:
- using the 'Broome' indirect cohort method PHE determined that vaccine effectiveness for PPV23 at one year was 48% (95%CI: 32-60), 21% (95%CI: 3-36) over two to less than five years, and 15% (95%CI: -3-30) for five years or greater;



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- there was additionally some evidence that effectiveness of PPV23 was higher for those not in risk groups, and those aged between 65 and 74 years relative to older adults;
  - evidence indicated that PPV23 did not provide protection against pneumococcal CAP in those aged 65 years and older;
  - there was evidence of PPV23 failing to provide protection in some high risk groups, notably Chronic Obstructive Pulmonary Disease;
  - PPV23 was ineffective in one trial among HIV-positive Ugandan adults;
  - non-randomised studies in risk groups provided conflicting data on efficacy but protection was likely to be short lived.
51. The Committee agreed with the findings of the sub-committee that whilst uncertainties remained about the efficacy of PPV23 in those aged 65 years and over without risk-factors, it was likely that there was some short-lived protection against vaccine type IPD, but there was unlikely to be any efficacy against vaccine type CAP.
52. The Committee agreed with the Sub-committee that PPV23 may fail to provide protection in some high-risk groups, especially in patients with COPD. Evidence of PPV23 efficacy in clinical groups at increased risk of pneumococcal disease was conflicting and duration of protection may be short-lived.
53. Members acknowledged that repeat vaccination with PPV could give rise to hypo-responsiveness, but further agreed that there was no evidence that this occurred when doses of PPV23 were given five years or more apart.

#### PCV13

54. The Committee considered information provided in presentations by the London School of Hygiene and Tropical Medicine (LSHTM), and the Chair of the Pneumococcal sub-committee, noting that:
- The CAPiTA study<sup>5</sup>, a double blind, randomised, placebo-controlled PCV13 efficacy trial in the Netherlands was a key source of data on the efficacy of PCV13 in adults;
  - The study enrolled 84,496 PPV23 naïve, immunocompetent adults aged 65 years and over who were not living in a nursing home or other long term care facility or needing semiskilled nursing care;

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<sup>5</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.

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- per-protocol analysis of the CAPiTA study indicated that PCV13 vaccine efficacy against a first episode of vaccine type CAP was 45.6% (CI 21.8-62.5;  $P < 0.001$ );
  - per protocol analysis of the CAPiTA study indicated that PCV13 VE against a first episode of non-invasive vaccine type CAP was 45.0% (CI 14.2-65.3;  $P = 0.007$ );
  - per protocol analysis of the CAPiTA study indicated that PCV13 VE against a first episode of vaccine type IPD was 75.0% (CI 41.4-90.8;  $P < 0.001$ );
  - modified intention to treat analysis of the CAPiTA study showed lower PCV13 efficacy against a first episode of vaccine type CAP of 37.7% (CI 14.3-55.1;  $P < 0.003$ );
  - while the number of deaths in study participants was low in the CAPiTA study, PCV13 vaccination did not demonstrate protection against all-cause death or death due to vaccine-type CAP or vaccine type IPD;
  - the CAPiTA study did not suggest efficacy in those who developed immunodeficiency after immunisation, and those with immunodeficiency at baseline were not enrolled;
  - there was evidence of PCV13 efficacy in some high-risk groups, such as HIV-infected individuals, however there was a lack of evidence on efficacy in many other clinical risk groups.
55. The Committee agreed with the sub-committee that CAPiTA was a well-conducted study. However, exclusion of immunocompromised individuals from the study meant a substantial proportion of those aged 65 years and older who were at risk of pneumococcal disease had been excluded from the analysis.
56. While the number of deaths in study participants was low, it was noted that the CAPiTA study showed no difference in mortality for vaccinated and unvaccinated cohorts. Mathematical modelling exercises using these data to estimate cost-effectiveness had predicted a reduction in mortality based on the product of the vaccine efficacy against pneumococcal pneumonia and the case-fatality ratio of pneumococcal pneumonia. However, this was not observed in the CAPiTA trial.
57. It was also important to note that there was a lack of evidence of PCV13 efficacy in many individual pneumococcal risk-groups and that evidence from CAPiTA did not suggest efficacy for those who developed immunodeficiency after immunisation.

## Cost-effectiveness

### *PPV23 vaccination*

58. The Committee noted that as 45% of those aged 65 years and over were in clinical risk groups, considerations regarding use of PPV23 in risk groups and in those over 65 years of age overlapped considerably.
59. The Committee noted that PHE had undertaken a qualitative analysis of the 2004 study<sup>6 7</sup> previously considered by JCVI in assessing the cost-effectiveness of PPV23 vaccination of adults 65 years and over. The Committee noted that the qualitative analysis had taken into account the changing epidemiology of pneumococcal disease in the UK, and changes to population demographics. The findings of this re-analysis indicated that; despite an estimated 30% decline in incidence of IPD attributable to PPV23 serotypes since the original study was considered in those 65-69 years of age; the findings of the original cost effectiveness analysis vaccination had not substantially changed. The Committee therefore agreed with the advice of the Pneumococcal sub-committee that the PPV23 programme for those aged 65 years and over should continue at this time.
60. The Committee agreed that there remained considerable uncertainty as to the level of protection against vaccine type IPD afforded by PPV23 in risk groups, and also death due to vaccine type IPD. However it was felt that the vaccine may provide some short-lived protection against IPD in risk groups, and would therefore provide some protection against the 11 capsular groups not covered by PCV13. The committee agreed that the PPV23 immunisation programme in risk-groups should continue at the current time and be reviewed again in two to three years in parallel with the routine PPV23 vaccination programme for those aged 65 years and over. These programmes would need to be considered together in order to consider the inherent difficulties in delivering a risk- or age based routine programme, where so many of those aged 65 years or over were in risk-groups.
61. It was noted that given the falling incidence of PPV23 vaccine-type IPD, the cost-effectiveness of the programme was likely to continue to reduce over time, unless PPV23 vaccine serotype replacement occurred as a result of the increasing indirect impact of the PCV13 childhood programme. It was agreed

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<sup>6</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>7</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.

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that PHE should work to define an incidence threshold of vaccine type IPD below which the PPV23 programme would no longer be cost-effective.

62. The Committee noted that the sub-committee had raised an issue with the Department of Health that there was no standard methodology for considering the discontinuation of vaccination programmes. This was of particular importance as the methodologies used had changed over time. It was noted that the Committee had begun trialling the methodology advised by the Working Group on Uncertainty after decisions had been made regarding introduction of the PPV23 programme, and there were considerable uncertainties associated with the evidence used to assess the cost-effectiveness of PPV23 vaccination, including the case fatality ratio for IPD. The Committee welcomed a response from the Department of Health that the Working Group on Cost-Effectiveness Methodology for Immunisation Programmes and Procurements (CEMIPP) had agreed to consider the matter.
63. The Committee agreed that work to define a threshold at which PPV23 vaccination would no longer be cost-effective should be undertaken, and supported by work to refine estimates of the case fatality ratio for IPD, and also take into account the advice of CEMIPP.

*PCV13 vaccination for those aged 65 years and over*

64. The Committee noted a pre-publication paper from PHE and LSHTM on the cost-effectiveness of vaccinating immunocompetent older adults with PCV13. The static cohort model assumed the continuation of the routine PPV23 immunisation programme for individuals aged 65 years and over. Additionally, members received a presentation from PHE on this cost-effectiveness model and noted in particular that it made the following assumptions:
- a single dose of PCV13 offered at 65 years of age, followed by PPV23 at a later visit;
  - the vaccination programme would be introduced in England in the autumn of 2016;
  - IPD due to PCV7 serotypes remained at the 2013/2014 incidence;
  - IPD due to the six additional serotypes in PCV13 (i.e. in PCV13 but not in PCV7) followed a similar pattern of decline to that of the seven serotypes after the introduction of PCV7 (but with a lag period of one year explained by the fact that there was no catch-up campaign for PCV13 as there had been with PCV7);

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- vaccine type CAP incidence as measured in the Rodrigo *et al.* (2015)<sup>8</sup> study, declined with the same dynamic as IPD
  - CFR of 30% for IPD and 10% for CAP;
  - vaccine efficacy as given in the CAPiTA per protocol analyses;
  - no waning of protection for ten years;
  - discounting rates of 3.5% for costs and benefits.
65. The Committee noted that in the base case analysis the cost per quality adjusted life year (QALY) gained was substantially higher than the accepted threshold of £20,000 and the maximum price per dose of vaccine using a threshold of £20,000/QALY was negative when administration costs were taken into account. The robustness of the outcome had been tested in a series of sensitivity analyses which varied the assumptions made on elements including costs, QALY loss, case fatality rate, incidence of IPD and CAP, vaccine waning, age at first dose and life expectancy. The outcome was shown to be particularly sensitive to the case fatality rate, waning of protection and the projected incidence of IPD. Sensitivity analyses indicated that the cost per QALY gained was lowest for the assumption of zero waning of protection but this was still markedly higher than the £20,000/QALY threshold. Assuming that the incidence of PCV13 vaccine type IPD and CAP showed no further reduction 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 was below a practical value, as indicated by the Department of Health.
66. The Committee noted that when a cost-effectiveness analysis undertaken by Pfizer the manufacturer of PCV13, was compared to the PHE/LSHTM analysis, if similar parameters were used the results were comparable. It was considered that the parameters used in the Pfizer analysis were favourable to the cost-effectiveness of the vaccine, and were not in keeping with the totality of the evidence available.

#### *PCV13 vaccination for clinical risk groups*

67. The Committee noted that the previous review of PCV13 vaccination of clinical groups at increased risk of IPD in the UK had been informed by a cost-effectiveness study conducted by the Health Protection Agency and LSHTM. This analysis had concluded that it was unlikely a PCV13 vaccination programme for all risk groups would be cost-effective. Vaccination of most individual risk groups, with the exception of those individuals with chronic liver

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<sup>8</sup> Rodrigo C, Bewick T, Sheppard C, Greenwood S, Mckeever TM, Trotter CL, Slack M, George R, Lim WS (2015) Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. *Eur Respir J* 45(6):1632-41.

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disease, was also considered unlikely to be cost-effective unless PCV13 effectiveness against non-bacteraemic pneumococcal pneumonia was assumed. The Committee noted that the Sub-committee had interrogated this and other relevant studies and had concluded that by the year 2015/16, routine vaccination of all risk groups and vaccination of most individual groups at increased risk of pneumococcal disease was extremely unlikely to be cost-effective. The Committee agreed with the sub-committee that a routine PCV13 immunisation programme for risk groups was unlikely to be cost-effective in 2015/16 and was highly likely to become less cost-effective as the full indirect effects of the childhood PCV13 immunisation programme were realised. The Committee agreed with the sub-committee that use of PCV13 vaccine in risk groups should remain limited only to those at the very highest risk of, or mortality from IPD. Such use of the vaccine remained justified while the full impact of the PCV13 programme had yet to be realised.

### Conclusions

68. The Committee concluded that there had been a significant reduction in PCV13 vaccine type disease in the UK across all ages through the direct and indirect impact of the childhood vaccination programme which had begun in 2006. The vaccine first used in the childhood programme, PCV7, had within seven years led to a near elimination of PCV7 vaccine type invasive disease in the UK. Since moving to use of the PCV13 vaccine in 2010, there had been a significant reduction in disease caused by the additional capsular groups in PCV13, and the Committee agreed that it was highly likely that this trend would be continued, with likely near elimination within the next three years.
69. The Committee agreed that the evidence indicated the indirect impact of the childhood vaccination programme in the UK was also having a significant impact on cases of vaccine-type pneumococcal community acquired pneumonia, similar in magnitude to the impact seen with invasive disease. Sentinel risk-groups, such as HIV-positive individuals, indicated that significant indirect protection against IPD was also being provided to those individuals in risk-groups in the UK.
70. It was agreed that evidence indicated the pneumococcal polysaccharide vaccine PPV23 provided some protection against invasive disease, although the protection afforded was likely short lived, particularly in risk groups. As the PPV23 vaccine covered pneumococcal capsular groups not in the PCV13 vaccine, the committee felt that continuation of a programme to vaccinate those aged 65 years and over and in clinical risk groups continued to be clinically justified at this time. A qualitative analysis of the data had indicated that it was likely that use of the vaccine remained cost-effective at this time, although it

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was important to note the considerable uncertainties associated with the data on vaccine effectiveness and impact which supported the analysis.

71. The Committee agreed that given the continued reduction in incidence of PCV13 vaccine type pneumococcal disease in the UK, the benefits associated with vaccination of additional groups with PCV13 vaccine would be limited. The Committee considered that the analysis it has reviewed on the cost-effectiveness of PCV13 vaccination of adults aged 65 years and over was robust, and indicated it was highly unlikely that a programme to vaccinate those aged 65 years and over in the UK would be cost-effective at this time. Should the incidence of PCV13 vaccine type disease in the UK continue to reduce, as was expected, the Committee agreed that in around three years there would be very little PCV13 vaccine-type disease to prevent in the UK and any benefits of additional PCV13 vaccination would be minimal. The Committee agreed that this position should be reviewed should PCV13 vaccine-type pneumococcal disease not decline as expected
72. A review of the evidence indicated that the pneumococcal risk-groups previously identified were still appropriate. The Committee noted that the Pneumococcal sub-committee had advised that PHE should be asked to consider a number of clarifications to descriptions in the Green Book of those in clinical risk groups and specifically consider references to rheumatoid arthritis, systemic lupus erythematosus and other related autoimmune conditions, neuromuscular disorders and epilepsy. JCVI agreed with the sub-committee and asked PHE to undertake the necessary considerations.
73. As the epidemiology of pneumococcal disease was still evolving, following the introduction of PCV13 into the childhood programme, the Committee agreed to consider reviewing the use of PPV23 in three years, at a time when it was anticipated that pneumococcal epidemiology may have achieved a steady state.
74. The Committee asked that work be undertaken to identify a threshold of PCV23 vaccine type disease at which point continuation of the PPV23 programmes was no longer cost-effective. As there were considerable uncertainties regarding the efficacy of PPV23 vaccine, and preventable mortality, the Committee also welcomed consideration by CEMIPP of appropriate methodologies for disinvestment. The Committee asked PHE and LSHTM to provide an update to the Committee in October 2016 on progress in modelling a cost-effective threshold for PPV23 vaccination.

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## Advice

75. Overall the Committee 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.

## Consideration of the Pneumococcal conjugate vaccine of choice for the UK childhood programme

76. The Committee reviewed data submitted by GlaxoSmithKline on their 10-valent pneumococcal conjugate vaccine. The Committee considered these data in light of earlier advice from the Committee that the 13-valent pneumococcal conjugate vaccine should be the pneumococcal conjugate vaccine of choice for the UK childhood immunisation programme. The Committee additionally considered commentary from PHE on the data provided, and data describing the epidemiology of capsular group 19A in areas with a PCV10 programme.
77. The Committee agreed that the epidemiological data in the surveillance report, presented as evidence of both direct and indirect protection from 19A, was difficult to interpret. There had been changes in rates of 19A in several countries including an increase in 19A IPD in the most recent epidemiological year, and that non- vaccine type disease has also increased.
78. While the two case control studies provided appeared to show evidence of cross protection from PCV10 against 19A in vaccinated children, the impact data from Finland and the Netherlands indicated some recent increases. The difference in behaviour of 19F and 19A and of 6A and 6B in Finland in 2014 suggested the situation is not clear cut. The impact of indirect effects of PCV10 in older age groups is not thus far as well documented as for PCV13. A claim that PCV10 induces less serotype replacement than PCV13 needs further investigation but is not supported by data from the Netherlands.
79. The committee reiterated the previous view that the full impact of the PCV13 programme had yet to be realised and that it is prudent to continue to monitor and define the full extent of the impact before making changes to the programme, particularly given the large direct and indirect effects documented in the UK surveillance. Further evidence of impact of PCV10 on serotype 19A and the indirect effects of this vaccine will help inform future deliberations about alternative programmes.



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### **VIII. HPV Vaccination of MSM**

80. The Committee received an update from the Chair of the HPV Subcommittee on the meeting held in June 2015, where consideration of a targeted vaccination programme for MSM was undertaken. The Committee noted that:
- the modelling had been updated following feedback from the stakeholder consultation and peer review and the results had not qualitatively changed;
  - a targeted programme for those MSM aged 16-40 attending GUM and HIV clinics would be cost effective, provided the combined cost of the vaccine and administrative fee was below a certain threshold price;
  - the Subcommittee had agreed that there should be no lower limit of age and that the findings regarding a programme to vaccinate those aged 16-40 years could be reasonably extrapolated to age 45, where data was less robust;
  - the Subcommittee had also agreed that prisoners who are MSM should also be able to access the HPV vaccine through prison sexual health services and transgender women should also be eligible; and
  - the Subcommittee was advising that a targeted vaccination programme for MSM up to the age of 45 attending GUM and HIV clinics was cost-effective, provided that the combined cost of the vaccine and administrative fee were within the threshold for the programme to be cost effective.
81. The Chair invited PHE to present the findings from the updated modelling work. The Committee were reminded that the initial findings presented to the Committee in October 2014 had shown:
- that a programme could be cost-effective provided that the combined price of the vaccine and administration was below a certain threshold;
  - the Department of Health had investigated the administrative cost and agreed that the administrative cost of vaccination in the school based HPV programme was a reasonable estimate to use for the administrative cost of the MSM programme;
  - A programme with the bivalent vaccine would not be cost-effective under any realistic price scenario.
82. The Committee noted that as a result of the stakeholder consultation, peer review, and feedback from the subcommittee a number of changes had been made to the model, including:

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- the estimated proportion of HIV positive MSM attending GUM clinics; those that were diagnosed HIV positive would attend at a high rate and those not diagnosed would attend at a similar rate to HIV negative MSM;
  - not all MSM attending would take up the offer of HPV vaccination and, of those that did not all would complete the three dose course;
  - anal cancer survival rates had been updated using results from a more recent trial;
  - the model had been recalibrated for anal cancer and now fitted better with the HPV prevalence estimates from the Mortimer Market GUM study and anal cancer incidence from the Office of National Statistics (ONS); and
  - a correction for discounting QALYs in the future had been made.
83. A number of smaller changes had also been made to the model including updates to demographic data, use of the third National Survey of Sexual Attitudes and Lifestyle (Natsal-3) data instead of Natsal-2 data, and cancer incidence and genital warts incidence had been averaged over a number of years rather than from a single year. The Committee noted that some of the changes would make vaccination more cost-effective while others would make it less cost-effective.
84. The Committee noted that the assessment had also been expanded at the request of JCVI to look at more subgroups in terms of age and HIV status by looking beyond 40 years up to 45 and then up to 74 years of age although PHE stressed that these analyses were highly speculative and uncertain because of the paucity of data in terms of sexual mixing and HIV prevalence beyond 40 and especially beyond 45 years of age. Similarly under certain assumptions a strategy targeting HIV positives MSM might be more cost-effective but was also subject to greater uncertainty around the attendance of undiagnosed HIV positive MSM and the duration of protection of the vaccine. Therefore PHE considered that the base case should be all MSM aged 16-40 attending GUM and HIV services.
85. The Committee noted the results from the updated model noting that:
- the results had not qualitatively changed and as such the overall conclusions had not changed;
  - the estimated threshold price per dose, including administrative costs, at which a targeted programme would be cost-effective for extending incrementally from a programme for HIV+ve MSM aged 16-40 to all MSM 16-40 was now higher compared to the original estimate presented in September 2014;

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- the threshold price per dose of vaccinating all MSM 16-40 was higher still when the option of an HIV+ve MSM only programme was excluded from the incremental analysis;
  - if herd effects were excluded, for example in a scenario where uptake was so low that benefits due to potential herd effects were small, the threshold price for cost effectiveness decreased, although it was still a positive price;
  - whether or not the programme would be cost-effective would depend on the price at which the vaccine was procured combined with the administrative costs;
  - at the list price of the vaccine, vaccinating HIV+ve individuals up to the age of 45 appeared cost-effective;
  - vaccinating all HIV+ve MSM up to 45 was also cost-effective at a practical threshold price, but not at the list price of the vaccine;
  - data informing analyses for MSM over 40 years of age were poor;
  - under the assumptions used comparing vaccination to no vaccination and at a realistic combined vaccine and admin price the cost effectiveness of vaccinating MSM aged 16-40 satisfied the criteria recommended by the Working Group on Uncertainty in Vaccine Evaluation and Procurement.
86. The Committee noted that the Department of Health was of the view that the uncertainty analysis indicated that it was almost certain that a programme to vaccinate MSM attending GUM and HIV clinics aged up to 40 years of age would be cost-effective, subject to procurement and delivery at a cost-effective price.
87. The Committee agreed with the HPV Subcommittee that the age for vaccinating all MSM could be extended to 45 as this came out at a practical price within the bounds of cost effectiveness and despite uncertainty in the data after 40 years of age it did not consider that the sexual behaviour of MSM would change between the age of 40 and 45. The Committee also agreed that the lower age limit of 16 years could be removed.

#### Monitoring and Surveillance

88. The Chair invited PHE to report on the plans to monitor vaccine uptake among MSM and assess the impact of the programme and noted that:
- uptake of vaccine in GUM and HIV clinics could be monitored using the genitourinary medicine clinic activity dataset (GUMCAD) and HIV and AIDS reporting system (HARS) respectively to record the number of doses received as well as whether HPV vaccination was offered and refused and whether the HPV vaccination schedule had previously been received in full;

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- residual sera from routine testing for HIV and syphilis in GUM clinics would be used to assess anti-HPV antibody concentrations to indicate whether a person has been vaccinated or not, and this could be used to validate the uptake data;
  - impact on HPV infection could be monitored by testing residual rectal swabs which are routinely taken for MSM in sexual health services for chlamydia testing;
  - the initial impact on disease could be assessed from the incidence of anogenital warts which was routinely reported through the GUMCAD surveillance system. The impact on cancer would be measurable in the much longer term via ONS cancer statistics.
89. The Committee agreed that monitoring and surveillance would be critical to the success of the programme and that PHE had put together a comprehensive plan. The Committee noted concerns on whether this would be robust enough based on the previous experience of the difficulty of collecting Hepatitis B (Hep B) vaccine uptake in GUM settings and because it was not possible to track individual MSM from one GUM clinic to another. However, the Committee noted that the Hep B vaccine for MSM was introduced before the GUMCAD surveillance system had been set up, and therefore it was difficult to know how good the current system was for estimating Hep B coverage given that a large number of MSM would now have received the vaccine.
90. PHE recognized there were limitations to the information that could be collected for HPV vaccination due to the data being anonymised, but indicated that the number of men who had one two or three doses could be reported and 12 to 18 months into a programme PHE should have an estimate of the number of MSM that had one dose and then completed two or three doses.

#### Implementation and delivery

91. The Committee noted the Sub-committee's view that GUM and HIV clinics were by far the most accessed sexual healthcare service by self-declaring MSM, who might not otherwise self-declare to a GP, and that MSM accessing GUM services were known to be a high-risk group within the MSM population in terms of risk behaviour and STI transmission. The cost-effectiveness analysis being considered was only possible because of the sexual health data available from GUM and HIV clinics. Data on partnership rates, numbers, or HPV prevalence in those MSM solely accessing GP services was limited.
92. The Committee however recognized that other providers might wish to offer the vaccine opportunistically (such as GPs), and as access to GUM services may vary geographically, restricting a service solely to GUM and HIV clinics could

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introduce concerns around equity of access. The Committee agreed that the advice of the Committee could only be based on the available evidence, which in this instance was on the impact and cost-effectiveness of vaccinating the GUM/HIV clinic-attending MSM population. The Committee considered that it might be possible for eligible MSM to be identified in GUM clinics be given the option to receive follow up doses elsewhere, but it was agreed that this was for DH, PHE and NHS England to consider, alongside any identified options for delivery.

93. In terms of implementation the Committee agreed it was important to recognise the complexities associated with commissioning and delivery of a programme involving GUM and HIV services. The Committee noted that sexual health was the responsibility of local government, whilst NHS England was responsible for commissioning primary care and national vaccination programmes. The Committee noted that work was required by DH, PHE and NHS England to identify potential routes for the commissioning and delivery of any programme to vaccinate MSM, and that this work would likely be challenging.
94. The Committee had considered evidence related to the scientific and economic assessment of a targeted programme for MSM attending GUM and HIV clinics, and it could therefore only make an informed decision and offer advice on the basis of that evidence. The Committee however agreed that its advice would not preclude delivery through other providers and that there was potentially scope for this, although it could not comment on the cost-effectiveness of such provision if it were to be considered incrementally over provision through HIV and GUM services.

#### Other groups

95. The Committee were reminded that alongside a targeted programme for MSM, some individuals in other groups might also be considered for vaccination on the grounds of having a risk profile for infection and disease progression similar to that of the MSM group attending GUM and HIV clinics such as MSM over 45, sex workers, HIV+ve women, HIV+ve men who are not MSM and women above the cut off age for receiving the HPV vaccine.
96. The Committee noted that the cost-effectiveness of a catch-up for women above 18 years who had not received the vaccine could be modelled although it was considered unlikely to be cost-effective based on the modelling used to inform the original advice in 2008 for the adolescent girls programme. Moreover this would be in the context of reduced risk of infection and disease due to the herd effects of the current programme.

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97. It was considered possible that vaccinating some subgroups, including some women over age 18 years at particularly high risk of HPV infection and/or disease may be cost-effective. However, it would be difficult to identify the data needed to parameterize a model of such subgroups. PHE agreed to look into the availability of data, and agreed that if data were sufficient, it may be possible to calculate a threshold risk for which vaccination would be appropriate.
98. The Committee agreed that individuals in certain groups, that might be considered to have a risk profile similar to that of the MSM group attending GUM and HIV clinics for which quantitative analyses were not possible due to data limitations. JCVI considered that there may be considerable benefit in offering the HPV vaccine to other individuals who have a similar risk profile to that seen in the 16 to 40 year old GUM attending MSM population, including some MSM over 45, sex workers, HIV+ve women, and HIV+ve men. As clinicians are able to offer vaccinations outside of the national programme using individual clinical judgement, HPV vaccination could therefore be considered for such individuals on a case-by-case basis.
99. Note: Following the meeting, the Department of Health agreed to consider vaccination of individuals in other groups from a national perspective alongside the advice of the Committee on the vaccination of MSM up to 45 years of age who attend GUM and HIV services, and will report back to the Committee at a future date.

### Conclusions and advice

100. Given the available data, the Committee advised that a targeted HPV vaccination programme for MSM aged up to 45 who attend GUM and HIV clinics should be undertaken, subject to procurement of the vaccine and delivery of the programme at a cost-effective price.
101. Before any programme could be undertaken, work is required by DH, PHE, local government and NHS England to identify the commissioning arrangements and potential routes for delivery of any programme to vaccinate MSM. The Committee noted that this work would likely be challenging.
102. The Committee further agreed that prisoners who are MSM should also be able to access the HPV vaccine through prison sexual health services and transgender women should also be eligible.

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103. JCVI considered that there may be considerable benefit in offering the HPV vaccine to other individuals who have a similar risk profile to that seen in the 16 to 40 year old GUM attending MSM population, including some MSM over 45, sex workers, HIV+ve women, and HIV+ve men. As clinicians are able to offer vaccinations outside of the national programme using individual clinical judgement, HPV vaccination could therefore be considered for such individuals on a case-by-case basis.
104. Note: Following the meeting, the Department of Health agreed to consider vaccination of individuals in other groups from a national perspective alongside the advice of the Committee on the vaccination of MSM up to 45 years of age who attend GUM and HIV services, and will report back to the Committee at a future date.
105. The Committee also highlighted the importance of the on-going assessment for the consideration of extending HPV vaccination to adolescent boys and noted the update from the HPV Subcommittee on this work and that the two models looking at this are currently in development.

#### HPV vaccine safety

106. The Committee were reminded that the issue of the safety of the HPV vaccine had also been considered by the HPV Subcommittee. The Committee noted that the safety of the HPV vaccine was currently being reviewed by the EMA and that it would be sensible to discuss this further when the results of the review were made public in the coming months.

#### 9 valent vaccine

107. The Committee noted that the HPV subcommittee had also considered a presentation by the manufacturer on the 9 valent vaccine and that further data would be considered in the future when it becomes available. The Committee noted that the impact and cost-effectiveness of the 9 valent vaccine would be included as an option alongside the other available vaccines in the models currently under development for considering the vaccination of adolescent boys.

### **IX. Update from the Varicella Sub-Committee**

108. Members heard an update from the chair of the JCVI Varicella sub-Committee which was reconvened in June 2015. Members were informed that;

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- the sub-Committee was reconvened to consider the impact and cost effectiveness of a universal childhood varicella programme, to consider the impact and cost effectiveness of targeted varicella vaccination programmes in adolescents and post-natal populations and the impact of the adult herpes zoster (HZ) vaccination programme;
- previously, the JCVI had recommended not to introduce a combined varicella- in children and HZ- in adults programme but it did recommend a universal HZ programme for adults aged 70 years up to and including 79 years, provided that a licensed vaccine was available at a cost effective price, and this programme started in 2013;
- the decision not to implement a combined universal varicella and HZ programme was largely based on the findings of cost effectiveness modelling and the predicted increase in herpes zoster incidence for the first 40 to 60 years following the introduction of the programme;
- the sub-Committee had heard a presentation on the epidemiology of varicella and HZ and it was apparent that more data were required to (1) explore the potential of A&E data in HES to capture the number of admissions due to varicella and HZ, (2) undertake investigations to determine whether NHS 111 hold data on consultations related to varicella, (3) investigate whether additional costs associated with issuing VZIG can be included in the van Hoek et al (2012) model, and (4) investigate why 30% of hospital admissions for children under 10 years of age have no other complications recorded on HES;
- the sub-Committee had been presented with data on the association between invasive group A streptococcal (iGAS) disease and varicella zoster infections and it was thought that additional data could be captured which may imply that there were more cases of iGAS associated varicella and that it should be investigated how the van Hoek et al (2012) model might be updated to include sequelae and life-long costs associated with varicella infection;
- a review of the licensed varicella vaccines had been presented at the sub-Committee meeting and it was highlighted that 1 dose varicella vaccination programme in children may prevent severe disease but still maintain circulating VZV and therefore boosting and prevention of HZ would continue. The sub-Committee had requested that a 1 dose childhood varicella vaccination programme be included in the van Hoek et al (2012) model;
- the sub-Committee had been presented with safety data on the varicella vaccines and the increased risk of febrile convulsions with the combined measles, mumps, rubella and varicella vaccine had been discussed and it



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was thought that parent's views on the acceptability of the combined MMRV vaccine with double the risk of febrile seizures would need to be sought;

- the impact of a universal varicella vaccination programme on the epidemiology of HZ had been heard by the sub-Committee and that many countries are monitoring HZ epidemiology since the introduction of varicella programmes however it is difficult to determine the impact of varicella vaccination on HZ epidemiology as HZ rates have been steadily increasing in other counties prior to the introduction of the varicella vaccine;

109. The committee heard that there will be a workshop involving modellers from various European countries to discuss and compare individual varicella and HZ models and there will be a report back from this at a future meeting.

#### PHE update on the impact of herpes zoster vaccination in England

110. PHE provided an update on an evaluation of the HZ programme which was introduced in England in September 2013. The committee noted that:

- a range of different surveillance systems had been implemented to monitor the impact and the effectiveness of the HZ programme;
- the HZ vaccine had been offered routinely to 70 year olds with a single year catch up programme for those aged 79 years;
- HZ is not notifiable in England and therefore the impact of the programme had been assessed using CPRD data with consultations for shingles extracted from 2000 onwards. Birth cohorts between the ages of 65 and 84 were assessed where there was a read code for HZ;
- prior to the introduction of the HZ programme, data from the UK showed a very stable trend in HZ incidence
- trends were compared between those age cohorts who were eligible for the vaccine and those which were not and a decline in consultations rates were seen in both the routine and catch up cohorts. The decline in consultations for shingles for the two cohorts who were vaccinated was estimated to be 22%. This figure was consistent with that which would be expected for a vaccine with 38% efficacy and coverage of around 60%.

111. It was noted that HZ incidence in the UK has been remarkably flat prior to the introduction of the HZ vaccine which would not have been predicted from modelling which takes into account changes in mixing and social structures. The data are also very different from the HZ epidemiology data collected from the US and Canada where a rise in HZ has been observed prior to the

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introduction of the varicella vaccine. If the original assumption was correct that changes in exposure to VZV increased the rate of Zoster in younger adults, members thought the only plausible explanation would be if there had been a rise in individuals attending A&E with HZ instead of primary care however this was not thought to be likely.

**X. Papers for Comment**

112. The Committee noted the papers provided

**XI. Any Other Business**

113. No other business was raised

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