JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

Minute of the meeting on 1 October 2014

102A-124A, Skipton House

80 London Road, London SE1 6LH

Members

Prof Andrew Pollard (Chair)
Dr Peter Baxter
Prof Judith Breuer
Dr Peter Elton
Prof Matt Keeling
Ms Alison Lawrence
Mrs Pauline MacDonald
Mrs Anne McGowan
Prof Robert Read
Dr Andrew Riordan
Prof Anthony Scott
Prof Claire-Anne Siegrist
Dr Maggie Wearmouth

Invited contributors

Prof Ray Borrow

Medical advisors

Prof John Watson (DH)

Apologies

Dr Anthony Harnden

Invited observers from Devolved Administrations and MHRA

Dr Elizabeth Reaney (DHSSNI)
Dr Andrew Riley (Welsh Assembly)
David Vardy (Welsh Assembly)
Dr Nicola Steedman (Scottish Govt)
Dr Phil Bryan (MHRA)

Observers and presenters

Dr Claire Cameron (HPS)
Dr Richard Roberts (HPW)
Dr Richard Smithson (PHA)
Dr Sandra Anglin (NHS England)
Dr Ruth Howlett-Shipley (MoD)
Elaine Burgess (Guernsey)
Dr Dipti Patel (NaTHNaC)
Prof Ian Feavers (NIBSC)
Dr Darina O'Flanagan (Eire)
Dr Mark Jit (PHE)
Dr Sema Mandal (PHE)
Dr Gayatri Amirthalingam
Dr Karen Powell (PHE)
Carolyn Heaney (DH)
Michelle Parkinson (DH)
Dr Peter Grove (DH)
Mr John Henderson (DH)
Joanne Yarwood (PHE)
Dr Kishore Parmeswaran(Isle of Man)
Dr Laura Yates (UKTIS)
Dr Linda Diggle (Jersey)
Dr Shamez Ladhani (PHE)
Dr Vanessa Saliba (PHE)

Secretariat

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

Welcome

1. The Chair welcomed all to the meeting. Apologies were received from Dr Gabrielle Laing and Mr Chris Liffen, it was noted that Prof Matt Keeling would join the meeting from 12:00. The Chair welcomed Professor Ray Borrow as an invited expert contributor on bacteriology for this meeting.

2. The Chair noted that applications for the roles of GP member and vaccinologist member had been received by the Department of Health (DH), and that interviews for the posts would be taking place in the coming weeks. No applications had been received for the health economist post, and this would be re-advertised shortly.

3. The Chair noted that Mrs Pauline MacDonald had tendered her resignation from the Committee as she would be leaving her current role to take up a post in Public Health England (PHE) as Programme Director for the Childhood Influenza National Senior Taskforce in November and would therefore be ineligible as a member of the committee. The Chair thanked her for her valuable contributions during her time on the Committee. The Chair further noted that Dr Gabrielle Laing had also tendered her resignation from the Committee, as a number of new commitments meant she could no longer dedicate sufficient time to the Committee. The Chair thanked her for her valuable contributions during her time on the Committee. It was noted that the secretariat would be working with the DH appointments team to ensure the posts were filled as soon as practicable.

4. The Chair advised the committee that he had held discussions with the secretariat regarding the appointment of one or more Deputy Chairs for the Committee who would provide additional leadership for the Committee, and provide the opportunity for all members to become more involved in the coordination of meetings. It was noted that these would be internal appointments which would not require a formal process via the DH appointments team, provided that Deputy Chairs were appointed from the existing membership of the Committee. The Committee agreed to the proposal and further agreed that Dr Andrew Riordan should be appointed as a Deputy Chair. Further consideration to appointment of an additional Deputy Chair would be undertaken following the appointment of new members under the current recruitment exercise.

5. The Chair reminded all that papers provided for the meeting included information provided in confidence. Attendees were asked not to circulate the papers more widely or discuss the data with others outside of the meeting.

6. The Chair noted that he had asked specified members to review each of the key topics for discussion at the meeting, and prepare questions for those presenting

information to the Committee. It was hoped that this preparation would allow the issues to be discussed in depth, and would ensure that the presenters were questioned adequately. It was agreed that this process would continue to be undertaken at future meetings. The Chair further noted that the draft agenda for each subsequent meeting should be circulated as early as practicable to allow members and deputy chairs to comment on the agenda and suggest additional items as necessary.

7. Each member agreed to update their conflicts of interest as held by the Secretariat, and noted that voluntary unpaid membership of data safety monitoring committees would not be considered a conflict of interest.

I. Minute of June meeting

8. The Committee agreed the Minute as an accurate record of the meeting held in June 2014, apart from the following amendments.
   - Prof. John Watson was not in attendance and should be removed from the attendees list;
   - Specified changes to the section on pneumococcal vaccination as specified in Annex A.

II. Matters Arising

9. The action points recorded in the minute of the June 2014 meeting were reviewed, and the Chair noted that:

   - a draft five year forward look had been prepared by the secretariat and was provided for comment and discussion under item 10;
   - the Minute of the February 2014 meeting had been amended regarding concomitant administration of live vaccines;
   - the Secretariat had contacted NICE regarding development of an updated cost-effectiveness analysis on use of RSV prophylaxis and were waiting for the opportunity to undertake further dialogue on the matter (discussed further under item 11);
   - PHE had agreed to provide the Committee with annual updates on pertussis epidemiology and the latest data from the evaluation of the maternal pertussis vaccination programme;
   - the Secretariat had contacted AstraZeneca for further information on the consistency of ovalbumin content of Fluenz® and were awaiting a response;
   - PHE had provided the Committee with a revised summary of the data and relevant papers on morbid obesity and influenza vaccination via

correspondence following the June 2014 meeting, and the Committee had concluded that the additional data allowed them to form clear advice that morbid obesity should be considered a risk factor for seasonal influenza vaccination;

- discussions were underway with modellers regarding preparation of an update to the PPV modelling;
- the Committee had agreed there was a need to convene a pneumococcal sub-committee during 2015 to consider the adult pneumococcal vaccination programme;
- representatives from industry had presented at the HPV sub-committee meeting held on 22 September 2014, and the Chair of the HPV sub-committee would provide her thoughts about the process under item 6;
- the Secretariat had collated relevant information on the use of HBV containing vaccines in the infant schedule, which would be considered under item 4;

10. The Chair advised the Committee that a five year forward look had been developed by the Secretariat to provide the Committee with anticipated timings of Committee work, and to allow the Committee to have an active role in planning future work of the Committee. It was agreed that the timeline would be reviewed regularly. The Committee noted that one key aim of this work was to ensure that information associated with proper deliberation and development of advice or recommendations by the Committee on key areas of future work was scoped early enough to ensure the best possible information would be available at the appropriate time. The Chair asked members to provide the Secretariat with comments and suggested amendments to the timetable provided. The Committee agreed that the timeline should include consideration of pandemic influenza, and that scoping work for norovirus vaccination should be undertaken during 2015. The Committee agreed to provide additional comments to the Secretariat by correspondence after the meeting.

Action: Committee members to provide comments on the five year forward look to the Secretariat by correspondence

11. The Committee noted that whilst the secretariat were exploring options for an update to the cost-effectiveness analysis for palivizumab with NICE, it would be appropriate to develop an interim position regarding RSV prophylaxis, which took into account those comments from the CRG which did not require further cost-effectiveness work. The Committee agreed that a specified member should review the guidance on RSV prophylaxis provided at the June 2014 meeting, and provide amendments for the Green Book to the Secretariat, which should be provided to the CRG by correspondence. The Chair also noted that further discussions on RSV prophylaxis would be included at the next meeting.

Action: Specified member to develop an interim position regarding RSV prophylaxis, and the Secretariat to write to the Chair of the CRG.

Cost-effectiveness working group

12. The Committee noted that the cost-effectiveness working group had held its first meeting which had been very positive. The working group had decided to set up subgroups to look at each of the key issues identified at the meeting. It was agreed that the minutes of the meeting would be circulated to Committee members for information.

Action: Secretariat to circulate the minute of the first meeting of the cost-effectiveness working group to members of JCVI

III. Anti-microbial Resistance (AMR)

13. The committee noted an oral update from Liz Stokle, programme lead for the PHE Antimicrobial Resistance (AMR) programme. The Committee noted that PHE held responsibility for overseeing and coordinating the health and social care sector response to the UK AMR strategy and worked closely with Defra and DH on these issues. The Committee noted that PHE held responsibility for four out of the seven key areas outlined in the UK AMR strategy including infection prevention control.

14. The Committee noted plans to set up a steering group on infection prevention control which would take the lead in developing a national strategy, including professional education and the public awareness. The committee noted that whilst new antibiotics and greater stewardship of existing antibiotics in hospitals and primary care were essential, vaccination was a third and equal pillar of the strategy. The committee noted the structure of groups involved in the oversight, coordination and implementation of the five year AMR strategy, including a high level steering group which would allow DH to advance the AMR strategy and its implementation. The Committee noted that the structure ensured appropriate accountability.

15. Views were sought from the Committee as to how the AMR team could work with the JCVI regarding AMR and it was noted that a key factor for successful working would be to optimise effort and avoid duplication. The Committee was asked to comment on future work of the JCVI with relevance to combatting AMR. The chair noted that the work of the JCVI had already played a role in reducing AMR for example through the implementation of the childhood pneumococcal vaccine programme as several antibiotic resistant clones of pneumococcus are covered by the PCV13 vaccine. However, it was noted that vaccines against the

most common health care associated infections were unlikely to advance to the point of application in the short term. The Committee agreed that it would remain an advocate of the development of such vaccines through activities including its annual Horizon Scanning exercise. The Committee commented that healthcare and social care settings would benefit considerably from vaccinations against a number of infections, including group B streptococcus and norovirus. The Committee noted the success of the rotavirus vaccination programme and the positive impact on hospitalisation rates. These infections are not associated with AMR per se but by reducing these and other diseases, and hospitalisations, the vaccines reduce the exposure of the population to unnecessary antibiotic therapy.

16. The Committee noted that some vaccines could have a profound effect on reducing AMR. The influenza vaccination programme would have reduced the number of individuals given antibiotics by lowering the number of individuals presenting with febrile illnesses in primary care, and by reducing the need for treatment of secondary pneumonia. The Programme would also have led to a reduction in the use of antivirals. The Committee noted that the impact of the strategic use of common vaccines in reducing antibiotic use was a contingency that may not previously have been fully appreciated by JCVI.

17. The Committee discussed whether cost-effectiveness analyses of vaccine programmes should take account of the potential benefits associated with reducing antimicrobial use and agreed that consideration should be given to including such benefits in future cost-effectiveness assessments if possible. It was suggested that the Health Protection Research Units might be undertaking modelling in this area, which should be explored.

Action: Secretariat to explore whether data are available on the potential impact of vaccination in preventing further increases in AMR.

18. The Chair suggested that members should review the JCVI five year forward look from the perspective of reducing AMR and provide comments to the Secretariat. In addition, members should consider possible vaccination programmes not currently included in the plan, such as gonococcal vaccines.

Action: Committee members to review the JCVI Five Year Forward Look Timeline from the perspective of reducing AMR and feedback comments to the Secretariat.

IV. Hepatitis B

19. The Committee noted that in 2009 the Secretary of State for Health had requested a recommendation from JCVI on universal hepatitis B (HBV) vaccination. After consideration of this request, JCVI advised they were unable to recommend a universal infant HBV vaccination programme at that time, as the evidence indicated that use of a stand-alone HBV vaccine in infants or adolescents was highly unlikely to be cost-effective, and whilst evidence indicated the use a HBV-containing multi-component childhood vaccine could be cost-effective, concerns regarding maintenance of protection against Hib disease had prevented the Committee from recommending the use of any available vaccine at that time. However, the request for a recommendation from the Secretary of State for Health was extant and the Committee could still develop a recommendation should the evidence allow it to do so.

20. The Committee noted the WHO position on HBV vaccination that "immunization [sic] of all infants as an integral part of the national immunization schedule should be the highest priority in all countries". The Committee additionally noted the provided papers, including several letters sent from Liver Disease charities.

Pertussis components in hexavalent vaccines

21. The Committee noted that a multi component vaccine would require diphtheria, tetanus, pertussis, polio, Hib and HBV components, and two vaccines currently licensed in Europe contained these components; Infanrix Hexa® produced by GSK and Hexyon® produced by Sanofi Pasteur MSD. The Committee further noted that Sanofi Pasteur MSD had a second multi-component HBV containing vaccine in development, however as this was yet to receive market authorisation it was not considered further.

22. The Committee noted that Infanrix Hexa® contained three pertussis components, and Hexyon® contained two pertussis components. The Committee was reminded by the Chair that there was been a long running debate on the protection afforded against pertussis by vaccines with various numbers of pertussis components, however, the UK currently held the position that vaccines should have no less than three pertussis components, following previous discussions by JCVI. After considering the evidence provided, the Committee concluded that although the evidence[1] was weak, it was the best

[1] Jefferson T, Rudin M and Di Pietrantonj C (2003) Systematic review of the effects of pertussis vaccines in children. *Vaccine* **21**(17-18): 2003-14.

available and supported maintenance of the current position that vaccines used in the UK should have at least three pertussis components, particularly given the recent increase in pertussis incidence in the UK.

Hib protection.

23. PHE introduced a paper on the potential impact of introducing a HBV containing 6-in-1 combination infant vaccine on invasive Hib disease in the United Kingdom.

24. The Committee noted that at this time control of Hib disease was excellent with only 15 confirmed cases in 2012 and 19 in 2013, mainly in older adults with co-morbidities. Concerns had previously been raised about using a HBV containing 6-in-1 combination vaccine in infants because Hib immunogenicity in a previously used precursor vaccine had been low and had contributed to a resurgence of Hib disease from the years 2000 to 2002.

25. The Committee noted that until recently only limited data were available regarding the protection afforded by Infanrix®-based vaccines. However, recent clinical trials had reported adequate immunogenicity, protection and antibody persistence against all vaccine antigens with Infanrix-Hexa®. Such studies had indicated that 85% of infants made responses above the putative protective threshold against Hib disease after the primary schedule, which was considered a sufficient level of protection until the booster at 12 months of age. The booster vaccination would additionally provide protection through a reduction of carriage in toddlers providing indirect protection to unvaccinated infants, adults and the elderly, as well as direct protection for those boosted. The Committee noted that it was on this basis that Infanrix-IPV-Hib® was currently in use in the infant programme, alongside Pediacel®, which provided comparable protection against Hib disease. The Committee additionally noted that, whilst not necessary for generation of a sufficient level of Hib protection in infants, the current use of a tetanus toxoid meningococcal C conjugate vaccine in the UK schedule would likely lead to an additional increase in the Hib response generated from the routine vaccines offered at three months.

26. Overall the Committee agreed that the evidence provided indicated that Infanrix®-based vaccines with a Hib component, if provided in the UK according to the current schedule, would provide sufficient protection against Hib disease in infancy.

Cost-effectiveness

27. PHE introduced a paper on the cost-effectiveness of HBV vaccination, based on a published paper by Siddique *et al*[2], which the Committee had reviewed previously in 2010 prior to publication. The Committee noted little change in the epidemiology of HBV from that outlined in the paper by Siddique *et al*, and that incidence and prevalence remained low across the UK. Overall a small decline in the number of cases had been observed, at a time when case ascertainment had likely improved.

28. The Committee noted that the cost-effectiveness study employed a Markov model of HBV infection which simulated the natural history of HBV infection and disease progression. A cohort rather than dynamic transmission model was used which omitted the effects of herd immunity and therefore could lead to a slight underestimation of the benefits of universal vaccination. However, as the direct effects of the vaccination programme predominate, the simple cohort model was considered acceptable. The model included scenarios for universal infant, universal adolescent and selective geographical programme of infant vaccination targeting high risk populations.

29. The Committee noted the model parameters, including:
    - incidence rates for HBV infection used were estimated using routine laboratory reports adjusted for underreporting;
    - estimated incidence rates in at-risk ethnic populations, applied to a cohort of 12.8% of live births in England in 2006, representing those infants born to mothers born in a country considered intermediate or high risk for HBV infections;
    - carrier-cirrhosis progression which was a good fit to both Taiwanese hepatocellular carcinoma incidence, and USA cirrhosis and mortality data;
    - female incidence rates three times lower than male incidence;
    - the universal programme being implemented in addition to current antenatal screening and selective vaccination from birth of children born to HBV infected women;
    - vaccine efficacy of 90% against acute and chronic infection in infants and adolescents;
    - 90% completion rates in infants and adolescents;
    - A selective geographical infant programme modelled on the BCG vaccination programme;
    - discount rates of 3.5% for costs and benefits.

30. The Committee noted that the model had been extensively peer reviewed, and had not attracted negative critique since publication. The Committee agreed that

[2] Siddiqui MR, Gay N, Edmunds WJ and Ramsay M (2011) Economic evaluation of infant and adolescent hepatitis B vaccination in the UK. *Vaccine* **29**(3): 466-75.

the modelling study was undertaken well, and provided sufficient evidence upon which to develop advice or form a recommendation.

31. The Committee noted that an adolescent programme was highly unlikely to be cost-effective. However, a universal infant programme using a HBV containing hexavalent vaccine demonstrated the potential to be incrementally cost-effective over a pentavalent vaccine, albeit at a price which would be only marginally higher. The Committee further noted that this margin increased by an order of three for a geographically selective programme targeting high risk populations.

32. The Committee considered whether the scenarios modelled accounted for the potential for protection against infection in adulthood following vaccination in infancy. A World Health Organisation (WHO) consensus statement indicated that HBV boosting was not required, although it was noted that this statement referred to use of the vaccine in countries with endemic disease. The Committee agreed that an accelerated infant schedule was likely to provide protection against chronic infection and carriage in adulthood, which was the primary objective of the programme, although it was unlikely to protect against acute infection. The Committee agreed that although this was not accounted for in the current model, the absence of this potential impact on transmission of HBV in adults was likely to only lead to a modest increase in the incremental cost-effectiveness, due to the low incidence of acute infections in the UK. The Committee indicated that it would be interested to review any future work on HBV cost-effectiveness modelling which took this potential impact into account.

33. The Committee noted that a geographically selective programme would be more cost-effective than a universal programme. However, the Committee considered that such a programme would be more difficult to implement, and completion rates could be lower for those within the high-risk populations in the UK. The Committee agreed that advice on such a programme should not be considered at this time, and the focus should remain on cost-effectiveness of a universal programme, as requested by the Secretary of State for Health. The Committee agreed to only revisit the potential benefits of a selective programme should a universal programme not be implemented on cost-effectiveness grounds.

Conclusions

34. The Committee agreed that universal HBV vaccination of infants in the UK was of considerable public health importance and in line with current global WHO advice. Evidence provided to the Committee indicated that whilst use of a stand-alone HBV vaccine in infants was highly unlikely to be cost-effective, replacement of the currently used pentavalent infant vaccine (DTaP-IPV-Hib) with a hexavalent infant vaccine (DTaP-IPV-Hib-HBV) could be cost-effective, if

such a hexavalent vaccine could be procured at a price which was only marginally higher that of the price of pentavalent vaccines.

35. The Committee therefore recommended that a universal infant programme using a hexavalent infant vaccine (DTaP-IPV-Hib-HBV) should be implemented, subject to procurement at a cost-effective price, and such a hexavalent vaccine should be considered the preferred vaccine for use in the UK schedule.

Babies born to HBV positive mothers

36. The Committee noted that a programme was currently in place for HBV vaccination of babies born to HBV infected mothers, with a schedule of 0, 1, 2, 12 months of age. The committee noted the schedule adopted in other countries including the Australian schedule, which simply deploys a birth dose in these high risk populations and then follows the routine HBV-containing routine schedule. The Committee asked PHE to consider from an implementation perspective whether these infants should also receive HBV containing vaccines in the routine infant programme, if a cost-effective price for HBV containing vaccines could be negotiated.

Action: PHE to assess the issues associated with provision of routine vaccinations containing a HBV component in infants born to HBV positive mothers, who would already have received HBV vaccine in early infancy, and provide a paper for JCVI to consider at a future meeting.

V. MenACWY Vaccination in adolescents

37. The Chair reminded the Committee that in January 2012 they had published a statement advising the use of meningococcal serogroup C (MenC) conjugate vaccine in adolescents. This advice had been given on the basis that the infant immunisation programme did not provide persistent protection against invasive MenC disease (IMD) in adolescence. In September 2013, a schools-based vaccination programme had begun in the UK and a catch-up programme for immunising university entrants had also now been introduced.

38. The Chair advised the Committee that current advice limited procurement to MenC conjugate vaccines, disallowing the potential procurement of quadrivalent meningococcal ACWY (MenACWY) conjugate vaccines in the adolescent vaccination programme. The Chair informed the Committee that a request had been received from PHE for JCVI to consider the potential use of MenACWY conjugate vaccines in place of monovalent MenC conjugate vaccines in this programme, particularly in light of a year-on-year increase in meningococcal

serogroup W (MenW) disease since 2009 in all age groups. The Committee noted that there was no available data on the incremental cost-effectiveness of MenACWY conjugate vaccine over use of MenC conjugate vaccine in adolescents in the UK. Therefore, in the absence of cost-effectiveness data the Committee could only comment on the acceptability of use of MenACWY conjugate vaccines in the adolescent immunisation programme.

39. The Committee received an update on meningococcal epidemiology in England and Wales from PHE. In particular the Committee noted that:

- the number of laboratory-confirmed cases of IMD in England and Wales decreased from 2,446 during 1999/2000 to 800 during 2012/13;
- in addition to a decrease in total cases of IMD since the introduction of MenC conjugate vaccine into the routine immunisation programme, there was a substantial reduction in MenC and meningococcal serogroup B (MenB) disease;
- historically, the incidence of MenW disease had been low, accounting for only 1-2% of IMD cases each year;
- an increase in MenW disease during 2000-2002 was associated with travel to Hajj, but MenW did not spread outside this community. The number of cases of MenW declined to pre-2000 levels following the introduction of a requirement of proof of MenACWY vaccination for entry into Saudi Arabia;
- a year-on-year increase in MenW disease had occurred since 2009. In 2013/14, 15% of all IMD was caused by MenW and, unlike the Hajj-associated outbreak, disease was not travel-related;
- analysis of MenW clinical isolates demonstrated that the increase in MenW disease since 2009 was almost entirely caused by the expansion of a single endemic hyper-virulent clonal complex (cc) 11 strain. This is particularly concerning because natural immunity against MenW is low across all age-groups;
- although the total number of cases of IMD caused by this clone remained low, expansion appeared to be continuing, with a notable increase in 2013/14;
- a particular concern is that in recent years, for the first time since the 2000-02 outbreak, MenW was associated with fatal outcomes in children and adolescents. All MenW-associated deaths occurred during the last two epidemiological years and all MenW infections were caused by cc11;
- since the Hajj-associated international outbreaks, a number of countries in Latin America, Sub-Saharan Africa, South Africa and the Far East have reported increases in endemic MenW disease caused by strains belonging to cc11;

- to date the UK is the only country in Europe which has reported a recent increase in endemic MenW:cc11 disease.

40. The Committee noted a presentation from PHE on the recent history of the incidence of meningococcal cc11 isolates worldwide. In particular the Committee noted that:

- MenC:cc11 isolates were a major cause of IMD in Europe in the late 1990s and have been associated with IMD in areas including North America, Europe and Australia;
- more recently, MenW:cc11strains have been isolated during the Hajj-associated outbreak (2000s), African epidemics (2002-2004), in South Africa, South America and in England and Wales since 2008;
- there had been an increase in MenW disease in South Africa in 2005 and incidence had subsequently increased in Brazil, Argentina and Chile;
- the increase in MenW incidence in Chile began in 2012 and was associated with an increasing case fatality rate (CFR). This resulted in the implementation of MenACWY vaccination for children aged 9 months to 5 years in October 2012, however MenW disease still continued to rise in those unvaccinated age groups;
- approximately 800 cc11 strains have been collected globally and core genome multi locus sequence typing (MLST) data used to determine relationships between the isolates;
- for cc11, there was no evidence of recent capsular switching between meningococcal serogroups W and C but there was switching between serogroups C and B;
- a W:cc11 strain was prominent at the Hajj (the ‘Hajj strain’) and this strain had recently been isolated in France, most cases being travel-associated. There remained an on-going problem in South Africa with a strain very closely related to the Hajj strain;
- in 2009 figures indicated that disease associated with the Hajj strain in England and Wales was very low;
- in the post-‘Hajj’ period in England and Wales, most MenW disease had arisen due to W:cc11. Since 2009, the UK W:cc11 isolates were very distant from the Hajj strain but very closely related to isolates from Argentina, Chile and Brazil;
- the CFR for MenW in Chile in 2013/14 was 28%;

- the current CFR for MenW (all MenW regardless of clonal complex) in England & Wales is 13% (13/98) having risen from 0% (0/34) in 2011/12 to 16% (9/58) in 2012/13;
- the current MenW clone circulating in the UK is likely to be covered by Bexsero®, in that pooled serum from vaccinated infants and adolescents killed a representative collection of UK MenW strains;
- although the incidence of MenC disease remained low and had not increased in recent years, nearly 90% of cases in England and Wales are currently caused by C:cc11 strains.

41. The Committee received a paper prepared by the JCVI secretariat on the potential for meningococcal replacement following the use of MenC or MenACWY vaccines. In particular the Committee noted that:

- there was some concern globally about the possibility of replacement disease as a result of the introduction of meningococcal conjugate vaccines into national immunisation programmes prior to their introduction in 1999;
- serogroup replacement had the potential to arise as a result of mechanisms including polysaccharide capsular switching;
- while there was evidence to suggest that capsule switching events occur in *Neisseria meningitidis*, there was no evidence to suggest that these events result in an increase in replacement disease following the introduction of MenC conjugate vaccines;
- studies in the United Kingdom and other countries worldwide reported that there was no evidence for replacement meningococcal disease following the introduction of Men C conjugate vaccines;
- Australia and the Canadian provinces using MenC conjugate vaccines had not reported replacement disease;
- regions that currently used MenACWY vaccines, including the United States of America and some Canadian provinces, had not reported replacement disease. However, the relatively recent licensure of these vaccines in some areas meant that data on their impact were currently limited and further surveillance was required.

42. The Committee received a report on the immunogenicity and safety of CRM- and TT-conjugated quadrivalent MenACWY vaccines in teenagers who had received a CRM- or TT- conjugated MenC vaccine at preschool age in a trial run by PHE. In particular the Committee noted that:

- protection after immunisation in early childhood with MenC conjugate vaccine was short-lived;

- use of a quadrivalent MenACWY vaccine had the potential to protect against serogroups in addition to Men C but concerns had been raised about whether this could compromise MenC response;
- in a randomised trial, teenagers who had received a single priming dose of MenC-CRM or MenC-TT between three and six years of age subsequently received a booster dose of either MenACWY-CRM or MenACWY-TT;
- both MenACWY vaccines induced protective serum bactericidal antibody (SBA) titres to all four meningococcal serogroups in most MCC-primed teenagers;
- overall, MenACWY-CRM vaccine gave significantly higher MenC SBA titres than MenACWY-TT but both vaccines gave titres far in excess of the protective level;
- MenACWY-TT elicited higher antibody levels in teenagers primed with MenC-TT;
- the post-booster SBA was likely to persist throughout adolescence;
- both MenACWY vaccines were well tolerated in teenagers and no attributable serious adverse events were recorded.

43. The Committee agreed that although the total numbers remained relatively low, the increase in the incidence of Men W disease in England and Wales was a substantial cause for concern and that future incidence was difficult to predict. Of particular concern was the fact that most cases of MenW disease in England and Wales were caused by W:cc11, the same clonal complex as the outbreak MenC strain which struck the UK during the 1990s, which was associated with increased virulence, increased fatality rates and disease in younger age groups.

44. The Committee agreed that the use of quadrivalent MenACWY conjugate vaccine in the adolescent programme had the potential to protect against meningococcal disease beyond serogroup C, including MenW. Data provided by PHE demonstrated that concerns that the use of MenACWY vaccine as a booster in the adolescent programme could compromise the MenC response appeared unfounded and that quadrivalent MenACWY conjugate vaccines gave equivalent protection to the monovalent MenC vaccine. The Committee particularly noted that use of both MenACWY-CRM and MenACWY-TT as a booster resulted in protective antibody levels. The Committee reviewed publications showing that the magnitude of the protection against MenC following these MenACWY boosters was far greater than had been observed in the studies of a first dose of MenC in the late 1990's, which had provided considerable direct and indirect protection in the UK population[3,4,5]. The

[3] Burrage M, Robinson A, Borrow R, Andrews N, Southern J, Findlow J, Martin S, Thornton C, Goldblatt D, Corbel M, Sesardic D, Cartwright K, Richmond P and Miller E. (2002) Effect of vaccination with carrier protein on

Committee further agreed that they had no concerns over the safety of quadrivalent MenACWY as a replacement for monovalent MenC vaccine in the adolescent immunisation programme.

45. The Committee noted that while the use of quadrivalent MenACWY vaccine in the adolescent programme was likely to protect against MenW disease in this age group, the vaccine was only licensed for use in individuals older than two years in the UK. The Committee expressed concern that infants would not be protected against MenW disease especially in light of its increased incidence in this age group. It was agreed that a degree of protection would likely be afforded through herd immunity following the introduction of MenACWY into the adolescent programme, but that this would take several years to become established, and require consistent use of the vaccine in adolescents. The Committee considered the data showing that the MenB vaccine, Bexsero®, was likely to provide infants and adolescents protection against infection with the MenW clone currently circulating in the UK. In February 2014, the JCVI recommended that Bexsero® should be offered to children at 2, 4 and 12 months dependant on a cost effective price for the vaccine being secured. The Committee agreed that infants would be likely to be protected against infection by MenW should Bexsero® be introduced into the infant programme. . The Committee noted that they had been unable to form a recommendation on the use of Bexsero® in adolescents due to the degree of uncertainty regarding duration of protection and protection against acquisition of meningococcal carriage and the significant risk that such a programme would result in a net loss of health in the population through displacement of other interventions within the health service.

46. The Committee considered the risks of replacement disease, in particular MenB, should quadrivalent MenACWY replace monovalent MenC vaccine in the adolescent immunisation programme. The Committee agreed that while there was strong evidence to suggest that capsular switching occurred in *Neisseria meningitidis*, there was no evidence to suggest that this would result in an increase in virulence or in replacement disease. The Committee considered the impact of the introduction of MenC vaccination on replacement disease globally and agreed that based on the currently available data there was no evidence

response to meningococcal C conjugate vaccines and value of different immunoassays as predictors of protection. *Infect Immun* **70**(9): 4946-54.

[4] de Whalley PC, Snape MD, Plested E, Thompson B, Nuthall E, Omar O, Borrow R and Pollard AJ (2013) Long-term seroprotection after an adolescent booster meningococcal serogroup C vaccination. *Arch Dis Child* **98**(9): 686-91.

[5] Snape MD, Kelly DF, Lewis S, Banner C, Kibwana L, Moore CE, Diggle L, John T, Yu LM, Borrow R, Borkowski A, Nau C and Pollard AJ (2008) Seroprotection against serogroup C meningococcal disease in adolescents in the United Kingdom: observational study. *BMJ* **336**(7659): 1487-91.

that this had occurred. In particular, the Committee noted that there was no evidence to suggest that an outbreak of meningococcal serogroup B disease in Quebec was a result of serogroup replacement. The Committee agreed that while data on the effect of MenACWY vaccine on replacement disease were limited, in part due to the relatively recent introduction of MenACWY into vaccination programmes in some regions of the world, there was no evidence to suggest that this had occurred in the USA or Canada.

Advice

47. The Committee agreed that the replacement of MenC monovalent vaccine with quadrivalent MenACWY vaccine in the adolescent and fresher programmes was likely to be beneficial in controlling IMD, especially MenW disease. However, it was noted that herd protection would take a number of years to become established and that initially the vaccine would provide only direct protection. They further agreed that they had no concerns over the safety of the quadrivalent vaccine or that the response to the MenC primary dose would be compromised. While data were limited, the Committee further agreed that there was currently no good evidence to suggest that the use of either monovalent MenC or quadrivalent MenACWY vaccines in routine immunisation programmes resulted in meningococcal replacement disease. In light of the additional benefits likely to be afforded by replacing monovalent MenC vaccine with quadrivalent MenACWY vaccine in the adolescent programme, and in the absence of cost-effectiveness analysis, the Committee agreed that they would advise the use of the quadrivalent vaccine if this could be procured at a comparable price to the monovalent vaccine.

Action: Secretariat to write to the Department of Health on behalf of the JCVI informing them of their advice with regard to the use of MenACWY vaccine in place of MenC vaccine in the adolescent and fresher vaccination programmes.

VI. Update from HPV Subcommittee

47. The Chair reminded the Committee that targeted HPV vaccination of men who have sex with men (MSM) and a programme to vaccinate all adolescent boys were options under consideration for the extension of the HPV vaccination programme in the UK. Assessment of the potential impact and cost-effectiveness of targeted vaccination of MSM had been prioritised by the Committee as MSM were at high risk of HPV infection as they received little indirect protection from the highly successful HPV vaccination programme in adolescent girls.

48. The Committee received an update from the Chair of the HPV sub-committee on the September meeting of the Subcommittee, where the main item under consideration was the cost-effectiveness of vaccinating MSM, alongside a summary report provided on the Subcommittee's deliberations and advice.

Modelling parameters and assumptions

49. The Committee noted a presentation from PHE on the results of the modelling and cost-effective analyses undertaken for a targeted vaccination programme for MSM in Genito-urinary Medicine (GUM) and HIV clinics. The Committee noted that the model considered vaccination of four possible scenarios for the vaccination of MSM attending GUM and HIV clinics: HIV positive MSM aged 16-25; HIV positive MSM aged 16-40; all MSM aged 16-25 and all MSM aged 16-40.

50. The modelling considered the impact of vaccination with either the bivalent or quadrivalent vaccines on anal, penile and oropharyngeal cancers, and anogenital warts (AGW), but not cancers of the oral cavity and larynx as there was not yet strong evidence of causation by HPV 16 for these cancers; and assumed
    - 100% acceptance, uptake and completion of a 3-dose schedule would be achieved in MSM attending GUM clinics;
    - lifelong protection against vaccine strains (protection for 20 years in sensitivity analyses);
    - duration of protection was the same regardless of HIV status;
    - cross-protection against high-risk non-vaccine HPV types had not been considered for either vaccine (due to the limited evidence available regarding the presence and longevity of cross-protection, and because HPV 16 and 18 accounted for a higher proportion of HPV associated non-cervical cancers, than cervical cancers);
    - the bivalent vaccine did not provide cross-protection against AGW (given the limited evidence regarding the impact and longevity of cross-protection);
    - vaccination would provide protection against future infection in seropositive individuals who had cleared their infection (as demonstrated in vaccination trials in females)
    - anal cancer incidence was taken to be higher among GUM attendees compared to non-GUM attendees (MSM) with the risk of HPV related cancer adjusted according to HIV status (anal and other cancers);
    - the age and time-dependent reduction in anal cancers due to vaccination had been applied to non-anal cancers (due to limited evidence of the natural history of the non-anal cancers);
    - HIV positive individuals would attend GUM clinics more frequently than HIV negative MSM, regardless of whether or not their HIV had been diagnosed, with 17.8% of HIV infected individuals assumed to be undiagnosed.

51. In terms of cost-effectiveness, vaccinating all 16 to 25 years olds had been shown to be weakly dominated by the options of vaccinating HIV positive MSM aged 16-40 years and all MSM age 16-40 years. As such vaccinating all MSM aged 16 to 25 years had not been considered further.

Costs and Benefits

52. Costs and benefits had been discounted to 3.5%, in line with the findings of the Working Group on Uncertainty. In the base case scenario an administration cost based on the cost of the vaccination of adolescent girls in schools was used. In sensitivity analysis a much higher fee had also been explored, based on the national non-mandatory tariff for consultations at GUM clinics. Additionally, in the base case scenario the list prices of the vaccines were used in the model, a threshold price at which the vaccines would be cost effective was also calculated.

Uncertainty

53. The Committee noted a number of uncertainties regarding the behaviours of HIV positive MSM, and the impact of vaccination in this group. The data were poorer for this group as the numbers were smaller so it was difficult to estimate the risk difference between HIV positive and HIV negative MSM in terms of cancer. The model assumed all HIV positive MSM were diagnosed with HIV infection as soon infected. This was likely to be an overestimate as according to PHE estimates between 10% and 20% of HIV positive MSM were undiagnosed. The Committee considered that for HIV positive MSM there was a greater uncertainty on duration of protection from HPV vaccination as there was no evidence available.

54. The Committee noted that lower uptake, within reasonable limits, would have a very limited impact on the cost-effectiveness of the programme. A lower completion rate could however have an impact on the cost-effectiveness of the programme, as three doses were likely required to achieve long term protection. This had not been examined in the modelling work undertaken, although the Committee agreed that the impact of lower uptake might possibly be balanced out by any increased attendance for HPV vaccination.

55. The Committee noted that was little evidence on the likely levels of uptake to expect and there was no data for MSM on the levels of immunity achieved from only two doses of vaccine. However, some studies had shown high level of willingness to be vaccinated and a small pilot study in north London indicated an 80% uptake of the offer to vaccinate.

Equity

56. The Committee noted that were a targeted programme for MSM to go ahead, then consideration would need to be given as to whether other adults aged 16-40 years of age should have access to HPV vaccination in GUM clinics. The Committee noted that the issue of equity in vaccination policy was the responsibility of the Department of Health, and advised that they consider this issue carefully.

57. The Committee agreed that any consideration of equity should take into account how HPV infection rates were higher in MSM in older age groups compared to older women, that MSM were afforded very little protection from the current HPV programme in adolescents, and that in females the peak in HPV incidence occurs early during the third decade of life, and then falls away rapidly over a relatively short time period. The Committee agreed that it could only consider the cost-effectiveness of vaccinating other adults at greater risk of HPV infection and disease, such as women who were HIV positive, and sex workers, if the evidence was provided. Should such evidence be identified, then the HPV sub-committee should review it accordingly.

Results

58. The Committee noted that the clinical impact on AGW was smaller than the impact on the HPV associated cancers, as the model assumed many MSM attend with an AGW presentation at their first visit to a GUM clinic. However, despite the larger clinical impact on cancer, the economic benefits of preventing AGW were of importance in the model as they occurred much earlier after vaccination and were as such less impacted by discounting. Because of this much of the net-benefits of a targeted programme were due to the prevention of AGW and the cost-effectiveness of HPV vaccination in MSM as such was greatly influenced by the prevention of AGW.

59. At the list price the quadrivalent vaccine was always the more cost-effective vaccine and the bivalent vaccine was significantly less cost-effective, as much of the total net health benefits were due to the prevention of AGW. However, if the current standard non-mandatory tariff price for GUM clinics was used, as opposed to an opportunity cost, then no option was cost-effective.

60. Under the criteria used by JCVI, vaccinating HIV positive MSM aged 16 to 25 years of age was cost-effective at the list price of the vaccine. Vaccinating HIV positive MSM age 16 to 40 years of age was also incrementally cost-effective under the base case assumptions. Extending vaccination to all MSM aged 16 to 40 years of age was not incrementally cost-effective when using the list price of

the vaccines. However, vaccination of all MSM aged 16 to 40 was cost-effective under the criteria used by JCVI at a threshold price below the list price.

Operational issues

61. The Committee noted that the model showed that a programme could be cost effective but key operational and delivery issues would need to be considered.

62. As sexual health is the responsibility of Local Authorities (LAs) in England and not NHS England, vaccinations undertaken in this setting, primarily HBV vaccination, were neither centrally commissioned nor procured. The Committee considered that obtaining the vaccine at a price which was cost-effective for MSM vaccination in GUM and HIV clinics was highly likely to depend on the vaccine being centrally procured.

63. The Committee advised that it would be very important to closely monitor uptake, completion levels and impact if the programme was implemented, as the success of the MSM programme would also influence the consideration of an adolescent boys programme.

Conclusions

64. The Committee noted that whilst there were a number of uncertainties regarding assumptions made in the model, they agreed with the advice of the HPV subcommittee that a programme to vaccinate MSM age 16-40 should be considered, provided that the programme could be undertaken at a price (administration and vaccines costs) which was cost effective. Vaccinating MSM aged 16-40 was preferred because of the greater uncertainty around a strategy of vaccinating only HIV positive MSM.

65. Although such a programme would be very likely to prevent HPV associated cancers in MSM, the model had indicated that an even more substantial benefit could be realised from the prevention of AGW. The Committee therefore considered that any vaccine used for a programme targeting MSM should provide specific protection against AGW.

66. The Committee concluded by advising that a programme for the vaccination of MSM aged 16 to 40 years of age should be implemented in GUM and HIV clinics in the UK using the quadrivalent HPV vaccine, subject to the programme being provided at a cost-effective price. The Committee recognised that the mechanisms and arrangements for commissioning and procuring HPV vaccine for use in GUM clinics were complex, and advised that the DH consider options for implementation, in collaboration with Public Health England, NHS England

and Local Authorities. Should a programme to vaccinate MSM in GUM clinics be undertaken, the Committee agreed it would be very important to monitor the uptake, completion and impact of vaccination to assess the programme's effectiveness.

67. The Committee advised that an interim statement should be issued on its advice for vaccinating MSM and that due to the number of assumptions and uncertainties around some of the data inputs, stakeholders should be invited to have the opportunity to comment on the validity of these and the interim advice of the Committee. The Committee also advised, for assurance purposes, that the modelling and cost effectiveness work undergo additional peer review in parallel.

Modelling for the use of HPV vaccine in adolescent boys

68. The Committee noted that work to model the impact and cost-effectiveness of vaccinating adolescent boys with HPV vaccine was dependent on the completion of work by PHE on an individual-based model for HPV screening, as the intention was to use the completed screening model as a basis on which to model adolescent male vaccination. The Committee noted that the screening model was now not due to be completed until early 2015. Although disappointed that modelling work on the cost-effectiveness of HPV vaccination of adolescent boys by PHE would not begin until early 2015 the Committee agreed that it would not be advisable to take any shortcuts in order to expedite the work, which could undermine the validity of the outputs. The committee noted that the individual based model would also be needed for other issues in HPV vaccination and for future tenders in procurement.

69. The Committee further noted that a team at Warwick University had started work to model the impact and cost-effectiveness of adolescent male vaccination.

70. The Committee noted that the cost effectiveness of an adolescent boys programme was not certain as the high coverage rates achieved for adolescent girls was highly likely to interrupt HPV transmission and provide indirect protection for boys to such an effect that there may be little additional benefit to be accrued from vaccinating most boys. However the Committee agreed that a detailed cost-effectiveness analysis was required to fully understand the potential benefits of such a programme.

VII. MHRA Vaccine Safety report

71. The committee noted the annual update from the MHRA on suspected adverse reactions associated with routine and/or commonly used vaccines in the UK reported via the Yellow Card Scheme during the period 1 July 2013 to 30 June 2014.

72. The Committee noted that no new risks had been identified. The MHRA had closely monitored new programmes including the use of Rotarix®, in particular monitoring for cases of 'intussusception' (IS). Numbers of cases of IS reported were not greater than expected given the background rate and the number of children vaccinated during the reporting period. Fluenz® and Zostavax® vaccines were also monitored closely, with no new issues emerging. The committee was already aware of the analysis of the pertussis vaccine in pregnancy which had been published in July 2014 and the MHRA indicated that they would be re-running the analysis in the new few months, following use of Boostrix-IPV® in the programme.

73. The Committee noted a potential issue following anecdotal reports of fatal outcomes occurring involving disseminated BCG in infants who were suspected to have been exposed to anti-TNF-α biologics in utero. The Committee was concerned that there was an issue with information exchange and rheumatologists needed to be involved in this aspect of their patient's primary care and ensure that the necessary information is conveyed to the mother.

Action: Secretariat to work with MHRA to determine if an update should be made to the Green Book in relation to the BCG vaccine and exposure to a TNF-α inhibitor in utero.

VIII. Rotavirus epidemiology and impact of vaccination

74. The Committee noted an update on rotavirus epidemiology from PHE, following introduction in July 2013 of the rotavirus vaccine Rotarix® into the routine childhood vaccination programme. The vaccine had been offered to all infants born from May 2013 onwards and the first rotavirus season has elapsed since the implementation of the programme. The Committee were informed that there had been a dramatic reduction in rotavirus cases across all age groups which was not considered due to a decrease in testing as the number of samples tested remained constant, while the proportion of positives had reduced. PHE would now be looking at Hospital Episode Statistics (HES) data to see if there is a similar reduction in hospitalisations due to rotavirus over the last year. Other countries, including some which had not introduced a rotavirus vaccination

programme, had also reported a reduction in the number of rotavirus cases last season but to a lesser extent than in the UK.

IX. Papers for Comment

75. The Committee noted the papers provided for comment.

X. Coverage

76. The Committee was informed about the routine childhood vaccination coverage rates for the quarter March to June 2013 for England, Scotland, Wales and Northern Ireland. These data were considered very positive, especially given continuing challenges following transition in England.

XI. AOB

77. The Chair informed the Committee that a letter dated 15 August 2014 had been received from Professor Paul Griffiths, Chair of the UK Panel for the Certification of Elimination of Poliomyelitis (PCEP). The letter summarised communications received from the European Regional Certification Commission for Poliomyelitis Eradication (ERCC) stating that it considers the risk of substantial transmission following importation of wild poliovirus in the UK intermediate. PCEP subsequently agreed that pilot environmental testing for polio should be initiated in the UK to provide assurance that polio is currently well controlled and to facilitate the detection of circulating virus should it be imported. The Chair informed the Committee that a reply had been sent to Professor Griffiths on 18 August stating that this information would be brought to the attention of the JCVI at the current meeting.

78. The Committee considered the potential for an open meeting, and options for engagement of the Committee with stakeholders. The Committee agreed to provide thoughts on how this might be achieved to the secretariat.

79. The Chair thanked the secretariat for their support in preparing the meeting and all those in attendance and closed the meeting.

Annex A – Changes to the June 2014 Minute - Pneumococcal disease

50. The Committee received presentations from Public Health England and from Professor David Goldblatt, Professor of Vaccinology and Immunology at the Institute of Child Health at University College London. The Committee noted:

- vaccine effectiveness for PCV13 was high;
- coverage of PCV vaccines were very good in the UK;
- a clear direct and indirect impact of PCV13 infant vaccination on each of the 13 vaccine serotypes;
- serotype 3 has the least impact, consistent with immunogenicity data, however cases of serotype 3 disease had still ~~significantly~~ reduced, despite earlier doubt about the vaccine's impact against this strain;
- a large effect of PCV13 on serotype19A disease was seen ;
- the full impact of the vaccine on invasive disease associated with PCV13 vaccine serotypes was unlikely to be seen for several more years;
- evidence was emerging to suggest some serotype replacement, although there was no single clear replacement serotype;
- there was a reduction of 1200 cases of invasive disease when comparing 2008/9 with 2012/13;
- the impact seen in the UK was consistent with those seen in the US and Australia;
- the correlate of protection used for licensing PCV vaccines of 0.35µg/mL lacked precision, and appeared too low for 9 of the 13 serotypes in PCV13;
- immunogenicity of the booster dose was likely to be important for the overall impact of the vaccine but was not currently factored into the calculation of correlates.

51. Additionally the Committee noted data provided by Pfizer on PCV13, GSK on PCV10 and Sanofi Pasteur MSD on PPV23. In particular the Committee noted data on the impact of PCV10 on acute otitis media and cross protection of PCV10 against non-vaccine serotypes.

52. The Committee agreed that the current infant pneumococcal vaccination programme (PCV13) in the UK was having a significant impact on invasive pneumococcal disease in infants and adults, but that the full impact of the programme was unlikely to have yet been seen. Data provided by GSK on the impact of PCV10 on acute otitis media, in addition to invasive disease, was difficult to extrapolate to the UK, where PCV7/13 had been used since 2006. These data ~~was~~ were thus not of sufficient weight to allow the Committee to advise any change from the current highly effective programme. Additionally, after reviewing the evidence provided to the Committee on cross-protection provided by PCV10 against non-vaccine serotypes, the Committee agreed it was not yet clear whether PCV10 could provide protection against serogroup 19A on a level being provided by PCV13. ~~expressed concerns that a shift from PCV13 to PCV10 could still have a negative impact on control of invasive pneumococcal disease in those serotypes contained in in PCV13 but not in PCV10.~~

53. Given that ~~the evidence~~ it was not yet clear whether PCV10 could provide protection against serogroup 19A on a level being provided by PCV13 ~~provided indicated offering PCV10 as an alternative to PCV13 in the UK could lead to an increase in invasive disease associated with those serotypes contained in PCV13 not contained within PCV10~~, that only limited evidence was available on the possible compensatory prevention of acute otitis media in a population already using PCV13, and the full impact of the current programme could not yet be fully assessed, the Committee concluded that PCV13 should remain the pneumococcal conjugate vaccine of choice for the UK at this time. The Committee further agreed that at this time it would be inappropriate to commission modelling to compare the impacts of PCV13 with those of PCV10 as the parameterisation would be insufficiently secure.