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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 06 June 2018

Skipton House, London Road, London

Members

Professor Andrew Pollard (Chair)
Dr Andrew Riordan (Deputy Chair)
Prof Matt Keeling
Prof Judith Breuer
Dr Fiona van der Klis
Alison Lawrence
Prof Adam Finn
Prof Rob Read
Prof Anthony Scott
Dr Maggie Wearmouth
Dr Peter Elton

Co-opted members

Dr Julie Yates (England)
Dr Lucy Jessop (NI)
Anne McGowan (Wales)
Dr Lorna Willocks (Scotland)

Secretariat

Andrew Earnshaw
Ruth Parry
Jonathan Crofts
Dr Andras Donaszi-Ivanov
Dr Mary Ramsay
Dr Gayatri Amirthalingam

Invited Speakers

Dr Richard Pebody (PHE)
Dr Marc Baguelin (PHE)

Invited observers from Devolved Administrations

Dr Syed Ahmed (Scotland)
Dr Gillian Armstrong (NI)
Dr Stephen Thomas (Wales)

Other invited observers

Dr Sandra Anglin (NHS England)
Dr Anna Clarke (Eire)
Dr Linda Diggle (Jersey)
Jacqui Dunn (IoM)
Dr Darina O'Flanagan (Eire)
Dr Dipti Patel (NaTHNaC)
Dr Michael Edelstein (PHE)
Cheryl Cavanagh (DHSC)
Dr Anne Kilgallen (DHSSNI)
Dr Yoon Choi (PHE)
Cheryl Cavanagh (DHSC)
Dr Vanessa Saliba (PHE)
Wing Commander Robert Lingfield (MoD)
Joanne Yarwood (PHE)
Dr Sema Mandal (PHE)
Dr Ian Feavers (NIBSC)
Dr Caroline Trotter (PHE)
Dr Claire Cameron (HPS)
Dr Richard Roberts (HPW)
Dr Tom Irving (DHSC)
Dr Sema Mandal (PHE)

Welcome

1. The Chair welcomed all to the meeting. The Chair reminded members and observers that the papers provided for the meeting included information provided in confidence. Attendees were asked not to circulate the papers more widely or discuss the information provided with others outside of the meeting. Attendees were asked not to discuss any considerations of the Committee with others outside of the meeting. Any requests for information should be directed to the Secretariat.

2. The Chair asked members to provide an update about any declarations of interest.

3. Apologies were noted from Prof. Maarten Postma, Prof. Anthony Harnden and Prof. Jonathan Van-Tam.

I. Minute of the February 2018 meeting

4. The Minutes of the February 2018 meeting were agreed with one change. The Bexsero® vaccine effectiveness data had been quoted with very wide confidence intervals. An additional sentence was proposed that reflected how there had been a large impact with the vaccine and that the vaccine effectiveness data had not demonstrated significance because of the small number of cases.

II. Matters arising

Research prioritisation process

5. The Committee noted a proposed list of research requests to be published alongside the minute of the meeting, which summarised earlier JCVI meeting discussions. There were no comments on the table of research requests.

CEMIPP consultation

6. The Committee had been working on a response to the CEMIPP consultation. The Chair referred members to the helpful lay summary of the CEMIPP report which had been published by DHSC and supplied in their meeting packs. There was now a further version of the response from the Committee which would be circulated for final comment ahead of the consultation deadline. Thanks were given to specified members for their work on the response. The main messages in the response were concerns regarding the potential for implementation of CEMIPP unilaterally for vaccines ahead of implementation more widely across the NHS and therefore favouring treatments over vaccines. Members were requested to respond to the most recent version as soon as possible following receipt.

Five year forward look

7. While the Committee kept all programmes under review, the Committee noted a summary document which detailed particular programmes that were to be reviewed in the coming five years. Potential new programmes (though no licensed products currently available) were also highlighted. Members commented on the potential for use of group B streptococcus vaccine, RSV vaccines/monoclonals, maternal pertussis-only acellular vaccine and cytomegalovirus (CMV) vaccine. The Committee noted their continued interested in vaccines for healthcare associated infections and improving health through all life stages. The Chair requested that the Committee look through the documents and feed back to the secretariat. A shorter overview of work to be undertaken in the next 12-24 months would be placed on the website when agreed.

New EMA process

8. The Chair notified the Committee that the EMA had proposed the inclusion of views from NITAGs in the licencing process. In the first instance they had requested that JCVI assist with an application they will receive regarding a new vaccine. EMA would provide documents about the vaccine and questions for the Committee to answer. The responses would be collated by the secretariat. A representative from the Committee would also be asked to go to an EMA meeting in the autumn. It was noted that JCVI would be giving advice to the EMA and not the company that was developing the vaccine.

III. Horizon Scanning

9. The Committee noted information collated by the secretariat during the 2018 horizon scanning exercise. The Committee discussed the findings, noting that the information provided was commercially confidential. It was noted the MSD Ebola vaccine was being used in the Ebola outbreak in the Democratic Republic of Congo.

IV. Influenza

10. The programmes in the UK were detailed for the benefit of visitors from other NITAGs.

Overview of the 2017/18 season

11. The Committee noted a presentation from PHE which provided an overview of the 2017/18 influenza season. On the influenza activity in the UK in 2017/18 season the Committee noted that:

    - it was a long season with peak activity reaching moderate levels of activity (GP ILI consultations), with the peak consultation rates the highest seen in England since 2010/11;
    - rates of consultations were highest in the older age groups with the lowest rates in children;
    - over 2000 outbreaks of acute respiratory infection were reported across the UK; dominated by care home outbreaks, with a relatively small number

of school outbreaks;
- this was the highest number of outbreaks notified through this reporting system since its inception;
- the rate of laboratory-confirmed influenza hospitalisations were very high with peak levels being the highest observed since 2010/11, with the burden being particularly notable in the older age groups;
- reports of increased use of point of care diagnostics were noted, which may have contributed to improving sensitivity of reporting;
- a large proportion of cases were due to influenza B;
- the rate of laboratory-confirmed influenza ICU admissions were very high - the highest peak rate observed since 2010/11, with the burden again being in the older age groups and a large proportion of the cases due to influenza B;
- all cause excess mortality was at similar levels to that seen in the 2016/17 season, but did not reach the level seen in 2014/15;
- individual paediatric surveillance for influenza-confirmed deaths reported a number of deaths due to influenza A and B in children up to the age of 17 years of age in England; some had underlying conditions but others were otherwise healthy; of those with available vaccination history, none had received the influenza vaccine during the season;
- the A(H3N2) viruses characterised this season were mainly of the 3C2a1b haemagglutinin genetic group early in the season, up to November when the numbers were relatively small;
- later circulation was dominated by 3C2a2; and
- the influenza B strains identified were dominated by viruses of the B/Yamagata lineage, which was well matched to the strain in the quadrivalent vaccine but was not found in the 2017/18 trivalent vaccine, although previous evidence of cross-protection had been demonstrated when a B lineage mismatch had occurred.

12. On vaccine uptake the Committee noted that:

- uptake in adults in England had increased in all groups compared with previous seasons, with 72.6% of the over 65 year olds, 48.9% of the under 65 year olds in at-risk groups, 47.2% of pregnant women and 67.6% of healthcare workers being vaccinated;
- in the children's programme uptake levels in England had increased in all age-groups;
- uptake in 2 year olds was 42.6%, in 3 year olds 44.0% and 4 year olds 62.6%;
- the largest increase was seen in 4-year olds, who were now targeted in school reception classes compared with the previous season when they were vaccinated in primary care;
- the uptake in school year 1 was 60.9%; year 2, 60.3%; year 3, 57.5% and year 4, 55.7% in England; and
- the uptake in the childhood programme in Scotland and Northern Ireland was higher than in England.

13. On the performance of the programme the Committee noted that:

- across the UK the number of weeks above the baseline threshold level for GP ILI consultation rates was longer in England and Wales (14 weeks) than in Scotland and Northern Ireland, where the primary school age programme had been fully rolled out; and
- all countries of the UK saw significant excess all-cause mortality.

14. On vaccine effectiveness the Committee noted that:

- using the established test negative case control (TNCC) study approach just under 4000 respiratory swabs were collected across the five GP sentinel schemes across the UK of which just over 3000 were used in the final analysis; 1768 were from controls. 420 cases were A/H3N2, 95 were A/H1N1 and 766 were flu B;
- for all ages the overall VE against influenza A and B was modest;
- vaccine effectiveness against A/H3N2 was low;
- vaccine effectiveness against A/H1N1 and influenza B was higher than against A/H3N2;
- in adults comparing ages 18-64 with 65+, low effectiveness against H3N2 was seen in both groups;
- there was evidence of effectiveness against H1N1 in young adults, but not enough data to estimate effectiveness against H1N1 in those over 65 years of age;
- effectiveness against influenza B was low, but most adults would have received TIV which did not contain the influenza B strain that had predominated in the 2017/18 season;
- small numbers received the quadrivalent inactivated vaccine (QIV), but the suggestion was of overall positive effectiveness; although again poor against A/H3N2, as seen with the adult inactivated vaccine.
- in the paediatric programme the overall effectiveness of LAIV was moderate; A/H3N2 showed no significant effectiveness, but there was significant effectiveness against influenza A/H1N1pdm09 and against influenza B;

15. The Committee noted data from Finland where LAIV was also used in young children. Their influenza season was similar to that in the UK. The findings with regard to effectiveness were consistent with those in the UK.

16. The Committee noted potential explanations for the low effectiveness against influenza A/H3N2, including emergence of the 3C2a2 group. There had been previous concerns that egg adaption may contribute to reduced vaccine effectiveness and recent publications indicated that this may be a problem. A number of investigators, including investigators at the Crick Institute were working on this.

17. The Committee noted proposed solutions to the potential factors leading to reduced vaccine effectiveness against influenza A/H3N2, including:

- immunosenescence might be addressed by the use of adjuvanted or high

dose vaccine in those over 65 years of age; the former would be available for all aged 65+ in the 2018/19 season; the high dose vaccine should be available in the 2019/20 season, if it is licensed in 2018;

- genetic evolution of the circulating strain with the emergence of the 3C2a2 genetic group may be addressed by the use of a well-matched vaccine; for the 2018/19 season there would be a switch to an A/Singapore strain that may be a better match to circulating strains; and
- the egg adaption issue might be addressed by the use of cell-culture based vaccines, which may be available in future.

18. The Committee noted the newly available vaccines for adults; an MF59 adjuvanted inactivated trivalent vaccine which was recommended for all those aged >65 years for the 2018/19 season; a high dose inactivated trivalent vaccine which was expected to gain UK licensure this autumn and be available for the use in 2019/20. Quadrivalent inactivated vaccine would be available for those aged less than 65 years old in at risk group for the 2018/19 season.

19. The Committee agreed that significant effectiveness was still being observed in the paediatric programme and noted the good effectiveness against both B strains and A(H1N1)pdm09. The performance of the A/H3N2 component of all the vaccines, however, was disappointing, but noted that strategies to address this were being investigated.

<u>Cost effectiveness analysis of vaccines for use in the 65+ programme</u>

20. The Committee noted a cost-effectiveness analysis carried out by Public Health England to assess, based on current evidence, the likely epidemiological impact of immunisation of those 65 years and over, with:
    - inactivated standard dose non-adjuvanted quadrivalent vaccine (QIIV);
    - trivalent adjuvanted vaccine (TIIV-ADJ); and
    - trivalent high dose vaccine (TIIV-HD).

21. The Committee noted the details of the model used for this analysis and the publication from which the health outcomes were derived. Vaccine coverage was based on PHE figures for 2016/17 and baseline vaccine efficacy based on a published meta-analysis by Belongia et al (2016).

22. The assumed additional protection from the new vaccines was described, noting that there were few published data on the adjuvanted vaccine; these were derived from existing publications (Belongia et al, 2016; Puig-Barberà, 2013; Wilkinson et al, 2017)

23. The likely impact on infections was touched upon and it was noted that the reduced burden for the quadrivalent vaccine was for the influenza/B viruses, whereas most for the high dose and adjuvanted vaccines is for the influenza A/H3N2 virus.

24. The incremental cost-effectiveness of the alternative vaccines for those 65+ was estimated based on a threshold analysis on a willingness to pay threshold of

£20,000 per QALY.

25. A sensitivity analysis sought to establish which parameters were driving the cost-effectiveness. The efficacy of each vaccine against each of the strains was varied +/- 5% in absolute terms; the vaccine coverage for the elderly population varied +/- 10% in absolute terms; a larger paediatric programme covering ages 2-16 years was tested and excess mortality as in Green *et al* used, which attributed more deaths to influenza than Cromer *et al*.

26. It was noted that the sensitivity analysis suggested that for the QIIV most of the uncertainty was around the additional B strain, for the adjuvanted vaccine, most of the uncertainty was around the potential efficacy against the A/H3N2 strain. Similarly for the high dose vaccines; the greatest uncertainty was around the potential efficacy against the A/H3N2 strain.

27. The impact of different mortality estimates was to increase the maximum incremental cost per dose, so quantification of mortality has an important impact on cost-effectiveness. Extending the paediatric programme had the effect of decreasing the willingness to pay for all three vaccines.

28. Evidence indicated superior efficacy for adjuvanted influenza vaccine and high-dose influenza vaccine, compared with standard dose products. While data comparing the two products were not available, the Committee agreed the PHE modelling used the most appropriate relative effectiveness data for parameterisation of the model. Overall the results indicated a similar willingness to pay for the high-dose and adjuvanted influenza vaccines, over the cost of the standard dose vaccine. The willingness to pay was higher for high-dose and adjuvanted vaccines, when compared with quadrivalent standard dose vaccine.

29. The Committee noted the Sanofi Pasteur cost-effectiveness model, which had a similar approach to that of Baguelin et al, 2013. The main difference was the use of higher hospitalisation and mortality rates derived from Matias et al, 2016. They concluded that the cost of the high dose vaccine was not dissimilar to the willingness to pay cost estimated if using the mortality data as per the Green *et al* paper.

30. The Committee noted that following its advice last October the adjuvanted vaccine would be the vaccine of choice in the elderly for the 2018/19 season. For the 2019/20 season there was the possibility of both the high dose and adjuvanted vaccines being available. Based on available data it was thought that they were both likely to be superior to standard dose non-adjuvanted vaccines in terms of effectiveness although there were no head to head studies to compare the two vaccines directly. It was agreed that in the light of the upcoming changes there would be the need to maintain the continued close scrutiny of the programme and vaccine effectiveness. Overall the Committee considered that both the adjuvanted and high-dose vaccines were suitable for the over 65 years programme, and were preferable to the trivalent and quadrivalent standard dose non-adjuvanted vaccines produced in eggs in that population.

<u>Pandemic-specific vaccine strategy</u>

31. The Committee noted the PHE approach to a pandemic specific vaccine strategy and the decision about which vaccine to purchase. The current advance purchase agreement is for an MF59 monovalent vaccine produced using egg-based technology. This vaccine was not currently licenced for use in children.

32. The strategy outlined a biphasic approach in which the first phase is the early use of vaccine; produced in less than 4 months which will have a larger population impact in reducing morbidity and mortality before the peak of the pandemic. This would require the use of technologies that are newly licenced or currently in the late stages of development.

33. The second stage would be a sustained response with higher volumes of vaccine being produced using current production technologies.

34. The technologies available for use in both phases of such a biphasic approach were outlined.

35. The Committee agreed that this strategy was a sensible approach.

V. Herpes Zoster vaccination

36. The Committee noted that that at the JCVI meeting in February 2018 it was agreed that on the basis of the data presented by GSK, the new non-live shingles vaccine produced by GSK had good efficacy with little evidence of decline with age and that it would be a suitable vaccine to offer to those who were eligible in the current programme, but contraindicated for receipt of Zostavax®.

37. At the sub-committee meeting in May 2018 PHE modellers presented the work they had carried out on modelling the cost effectiveness of the new vaccine, Shingrix® versus Zostavax® in the current programme for adults aged 70-79 years. The economic analysis showed that a programme using Shingrix in this age group is highly likely to be cost-effective. The committee noted there were few limitations which included the limited follow up efficacy data for Shngrix to 4 years , It was agreed that some minor changes needed addressing but that none of these were likely to change the outcome.

38. It was noted that it was an incremental analysis and that the two doses and administration cost were taken into account. Further modelling on the overall optimal age for Shingrix was due to start.

39. The Committee was content that Shingrix® was an effective and cost-effective vaccine for use in the current programme for those between their 70th and 79th year. The vaccine should therefore be considered for use in the national programme in the UK.

40. It was noted that specialist clinical groups may wish to make their own recommendations with regard to use of the vaccine for immunocompromised individuals outside of the national programme, when stocks become available but that guidance on definitions of ‘immunocompromised’ was required to ensure

consistency of approach across specialisms.

41. A proposed implementation pilot was described which would consider, once vaccine was available, the acceptability of a two dose schedule offered at a 1 year interval, potentially alongside another adjuvanted vaccine, ie influenza.

VI. HPV

42. The Chair reminded the Committee that an interim statement on HPV vaccination for adolescent boys had been published in July 2017. The interim statement had been subject to stakeholder consultation, and the sub-committee had reviewed the responses received, and requested a number of sensitivity analyses be undertaken. The Chair updated the Committee on work undertaken in preparation for the Committee to finalise its review of HPV vaccination in adolescent males, noting that the HPV sub-committee had met on 18 May and had developed advice for the Committee.

43. The HPV sub-committee and the main Committee had been reviewing two modelling exercises, being undertaken by the University of Warwick and by Public Health England. Overall the findings from the two modelling exercises were similar when interrogated; however, the sub-committee had been informed that there was likely to be a considerable delay in finalising the PHE modelling for peer review. As such, the discussions would focus on the work from the University of Warwick, which the sub-committee had considered robust and appropriate for the development of advice.

44. The HPV sub-committee Chair provided the Committee with an update following the sub-committee meeting held on 18 May 2018, alongside a presentation from the University of Warwick. The Committee noted that:

- the modelling undertaken by the University of Warwick and Public Health England assumed a programme for adolescent boys with vaccination at the same age as the current programme in adolescent girls (12-13 yrs of age);
- the University of Warwick and the Public Health England models were in overall agreement and provided similar findings and conclusions when examined;
- when the University of Warwick model was fitted to female only prevalence data (as was done in the PHE model), it provided very similar results to the PHE model;
- the model results were also in line with published evidence including a meta-analysis of published models;.
- given further delays in preparing the PHE model for peer review, the sub-committee had agreed that the robust modelling undertaken by the University of Warwick was sufficient for it to finalise its advice to JCVI;
- all HPV attributable diseases were included in the modelling from the University of Warwick;
- when considering the model from the University of Warwick, under the

standard methodology (£20k/QALY, 3.5% discount rate, incremental on the girls' programme), extension of the programme to adolescent boys was highly unlikely to be cost-effective;

- under the standard methodology, and fitted to female only prevalence data, extension of the programme to adolescent boys was likely to be cost-effective but at a very low, and unrealistic vaccine price;
- sensitivity analyses with a higher attributable fraction for oropharyngeal cancer (60% or 100%) made the vaccine more cost-effective, with a very low but not realistic vaccine price; these analyses failed the uncertainty test;
- a sensitivity analysis using a lower discount rate (20k/QALY, 1.5% discount rate, incremental on a girls' programme), showed a programme to be cost-effective at what was likely to be a realistic price;
- a 1.5% discount rate sensitivity analysis was standard practice for modelling reviewed by the Committee;
- the sub-committee agreed that, if in the development of policy there were sufficient arguments to consider gender-neutral vaccination on the grounds of equality, the most appropriate analysis would be one where no vaccination was used as the comparator rather than a girls' programme;
- using the alternative comparator a gender-neutral programme would be highly cost-effective;
- the subcommittee, being mindful that JCVI was a scientific advisory committee and equality was not within its remit, advised that the JCVI provided the findings using an alternative comparator to DHSC for consideration;
- data presented on mixed schedules looked promising;
- a presentation on data available on a single dose schedule indicated less cross-protection than was seen with two doses, but good protection out to 7 years;
- one dose data were only available from opportunistic studies, but formal studies were now underway and would likely report in the next few years;
- the sub-committee had agreed to review this issue once data were available from these studies;
- the sub-committee had considered vaccine supply, noting the rollout of HPV vaccines to a large number of countries being undertaken by Gavi; and
- the sub-committee had considered it was important to note that with a finite supply of vaccine, additional use of vaccine in countries such as the UK could have an impact on womens' health internationally.

Discount rate

45. While some HPV associated cancers can occur in the third decade of life, a proportion occurs much later. The HPV sub-committee had considered that vaccination at age 12-13 years to prevent disease so far in the future, meant that a 1.5% discount rate would be appropriate. The sub-committee also considered that this was in line with NICE Health Technology Assessment guidance, which indicated that a 1.5% discount rate can be considered where the impact of a lifesaving intervention is sustained over a period of at least 30 years. 1.5%

discounting was also the standard under previous NICE Public Health guidance.

46. The Committee considered that use of a lower discount rate would be appropriate for considerations regarding HPV vaccination.

Indirect protection

47. The Committee considered it was important to acknowledge that many of the benefits from extending the programme to boys were associated with a reduction in cervical cancer in girls, and genital warts in MSM.

48. The Committee noted that coverage levels in girls were an important factor in the cost-effectiveness of extending the programme. The lower the uptake in girls the more cost-effective vaccination of boys became. The Committee recognised that despite the high uptake seen in girls, there was a good argument for a gender-neutral programme in terms of providing some short-term resilience to the programme. Dramatic changes in coverage seen in some European countries were noted. Overall the Committee considered that a gender-neutral programme was likely to be more robust with respect to potential short-term fluctuations in uptake.

HPV and oropharyngeal cancer

49. The attributable fraction for oropharyngeal cancer was considered, given two recent studies in Scotland which indicated attributable fractions of 50% and 60%. However it was noted that changing the attributable fraction did not change the overall findings under the standard analysis. Overall the Committee concluded that there were varying data on the attributable fraction, and although this was important, would not materially change their conclusions from the analyses considered.

Equality

50. The Committee considered the issue of equality, which had been raised by stakeholders. It was agreed that the position of the Committee was that, although equality was an important consideration, as an expert scientific advisory committee JCVI was not in a position to advise on equality issues. Such issues should be considered by the UK Government in the development of Government policy.

51. The University of Warwick had undertaken an analysis using an alternative comparator, to ensure DHSC had all the information required in the development of policy. The Committee noted that when using an alternate comparator of no vaccination, a gender-neutral programme was highly cost-effective. The Committee agreed that this approach was not being formally adopted and was to inform DHSC only.

52. The Committee noted that there may potentially be further economies of scale when procuring double the volume of stock, and this should be considered by DHSC in the development of policy, and by PHE in the procurement of vaccine.

Conclusions

53. The Committee agreed that the findings from modelling undertaken by the University of Warwick, taken together with the results from PHE and other published evidence, provided sufficient evidence to formulate a position on HPV vaccination in adolescent boys.

54. The consideration of HPV vaccination in boys was a complex issue and JCVI had to take into account the wider issues of health economic methodology and be aware of the arguments made on equality issues. There was evidence of benefit in vaccinating boys and a gender neutral programme would provide resilience against short-term fluctuations in uptake as well as offer the prospect of better control of the main cancer-causing types of HPV. Gender-neutral vaccination would also provide optimal protection in MSM in the long term.

55. Under the standard economic methodology, the findings of the modelling work by Warwick University predicted that extending the HPV programme to adolescent boys would not be a cost-effective use of health service resources in the UK setting. Increasing the attributable fraction of HPV for oropharyngeal cancer did not alter this conclusion. On consideration of these results JCVI agreed it would not be able to advise extension of the programme to adolescent boys.

56. Because of the long natural history of HPV associated disease the Committee agreed that it could be reasonably argued that a 1.5% discount rate would be more appropriate. A lower discount rate would better take into account the longer term impact of HPV vaccination in cancer prevention, and the life years lost to cancer. The Committee agreed that they supported taking this approach. Using a 1.5% discount rate it was likely that a gender neutral programme would be cost-effective, and on the basis of these findings the Committee agreed they would advise extending immunisation to adolescent boys, with vaccination offered at the same age as adolescent girls (12-13 years).

VII. Pneumococcal schedule

57. The Committee were reminded that in October 2017 they had advised moving to a 1+1 schedule for PCV13, based on epidemiological, immunogenicity and modelling data presented to the Committee. This advice had generated a great deal of interest from charities and representatives from industry, and the JCVI had decided to offer a limited stakeholder consultation. The consultation initially ran from January 2018, and had been extended given requests from stakeholders, which had been considered at the February 2018 meeting.

58. The Committee noted an update from the Chair of the Pneumococcal sub-committee on the meeting held on 10 May 2018. The sub-committee had reviewed evidence regarding a reduced dose pneumococcal vaccination programme in childhood, evidence provided during the stakeholder consultation, and updated modelling on the impact of a reduced dose schedule.

59. The May 2018 meeting of the Pneumococcal sub-committee had focused on the

responses to the consultation, and on data presented by invited experts on epidemiology, immunology and modelling. The Committee noted that:

- there had been a comprehensive review of the evidence base before JCVI had provided advice in 2017, and this had been considered at the May 2018 Pneumococcal sub-committee meeting, alongside the latest evidence;
- PHE had confirmed their previous epidemiological assessment that vaccine-type disease was largely under control;
- the behaviour of serotype 3 IPD since PCV13 was introduced in the UK was compatible with limited effect of the vaccine, with serotype 3 IPD cases increasing rapidly in the last 3 epidemiological years, especially in older adults;
- the most up-to-date data showed that serotypes 3 and 19A had predominated in most vaccine type IPD cases in infants under two years in recent years, with the majority of cases having been appropriately vaccinated for age;
- immunogenicity data indicated that 2+1 and 1+1 schedules were broadly comparable in terms of immunogenicity, with four serotypes showing slightly lower responses and four serotypes showing slightly better responses with a 1+1 schedule after the 12 month booster; the remaining serotypes showed equivalent immunogenicity with a 1+1 schedule compared with a 2+1 schedule, including serotypes 3 and 19A;
- sensitivity analyses were conducted for 2+1, 1+1, 2+0 and 0+1 schedules;
- modelling of 1+1, 0+1 and 2+0 schedules indicated maintenance of herd protection with a 1+1 schedule;
- given the level of herd protection seen in modelling of a 0+1 schedule, effectiveness of the priming dose had little impact on the findings;
- the model had been adjusted with slightly different case/carrier ratios, and a more realistic vaccine coverage of 92% (instead of 73% considered in October 2017);
- the model predicted a very small increase in IPD cases in under two year olds in the next five years;
- by using the latest evidence, the sub-committee had extrapolated non-invasive disease rates using IPD rates, and concluded that any increase of non-invasive disease would be small;
- the sub-committee had agreed this increase would not cause any considerable increase in antibiotic use or hospitalization; and
- the modelling predictions agreed with the direct calculations on predicted additional cases presented in the October 2017 meeting, which strengthened the predictive value of the modelling results.

60. The Pneumococcal sub-committee Chair summarised the discussions undertaken on the consultation responses. The Committee noted that:

- the sub-committee has considered a 1+1 schedule would rationalise health service resources, simplify the vaccine schedule, reduce the needle burden in infants (3-3.5 million fewer doses administered over 5 years) and allow space in the schedule for new vaccines to be introduced;

- there was compelling evidence that a 1+1 schedule would have a minimal impact on both invasive and non-invasive disease;
- carriage data from infants had been used in development of the model;
- while stakeholders had raised concerns about geographical areas with low vaccine coverage, the model considered in October 2017 has used a significantly lower coverage value (73%), which was lower that the lowest coverage by area in England and Wales (~80%);
- PHE was committed to working with NHS England to improve the vaccine coverage in low coverage areas and communities;
- meningitis was a rare complication of IPD, and the sub-committee agreed it was likely that only a small proportion of the additional cases predicted would present as meningitis (UK data indicates around 5% of IPD cases present with meningitis);
- assessments of equality were not within the remit and expertise of the JCVI, any such analysis needed to be undertaken by the DHSC;
- the robust surveillance system in place in the UK for IPD would ensure that the JCVI could react swiftly should it become necessary to re-consider the advice;
- should the advice on a 1+1 schedule need to be re-considered, there should be no need for a cost-effectiveness analysis;
- while procurement and programme costs were not within the remit of JCVI, cost-effectiveness was an important part of the Committee's remit; and
- given the very small increase in cases predicted, the extra dose in a 2+1 schedule was unlikely to represent a good use of public money.

61. The Committee noted that after consideration of the evidence, the Pneumococcal sub-committee had fully supported the advice of JCVI to move to a 1+1 schedule in the UK, particularly given the excellent control of disease seen.

<u>Epidemiology update from PHE</u>

62. The Committee noted a presentation from PHE on vaccine-type disease in the first year of life, where any impact of moving to a 1+1 schedule was likely to be seen. The Committee noted that:
    - over the last 5 years, there had been 85 vaccine-type IPD cases (averaging around 17 cases per year) in those less the two years of age;
    - serotype 3 and 19A were responsible for most of the IPD cases seen in this age group;
    - 7F used to be the most common cause of meningitis, although there was now very little 7F disease; and
    - data on the vaccination status of cases indicated the majority of cases were in those who had been appropriately immunised for their age.

<u>Adult vaccination and alternative vaccines</u>

63. The Committee noted that the sub-committee had considered adult pneumococcal vaccination. When use of PCV13 had last been reviewed in 2015, it had been considered that the six serotypes in the 13-valent vaccine, but not in the seven valent vaccine (PCV13-7), would decline in the same way as the seven

serotypes in PCV7. That extrapolation had formed part of the assessment for not advising the use of PCV13 in adults. While two of the additional PCV13 serotypes not in PCV-7 (serotyped 3 and 19A), had not declined in the way predicted, the modelling undertaken at that time had examined this eventuality in the sensitivity analysis. The modelling in this scenario still found PCV13 vaccination in the elderly to be not cost-effective. It was therefore considered that no further review of PCV13 vaccination in the elderly was required at this time.

64. The sub-committee had noted that there were higher-valency pneumococcal vaccines in the pipeline, and that modelling would need to be reviewed in preparation for these vaccines being considered by the Committee. It was agreed that PHE would consider the modelling requirements once more information on the vaccines was available.

65. The sub-committee had considered the use of PPV23 in the elderly. IPD from serotypes in PPV23 but not in PCV13 had increased quite considerably in adults since 2015. When also considering how the PCV13 serotypes had not decreased as much as predicted, the sub-committee had considered that PPV23 was likely to be more cost-effective than when the programme was reviewed in 2015. The sub-committee had also considered whether revaccination with PPV23 should be considered further, noting that this had been considered by the German NITAG (STIKO) which had advised revaccination every six years. While the immune response to PPV23 declines with age, the incidence of disease increases. So additional doses could potentially offer additional protection.

66. The Committee noted that revaccination with PPV23 had not been modelled in the UK setting and that there were little immunological or efficacy data on repeat doses with PPV23. It was agreed the sub-committee should consider the matter further and report back to the Committee.

Conclusions

67. The Committee considered the report from the pneumococcal sub-committee and agreed with the findings presented. They agreed that there was compelling evidence that a 1+1 schedule would have a minimal impact on both invasive and non-invasive disease. A 1+1 schedule would rationalise health service resources, simplify the vaccine schedule, reduce the needle burden in infants and allow space in the schedule for new vaccines to be introduced. Additionally the use of a 1+1 schedule was likely to represent better use of public money.

68. The Committee agreed that the sub-committee had fully reviewed all stakeholder responses, and that all points raised had been considered appropriately. The sub-committee had fully supported the JCVI advice of October 2017 to move to a 1+1 schedule for PCV13 in the UK.

69. The Committee concluded that the PCV programme in the UK had been highly successful, with large and sustained decreases in PCV13 serotype disease across the population and especially in young children. High vaccine uptake in the UK combined with good vaccine effectiveness provided the UK with an opportunity to move to an alternate schedule. Given the success of the

programme, both in those vaccinated, and the wider population through indirect population protection, the Committee continued to agree that a move to a 1+1 schedule was appropriate for the UK situation. The Committee, therefore, advised a revised schedule for PCV13 vaccine, with vaccination offered at 12 weeks and at 12 months.

70. JCVI agreed it would keep IPD rates under careful review following a change to a 1+1 schedule, and would re-evaluate the advice according to the evidence where necessary. DHSC had confirmed that there would be no requirement for a cost-effectiveness analysis for the Committee to amend its advice, should that be required. The Committee also agreed that efforts to sustain coverage, especially at 12 months of age should continue to be a focus of the programme.

VIII. Coverage

71. The Committee noted the latest coverage data from across the UK. The Committee commented on the potential for data to be available on timeliness of vaccination, particularly for the booster doses at 12 months.

72. The Committee noted measles outbreaks had occurred in the final quarter of 2017 in England and Wales, often in under-vaccinated populations and young adults, and associated with importation. Work was underway to try and target younger adults. The Committee expressed concern about the lack of clarity on funding for catch-up programmes.

Prof Andrew Pollard (Chair)
Professor Pollard receives no personal payments from the manufacturers of vaccines He is Director of the Oxford Vaccine Group in the Department of Paediatrics, University of Oxford and has current research funding from the Bill and Melinda Gates Foundation, the National Institute for Health Research, the European Commission, Medical Research Council, Wellcome Trust, Innovate UK, Meningitis Research Foundation, and the Global Alliance for Vaccines and Immunisation. He chairs the scientific advisory group on vaccines for the European Medicines Agency and is a member of WHO's SAGE. Other investigators in the Department conduct research funded by vaccine manufacturers and the Department has received unrestricted educational grant funding for a three day course on paediatric infectious disease from Gilead, MSD, GSK and Astra Zeneca.
Prof Anthony Harnden (Deputy Chair)
Professor Harnden has no registered conflicts of interest.
Dr Andrew Riordan (Deputy Chair)
Dr Riordan has no registered conflicts of interest.
Prof Judith Breuer
Professor Breuer has no registered conflicts of interest
Dr Peter Elton
Dr Peter Elton has no registered conflicts of interest
Prof Adam Finn
Professor Adam Finn receives no personal payments from the manufacturers of vaccines. Professor Finn undertakes unpaid advisory work for Astellas on a klebsiella-pseudomonas vaccine. Professor Finn's Department receives funding for consultancy work from VBI vaccines on a developmental Hep B vaccine, and Bionet on a developmental pertussis toxin vaccine. The University of Bristol conducts research funded by GSK on meningococcal carriage, by Pfizer on pneumococcal carriage and transmission.
Prof Matt Keeling
Professor Matt Keeling has no registered conflicts of interest.

Dr Fiona Van der Klis
Dr Fiona van der Klis has no registered conflicts of interest
Ms Alison Lawrence
Ms Alison Lawrence has no registered conflicts of interest
Mrs Anne McGowan
Mrs McGowan receives no payments from the manufacturers of vaccines Mrs McGowan's employer Public Health Wales develop educational materials with funding from Pfizer, Sanofi Pasteur MSD, Novartis, Astra Zeneca and Wyeth.
Prof Maarten Postma
Professor Postma has received honoraria from SPMSD (health economics) MSD (health economics), and is an advisor to companies on Rotateq and Rotarix vaccines. Professor Postma works for the University of Groningen which receives grants from SPMSD and GSK for work related to influenza vaccines. Professor Postma attends advisory boards unrelated to vaccines or vaccine industry Professor Postma organized a conference which was financially supported by Pfizer relating to Health Economics.
Prof Robert Read
Professor Read receives no payments from the manufacturers of vaccines. The University of Southampton receives CASE studentship awards from Novartis and GSK.
Prof Anthony Scott
Professor Scott receives no payments from the manufacturers of vaccines. Professor Scott is Director of the Vaccine Centre and the Director of the Health Protection Research Unit at the London school of Hygiene and Tropical Medicine, which receives funding from PATH for research into whole cell pneumococcal vaccines. Professor Scott is also a scientific advisor to PATH on whole cell pneumococcal vaccination
Dr Maggie Wearmouth
Dr Wearmouth has no registered conflicts of interest
Dr Lucy Jessop (co-opted member)

Dr Lucy Jessop has no registered conflicts of interest
Dr Lorna Willocks (co-opted member)
Dr Lorna Willocks has no registered conflicts of interest
Ms Julie Yates (co-opted member)
Ms Julie Yates has no registered conflicts of interest