# JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

## Minute of the meeting on 01 June 2016

## Wellcome Collection

## 183 Euston Road, London NW1 2BE, UK.

**Members**

Professor Andrew Pollard (Chair)
Dr Andrew Riordan (Deputy Chair)
Prof Anthony Harnden (Deputy Chair)
Dr Peter Baxter
Prof Judith Breuer
Dr Peter Elton
Prof Adam Finn
Dr Fiona van der Klis
Ms Alison Lawrence
Mrs Anne McGowan
Prof Maarten Postma
Prof Robert Read
Dr Maggie Wearmouth

**Co-opted Members**

Julie Yates
Lucy Jessop
Lorna Willocks

**Invited Experts**

Prof Ray Borrow
Prof John Cairns
Dr Hannah Christensen

**Medical Adviser**

Professor John Watson

**Secretariat**

Andrew Earnshaw
Jonathan Crofts
Catherine Mackenzie
Dr Mary Ramsay

**Invited observers from Devolved Administrations**

Dr Nicola Steedman (Scottish Government)
Dr Anne Kilgallen (DHSSNI)

**Invited observers the MHRA**

Dr Phil Bryan (MHRA)

**Other invited observers**

Ms Joanne White (PHE)
Dr Claire Cameron (HPS)
Dr Richard Roberts (HPW)
Ms Sandra Anglin (NHS England)
Ruth Howlett-Shipley (MoD)
Dr Linda Diggle (Jersey)
Jacqui Dunn (IoM)
Dr Dipti Patel / Dr Vanessa Field (NathNac)
Dr Darina O'Flanagan (Eire)
Dr Peter Grove (DH)
Dr Shamez Ladhani (PHE)
Dr Sema Mandal (PHE)
Dr Vanessa Saliba (PHE)

Elaine Burgess (Guernsey)
Dr Caroline Trotter (PHE)
Pauline MacDonald (NHSE)
Helen Campbell (PHE)
Joanne Yarwood (PHE)

**Welcome**

1. The Chair welcomed all to the meeting. Apologies were received from Prof Anthony Scott, Claire Anne Siegrist and Dr Christian Schnieder.

2. 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 data with others outside of the meeting.

3. Conflicts of interest were checked by the secretariat prior to the meeting and members given the opportunity to provide updates.

**I. Horizon Scanning**

4. The Committee welcomed the information that had been provided in confidence by organisations involved in the development of vaccines, and noted the timetables for their licensing. Where appropriate vaccines would be considered in more detail by sub-committees.

5. The Committee indicated that it would welcome information on the concomitant use of the newly licensed vaccine Vaxelis® with Bexsero®.

**Action: Secretariat to approach industry for information regarding concomitant use of Vaxelis with Bexsero®.**

6. The Committee noted information about vaccines in development against a number of nosocomial infections. The committee welcomed work in this area, and asked the secretariat to consider establishment of a sub-committee in 2017 to consider use of such vaccines in more detail.

**Action: Secretariat to work with Chair to establish a nosocomial infection sub-committee.**

- The Committee noted timescales for the potential licensure of new RSV vaccines and considered what evidence would be required for decision making and the need for an assessment of the impact and cost-effectiveness of vaccination strategies. The Committee noted that

modelling was underway in this area, but agreed that further work was needed to estimate the burden of disease in the over 60's in the UK specifically. The Committee agreed to consider this in more detail at the October 2016 meeting.

**Action: Secretariat to identify work underway to assess the impact and cost-effectiveness of RSV vaccination in those 60 years of age and over and identify sources of data on the burden of disease in this age group**

7. The Committee noted timescales for licencing of a new inactivated herpes zoster vaccine, and that work was underway to assess the relative impact and cost-effectiveness of this vaccine and the currently licensed live herpes zoster vaccine. This would be presented to the Varicella sub-committee in early 2017.

8. It was agreed that specific influenza vaccines identified by the report (pandemic and elderly seasonal) would be considered as part of the JCVI's review of influenza vaccines in 2018.

9. JCVI agreed that development of alternative (or novel) vaccine delivery mechanisms would be welcome.

## II. Minute of the February 2016 meeting

10. The Committee agreed the minute of the February 2016 meeting was an accurate reflection of the discussion and the minute was approved with one change to the list of attendees.

**Action: Secretariat to amend the minute of the February 2016 meeting accordingly.**

## III. Matters arising

<u>Actions from the previous meeting</u>

11. The Committee noted that the secretariat was working to identify data on mixed schedules of PCV10 and PCV13 and feedback would be provided at a future meeting.

12. The Committee noted that Pfizer has provided additional information as requested by the Committee, and this was being considered by Public Health England. This, and any additional information provided would be provided to the Committee at a future meeting. The Committee noted that the final 'JCVI statement on adult pneumococcal vaccination in the UK' had been published.

Meeting papers

13. The Committee discussed the possibility of using electronic papers only. It was agreed that this approach would be trialled in coming meetings, and that any specific concerns should be raised with the secretariat.

Tuberculosis vaccination (BCG)

14. Public Health England provided an update on the procurement of BCG vaccine in light of the global shortage. Alternative vaccine sources had been identified and Public Health England had obtained a supply of WHO pre-qualified vaccine. This would be available for use shortly. In the longer term PHE would be looking to obtain more of the vaccine until such time as a licensed vaccine became available again.

15. The Committee noted that it was due to review BCG vaccination in October 2016, and a PHE BCG working group had been considering an update to the Green Book: Immunisation against infectious disease. The Committee agreed that they would consider in October 2016 whether a BCG sub-committee should be formed to consider new data in detail.

**Action: PHE to provide a report on the latest evidence on BCG vaccine at the October 2016 meeting**

Maternal pertussis vaccination

16. The Committee welcomed the letter to service providers from PHE on maternal pertussis vaccination, which set out the February 2016 advice from the Committee on the timing of vaccination. Work was underway to reflect this change in GP contracts for 2017/18.

Meningococcal Group B adolescent carriage evaluation

17. The Committee received a presentation on the ongoing work to develop a baseline of meningococcal carriage from Public Health England. The Committee noted that:

- 2,100 carriage isolates had been collected from across 10 sites in the UK by the UKMenCar carriage study, and work was ongoing to whole genome sequence these to determine whether the isolates were vaccine–preventable;
- an interim report would be provided to the Committee at its October 2016 meeting, with full results expected in 2017;
- the results would be used to inform the design of a further study to assess the effectiveness of meningococcal group B vaccines in reducing carriage.

**Action: Public Health England to provide an interim report on the adolescent meningococcal group B study for the October 2016 JCVI meeting**

18. The Committee additionally noted that the University of Bristol had an on-going study on meningococcal carriage density, and transmission. The group was also working on better-tolerated methods of sampling (particularly from saliva) which they hoped would be available by 2017.

SAGE decisions on Polio and Dengue

19. The Chair advised the Committee that the globally co-ordinated move from trivalent to bivalent oral polio vaccine (OPV) occurred in April 2016. This was part of the phased approach to switch to inactivated polio vaccine and prevent circulation of attenuated vaccine type virus, following global eradication of polio type two. It was noted that significant progress had been made in recent years towards polio eradication, although challenges still remained – including a global shortage of IPV vaccine.

20. The Committee noted that SAGE had advised the use of the dengue vaccine Dengvaxia® in endemic areas for those over 9 years old. It was noted that a second dengue infection was often more severe than a first infection, and as such vaccination in those over 9 years of age, who were in endemic areas where there was a high rate of dengue seropositivity, would reduce the risk of more severe infection .

**IV. Travel subcommittee report**

21. The Committee received a report from the chair of the Travel sub-committee which met on 6 May 2016 and noted that the subcommittee:
    - discussed potential new vaccines for future consideration, including the dengue vaccine now licensed in a number of countries outside of Europe, including Mexico and the Philippines (discussed under matters arising) and Ebola vaccines which were potentially close to licensure;
    - discussed scenarios under which dengue and Ebola vaccines might have relevance for travellers, and other groups such as the military and aid workers;
    - agreed that a new rapid schedule for the vaccine IXIARO® could be given to travellers aged 18-65 years at 0 and 7 days as per the SPC and the Green Book should be updated accordingly;
    - noted that there was also good potential for IXIARO® to be given to adolescents but that the sub-committee would like to see data from the manufacturer to support this;

- reviewed the issue of influenza vaccination and the Haj which may become a mandatory requirement by the Saudi Ministry of Health; the Subcommittee noted that overall the evidence supported the benefits of flu vaccination in Hajjis but noted the problem of the seasonality of flu in relation to the timing of the Haj which changes year to year, and the availability of the northern or southern hemisphere vaccine for Haj travellers;
- the latter was a complex issue as stocks of southern hemisphere vaccine were not held in the UK and GPs returned unused stock of northern hemisphere vaccine at the end of the UK flu season; the Subcommittee noted that the issue of the timing of the Haj and vaccine availability would be a challenge to resolve were vaccination to become a mandatory requirement and would require coordination at the international level;
- agreed that in the short term current advice needed strengthening to ensure awareness in the Muslim community about routine seasonal flu vaccination in at risk groups;
- discussed whether PCV13 should be offered to travellers over 65 years of age in circumstances where countries did not have a programme for infants that provided herd protection to older age groups;
- agreed that PCV13 could be offered to travellers over 65 staying longer than a month, working with local communities, or in close contact with the local population, in countries without established programmes but that a list of countries would need to be worked out and such a list would need to be regularly updated;
- agreed to consider the issue of Men C vaccine for infants visiting countries without established herd protection from adolescent programmes now that the infant dose is to be removed from the UK schedule this summer.

22. The Committee noted the findings of the Travel sub-committee.

**V. HPV Subcommittee report**

23. The Committee received a report from the chair of the HPV subcommittee which met on 26 February 2016 to consider an update on the work looking at extending vaccination to boys, progress on the recent advice to vaccinate GUM attending MSM, data presented by the manufacturer on two dose schedules for the 9 valent vaccine, the potential of one dose schedules, and an update from MHRA on vaccine safety.

24. The Committee noted the HPV sub-committee's recommendation that the 9 valent vaccine was suitable for use in the UK programme under a two dose schedule and should therefore be considered in the next round of tendering to procure HPV vaccine for the programme. The 9 valent vaccine was preferred for the programme because of the additional protection it offered compared with the bivalent and quadrivalent vaccines, provided it could be procured at a cost effective price.

25. The Committee noted that modellers at the University of Warwick had estimated that the 9 valent vaccine could eventually prevent an additional 300 cervical cancer cases a year if the programme switched to using this vaccine. These cases would be in addition to the cases of cervical cancer predicted to be eventually prevented by the programme using the quadrivalent vaccine.

26. The Committee noted that separating the doses for the nonavalent vaccine by more than 6 months generated a stronger antibody response than a 0, 6 schedule. The Committee agreed with the subcommittees concerns over the length of follow-up planned in the two dose trials and that a longer follow-up, without a boosting 3rd dose, was needed in the trials.

27. The Committee noted that the modelling work by Warwick University indicated that extending vaccination to boys, with a two dose schedule, was highly unlikely to be cost effective. This was based on looking at the impact and cost-effectiveness of having a gender neutral programme from 2015 and examining the cost effectiveness of this incrementally on a girls only programme and taking into the account the gains already made since the introduction of the girls programme in 2008.

28. The results showed that the threshold price for the vaccine (willingness to pay) at which a boys programme would be cost effective was close to zero with confidence intervals that included zero. Warwick had also conducted an uncertainty test which showed that it was highly unlikely that extending vaccination to boys would be cost effective.

29. The Committee noted the girls programme continued to be cost-effective and that high coverage in girls meant a large proportion of the potential health benefits from HPV vaccination for both sexes were achieved by the girls programme. The additional benefit that could be gained from vaccinating boys was therefore relatively small.

30. The Committee agreed that assessing the cost effectiveness of a boys programme incrementally on the girls programme was according to the Governments rules on cost-effectiveness analyses and that it was appropriate that the comparator should be based on the current ‘real world’ epidemiological situation.

31. The Committee thanked Warwick for their work but was reminded by the Chair that the Public Health England model was the main model that would be used for the consideration of gender neutral vaccination and that this was expected in early 2017.

32. The Committee considered the potential for one dose schedules and agreed that more data were needed to support this consideration. The Committee noted that the Subcommittee had specifically asked for research in this area as part of its recommendations and had also requested that Warwick explore modelling a one dose schedule for boys.

33. The Committee noted the progress with regards to the advice for a targeted programme for MSM and welcomed the planned introduction of a pilot by PHE.

34. The JCVI Chair summarised the advice with regards to the 9 valent vaccine:

- the Committee was satisfied from the immunogenicity and safety data presented by the manufacturer that the 9 valent vaccine could be used in the girls programme under a two dose schedule;
- the 9 valent vaccine was the preferred vaccine for the programme because of the additional health benefits that it provided in protecting against the 5 additional cancer causing HPV types;
- the choice of the 9 valent vaccine for the programme would however be determined by the incremental cost-effectiveness of the 9 valent vaccine and whether this offset any differential in cost between the tendered price for the 9 valent vaccine and that tendered for any of the competitor vaccines.

## VI. CEMIPP Report

35. The Cost-Effectiveness Methodology for Immunisation Programmes and Procurements Committee (CEMIPP) was established to examine whether changes should be made to the way in which JCVI assessed the cost-effectiveness of vaccination programmes. CEMIPP had a near final report that had been provided to the Committee for information. The final report would be provided to the Department of Health later in 2016.

36. The Committee received a presentation on CEMIPP's work from its Chair, Prof. John Cairns. The Committee heard that CEMIPP was considering the following areas of cost-effectiveness analysis:
    - perspectives on costs and outcomes (incl. how broadly costs and benefits should be considered);
    - incremental analysis;
    - discounting rate and time horizon;
    - measuring and valuing health effects (incl. the relative value of QALYs);
    - the relationship between cost and outcome (incl. non-linearity); and

- appraisal of evidence (incl. QALY price thresholds, uncertainty analysis and disinvestment).

37. The Committee welcomed the principle of a clearer framework for cost-effectiveness analysis. The Committee also requested to continue to be regularly consulted on the development and consideration of any proposed changes by both CEMIPP and the Department of Health.

38. The Committee considered that more primary evidence was needed to quantify some of the wider issues that could feed into cost-effectiveness analysis. This included peace of mind, preference for prevention over cure, preference for protection of specific age groups and the difficulty in collecting evidence for specific age groups.

39. The principle of incremental analysis as a method for achieving the best outcomes with a finite budget was recognised. However, there were concerns that the method did not adequately value control of disease. Under incremental analysis a programme could be highly cost effective, but a smaller element within that programme may not be cost effective and therefore rejected.

40. It was noted that should JCVI adopt the recommendations of CEMIPP it may then be operating differently to other bodies such as NICE.

41. The time period over which costs and benefits are taken into account ("time horizon") should be flexible to allow for individual vaccine circumstances.

42. It was noted that careful consideration would need to be taken by the Department of Health as to how any changes to cost-effectiveness methodology would affect previous JCVI decisions. This would include programs that had already been implemented.

43. The Committee identified risks around disinvestment. The frequency of disinvestment appraisal needed to be proportionate. Any disinvestment analysis also needed to take into account the risk of pre-vaccine disease burden returning to avoid frequent stop-start scenarios. It was noted that the Committee currently took these elements into account when considering disinvestment, and they were an integral part of disease modelling.

## VII. Meningococcal vaccination

Previous recommendations of the Committee and implementation

44. The Chair reminded the Committee that they had undertaken a comprehensive and detailed assessment of the evidence on group B meningococcal (MenB) vaccines in development, and on the impact and cost effectiveness of a range of potential MenB immunisation strategies in 2013 and 2014.

45. A key component of the assessment undertaken by JCVI was a study on the impact and cost-effectiveness of different vaccination strategies using Bexsero® conducted by the University of Bristol and London School of Hygiene and Tropical Medicine. This study was undertaken to investigate the impact and cost effectiveness of routine infant and / or adolescent immunisation programmes with and without catch-up campaigns, with and without the removal of an infant MenC dose, with alternate schedules, and with a routine toddler immunisation programme.

46. It was noted that JCVI had recommended a routine programme with a 2, 4, 12 month schedule, subject to procurement at a sustainably cost-effective price. JCVI had considered the cost-effectiveness of a catch up in those aged 1-4 years of age and concluded that in view of the marginal cost-effectiveness of even the routine programme, the priority should be implementation of the routine infant immunisation programme.

47. Members noted that the programme had begun in September 2015. At the time of the meeting in June 2016, all children up to 13 months of age would have been eligible for vaccination with Bexsero® as part of the routine programme. The Committee noted that information regarding the price of Bexsero®, other than the list price, was commercially confidential and they would have to make their considerations without this information.

*Uncertainty*

48. The Committee noted that in 2014 there had been considerable uncertainties with regard to the potential direct and indirect impact of a routine programme, and similar or greater uncertainties with regards to catch-up programmes. The Committee's recommendation for the use of Bexsero® in the routine childhood immunisation programme had been dependent on procurement of the vaccine at a cost-effective price. As the cost-effective threshold price was very low, concerns had been raised over whether it would be possible to negotiate a cost-effective price for Bexsero®. This was why JCVI had stated that any routine programme should only be considered if it was sustainable.

49. The Committee agreed that given the borderline cost-effectiveness of the routine use of Bexsero® in the infant programme, the considerable uncertainties with regard to the potential impact of a routine programme, and similar or greater uncertainties with regards to catch-up programmes, it had not been in a position to advise or further examine the question of a catch-up programme in 2014. The Committee had agreed in 2014 that a programme to vaccine those aged 1-4 years of age was unlikely to be cost-effective. The Committee agreed that quite rightly the focus of their deliberations had been on the routine infant programme, where there was the greatest potential benefit and the least uncertainty.

50. The Committee also noted that in 2014 they had concerns around the acceptability of a vaccine which was reactogenic and had a high incidence of post-vaccination fever when given concomitantly with other childhood vaccines. Concerns had been raised that this might negatively impact delivery of the other routine vaccines in the programme, and the Committee had considered it important to start the programme in those with the highest burden of disease, and assess the impact of this aspect on the other vaccines in the routine childhood programme before considering wider use.

51. The Committee was now in a position to consider the first provisional data on vaccine effectiveness from the routine programme which began in September 2015. The Committee agreed that the meeting represented the earliest possible opportunity to consider these data.

Parliamentary and media activity

52. The Chair advised the Committee that a member of the public had created a petition on the Government e-petitions website calling for all children up to age eleven to be offered Bexsero® routinely. The tragic death of a two year old child from group B meningococcal disease, and a high profile case of group W meningococcal disease had resulted in a surge in signatures to the petition. When the petition closed it had received over 800,000 signatures, the highest number of signatures received by a Government petition as of 1 June 2016.

53. Given the heightened interest in extending the use of Bexsero®; and the fact that new data were about to become available on the impact and acceptability of introducing Bexsero® into the routine programme; the Chair advised the Committee that he had written to the Public Health Minister asking whether the Government would like JCVI to consider the cost-effectiveness of a small scale catch-up programme for children aged 12 to 23 months of age. This age range was from a clinical perspective, the next priority for vaccination after infants. The Minister had responded by asking JCVI to consider this.

54. Following on from the petition, the Parliamentary Petitions Committee had agreed that the issue should be debated in Parliament, and had requested a period of evidence gathering on the issues raised. Two Petitions/Health Select Committee evidence sessions were undertaken where experts, parents and charities were questioned on the issues raised. The process had culminated in a parliamentary debate on the petition and issues raised.

55. It was noted that in evidence provided by the Meningitis charities, they had strongly supported wider use of Bexsero®, although their call had been for vaccination of all children less than five years of age, as opposed to the petition which had called for vaccination up to eleven years of age.

56. The Committee noted that the question of vaccinating a smaller cohort had been raised at the Petitions/Health Committee meeting, and the Chair had responded indicating that JCVI would be considering this, as per correspondence with the Public Health Minister.

57. The Committee considered it important to evaluate each potential option raised, including catch-up vaccination for all children up to eleven, five and two years of age. The Chair noted considerations made at the meningococcal sub-committee, where it was agreed that any catch-up programme for those aged less than two years of age would need to be undertaken by December, before the meningococcal season typically began. After that date, the risk of disease falls following the winter season and most of those under 2 years of age would have been vaccinated in the routine programme.

*Concerns around the Methodology used by JCVI*

58. The Committee noted that during JCVI's deliberations on the use of Bexsero® in the routine programme during 2013 and 2014, the Committee had asked for a working group to be formed to review whether the cost-effectiveness methodology used to assess vaccination programmes was appropriate. This working group, the Cost Effectiveness Methodology for Immunisation Programmes and Procurements (CEMIPP), had considered such issues and the draft report had been presented to the Committee earlier in the meeting. It was noted that the final report of CEMIPP would be for the Department of Health to consider, and it would not be appropriate to use methodological approaches discussed at the time of the meeting. It would be for the Department of Health to consider the findings of CEMIPP and report its conclusions to the Committee. The Committee agreed that the existing methodology for assessing cost-effectiveness should be used in their deliberations.

*Concerns on whether JCVI had fully taken into account the impact of meningococcal disease*

59. Members noted draft minutes of the May 2016 Meningococcal sub-committee, where questions were raised during the Parliamentary process as to whether JCVI had fully taken into account the impact of meningococcal disease on those affected. The sub-committee had agreed that during their deliberations in 2013 they had advised JCVI to apply a 'quality of life adjustment factor' (QAF) of three (x3) to long term sequelae. This was the equivalent to assessing the cost-effectiveness of immunisation against a threshold of around £45,000 per QALY. JCVI had agreed with the advice of the sub-committee and this had been included in the analysis used for decision making by the JCVI in 2014.

60. The decision to use a QAF of three (x3) had been based on concerns that quality of life losses associated with meningococcal disease had not been fully captured within the cost-effectiveness analysis; wider concerns regarding the measurement of the impact of IMD in children; the innovative nature of the MenB vaccine Bexsero®; and the differential societal value of equal QALY measures of severe and relatively mild disease. The Committee agreed that everything which could reasonably be taken into account had been, and that the analysis had been well conducted.

<u>Meningococcal epidemiology and vaccine effectiveness</u>

61. The Committee noted data which indicated that before the introduction of Bexsero® into the routine programme the highest incidence of invasive Meningococcal B (MenB) disease was seen in those less than 12 months of age. The next highest incidence of invasive disease was seen in those aged 12 to 23 months. Very low levels of disease were seen in those aged two years and over.

62. The Committee noted early data on effectiveness following the first and second doses of Bexsero® in the routine programme, noting a considerable reduction in cases of meningococcal disease in the vaccine eligible cohort. While the numbers vaccinated were still relatively small, and the confidence intervals around estimates of effectiveness were relatively wide, the Committee agreed that the vaccine effectiveness data in the routine cohort who were eligible for vaccination were very encouraging, particularly following two doses of vaccine. The Committee noted work was continuing across the UK to assess the effectiveness and impact of vaccination with Bexsero®. It was anticipated that the first data would be ready for publication in autumn 2016.

63. The Committee agreed with the conclusions of the Meningococcal sub-committee that the epidemiological data indicated a substantial drop in invasive group B meningococcal disease incidence after the second birthday, and it would be appropriate to consider the cost-effectiveness of vaccinating those aged 12 to 23 months, alongside other options, as children in this age range would benefit the most from any catch-up programme undertaken.

Acceptability of the programme and uptake

64. The Committee noted that in 2014 concerns had been raised at the Committee regarding acceptability of a vaccine which was reactogenic and had a high incidence of post-vaccination fever when given concomitantly with other childhood vaccines. The Committee noted that Bexsero® had been very successfully introduced into the routine programme, and the vaccine appeared to be well tolerated.

65. The Committee noted that during trials with Bexsero® there was increased injection site pain when the vaccine was given to older children. The Committee agreed that use of Bexsero® in older children might be less acceptable to parents than it appeared to be in infants.

Cost-effectiveness of catch-up vaccination programmes using Bexsero®

66. The Committee received a presentation by Dr Hannah Christensen from the University of Bristol on modelling the impact and cost-effectiveness of Bexsero catch-up strategies, the Committee noted that:

- the model used was the same transmission dynamic model used in the 2014 analysis considered by the Committee;
- the model was age structured (0-99y), with the inclusion of demographic data;
- the cost-effectiveness threshold was £20,000 per QALY;
- discount rates of 3.5% and 1.5% were used for costs and benefits;
- the base case assumed 88% strain coverage and 95% vaccine efficacy;
- disease incidence and case fatality rates were based on HES data from 2005/6 to 2011/12;
- a scenario analysis was undertaken using more recent disease incidence, which was potentially more suitable for the modelling of catch-up programmes;
- a Quality Adjustment Factor (QAF) of 3 and litigation costs were included;
- scenario analyses were undertaken using lower strain coverage and reduced herd effects (vaccine conservative scenario);
- catch-up vaccination of children aged 12 to 23 months was undertaken incrementally on the infant programme;

- catch-up vaccination of children aged 24 to 35 months was undertaken incrementally on the infant programme and a catch-up for those aged 12-23 months;
- catch-up vaccination of children aged 36 to 47 months of age was undertaken incrementally on the infant programme and catch-up programmes for those aged 12-35 months of age; and
- the prices presented took into account the most up to date information on GP delivery costs.

67. The Committee agreed that as meningococcal disease incidence between 48 months and eleven years of age was significantly lower than that seen in younger children, the incremental cost-effectiveness of vaccinating children in this age range was likely to be proportionately less cost-effective.

68. The Committee noted that the University of Bristol was currently undertaking work on the weighting of QALYs by age, and this could be provided to the Committee once completed.

<u>Advice of the Meningococcal sub-committee</u>

69. The Chair of the Meningococcal sub-committee advised the Committee that the Meningococcal sub-committee had met in May 2016, where they had considered the modelling presented on the cost-effectiveness of catch-up vaccination programmes.

70. The sub-committee Chair reminded the Committee that they had previously agreed that the introduction of Bexsero® into the routine programme would provide some protection to infants against other meningococcal capsular groups, including meningococcal C disease. Control of meningococcal C disease was also being maintained by an adolescent Men C (and later Men ACWY) vaccination programme. The Committee had previously agreed that the infant dose of MenC vaccine in the programme could be removed from the schedule, subject to the introduction of Bexsero®, in the context of the successful implementation of the adolescent MenC programme. Given this circumstance, it had been agreed that it would be reasonable to add the cost of the MenC vaccine and the associated administration costs to the threshold price per course for use of Bexsero® in the routine programme. This meant the cost-effective threshold price per dose for Bexsero® had increased by a fixed amount over the price considered by the Committee in February 2014. This cost was not known to Committee members, as the price paid for MenC vaccine was commercially confidential information. The sub-committee had agreed that this addition could not be made to the price per dose of any catch-up programme, as removal of the infant MenC dose from the schedule was not contingent on a catch-up

programme with Bexsero® being undertaken, and all infants proposed for a catch-up would already have received the MenC dose.

71. The sub-committee had agreed that the base-case scenario for vaccination of those aged 12 to 23 months indicated a positive vaccine price at which a programme could be undertaken. The evidence indicated that catch-up vaccination programmes to vaccinate children two years of age and over were unlikely to be cost-effective in the conservative vaccine scenarios. The cost-effective price for a catch-up programme for those aged 12-23 months was significantly lower than the list price of the vaccine, and likely to be lower than the price per dose for the routine programme (once cost savings associated with removal of the MenC dose were taken into account).

72. The Committee agreed with the findings of the Meningococcal sub-committee regarding the threshold price per dose at which a catch-up programme for those aged 12-23 months would be cost-effective, and that the threshold price could not be increased with respect to the removal of the infant MenC dose from the schedule. The Committee agreed that a catch-up programme for those aged 12-23 months could be cost-effective, albeit at a threshold price which was likely lower than that for the routine childhood programme. The evidence indicated that vaccination of those aged 24 to 47 months was unlikely to be cost effective. Vaccination of those aged 48 months to eleven years of age was highly unlikely to be cost-effective given the very low levels of disease seen in this age group.

*Issues and risks with undertaking a catch-up vaccination programme*

73. The sub-committee chair advised the Committee that were a number of issues and risks associated with undertaking a catch-up vaccination programme, including the very low vaccine price identified, the potential need for negotiations with the manufacturer on vaccine price (should this price be lower than the price of the current contract), the need to deliver the catch-up program before December 2016, the availability of vaccine in the short timeframe being considered, and health service system capacity (with one or two appointments per eligible child at an age where no vaccination appointments were scheduled).

74. A major risk identified by the Meningococcal sub-committee was that a timely catch-up programme would likely not allow for new vaccine manufacture and therefore might be dependent on use of the ‘buffer stock’ held by Public Health England for the infant programme. This could potentially put the running of the infant programme at risk. The sub-committee had asked the Department of Health and Public Health England to consider this issue and provide an update to the Committee at the June meeting.

75. The Committee agreed with the findings of the meningococcal sub-committee, noting that use of vaccine buffer stock from the infant programme to vaccinate those aged 12 to 23 months would increase the level of operational risk for the infant programme. It was also agreed that system capacity in primary care was a real issue, and that the lead in time from advice to the start of a catch-up programme would make achieving a programme by December 2016 challenging.

Vaccine availability and scenarios for catch-up programmes

76. The Committee noted a paper from Public Health England outlining short-term vaccine availability and what could be achieved in the time available, given that the timeframe did not allow for new vaccine manufacture. Given the early data on vaccine effectiveness following one and two doses in infancy, the Committee agreed that a one dose programme would not be desirable, and any catch-up programme should use a two dose schedule.

77. The Committee noted the constraints around vaccine supply, given that vaccines were made to order and there was a long lead in time from placing an order to delivery of the vaccine. For any substantial purchase of vaccine it would typically take six to nine months from order to delivery. Any catch-up programme requiring implementation before the end of 2016 would mean the use of buffer stock which was held to support the running of the infant programme.

78. No options were available which would allow for the vaccination of all those aged up to 23 months of age. The Committee however noted that by the start of the meningococcal season all children aged 12 months to 19 months of age would have been offered Bexsero® as part of the routine programme.

Education

79. The Committee noted that Public Health England continued to ensure that all their communications highlighted the signs and symptoms of meningococcal disease and that currently available vaccines did not cover all strains of the disease. Communications continued using social media, Universities UK, schools and other partners to focus on the need to share with and engage young people and their parents about the need for vaccination, and awareness of meningococcal disease.

Discussion

80. The Committee agreed that this was the first opportunity for the Committee to consider evidence from the introduction of Bexsero® into the routine vaccination programme, which had begun in September 2015. Evidence from the routine programme provided the Committee with indications that the programme was likely to be highly effective. Concerns the Committee had in 2014 with regards to the acceptability and tolerability of introducing Bexsero® into the programme had not been borne out, with very high vaccine uptake being seen and evidence of a wider positive impact on the programme.

81. Now that the Committee had 'real world' evidence from the use of Bexsero® in the UK; which was the first country in the world to introduce Bexsero® as a publicly funded routine programme; the Committee agreed that a programme to vaccinate those aged 12 to 23 months with Bexsero® would likely be publically acceptable and effective, though this was untested in any country.

82. The cost-effective threshold price for a catch-up programme for those aged 12-23 months was likely to be lower than that for the routine programme (because of the additional savings in the routine programme from removal of a dose of MenC vaccine in infancy), and was potentially lower than the price paid for vaccine held by Public Health England for use in the infant programme. The Committee agreed that evidence indicated a catch-up programme to vaccinate those aged 12-23 months of age was likely to be cost-effective, subject to procurement of the vaccine at a (very low) cost-effective price, and lower than the cost-effective price for the current infant programme.

83. Catch up vaccination to older ages, including up to three years, four years and eleven years of age, were not cost-effective, primarily due to the very low levels of disease seen in these age groups.

84. The Meningococcal sub-committee had asked the Department of Health and Public Health England to examine the potential to operationalise a catch-up programme for those aged 12-23 months, with the catch up to be completed no later than the start of the meningococcal season in winter 2016. The Committee noted feedback from the Department of Health and Public Health England that given the lead time for procurement of new vaccine, any catch-up programme for delivery in 2016 would require use of the buffer stock from the infant programme. It was noted that the manufacturer had been continuing to build capacity and reliability into the manufacturing process; however use of Public Health England's buffer stock would increase the risk of supply interruption to the infant programme. The Committee were strongly of the view that any decision to use buffer stocks that would put the infant programme at risk should be avoided.

85. The Committee agreed that as the highest rates of meningococcal disease were seen in infants, and early evidence from the routine programme with Bexsero® indicated very good vaccine effectiveness, the routine programme remained the priority. Increasing operational risk to the infant programme was a serious concern and any failure to deliver it could reduce confidence in the programme and put those most likely to benefit from vaccination at risk. The Committee noted that meningococcal disease rates were seasonal, with a peak in cases occurring in the winter months. By 1 December 2016 all children between 2 months and 19 months of age should have been offered Bexsero® vaccine as part of the routine programme.

Conclusions

86. The Committee was acutely aware of the fact that wider use of Bexsero® in the UK could potentially prevent further tragic losses of life from meningococcal disease in childhood, and that there was significant public opinion supporting such use. The Committee agreed that wider use of the vaccine would be desirable from a public health perspective, now that very early estimates of vaccine effectiveness were available and evidence indicated that the vaccine was well accepted and its introduction had not had any adverse impact on the wider programme. The Committee agreed that new evidence gave them greater confidence in the vaccine, and reduced some of the uncertainties which had been a focal point of discussions in 2014. The Committee were greatly reassured that the initial evidence indicated that the programme was already likely to be saving lives which would otherwise have been lost to meningococcal disease.

87. When considering the cost-effectiveness of wider use of Bexsero® in the UK, the Committee concluded that a programme to vaccinate children aged 12-23 months of age could be cost-effective, albeit at a threshold price which was likely lower than that determined for the routine programme. Programmes to vaccinate older children, up to four years and eleven years of age were unlikely to be cost-effective, and the Committee therefore agreed that only a programme for those aged 12 months to 23 months of age should be considered.

88. The Committee however noted there was unlikely to be any vaccine available to deliver any programme to those aged 12 to 23 months of age before the 2016/17 meningococcal season. The Committee were also concerned about the serious risks to the infant programme that the use of Public Health England's buffer stock could present. Given these concerns, the Committee agreed that they could not advise the Department of Health to consider such a catch-up programme. The Committee remained committed to its recommendation on the use of Bexsero® in the routine infant programme.

89. The Committee welcomed the continuing work of Public Health England to increase awareness of meningococcal disease across the population.

Meningococcal ACWY vaccination

90. The Committee noted that work to assess the impact and cost-effectiveness of continuing the MenACWY vaccination programme had been delayed due to resources being re-allocated to work on the cost-effectiveness of catch-up programmes with Bexsero®. The Committee noted that the work would be provided for the October 2016 meeting.

**VIII. Influenza vaccination**

91. Public Health England provided the Committee with an overview of the 2015/16 season presenting the latest surveillance data.

Epidemiology

92. The Committee noted that the influenza season began relatively late in comparison to recent seasons and continued showing noticeable impact and activity into the late spring. Influenza A(H1N1)pdm09 viruses predominated in the first half of the season after which influenza B viruses predominated. Both of these influenza types tended to affect the younger age groups. The season was characterized by numerous reports of outbreaks in school and hospital settings. Peak activity in General Practitioner (GP) consultations occurred around week11 and continued above base line for 14 weeks in England but got no higher than within the medium threshold range of activity.

93. Although new genetic clades emerged at the end of 14/15, antigenic characterization data from 15/16 showed a good match between the influenza vaccine A(H1N1)pdm09 strain and the circulating wild type A(H1N1)pdm09 viruses. The main circulating B strain in 15/16 was similar to the influenza B/Victoria-lineage component in the quadrivalent vaccine, which was not the B strain present in the trivalent vaccine.

94. The main burden of influenza occurred in secondary care in hospitals and ICUs wards affecting mainly young adults. This was mostly caused by the A(H1N1)pdm09 virus. ICU admissions and rates were higher than in the 14/15 season. Extra Corporeal Membrane Oxygenation (ECMO) use due to influenza was also more than five times higher than the previous season and 50 percent of the ECMO use confirmed as influenza was for individuals with a BMI greater than 40 (morbidly obese) though their vaccination status was unknown. The

Committee noted that a recent publication[1] estimated ECMO costs over and above ICU admissions to be £75, 000 per bed occupancy. Age specific excess all-cause mortality was seen in the 15-64 age group, with the cumulative excess mortality rate in this age-group the highest seen in the last 5 seasons.

Vaccine uptake

95. Vaccine uptake in the >65 year olds was slightly lower in the UK (except in Northern Ireland) compared to the previous season, however, uptake in at risk groups <65 years old showed a larger drop compared to the previous season across the UK. In England uptake in the at-risk groups below 65 years of age was lowest in the morbidly obese and highest in diabetics. Uptake among healthcare workers declined in England and Scotland from 55 to 51% and 33 to 32% respectively. Possible reasons for the drop in uptake of influenza vaccination this season included: the negative publicity from last season over the very low mid-season VE estimates in 2014/15; having to keep pace with the increasing denominator size of the over 65 population, within risk groups and pregnant woman (more were vaccinated this year than last year); and data transfer issues from pharmacies now offering vaccination (England only).

96. In the childhood programme in England a slight drop off in uptake was observed for children aged 2 to 4 years old vaccinated via primary care while in primary school children in years 1 and 2 - rolled out for the first time in 2015/16 - the uptake was 54% in England. Uptake was 58% in the five pilot sites that vaccinated all primary school aged children. Analysis of uptake data showed an association between lower uptake and deprivation, black and minority ethnic groups, and children from Muslim families in 14/15.

Vaccine effectiveness

97. Estimates of overall vaccine effectiveness (VE) (any vaccine) showed a positive and significant protective effect against laboratory confirmed influenza A or B (52%), Influenza A (52%), Influenza B (54%) and influenza A(H1N1)pdm09 (56%) for all ages. Breaking this down by age showed good protection against influenza B in all ages up to 64 years, despite the mismatch of the influenza B strain in the trivalent vaccine which is targeted at adults, and good protection against A(H1N1)pdm09 in all age groups except in the under 18 year olds. The latter showed a positive but low VE estimate, which was statistically non-significant. Stratifying the data in children aged 2-17 years old by live attenuated influenza vaccine (LAIV) or inactivated influenza vaccine (IIV) showed overall good protection for the LAIV vaccine. Against influenza B, VE was high, with moderate

[1] Peek GJ et al. Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR). Health Technol Assess. 2010 Jul;14(35):1-46. doi: 10.3310/hta1.

(non-significant) protection against A(H1N1)pdm09. IIV showed good protection against H1N1pdm09, and non-significant protection against B. Pooled VE data for the past three seasons in 2-17 year olds showed the LAIV vaccine overall gave good protection, in particular against influenza B and influenza A(H3N2) but moderate, non-significant protection, against influenza A(H1N1)pdm09. IIV gave good protection against A(H1N1) but no evidence of any protection against influenza B or influenza A(H3N2).

Impact

98. The Committee reviewed early data on the impact of the childhood programme for 2015/16 in the pilot sites in England where all primary school aged children were vaccinated, compared to non-pilot sites. The preliminary data for 2015/16 indicated a similar positive impact on a range of influenza indicators to that seen in the 2014/15 season. A strong positive cumulative impact on GP consultation rates was observed in the pilots whilst the impact on more severe influenza hospitalisations and ICU admissions was not so marked. Early data from Scotland and Northern Ireland, where all primary school aged children were vaccinated (with high uptake rates), showed reductions in GP influenza-like illness (ILI) consultation rates for 5-14 year olds. Scotland and Northern Ireland also had a milder influenza seasons than England and Wales which did not get above pre-epidemic baseline thresholds, whereas England and Wales were above baseline epidemic levels for 14 weeks this season. The Committee agreed that it would like to see the finalized impact data for 2015/16 at the October meeting.

Conclusions

99. The Committee agreed that the 2015/16 influenza season was dominated by A(H1N1)pdm09 and then later by influenza B and had a moderate impact at primary care level but impacted more in secondary care and ICU admissions. Morbid obesity had again been highlighted as an important risk factor for severe disease. The Committee noted that despite the advice that this group should receive influenza vaccination, morbid obesity was not yet included in the section 7a agreement. This meant that GPs did not receive remuneration for vaccinating this risk group. The Committee noted that the latest evidence presented on morbid obesity would be considered in the next round of section 7a negotiations conducted by NHS England for the 2017/18 season.

100. The Committee noted that the VE of the LAIV was good against influenza B, but moderate against A(H1N1)pdm09. The Committee agreed that there was reassuring positive evidence emerging from the pilot sites of both direct and indirect impacts on influenza due to the childhood programme. There had also been a successful national roll-out in primary schools year 1-2 of the childhood

programme, which was a large undertaking, with school delivery by far the most successful means of delivery. The Committee noted that work was underway to improve coverage for next season and that an economic evaluation of the trivalent IIV compared to the quadrivalent IIV was also in development.

101. The Committee noted that early VE estimates in the United States (US) for the LAIV had been disappointing and would be reviewed later in June at the annual US Advisory Committee on Immunisation Practices (ACIP) meeting. The Committee noted this was not the first time the effectiveness of the LAIV had been disappointing in the US and that last year the LAIV had lost its preferential status as the vaccine of choice for children in the US. The Committee agreed the observations in the US were in contrast to the encouraging impact of the childhood programme in the UK. The Committee agreed to monitor the outcome of the ACIP meeting and consider any potential insights from this of relevance to the UK programme and policy.

**IX. Coverage**

102. The Committee noted the latest data on coverage for the UK childhood programmes and the continuing excellent coverage being seen across the UK.

| **Prof Andrew Pollard (Chair)** |
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| Professor Pollard receives no personal payments from the manufacturers of vaccines<br><br>Since taking up his role with JCVI he no longer takes on research grants from industry sources. Grants already set up prior to appointment were from Pfizer (epidemiological studies of meningitis in children and nasopharyngeal carriage of pneumococci, MenB vaccine study in adolescents and Okairos (RSV vaccine), and these past projects ended in 2015 or before.<br><br>He is Director of the Oxford Vaccine Group in the Department of Paediatrics and has current research funding from the Wellcome Trust, The Bill and Melinda Gates Foundation, The Medical Research Council, the World Health Organisation, the National Institute for Health Research, the European Commission and the Global Alliance for Vaccines and Immunisation. He chairs the scientific advisory group on vaccines for the European Medicines Agency.<br><br>Other investigators in the Department conduct research funded by vaccine manufacturers and the Department has received unrestricted educational grant funding from Novartis, 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. |
| **Dr Peter Baxter** |
| Dr Peter Baxter 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 has no registered conflicts of interest |
| **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<br><br>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 GSK (MenB vaccine), Novartis (non-vaccine), Pfizer (scientific advisory board), AbbVie (non-vaccine).<br><br>Professor Postma works for the University of Groningen which receives grants from Astrazeneca, Sanofi Pasteur MSD and GSK for work related to influenza vaccines. The University also receives funding from Pfizer and AbbVie for work unrelated to vaccines. |
| **Prof Robert Read** |
| Professor Read receives no payments from the manufacturers of vaccines.<br><br>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.<br><br>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 |
| **Prof Claire-Anne Siegrist** |
| Professor Siegrist receives no payments from the manufacturers of vaccines.<br><br>Professor Siegrist is the Head of the Vaccinology and Immunology Unit at the University Hospitals of Geneva, which receives funding from Sanofi Pasteur MSD for research into vaccine adjuvants, and independently undertakes research into the use of Prevenar 13® |

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