

JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

Minute of the meeting on 3 February 2016 Oxford Martin School Oxford

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
Prof Anthony Harnden
Dr Fiona van der Klis
Ms Alison Lawrence
Mrs Anne McGowan
Prof Maarten Postma
Prof Robert Read
Prof Anthony Scott
Prof Claire-Anne Siegrist
Dr Maggie Wearmouth

Co-Opted Members

Julie Yates – England
Lucy Jessop – Northern Ireland
Lorna Willocks – Scotland

Medical Adviser

Professor John Watson

Secretariat

Dr Mary Ramsay
Mr Andrew Earnshaw
Mr Jonathan Crofts
Dr Karen Homer

Invited observers from Devolved Administrations

Dr Nicola Steedman (Scottish Government)
Dr Anne Kilgallen (DHSSNI)
Dr Andrew Riley (Welsh Assembly Government)

Invited observers the MHRA

Dr Phil Bryan (MHRA)

This minute will remain draft until ratified by JCVI at its next meeting
The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

Other invited observers

Dr Dorian Kennedy (DH)
Dr Caroline Trotter (PHE/University of Cambridge)
Ms Pauline MacDonald (PHE)
Ms Joanne White (PHE)
Dr Claire Cameron (HPS)
Dr Richard Roberts (HPW)
Ruth Howlett-Shiple (MoD)
Dr Linda Diggle (Jersey)
Jacqui Dunn (IoM)
Elaine Burgess (Guernsey)
Dr Dipti Patel / Dr Vanessa Field (NaTHNaC)
Dr Stephen Inglis (NIBSC)
Dr Darina O'Flanagan (Eire)
Dr Peter Grove (DH)
Dr Shamez Ladhani (PHE)
Dr Sema Mandal (PHE)
Dr Gayatri Amirthalingam (PHE)
Dr Michael Edelstein (PHE)Helen Campbell (PHE)

Welcome

1. The Chair welcomed all to the meeting and informed members that no apologies had been received.
2. The Chair welcomed Professor Maarten Postma as the new Health Economist member of the JCVI. The Chair also welcomed Dr Marybeth Maritim, Chair of the National Immunisation Technical Advisory Group (NITAG) for Kenya, to the meeting. Dr Maritim was attending the meeting at the invitation of Professor Anthony Scott and the members were informed that Dr Maritim would be meeting to discuss the workings of the Committee with the JCVI Secretariat later in the week.
3. The Chair advised members that Mr Chris Liffen had decided to leave the JCVI and he thanked Mr Liffen for his contributions to the Committee. The members were informed that recruitment for a new lay member would begin shortly.
4. Members and observers were reminded that papers 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. The Chair reminded members that this also applied to the papers provided at the JCVI retreat which took place on 02 February 2016.
5. Conflicts of interest were checked by the Secretariat prior to the meeting and members were given the opportunity to provide updates.

I. Minute of the 07 October 2015 meeting

6. The Committee agreed that the draft minute of the meeting of 07 October 2015 was an accurate record subject to three amendments.
7. The Committee noted that Co-opted members (Julie Yates, England; Lucy Jessop, Northern Ireland; Lorna Willocks, Scotland) had been omitted from the list of attendees for the October meeting and that this should be corrected in revised draft.
8. The Committee noted that Dr van Hoek's affiliation had an incorrect abbreviation in the list of attendees for the meeting and that LHSTM should be revised to read LSHTM.
9. The members requested that the line in paragraph 35 reading 'The Committee noted that in October 2014 the JCVI had advised that the dose of meningitis C conjugate (MenC) vaccine...' be amended to read 'The Committee noted that in October 2014 the JCVI had advised that the dose of meningococcal C conjugate (MenC) vaccine...'

Action: Secretariat to amend the draft minute of the meeting of 07 October 2015 accordingly.

10. The members noted that correspondence had been received from GSK in which the vaccine manufacturer requested that the draft minute of the October 2015 meeting of the JCVI be amended. The Chair informed the Committee that the correspondence and GSK's request for amendments to the draft minute would be considered under Item II (matters arising).

II. Matters arising

Correspondence from GSK

11. The Committee noted a letter from GSK to Professor Pollard dated 1st December 2015, Re: '*Draft minute of JCVI meeting on 7 October 2015 regarding consideration of the pneumococcal conjugate vaccine (PCV) of choice for the UK paediatric immunisation programme, points 76-79 ("Draft Minute")*'. In this correspondence, GSK requested that JCVI clarify the process followed and the data reviewed during its consideration of advice with regard to PCV use in the childhood immunisation programme.
12. The members noted that the Secretariat had prepared an extensive response to GSK's concerns on behalf of Professor Pollard in a letter dated 11th December 2015. This letter detailed the process followed and assessment of the data reviewed during the JCVI's consideration of the PCV paediatric immunisation programme. The response also contained supporting information provided by Public Health England (PHE).
13. In a letter to Professor Pollard dated 25th January 2016, GSK acknowledged the extensive response provided by the JCVI but expressed their concern that there remained areas of uncertainty with regard to the interpretation of international pneumococcal serotype surveillance data. GSK additionally proposed alternative wording to paragraphs 77 and 78 of the draft minute of the October 2015 meeting of the JCVI.
14. The JCVI considered in detail the amendments to the draft minute of the October 2015 JCVI meeting proposed by GSK. The Committee agreed that in principle it had no objection to amending the draft minute of a meeting where proposed changes provided clarification or important corrections of fact. The members noted that this had been done previously, where concerns were raised that highly specific comments made about the UK vaccine programme could have an impact in relation to immunisation programmes in other countries. However, the Committee agreed that amendments to a draft meeting minute should not be made where this would result in changing the record of the deliberations or the conclusions of the JCVI, or where there was no need for further clarification. The members further agreed that the changes to the draft minute of the October 2015 meeting of the JCVI requested by GSK should not be made.

Discussion on PCV10 and PCV13

15. The Committee acknowledged GSK's concerns with regard to the impact of its advice on competition during the national procurement for the PCV paediatric immunisation programme, noting that at present only one vaccine was eligible for this process in the UK. The members therefore considered at length areas of uncertainty which meant that JCVI was unable to consider revising its advice at the current time and additional areas of research which could provide data which might inform potential policy changes in the future.
16. The Committee noted that evidence on the impact of the PCV13 childhood immunisation programme (direct effectiveness, carriage, herd effects) from its use in the UK and elsewhere was extensive but the same granularity of data from high income settings with strong surveillance systems were not yet available for PCV10. It was noted that further data even for PCV13 were still emerging, especially with regard to replacement disease in adults, and members agreed the importance of on-going surveillance given the dynamic nature of the situation.
17. Members noted that pneumococcal serotype 19A disease had initially decreased following the introduction of PCV13 into the childhood immunisation programme in the UK but had risen slightly recently, however larger rises had been noted in some countries using PCV10. The Committee agreed that the reasons for this were currently unclear and agreed that they would like to see additional serotype 19A surveillance data from countries using PCV13 or PCV10 in childhood immunisation programmes. Members noted that although PCV10 is used in childhood immunisation programmes in several areas of the world, the force of infection is much greater in many of these countries and surveillance data therefore could not be extrapolated to the UK setting.
18. The Committee agreed that it would like to see further PCV10 impact data, in particular effects of vaccination on serotype-specific carriage in children, herd immunity and replacement disease in adults, from countries including the Netherlands and Finland that are more similar to the UK, so that any assessment can be made with comparable data. Such data could be used to adequately populate disease models and assess the potential for positive or negative changes in rates of disease should alternative immunisation programmes be considered in the UK. The committee also noted the emerging data on the apparent impact against serotype 3 in the US and UK data where PCV13 is used. The JCVI considered the benefits of a head-to-head study comparing the impact of PCV10 and PCV13 but acknowledged the inherent difficulties in obtaining these data.

19. The committee also considered that, if both PCV10 and PCV13 were used at the same time in the programme, further modelling data were needed to assess whether a particular balance of PCV10 and PCV13 immunised children in the population would be required to maintain herd immunity against all serotypes. The Committee discussed the possibility of conducting an implementation pilot in the UK, but acknowledged the operational and cost implications of such a pilot. JCVI concluded that there were no new data to inform a change to the current PCV13 programme, which has had a substantial impact against pneumococcal disease in children in the UK. However, JCVI await further data on PCV10 programmes elsewhere with interest.
20. The JCVI further considered the circumstances under which PCV10 might be considered as an additional or alternative component of the PCV childhood immunisation programme or whether a change to the number of PCV doses in the programme could be considered. Members noted that PHE was due to report on a trial with a 1+1 schedule for PCV13 in 2017. The Committee considered whether there is a need to have all three doses of the same PCV in the childhood programme given that the current high levels of coverage of PCV13 are unlikely to be required to maintain herd immunity to PCV13 serotypes once full control has been obtained. The members agreed that conceptually it was likely that a mixed 1+1 or 2+1 schedule would give herd protection but further agreed that the Committee should review data on PCV10 as a booster dose after a PCV13 prime and PCV13 as a booster dose after a PCV10 prime when this information becomes available.

Action: secretariat to see data on mixed schedules from the manufacturers and academic groups and DH to consider research in this area if data do not exist.

21. The Department of Health (DH) welcomed the detailed consideration which JCVI had given to the childhood pneumococcal immunisation programme and clarification of the additional evidence that would be required in order for the Committee to be able to review its current advice in this regard. The Department acknowledged the importance of competition in tender processes, noting the current cost of the infant PCV vaccination programme.

Other correspondence

22. The Committee noted correspondence from Pfizer dated 06 November 2015. This letter provided information which the vaccine manufacturer believed would be of interest to the JCVI and stated that more information would be provided within around two weeks. The members noted that this additional information had not yet been received.

Action: Secretariat to request additional information from Pfizer.

Status of the actions identified in the draft October 2015 meeting minute

23. The Secretariat had invited Professor John Cairns to provide an update on the work of the Cost Effectiveness Methodology for Immunisation Programmes and Procurement (CEMIPP) working group to the JCVI at the October 2015 meeting but he was unable to attend. The Committee noted that Professor Cairns had given a presentation to the JCVI at the retreat which took place on 02 February.
24. The Committee had requested the Secretariat to work with the reporters of coverage data across the devolved administrations to standardise the coverage data and produce a template of key indicators. Members noted that standardised coverage data had been provided and that this would be considered under Item XI.
25. After extensive deliberation and consideration of a body of new evidence, at the October 2016 meeting the JCVI concluded that it would not explicitly advise against prophylactic use of paracetamol, but also not encourage the use of prophylactic paracetamol except when Bexsero® was administered concomitantly with other infant vaccines. The Committee agreed it would be important that the wording in the Green Book distinguish between prophylactic use of paracetamol and treatment of fever. The Secretariat was requested to work with members of the Committee to make changes to the wording in the Green Book about the use of prophylactic paracetamol. Members noted that revised wording was being produced and that this would be circulated shortly.
26. At the October 2015 meeting, it was agreed that PHE and DH would identify and fully assess the uncertainties associated with a permanent extension to the MenACWY programme, and report back progress to the Committee at the February 2016 meeting. The Chair informed the members that discussions had been undertaken and that this issue would be further considered under Item V.

Feedback from the 02 February 2016 JCVI retreat

27. A retreat for JCVI members was held on 02 February 2016 at St Cross College, Oxford. The format for the day was based around a series of presentations followed by round-table discussions. The JCVI received a report on the coordination of the modelling studies which support JCVI decisions and a presentation on the operational aspects of implementing JCVI recommendations. The members additionally received an overview of the vaccine procurement process and the role of clinical adjudication.
28. The Committee received a presentation from Professor Cairns at the retreat which summarised the main findings of the CEMIPP Working Group to date. Professor Cairns was invited to give a more formal presentation to the JCVI at the June 2016 meeting, by which time it is anticipated that CEMIPP will have reported.

29. The Chair reminded the members that the scope and remit of the JCVI had also been considered at the retreat, along with its relationship with stakeholders. The members had also discussed the expertise that the JCVI would need in the future to meet the needs for vaccine advice in the longer term. The members agreed that the remit of the JCVI would be considered further at a future meeting and that the breadth of expertise within the Committee should be maintained while perhaps recruiting new members with additional areas of expertise in the future. During the retreat, the members also considered their role in encouraging vaccine research which would support the decision making process of the JCVI.
30. The members agreed that the retreat had been a useful exercise and that it had provided an opportunity for the Committee to consider in depth a range of topics.

Update on the outcomes of the spending review

31. The JCVI received an update on the outcomes of the Spending Review from Professor John Watson. Professor Watson informed the members that Spending Review settlement had been agreed with the Department of Health, noting that DH had used a different approach to the NHS and other Arms' Length Bodies. DH was currently working through its priority setting to decide how to allocate resources. Future National Immunisation Programme assumptions were being worked into these priorities, although no details were available at the time of the meeting.

III. Adult pneumococcal vaccination – Consultation responses and final decision

32. The JCVI Pneumococcal Sub-committee met three times during 2015 to consider adult pneumococcal vaccination and the Sub-committee reported to the JCVI at the October 2015 Committee meeting. The *'Interim JCVI statement on adult pneumococcal vaccination in the UK'* was published in November 2015 for stakeholder consultation. Manufacturers of pneumococcal vaccines were specifically asked to provide submissions in response to the interim statement. Only Pfizer had provided a response on the topic of adult pneumococcal vaccination. The Pfizer response had been provided to the Pneumococcal sub-committee, JCVI members and observers, and to the relevant officials in PHE for consideration in advance of the meeting.
33. Pfizer's response to the interim statement included information on a clinical group at increased risk of pneumococcal disease for whom routine immunisation with PCV13 was not currently recommended. The Committee considered the data provided by Pfizer, especially in light of the indirect protection afforded by the childhood PCV13 immunisation programme, and agreed that there was currently insufficient information on which to base a change in their advice in this regard.

34. The Committee concluded their deliberations by agreeing that they were content that the '*Interim JCVI statement on adult pneumococcal vaccination in the UK*' should be published as final without any amendments.

Action: Secretariat to publish the final '*JCVI statement on adult pneumococcal vaccination in the UK*'.

IV. Maternal pertussis vaccination

35. The Committee noted a presentation from PHE on the latest pertussis epidemiology. Following the introduction of the temporary vaccination programme for pregnant women in 2012 in response to a national outbreak of pertussis, infant disease had returned to levels similar to that seen pre-2012, but disease in all other age groups remained substantially higher than those seen pre-2012. Pertussis activity was also exceeding that seen in 2012 in five to nine year olds. Data from England indicated that vaccine effectiveness for the maternal programme remained at around 90%, where the vaccine is provided at least 1 week prior to delivery. The Committee noted that coverage for the maternal programme was around 60%, with higher uptake seen in the winter months, believed to be the result of the additional offer of maternal influenza vaccine during this period. Data from the Clinical Practice Research Datalink (CPRD) indicated coverage rates 15 percentage points higher, which was considered likely a reflection of how the denominator was calculated and pregnancies identified.
36. The Committee noted that studies had been undertaken to assess whether maternally derived antibody concentrations to pertussis, diphtheria, and tetanus might interfere with infants' response to the same vaccine antigens and those conjugated to diphtheria toxin (CRM) or tetanus toxoid (TT). Whilst an impact on some antibody levels were seen, the majority of infants achieved protective antibody thresholds (where there is a defined correlate of protection) after primary immunisation, and there was no indication that the lower antibody levels were having a clinical impact based on current surveillance data.
37. Given continuing heightened pertussis activity in those over one year of age the Committee agreed that the maternal pertussis immunisation programme remained important in the control of pertussis in those less than one year of age. The Committee noted that there was no licensed whole-cell vaccine available for use in the UK, although consideration could be given to the use of whole cell vaccines at a future date. It was noted that a European Commission Innovative Medicines Initiative programme would assess the comparative immunogenicity of whole cell and acellular vaccines in several countries in Europe. It was noted that modelling could be used to identify the optimal pertussis programme for children, and that this would be of interest to the Committee.

Timing of maternal vaccination

38. The Committee noted a paper¹ indicating that optimal neonatal pertussis antibody concentrations were elicited following maternal vaccination between 13 and 33 weeks gestation. It was noted that the current UK advice to ideally vaccinate between weeks 28 and 32 had been based on consideration of evidence on the period of optimal maternal antibody transfer. It was noted that vaccination earlier in pregnancy, as well as potentially improving neonatal antibody levels, would also be operationally easier, particularly given that a number of routine appointments were offered before week 28. A change in advice permitting earlier vaccination in pregnancy would provide additional benefit where delivery was premature. The Committee agreed there were no safety issues with earlier pertussis vaccination in pregnancy
39. JCVI noted the study and agreed the evidence indicated vaccination earlier than week 28 in pregnancy would be likely to improve neonatal antibody levels and would increase opportunities during pregnancy for vaccination. The Committee agreed that vaccination should now be advised from the 16th gestational week of pregnancy, with consideration to be given by PHE to the option of offering the vaccine at the same time as, or at any time after, the routine 20 week anomaly ultrasound scan.

V. Meningococcal vaccination

Meningococcal B vaccination programme

40. The Committee noted that the meningococcal B vaccination programme had begun on 1 September 2015. Early data from the programme were presented to the Committee by PHE, and it was noted that:
- 186 Men B cases had been confirmed in England between September 2015 and January 2016, compared with 200 and 201 cases during the same months in the 2014/15 and 2013/14 epidemiological years;
 - MenB was responsible for 55% of all invasive meningococcal disease (IMD) cases, compared with 56% in 2014/15 and 66% in 2013/14;
 - since 01 September 2015, there were 15 laboratory-confirmed IMD cases in infants aged ≥ 3 months at diagnosis and eligible for the MenB vaccine, with eight due to MenB, five due to MenW and two due to MenY;
 - three of the eight MenB cases received a single dose of Bexsero® and developed disease before receiving a second dose;
 - no cases had been seen in infants who had received two doses of the vaccine;
 - Coverage levels for the vaccine were good, and comparable to routine vaccinations offered at the ages the meningococcal B vaccine was offered;
 - the number of yellow card reports received were as expected, and there were no concerns identified from the reports received;

¹ Eberhardt et al (2016) Maternal immunization earlier in pregnancy maximizes antibody transfer and expected infant seropositivity against pertussis. Clin Infect Dis. Jan 20. pii: ciw027.

41. The Committee agreed that the results were encouraging, although given the historical backdrop of falling invasive meningococcal B disease, it was too early in the programme to have confidence that the comparative reduction in disease was an effect of the programme. The Committee indicated it was keen to see an update to this data at a future 2016 meeting.

Meningococcal epidemiology

42. The Committee noted that in October 2014 they had advised that the meningococcal C conjugate (MenC) vaccination programme in adolescence be replaced with a meningococcal ACWY conjugate (MenACWY) vaccination programme. In February 2015 they had reviewed in detail the on-going increase in meningococcal W (MenW) cases and advised the implementation of a vaccination programme for teenagers aged 14 to 18 years as soon as possible, stating:

“The continuing rise in cases of MenW across the population was a cause for significant concern. Levels of disease were consistent with an outbreak situation, with cases and deaths occurring in all age ranges, constituting a public health emergency. Cases seen to date were likely the start of a much larger outbreak, one potentially of the same order as that seen with MenC in the 1990’s”

43. The Department of Health had accepted the advice. The MenACWY vaccine had replaced the MenC vaccine in the time-limited ‘freshers’ programme from August 2015, and in the routine adolescent schools programme in 2015/16 academic year. In addition, a catch-up campaign was being implemented offering MenACWY vaccine to all adolescents aged 14 to 18 years. School leavers had been prioritised for the first phase of the catch-up. The committee noted that it had intended that the adolescent programme would continue with MenACWY once the catch-up was complete, and would not revert back to the MenC programme.

44. The Committee further noted that:

- in 2014/15 MenB had accounted for 58% of all invasive meningococcal disease (IMD) cases, followed by MenW (24%), MenY (13%) and MenC (4%),
- cases of both MenW and MenY IMD reported in 2014/2015 were the highest since the start of enhanced IMD surveillance in England in the late 1990’s.
- MenW IMD had increased by 85% from 95 cases in 2013/2014 to 176 cases in 2014/15, and MenY had increased by 12% from 83 cases to 93 cases respectively;
- cases of MenW continued to increase in the current epidemiological year and were higher to 31 December 2015, with 87 cases, than to the equivalent point in each of the last 5 years (9, 21, 43 and 64 cases);
- increases had been observed in all age groups other than those aged 15-19 years who had been targeted by the MenACWY vaccination programme and in whom cases were lower than this time last year; and

- coverage of school leavers from the 2014/15 academic year in England was disappointing at around 30%.

45. The Committee discussed the data, commenting on how low coverage was being reported in certain areas, and welcoming comments on work to improve coverage going forward.

Modelling the cost-effectiveness of continuation of the MenACWY vaccination programme

46. The Committee noted continuing dialogue between PHE and DH regarding the modelling work to ascertain the cost-effectiveness of continued MenACWY vaccination in teenagers beyond the MenW outbreak, and efforts to assess the uncertainties in this assessment. The Committee noted, and supported, the intention that the PHE Vaccine Preventable Invasive Bacterial Disease Forum (whose members include microbiologists, clinicians, epidemiologists and public health specialists) be consulted, to define plausible scenarios for the course of the epidemic in the absence of vaccination, and to make projections about the risk of further MenW (or Y) outbreaks over the next 100 years.
47. The Committee noted that discussions were continuing regarding the timeframe for consideration of the cost-effectiveness analysis, and whether guidelines for appraisal and evaluation in Government indicated that an incremental analysis on the existing catch-up programme was required. It was noted that the Committee had advised a routine programme prior to advising a catch-up, which potentially provided support to a non-incremental analysis. The Committee also heard comments about the rationale for both approaches.
48. The Committee agreed that discussions should continue between PHE and DH. It was agreed that the Committee should, at a future meeting, consider both analyses. Given the potential for the catch-up to alter the cost-effectiveness of continuation of the routine programme (in an incremental analysis), considering both analyses would allow for commentary on this.

VI. Influenza vaccine development

49. The Committee received a presentation on egg adaptation of influenza virus vaccine strains from Dr John McCauley director of the WHO collaborating center at the Francis Crick Institute Mill Hill Laboratory where characteristics of flu viruses are monitored.
50. The Committee noted that:
- current influenza vaccines are predominantly produced using eggs;
 - influenza virus strains that are used for the inactivated vaccines, the live attenuated vaccine and even cell cultured vaccine are initially isolated in eggs and selected for genetic and antigenic characteristics that match those in circulation;

- candidate vaccine viruses are then created which can then be mass produced through propagation in eggs;
 - the only licensed vaccine which does not use eggs is one that uses recombinant haemagglutinin expressed in the baculovirus, though this is only licensed in the US and not widely used.
51. It was further noted that the phenomenon of egg adaptation had been known for a long time and propagation in eggs resulted in associated antigenic change in the virus. Propagation through cell culture of strains initially isolated in eggs does not reverse the egg adaptation. As a result most influenza vaccine viruses have adapted to eggs including AH3N2, B, and AH1N1 and vaccine strains propagated in eggs show marked differences to those propagated in cells.
52. The effect of egg adaptation seems more noticeable in the AH3N2 virus and since 1968 there had been a considerable decline in ability of AH3N2 vaccine viruses to bind to human receptor analogues (similar to sites the virus uses to bind to cells in the respiratory tract) and also to red blood cells.
53. It had been difficult to quantify the effect of egg adaptation on vaccine effectiveness (VE), however, because there were also other factors which influence VE such as natural genetic drift in circulating strains resulting in mismatches with the vaccine strains used. The latter was observed during the 2014/15 season in the UK when VE against AH3N2 was lower than expected.
54. In 2012/13, however, there had been a good match between vaccine and circulating strains but despite this a low VE was observed in Canada for the AH3N2 vaccine strain which was attributed to egg adaptation (Skowronski et al). Variable effectiveness for AH3N2 had also been observed in 2013/14 in Europe and an upcoming publication of some meta-analysis on VE may shed further light on the effect of egg adaptation.
55. It was noted that an additional complicating factor was that the egg adaptation of AH3N2 influenza viruses changed as the virus evolved, resulting in many variables that needed to be taken into account when assessing VE including genetic drift, the predomination of different strains in different parts of the world and geographic areas and differing types circulating in different seasons.
56. Although the propagation of cell cultured isolated virus was appealing, there are currently no licensed vaccines for this method, and no real incentives for industry to adjust their methodologies. There remained concern about whether the methodology would be able to meet the massive scale up that would be required to meet global needs.

57. The Committee agreed that changes affecting the effectiveness of the AH3N2 component of the vaccine were of important clinical significance owing to the impact that the AH3N2 virus can have on morbidity and mortality in the elderly. The committee thanked Dr McCauley for his presentation and agreed to monitor the situation closely for further developments and reports on this important issue.
58. The Committee received an oral update from the Deputy Chief Medical Officer at the Department of Health on recent international meetings that had been undertaken to consider how there could be improvement in how influenza vaccines are developed. The aim was to see if timelines could be shortened and flexibility incorporated in the process so as to be better able to respond to the potential for drifted strains occurring during the flu season.
59. It was noted that at present to start vaccinating in September in the Northern Hemisphere the decision on vaccine composition had to be made in the preceding February using data gathered on circulating strains from the previous season and from around the world.
60. The Committee discussed whether surveillance could be improved to inform better vaccine strain selection, whether the process of strain selection itself could be improved and shortened, whether steps in manufacturing could be shortened and whether there was any flexibility in delivery of vaccination and in the vaccination programmes themselves.
61. It was considered that based on current technology there was little room for manoeuvre and only very small savings could be made on current timelines. The process for developing the flu vaccine for each season remains very difficult to change once it has started and immunisation programmes are very intolerant to changes in timing of the arrival of vaccine due to the preparation and planning that goes into them. Flexibility might change if there was an existing technology capable of scaling up at short notice, though currently there seems little appetite for investment in methods such as cell propagation.

VII. MHRA safety report

62. The Committee noted a written report from the MHRA and a verbal update from an MHRA representative. The Committee noted the update on UK suspected adverse reactions (ADRs) associated with routine and/or commonly used vaccines reported to the MHRA via the Yellow Card Scheme during the time period of 1 July 2014 to 31 December 2015. The MHRA reminded the Committee that a report of a suspected ADR to the MHRA does not necessarily mean that it has been caused by the vaccine, as many factors have to be taken into account in assessing the relationship between a vaccine and suspected reaction such as the possible role of underlying or undiagnosed illness. The Committee noted that overall the MHRA had not identified any significant new safety issues in the period under consideration. The Committee thanked the MHRA for the report, and continued to be reassured regarding the safety of vaccines used in the UK.

63. The Committee further considered the European Medicines Agency (EMA) report on “whether there is evidence of a causal association between HPV vaccines and CRPS and/or POTS, and if available information may require updates to the advice to healthcare professionals and patients, including changes to product information or other regulatory measures on the marketing authorisations concerned”. It was noted that the overarching conclusion of the report was that “Taking into account the totality of the available information the Pharmacovigilance Risk Assessment Committee (PRAC) concluded that the evidence does not support that HPV vaccines (Cervarix, Gardasil, Gardasil 9, Silgard) cause CRPS or POTS” and that “The benefits of HPV vaccines continue to outweigh their risks”.
64. The Committee agreed that the EMA report followed extensive study and was a thorough review of the position. The Committee were reassured by the findings of the MHRA report, and the report from the EMA with respect to HPV vaccination. The Committee remained of the view that it had no concerns regarding the safety of the HPV vaccines.

VIII. Ebola Vaccines

65. The Committee received an update from Adrian Hill of the Jenner Institute Oxford University on the work on the Ebola vaccines that had been developed. The Committee noted that:
- prior to the Ebola epidemic that started in 2014 there were several Ebola vaccines which had already been made and were ready for testing;
 - these vaccines used either an adenovirus based platform expressing Ebola glycoproteins or a vesicular stomatitis virus (VSV) based platform encoding the same Ebola proteins; and
 - since the start of the epidemic in West Africa six viral vectors have been used for Ebola vaccines using adenoviruses, VSV or the modified vaccinia virus Ankara (MVA).
66. Preclinical data in monkeys using the Chimpanzee adenovirus vaccine candidate ChAd3 EBO Z indicated it induced strong antibody and T-cell responses. ChAd3 EBO Z also gave 100% protection against a high challenge of Ebola virus which could be boosted after a year using an MVA vector expressing Ebola antigens (MVA boost). For the ChAd3 vaccine protection was both antibody and T-cell dependent and high antibody titres correlated with protection.
67. The ChAd3 vaccine was taken forward by a consortium coordinated by WHO for accelerated development and phase 2 trials in humans for safety and immunogenicity. The vaccine generated good seroconversion rates and had a good safety profile but the antibody and T-cell levels elicited were much lower than that seen in macaques. Because of the low response levels it was decided to trial boosting by MVA after a single dose of ChAd3. A 20 fold increase in antibody was observed after boosting and the boosting regime was highly immunogenic with good levels of neutralizing antibody demonstrated and had a good safety profile. Boosting gave a good response as early as one week after the priming dose.

68. Another group funded by the European Commission Innovative Medicines Initiative had also developed an adenovirus based vaccine using adenovirus 26 for the priming dose with an MVA boost. The VSV vaccine has also made rapid progress although there was some initial concern on safety with arthritis observed in some in European recipients in some phase 1/2 trial sites.
69. The implementation of phase III efficacy trials for the various Ebola vaccines had been limited by the declining incidence of Ebola as the epidemic has been brought under control. Of the planned efficacy trials only one was able to go ahead fully which was a ring vaccination trial using the VSV vaccine. This showed a very high vaccine efficacy and more importantly it was discovered that protective antibody levels did not have to be as high as first envisaged and a single dose was sufficient to provide short term protection in an outbreak situation. The VSV based vaccine was on its way to licensure and this was likely to be followed shortly by the adenovirus based vaccines.
70. The Committee noted that two dose regimes were likely to provide the best way of inducing longer-term protection, and various on-going trials in West Africa were examining this issue with a ChAd3 MVA combination, which appeared to be showing good duration of immunogenicity so far, after 18 months of follow up. ChAd vaccines have been researched for longer and more widely tested as a vaccine platform for other diseases and have accumulated more information on safety. The ChAd vaccines also generate T-cell based immunity unlike VSV and can be used for priming or boosting in combination with MVAs. VSV may not be suitable as a booster due to the likely requirement for replication to produce good immunogenicity.
71. It was considered that the main roles envisaged for the Ebola vaccines were in bio-defence and in immediate outbreak control where a single dose should be sufficient to prevent disease and protect contacts of cases. Such vaccines could also be used to protect healthcare workers (and other frontline staff) and other aid workers deployed to affected areas. The technology of viral vector based vaccines also had the potential to provide a common platform adaptable to other emerging diseases with epidemic potential. Vaccines could be developed and held in small stocks to be used in the right place at the right time to be used against potential epidemics.

IX. BCG Vaccines

72. The Committee noted that there were continuing supply problems from the only European licensed manufacturer of BCG vaccine. PHE had to date successfully prioritised the available vaccine, but were considering whether to procure a WHO pre-qualified vaccine from a non-European licensed manufacturer. It was noted that such vaccines were very widely used outside of Europe. A representative from NIBSC indicated that they had not to date tested any relevant product, but indicated they would be content for the importation of a specified quantity. Overall the Committee agreed that as long as NIBSC and the MHRA were content with the importation of a specific product, and that PHE advised healthcare professionals regarding use of an

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unlicensed vaccine, that they would be content for the use of an unlicensed BCG vaccine in the UK.

X. Travel Sub-committee

73. The Committee noted a draft agenda for the next Travel Subcommittee meeting which was planned to take place in the coming months; however, there was insufficient time for the Committee to discuss the suggested agenda items. The Committee looked forward to hearing about the outcome of the meeting.

XI. Coverage

74. The Committee agreed that the Coverage data remained very positive.

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Prof Andrew Pollard (Chair)

Professor Pollard receives no personal payments from the manufacturers of vaccines

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.

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.

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

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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 GSK (MenB vaccine), Novartis (non-vaccine), Pfizer (scientific advisory board), AbbVie (non-vaccine).

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.

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

Prof Claire-Anne Siegrist

Professor Siegrist receives no payments from the manufacturers of vaccines.

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

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