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

JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

Minute of the meeting held on 02 October 2019

Wellington House, Waterloo Road, London

Members

Prof Andrew Pollard (Chair)
Prof Anthony Harnden (Deputy Chair)
Professor Jeremy Brown
Alison Lawrence
Dr Fiona van der Klis
Prof Simon Kroll
Prof Wei Shen Lim
Prof Adam Finn
Prof Rob Read
Prof Anthony Scott
Dr Maggie Wearmouth
Dr Martin Williams
Dr Kevin Brown
Dr Rebecca Cordery

Co-opted members

Dr Jillian Johnston (NI)
Dr Lorna Willocks (Scotland)
Mrs Anne McGowan (Wales)
Dr Julie Yates (England)

Medical Advisor

Prof Jonathan Van Tam

Secretariat

Andrew Earnshaw
Ruth Parry
Jonathan Crofts
Chris Lucas
Dr Mary Ramsay
Dr Gayatri Amirthalingam

Invited speakers

Dr Richard Pebody (PHE)
Dr Edwin van Leeuwen (PHE)
Alastair Ikin (DHSC)
Dr Shamez Ladhani (PHE)
Prof Matthew Snape (NISEC)
Dr Katherine Russell (PHE)

Invited observers from Devolved Administrations

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

Other invited observers

Dr Sandra Anglin (NHS England)
Matthew Olley (NHS England)
Dr Linda Diggle (Jersey)
Dr Jacqui Dunn (IoM)
Joana Rocha (Guernsey)
Nicola Brink (Guernsey)
Alex Hawkins-Drew (Guernsey)
Dr Dipti Patel (NaTHNaC)
Gary Holden (MoD)
Joanne Yarwood (PHE)
Dr Sema Mandal (PHE)
Julie Nugent (PHE)
Dr Sarah Tarr (PHE)
Dr Jamie Lopez (PHE)
David Green (PHE)
Dr Richard Roberts (PHW)

Dr Michael Edelstein (PHE)
Dr Louise Newport (DHSC)
Sarah Hicks (DHSC)
Tom Irving (DHSC)
Anna Clarke (Eire)
Lucy Jessop (Eire)
Carline Trotter (PHE)

Welcome

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

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

3. The Chair welcomed Dr Rebecca Cordery as the new public health expert member, and Dr Kevin Brown as the new virology expert member.

I. Minute of the June 2019 meeting

4. The Minutes of the June 2019 meeting were agreed.

II. Matters arising

HPV programme update

5. The Committee noted that an article had been published providing commentary on their advice regarding HPV vaccination, and the Committee wanted to make it clear that they still considered the standard methodology to be 3.5% discounting for costs and benefits using a £20,000/QALY threshold.

6. PHE informed the Committee that work had been undertaken to implement a gender-neutral HPV programme from the 2019/20 academic year. Both boys and girls were being vaccinated, and the suite of materials to support the programme had been updated to reflect the wider offer of vaccine. Anecdotal feedback from the front-line indicated a very positive response, and that the new programme had been well-received.

BCG and SCID screening

7. The Committee noted that a pilot screening programme for Severe Combined Immunodeficiency (SCID) was being considered, and that this had implications for the targeted neonatal BCG programme. The Committee had considered this issue in October 2018 and agreed it would be necessary to move the programme from birth to after SCID screening results were

available, as vaccination before testing would not be acceptable (due to the risk of disseminated BCG in SCID infants). However, deferring vaccination would potentially require a change in delivery setting from secondary care to the community, and the Committee raised concerns about the challenges this would present, and the risk of reduced uptake.

8. Further work had been undertaken by the National Screening Committee, which considered the potential impact of delaying BCG vaccination until after screening results were available. It was noted there could potentially be a small increase in TB cases as a result of the change in programme, but contrasted with a reduction in morbidity and mortality associated with earlier diagnosis of SCID.

9. The Committee noted comments on the potential impact of a change in setting on uptake of the vaccine and noted PHE would be considering how to maintain uptake levels. PHE were working on methods for improving data collection and identifying a denominator to allow coverage to be measured. The Committee agreed that the impact of the change should be monitored and considered by the Committee in the next two years.

10. Members commented on the modelling undertaken, and whether the change in timing was proportionate given the potential rates of BCG disseminated disease compared to the potential increase in TB disease, given that SCID was very rare. The cost-effectiveness was not explicitly stated in the report provided, and it was considered important to have this information made available to the Committee. Questions were also raised about whether the long-term impact of TB disease had been adequately captured.

11. The Committee noted arguments that achieving consent for vaccination, before the results of screening were available, would be challenging.

12. The Committee agreed that further information from the modelling and screening teams should be provided to the Committee for a future meeting. The Committee's advice remained as agreed in October 2018.

<u>Letter on PCV vaccination in older adults</u>

13. The Chair advised the Committee that they had received a letter from Pfizer asking that the Committee's advice on pneumococcal conjugate vaccination in older adults be reviewed, in light of the latest epidemiological data.

14. It was noted that the data highlighted by Pfizer included a prospective cohort study over 10 years in patients hospitalised with pneumonia in Nottingham. The data showed that in these patients there had been an increase in pneumonia admissions and an increase in PCV13 serotype disease, mostly serotype 3 (roughly 40%). It was noted that it has been difficult to demonstrate direct or indirect effectiveness of the vaccine against this serotype. There was also an increase in non-PCV13 vaccine type disease. It was noted that a cohort study in adults was underway in Bristol, where preliminary data confirmed the Nottingham results and the rise of PCV13 types in adult pneumonia and meningitis patients.

15. The Chair reminded members that this issue had been reviewed by the Committee in 2015, where they had agreed that vaccination with PCV13 in older age groups was not cost-effective. JCVI would not be able to consider the Pfizer questions raised in the letter without reviewing the model in detail. The Committee agreed that when the pneumococcal sub-committee began considerations of higher valency pneumococcal vaccines in development, that this issue should also be given consideration.

16. The Committee noted that pre-filled syringes of Pneumococcal polysaccharide vaccine (PPV23) were being used due to a shortage of vials, although pre-filled syringes were more expensive. This raised a question around whether PPV23 remained cost-effective, especially with changes to the circulating serotypes and development of higher-valency pneumococcal conjugate vaccines. PHE noted that the previous static model prepared by PHE could be updated, if this was identified as a priority by the Committee.

17. PHE noted that based on the model, PPV23 was likely to remain cost-effective at the higher price. A sensitivity analysis undertaken previously, had tested the impact of higher administration costs on the cost-effectiveness of the vaccine, and when this was considered, alongside changes to disease serotypes and incidence, it was considered likely that the vaccine remained cost-effective for use in the UK. However, PHE noted that the model could be refined to take account of serotype changes and higher valency vaccines, in addition to PPV23. This could also include impact of vaccination on rates of pneumonia.

18. DHSC noted that the Mathematical & Economic Modelling for Vaccination and Immunisation Evaluation (MEMVIE) group at Warwick were working on a second opinion model, for the cost effectiveness of the childhood PCV13 programme. It planned to extend this to the adult PPV23 programme.

19. Data on serological response in all elderly patients by age cohort, alongside data on the timings of vaccination, could be incorporated into the modelling undertaken.

20. The Committee agreed that the continuing cost-effectiveness of the PPV23 vaccination programme could be reviewed alongside other issues, including the potential use of higher valency pneumococcal conjugate vaccines and the cost-effectiveness of PPV23 vaccination strategies.

DHSC Vaccine Strategy

21. The Committee noted that in the ‘Prevention Green Paper’ published in July 2019, DHSC committed to publishing a ‘vaccine strategy’. On 18 August the Prime Minister had called for health leaders to renew their efforts to meet 95% uptake for both doses of MMR.

22. It was noted that the UK had lost its ‘measles-free status’ with the WHO, and this had led to the vaccine strategy being brought forward. The strategy was being developed by DHSC, who were writing to stakeholders, including JCVI, to seek views on issues to be considered in the strategy. The idea was to set

out a clear vision for maintaining the UK's world-leading position over the next decade, with a shorter-term focus on improving vaccine coverage, including for MMR.

23. Regarding mandating vaccination, it was noted that the Secretary of State had made public statements regarding this, which had been underpinned by significant concerns regarding the continued small decline in vaccine uptake across the programme. These statements were signals that there was no complacency in Government regarding the small but sustained reduction in coverage for childhood vaccines, and that Ministers were prepared to look at all options. It was noted that the advice of JCVI could be sought in the future on policy options being considered.

24. Members questioned whether the Government would be seeking the views of the public and patient advocacy groups. It was noted that the Government was seeking the views of specific professional groups and charity groups.

25. The Committee agreed that a formal scientific analysis of the potential positive and negative impact of mandatory vaccination should be undertaken if this approach was actively pursued, to ensure that due consideration of all consequences was made.

<u>Ebola post-exposure prophylaxis</u>

26. The Chair summarised the position regarding the ongoing outbreak of Ebola in the Democratic Republic of the Congo (DRC), and the discussions undertaken on holding a stock of Ebola vaccine in the UK for use in post-exposure prophylaxis, should any cases be identified in the UK. PHE had been asked to advise on use of vaccine in pregnant or immunosuppressed individuals, should they require post-exposure prophylaxis, and which vaccines might best be used in that situation.

27. The Committee noted that there were two vaccines available for use in western Europe. One vaccine was the vesicular stomatitis vaccine (VSV), which was trialled in the 2014 Ebola outbreak and had been used in DRC during the current outbreak and had been shown to be effective in a ring vaccination protocol (Merck). This was a live replication-competent vaccine, and there were no good data to inform considerations on whether it would be appropriate for use in immunosuppressed individuals. The other vaccine was a prime-boost with two separate compositions, neither of which was replication-competent (J&J). While there were no specific concerns about use of this vaccine in immunosuppressed individuals, there were no efficacy or effectiveness data available for this vaccine.

28. The Committee noted a paper from PHE on use of vaccine for post-exposure prophylaxis in immunosuppressed individuals, including pregnant women. It was noted that this covered available evidence on immunogenicity of the J&J vaccine, and the response over the first seven days following vaccination. Safety data for both vaccines were provided, alongside any data on use in pregnant women and immunosuppressed individuals. Alternative prophylaxis options were also considered.

29. Immunogenicity and safety data from use in pregnant or immunosuppressed individuals were limited for both vaccines. There were reasonable data on safety in individuals with HIV. It was noted the Merck vaccine was now being used in DRC in pregnant and lactating women.

30. There were some data available on the kinetics of the immune response to the J&J vaccine, which indicated there was unlikely to be a substantial immune response in the first seven days, although evidence did indicate some response by 14-15 days. Most studies only had data on responses between 26 and 56 days. In data on the Merck vaccine, there was no evidence of an immune response in the first seven days, but some evidence of a response by 14 days, and clearer evidence of a response by 28 days. There were some data on post-exposure use of the Merck vaccine.

31. Overall, use of vaccine in pregnant women and immunosuppressed individuals would require consideration of the potential risk of Ebola disease compared with the potential for adverse effects from the vaccines, and evidence on vaccine efficacy/effectiveness. Monoclonal antibodies or other therapeutics could also be considered for use in some cases. PHE advised that there wasn't sufficient evidence on immunogenicity and safety in pregnant women and immunosuppressed individuals, to advise use of one vaccine over the other, and that there still should be a case-by-case assessment, bearing in mind that the individual's perception of risk may vary. The paper provided set out an operational framework to inform this.

32. The Committee agreed with the findings and conclusions of the paper, which would be used to update the UK Ebola Vaccination Policy.

<u>Letter from CMO on meningococcal ACWY vaccination</u>

33. The Chair noted that the former CMO had written to him on MenACWY conjugate vaccine. This followed issues regarding an increase in MenC disease in the Yorkshire and Humber region, and the Committee's considerations regarding the need to improve coverage in older adolescents with the MenACWY vaccine, particularly in those not moving on to University. The letter indicated that work was being considered regarding improving coverage in this group and that, in April, an EMIS reminder was turned on as default across its English estate. The CMO indicated an intention to write to GPs to encourage increased coverage.

III. Pandemic influenza preparedness

34. The Committee noted that the Influenza Sub-committee had met on September 9 to continue the work started in June to consider potential pandemic specific influenza vaccines and modelling on the potential impact of vaccination strategies in a range of pandemic scenarios.

35. The Hine report had recommended that JCVI advise DHSC on pandemic vaccination strategies and planning. The Committee had already learnt that there were promising pandemic specific vaccines (PSVs) based on new technologies but these would not be available for the next few years.

36. The PSVs which were available were all egg manufactured and were the ASO3 adjuvanted vaccine, the MF59 adjuvanted vaccine and the Pandemic Live Attenuated Influenza vaccine (PLAV). Timelines for the availability of these vaccines were approximately five to six months from the declaration of a pandemic and dependent on a number of factors.

37. Potential pandemic scenarios, vaccination scenarios, and the impact of vaccination strategies had been modelled by PHE. Vaccine available at six months would miss the first wave of a pandemic and most of a second wave if there was one, like in the 2009 pandemic, but could be available for a third wave if such an event were to occur, like in the 1918 pandemic.

38. The Committee received an update from PHE on the work they presented in June, modelling pandemic scenarios and the potential impact and effectiveness of a pandemic vaccine strategy. The following was noted:

- availability of vaccination after the start of the pandemic was now modelled starting at 4 months and 6 months using one (at 30% vaccine effectiveness-VE) or two doses (70% VE);
- VE in the elderly was modelled at 10% and 30% for one and two doses respectively;
- vaccination strategies were: everyone evenly, high risk (2-65, then elderly then everyone else), and paediatric (2-16-year olds then everyone else);
- combinations of low (2009-like) and high transmissibility (1918-like) and low (2009-like) and high severity (1918-like) pandemics, starting in the winter or spring, were modelled;
- the model fitted well with the timing and peaks of the actual 2009 pandemic which started in the Spring and was also able to reproduce the 1918 pandemic reasonably well, which in the UK started in early June;
- estimated deaths were approximately 1200 and 250,000 in 2009 and 1918 respectively;
- a spring pandemic of low or high transmissibility had two, and three waves respectively; winter pandemics of either transmissibility had only one wave in the winter;
- mortality was the greatest contributor to QALY loss in a pandemic of high severity while in a low severity pandemic QALY loss was shared equally between mortality and morbidity; hospitalisation was the biggest contributor to healthcare costs in both scenarios;
- vaccine available six months into a 2009 like Spring pandemic of low or high severity would arrive at the tail-end of the second wave and result in an approximate 9% reduction in mortality using a vaccine with 70% VE;
- vaccine available six months into a 1918 like Spring pandemic of low or

high severity would arrive mid-way through the second wave and prevent the third wave occurring, resulting in an approximate 50% reduction in mortality at 70% VE; vaccine available at 4 months would have a considerable impact in all Spring pandemic scenarios;

- vaccine available six months into a Winter pandemic would arrive long after the first and only wave of a 1918/2009 type pandemic and have no impact;

- vaccine available at 4 months would have a minimal impact preventing only 1% of deaths in a 2009 type pandemic;

- for all Spring pandemics a paediatric first was the optimal strategy while a risk group first strategy was the optimal strategy in most Winter pandemics (with early vaccine availability); and,

- in general, higher uptake was better though under the most optimal scenario a programme could interrupt a pandemic even with low uptake;

- vaccine arriving late meant there was no time to distribute all the doses; and

- higher VE was generally the better option though there was a trade-off between reaching more people (one dose) and a higher efficacy (two doses).

39. The Committee received a presentation from DHSC on the costs and benefits of having early access to a pandemic specific vaccine and noted that:

- the costs and benefits of having early access to pandemic specific vaccine were assessed using DHSC's cost benefit methodology for countermeasures;

- this follows the standard practice for central government economic appraisals set out in the HMT Green Book and therefore differed from the cost-effectiveness methodology followed by JCVI for vaccines and vaccination programmes;

- the health, economic and cost savings of a PSV were compared with the opportunity cost of securing vaccine as early as possible;

- eight different pandemic scenarios were considered with a probability of 0.5% occurring in any given year based on the fact there have been 4 pandemics in the last 100 years;

- most of the benefits generated by vaccination during a pandemic were expected to come from the monetised QALY gain, with the economic benefits, NHS cost savings and National Pandemic Flu Service (NPFS) cost-savings being small in comparison;

- the expected benefits were heavily dependent on the Spring 1918 multi-wave pandemic scenario, with the vaccine being delivered too late to reduce the severity of the shorter winter pandemics; and,

- the results from the economic analysis suggested that on balance having early access to a PSV during a pandemic was likely to generate a positive net benefit for society and be a cost-effective use of resources.

40. In conclusion the following important points were highlighted

- Currently there were only three PSV products available, two inactivated adjuvanted (MF59 Seqirus, AS03 GSK) and one live attenuated (AstraZeneca), for use in a pandemic, and all relied on the use of eggs in their manufacture; no new technologies were available for the next three to five years;

- timelines for availability for these PSVs were no earlier than 5 to 6 months (some might even be longer); there was some variation on exact timing of delivery for available products which depended on a range of factors including manufacturing, regulatory pathways and volume of vaccine required;

- the benefit of a PSV strategy depended on when the first wave occurred and whether there was a second wave or a third wave and the timing of these;

- PHE modelling indicated there could be a benefit in having early access to a pandemic vaccine available at 6 months in some pandemic scenarios, principally those which are a multi wave pandemics that start in the Spring;

- even more benefit could be achieved if a PSV were available by 4 months, but this timeline was not currently achievable for the available PSVs according to manufacturing and regulatory time frames;

- in the Spring multi-wave pandemic scenarios where there was a benefit in using a PSV (available at 6 months) a strategy of vaccinating children first (followed by other groups) was the optimal strategy compared with vaccinating at-risk groups first; and

- a strategy of vaccinating high-risk groups first was only likely to be an optimal strategy in the event of a PSV being available very late in a pandemic, at the tail end of a wave.

41. The Committee agreed that it would be important to have early access to more than one vaccine for a) security of supply and b) and because there may be differences in the population you target where different vaccines may be appropriate.

42. Because a paediatric strategy was an important part of a PSV strategy in the scenarios modelled where there was most benefit, the Committee agreed

that there should be an appropriate vaccine available for use in children. This added complexity because:

- safety concerns remained over the use of adjuvanted vaccines in children as narcolepsy had been demonstrated with the ASO3 vaccine, and for the MF59 adjuvanted vaccine, though there has been no signal reported, there was not enough exposure data on children to give confidence to rule out the potential risk of an association with narcolepsy;

- using an adjuvanted vaccine might still be the most reliable choice in terms of the high VE demonstrated but concerns over narcolepsy meant it would be difficult to justify their use in children in a pandemic of low severity;

- there were theoretical concerns over using PLAIV in a highly LAIV vaccinated paediatric population, which should be investigated, and a PLAIV was unlikely to be suitable for adults;

- there might still be scenarios of high severity where it would still be appropriate to vaccinate children with an adjuvanted vaccine where the benefits outweighed the risk of rare but serious AEFI such as narcolepsy; and

- for adults either of the adjuvanted vaccines would probably be suitable.

43. Although it was not for the Committee to decide, it was noted that other interventions during a pandemic such as school closure could be used to delay/interrupt a pandemic and potentially increase the impact of a PSV by precipitating a pause in transmission and generating a second wave.

44. The Committee asked DHSC to consider engagement with current and potential future manufacturers to emphasise the substantial health benefits and cost savings from the further shortening of timelines which could allow a) an acceleration of safe access to novel vaccines and b) improvements in their understanding of the pandemic mock up file to shorten regulatory timelines.

45. DHSC were also asked to consider engagement with the MHRA to consider strategies to improve the speed of the regulatory process.

46. The Committee agreed that the PSV landscape should be reviewed again in three years because new pandemic vaccine technologies might then be available with shorter manufacturing timelines.

IV. Annual NISEC update

47. Matthew Snape, Assistant Professor in Paediatrics and Vaccinology, Oxford University presented on the National Immunisation Schedule Evaluation Consortium (NISEC). It was noted that NISEC included members of the UK Paediatric Vaccines Group and was funded by NIHR. It was noted that it had

a paediatric focus, but there was one member of the steering group with an adult focus. It was noted that it implemented studies of relevance to the UK immunisation schedule.

48. The Committee noted that work underway included:

IMAP3

- IMAP3, a follow-on from IMAP 2 which evaluated the use of 2 different pertussis-containing vaccines in pregnancy and the impact on the response to infant immunisation in the offspring;
- IMAP3 was following infants through to 3.5 years of age, to determine if there was any impact of maternal vaccination on pre-school boosters;
- 75% of the original participants had been retained and the results were expected at the end of October 2019;
- they would also be looking at the persistence of DTaP vaccines and the impact on pre-school boosters;

OPTIMUM

- The OPTIMUM study included 354 women randomised to receive the DTaP-IPV vaccine at three different time points during gestation;
- the infants would be involved in the study from birth to age five months;
- the study was co-funded with the Thrasher Research Foundation;
- the primary outcome measure was to measure antibody concentrations against pertussis toxin (PT) in cord-blood of term infants at delivery;
- recruitment completion was expected in February 2020;

What's the story?

- "What's the story?" was a sero-epidemiology study recruiting 2300 participants aged 0-24 years;
- the study aimed to be representative of the English population;
- the study was inspired by the cluster of diphtheria cases in Yorkshire and Humber in 2017/18, and the cluster of group C meningococcal disease in under 1-year olds;
- some work had been done on residual samples;
- the primary objective was to evaluate the feasibility and added public health benefit of a UK population based sero-epidemiological programme in 0 to 24-year olds;
- the consortium also aimed to undertake analyses of blood from

Sched 3 study participants 5 to 13 months of age, to examine the immunogenicity of the 2+1 schedule of 4CMenB against hyperinvasive MenW and clinically relevant MenC strains; and

- blood was also drawn at 2 years of age to examine the persistence of immunogenicity following the 2+1 4CMenB schedule for:
    - 3 MenB strains
    - MenW
    - Clinically relevant MenC strains.

49. The Committee noted that the results for the MenB arm should be available by the end of 2019.

50. Other studies were being considered, and the Committee noted that:

- Shingrix® studies were on hold until vaccine was available from the manufacturer;
- the 'Be on the team study', which aimed to examine whether immunisation of teenagers with group B meningococcal vaccines influenced pharyngeal carriage;
- throat swabs would be collected at baseline and 12 months, recruitment was at 87%;
- a study was considering alternative DTaP-IPV-Hib-HepB vaccine, Vaxelis®, where there was no co-administration data with MenB vaccine; and
- an H7N9 MF59 adjuvanted vaccine study in children.

51. The Committee thanked NISEC for the update.

V. Seasonal influenza vaccines for 2020/21

52. The Committee was reminded in September 2019 the Influenza Sub-committee had provided advice on vaccines for use in the 2020/21 season. The advice had been provided to the Committee by correspondence and a statement had been drafted, shared, agreed and then subsequently published.

53. The main Committee noted a letter from Sanofi Pasteur in which the manufacturer had raised concerns about the new seasonal influenza vaccine advice.

54. The Committee received a presentation from PHE covering the issues raised by the manufacturer and the evidence the Influenza Sub-committee had reviewed in its considerations. This included published evidence on the high dose trivalent influenza vaccine (TIV HD), adjuvanted trivalent influenza vaccine (aTIV), the cell cultured quadrivalent influenza vaccine (QIVc), and the egg cultured quadrivalent influenza vaccine (QIVe), and additional evidence provided by industry.

55. The Committee noted that for QIVc:

- QIVc avoided the problem of egg adaptation which affected mainly the A(H3N2) vaccine strain of egg-cultured vaccines;
- Sanofi Pasteur and Seqirus had presented to the Sub-committee the latest evidence for their respective vaccines, TIV HD, and aTIV/QIVc;
- on QIVc all the evidence came from the 2017/18 season, and mostly concerned its effectiveness compared with QIVe;
- an important study by the FDA (Food and Drug Administration) and CMS (Centers for Medicare & Medicaid Services) (Izurieta *et al*) in those aged >65 years old, demonstrated significant relative vaccine effectiveness (rVE) for QIVc against influenza hospitalisations and office visits compared with QIVe;
- a study by the manufacturer indicated a significant VE against influenza like illness (ILI) in 18 to 64-year olds, and a study by the Kaiser Permanente Northern California Institute in 4 to 64 year olds showed a significant rVE compared with QIVe against an influenza laboratory confirmed end point for influenza B but not influenza A;
- results from two test-negative case control studies in young adults from the US Department of Defence and Kaiser Permanente Southern California showed non-significant but positive point estimates for QIVc compared with QIVe; and
- early data for the 2018/19 season in the US had also been presented at the OPTIONS conference in August this year, which showed non-significant point estimates

56. In summary, the study results were mixed but with some evidence indicating QIVc performed better than QIVe in the 2017/18 season.

57. The Sub-committee had also looked at data presented on the vaccines recommended for the elderly, aTIV and TIV HD. The Committee noted that:

- aTIV had been used in the UK in 2018/19 with encouraging VE results against GP and hospital lab confirmed endpoints and no significant all-cause excess mortality had been observed;
- both manufacturers had presented direct comparisons between aTIV and TIV HD; Sanofi Pasteur had referred to the Izurieta *et al* paper which showed TIV HD to have performed significantly better in terms of rVE compared with aTIV;
- Sanofi Pasteur had also conducted a retrospective analysis of health insurance claims data comparing the two vaccines over the 2016/17 and 2017/18 seasons for a range of non-specific clinical endpoints, including respiratory and cardiac disease, with results indicating a positive significant rVE for TIV HD over aTIV;
- Seqirus had also conducted a retrospective cohort study

comparison of aTIV vs TIV HD using health insurance claims data from 2016/17 and 2017/18; and

- this indicated a significant rVE for influenza related office visits but no significant difference in VE for the two vaccines against a range of other non-specific clinical indicators.

58. The Committee noted that at the Sub-committee meeting there had been a lot of discussion over the methodological approach of the two 'head to head' studies regarding the time periods and censoring of influenza and non-influenza periods and how these were adjusted for. There had been some concern over a potential bias in both study approaches. The conclusion of the Sub-committee was that on balance it could not say whether one vaccine was better than the other based on the available evidence.

59. It was noted that the Committee had adjusted its advice for vaccines for the elderly saying that TIV HD and aTIV were preferable, but that QIVc could also be considered. This was because there was more evidence and stronger evidence in support of TIV HD and aTIV (compared with standard inactivated influenza vaccines) than there was for QIVc. Data from QIVc came from only one season, 2017/18, in which A(H3N2) was the predominant type in circulation.

60. The Committee's advice for QIVc in the under 65 at risk groups had also been adjusted to highlight a slight preference for QIVc because of the issue of egg adaptation (in an egg-adapted AH3N2 season), however, QIVe was still considered a suitable vaccine for this group, and likely to be similar in H1N1/B seasons or in years in which egg-adaptation was not a major H3N2 issue.

61. The Committee also noted the manufacturer had also highlighted in their letter that the quality of the evidence in support for TIV HD was better than that for aTIV, because of the number of randomised control trials conducted. The Committee did not feel this was enough to distinguish between TIV HD and aTIV, and that new supporting data from further seasons were needed.

62. The Committee agreed that it would like to see more data from the UK on the performance of the vaccines being used, as currently most of the evidence came from studies in the US and Europe. Overall the Committee agreed that the available evidence supported the position that TIV HD and aTIV were preferable to standard egg-based influenza vaccines for those aged 65 years and over, but the evidence was insufficient to distinguish between the two vaccines on the grounds of their relative vaccine effectiveness.

VI. Tick Borne Encephalitis

63. The Chair noted that PHE had recently found Tick Borne Encephalitis Virus (TBEV) in a small number of ticks in England, and that a possible case of Tick Borne Encephalitis (TBE) had been identified.

64. The Committee noted that TBEV was a flavivirus normally transmitted

through the bite of an infected tick. The reservoir for TBEV was small rodents, but other domestic and wild animals could support virus circulation through tick infestation. There were three subtypes – European (transmitted by Ixodes ricinus), Far-Eastern (I. persulcatus) and Siberian (I. persulcatus). I. ricinus was the most widely distributed tick species in the UK, and was also the vector for Lyme disease.

65. The incubation period was 7 days, with two thirds of cases asymptomatic. For symptomatic cases there were two phases with non-specific symptoms in the first viraemic phase and an asymptomatic interval followed by a second phase involving the central nervous system. European virus was associated with milder disease than others, with only 20-30% going on to the second phase. 10% of those patients may develop severe neurological sequelae with a mortality rate of 0.5-2%.

66. TBE was an important zoonotic infection across central, northern and eastern Europe, with incidence highest in Germany, Estonia, Lithuania and the Czech Republic. It was also seasonal in Europe with peaks in May-November. All cases identified in the UK had previously been travel-related.

67. A recent PHE Health Protection Research Unit study undertook surveillance for tick borne viruses using collected ticks from culled deer and from environmental dragging. This included testing for TBEV, which was found in two areas:

    - in the New Forest, where one pool of five ticks out of 2000 were found to be TBEV positive, with a strain similar to one previously seen in the Netherlands; and
    - in Thetford Forest, where five ticks out of 192 removed from deer were TBEV positive (99% homology to a strain of Central European TBEV).

68. PHE had concluded that there were two different strains in the UK from two separate introductions, potentially from birds or imported animals. However, Lyme disease continued to be the most common tick-borne infection in the UK.

69. In August 2019 German authorities informed PHE of a case of TBE in an individual who lived in a non-endemic area of Germany. They had been diagnosed with TBE following discovery of a tick after a trip to the New Forest in July. It was considered as a highly probable case of TBE by PHE.

70. PHE has undertaken several actions following this case including:

    - sharing key information locally (Thetford Forest and New Forest) and nationally;
    - the Rare and Imported Pathogens Laboratory (RIPL) were testing cases of unidentified acute encephalitis in these areas for evidence of TBEV exposure, with three samples tested and confirmed negative; and

- samples sent to RIPL for neuroborreliosis, with a general acute encephalitic presentation, which were negative for Lyme disease were being automatically screened for TBEV, with no evidence of exposure to date.

71. Two studies were also planned to inform this issue:

    - a retrospective study estimating population seroprevlence in regions around the affected areas using blood donor samples from NHS Blood and Transplant; and
    - a study testing for TBEV in groups at high risk of tick bites, including game keepers, deer stalkers, farmers and forestry workers.

72. It was noted that WHO recommend vaccination for people of all ages where TBE is highly endemic (>5 cases/100,000 population) or for severely affected groups in areas where incidence was moderate or low. WHO also recommended vaccine for travellers to endemic areas if activities included outdoor pursuits.

73. PHE had taken the view that the actions summarised were proportionate to the situation and asked the Committee for comment. The aim was to improve the understanding of the distribution of infected ticks in England and investigate for evidence of autochthonous infections in order to inform future recommendations around the use of TBE vaccination in high-risk groups, such as those in forestry jobs. They also asked the Committee if additional actions were required.

74. Overall the Committee agreed with the actions being undertaken by PHE. It was suggested that PHE expand the testing of cases to include other meningo-encephalitis presentations rather than just neuroborreliosis. PHE noted that they were testing both encephalitic neuroborreliosis and other no-cause encephalitis presentations found locally.

75. The Committee queried the positivity rate for testing using PCR and PHE noted that some commercial serology tests were poor and testing was best at early stages of infection. Therefore, PHE were following up with neutralisation testing. It was noted that there were other encephalitis studies over previous years which could be reviewed for potential samples.

76. The Committee noted that WHO recommended that where vaccination was undertaken, older adults should be vaccinated as a priority, as disease was more severe in this age group.

77. The Committee noted that in endemic countries there were questions around booster vaccination, and this would require consideration in the event of vaccination being advised.

78. The Committee agreed that this issue should be further reviewed, once more data were available, especially around whether certain occupational groups were at increased risk, and requested that at that time information be

provided on the vaccines, their formulation and efficacy.

VII. Update from the Travel Sub-committee

79. It was noted that the Travel sub-committee had met on 14 June 2019. The Travel sub-committee Chair noted that they had discussed four key topics. On influenza vaccination for travellers they had considered that:

- travellers eligible for the vaccine in the UK should be encouraged to receive it in the UK each year;
- this was particularly important for those attending 'mass gatherings' such as the Hajj or those travelling on cruise ships; and
- those intending longer stays in the southern hemisphere could consider vaccination after arrival, where available.

80. On HPV for male travellers:

- the increased risk of STD to travellers was well known;
- these STD risks should be expanded to include HPV;
- the HPV vaccine was available privately; and
- barrier forms of contraception should also be advised.

81. On Japanese encephalitis vaccination:

- the vaccine is offered as two doses 28 days apart with a booster at 1-2 years;
- where there is continued risk of exposure an additional booster dose is recommended at 10 years in those aged 18 to 64 years;
- there was no recommendation for a second booster in place for those under 18 or over 64 years of age;
- the evidence in young children indicated the protection would not extend beyond 10 years, and an additional booster could be considered, where appropriate; and
- NaTHNaC and HPS had agreed to prepare an update to current guidance.

82. On yellow fever and measles vaccine guidance:

- Green Book guidance focusses on MMR, and indicated that measles protection may be sub-optimal where the MMR vaccine is given with yellow fever vaccine;
- the Sub-committee considered evidence on whether the response to the yellow fever vaccine may also be attenuated in this circumstance;
- data from Brazil suggested this may be the case; and

- the sub-committee considered that where yellow fever and MMR are given together or within one month of each other, an additional dose of yellow fever vaccine should be given at 10 years.

83. The Sub-committee had also noted the continuing work on the safety of yellow fever vaccine by the Commission on Human Medicines, and had agreed that they would re-convene once the CHM findings were reported.

VIII. Annual meningococcal update

84. The Committee received a presentation from PHE on meningococcal epidemiology in England and vaccine effectiveness estimates. The Committee noted that:

- Men B vaccination had been implemented in 2016, in a 2+1 schedule with a small catch-up in 3 and 4-month old infants;
- 95-96% received one dose, and more than 90% received the second dose;
- at two years of age around 88% had received the advised three dose schedule;
- PHE first reported a large reduction in disease within the first ten months of the programme;
- over the first three years there were 361 cases of invasive meningococcal disease (IMD), two thirds of which were MenB IMD and just over half of these were confirmed by culture, which was important in determining if the infecting strains were vaccine preventable;
- in the first eight weeks of life (too young for vaccination), there was little observable change in disease following introduction of the programme;
- in the nine to 17-week-old infants (eligible for one dose), there was little reduction in disease;
- in the 18 to 52-week-old infants (eligible for two doses) there was a 28% reduction in MenB IMD in the first year of the programme (only part of the cohort vaccinated), a 77% reduction in MenB IMD in the second year of the programme and a 70% reduction in MenB IMD in the third year of the programme;
- in one year old children, there was a 57% reduction in the first year of the programme (only part of the cohort vaccinated), and an 80% reduction in the second year of the programme;
- in two-year-old children, there was a 57% reduction in the second year of the programme (part of the cohort vaccinated), which indicated protection until at least the third birthday;
- using the screening method, vaccine effectiveness for one dose was 24.1%, for two doses was 52.7% and after three doses was 58.9%, the estimate of effectiveness against vaccine preventable

MenB IMD was 70.5%;

- after 3 million doses of 4CMenB, there were no new safety concerns;
- it had been estimated that 277 cases of MenB IMD had been prevented in the first three years of the programme;
- the UK experienced a national MenW outbreak beginning in 2009;
- MenACWY vaccination started August 2015, with the aim of vaccinating all 13-18-year-olds over a three-year period;
- there was an impact in school leavers (17-18-year-olds) within 12 months of the start of the programme, despite 36% vaccine coverage; and
- 2017-18 was the first year with an overall decline in MenW cases across the population.

85. The Committee questioned whether the decrease in MenW IMD in young children was associated with the herd-immunity from the MenACWY programme or direct protection from the 4CMenB programme. PHE noted that using novel methods they were working to identify the proportion of the impact from each element of the programme, and so far, they had identified a clear impact from the 4CMenB programme.

86. Questions were asked about the impact of the 4CMenB programme on circulating strains. PHE noted that an infant programme should have no impact on strains circulating in adolescents (the main carriers of meningococcal bacteria) and as such there should be no change in the circulating strains attributable to the programme.

87. On compliance with prophylactic paracetamol, PHE noted that through the use of focus groups, evidence indicated that around 80% of parents were content to and did provide prophylactic paracetamol, around 10% provided prophylactic paracetamol, but had some reluctance in doing so, 5% provide it in response to fever in the infant, and the other 5% did not provide it.

88. It was noted that an ongoing meningococcal carriage study indicated around a two-thirds reduction in MenW carriage in year 12 (England) students, since the last (pre-MenACWY vaccination) study. A recent study in Portugal had indicated similar vaccine effectiveness results to those in England for 4CMenB, and no sequelae in those vaccinated with one or more doses who had MenB IMD. PHE were following every MenB IMD case for sequelae and would have the first results in the coming months.

89. It was noted that the Austrian NITAG had recommended booster doses of 4CMenB for at-risk groups, and PHE agreed that they would prepare a paper for JCVI to consider on this.

IX. Coverage

90. In England since the last JCVI meeting, data published indicated a continuation of the trend of small but continued declines in all antigens measured at one, two and five years of age, although the most recent data indicated a small increase in coverage. The Shingles programme had changed data collection method, and although not comparable to previous data, it indicated a 32% uptake in the routine cohort at age 70 years, and 33% uptake in the 78-year-old catch-up cohort.

91. In Scotland, since the last meeting, the quarterly data since the end of 2018 were starting to show some small increases in coverage following a trend of small but continued declines in coverage for all antigens measured at one, two and five years of age. Vaccine delivery for the childhood programme was moving from general practice delivery to more centralised (Health and Social Care partnership) delivery. It was too early to say whether the change in setting was associated with the small increase in coverage seen.

92. In Wales, the trend of small but continued declines in coverage for all antigens measured at one, two and five years of age had levelled-off in the most recent quarterly data. Having undertaken a data review, an issue had been identified with data extraction, which had resulted in an under-reporting of coverage figures for the preceding two years. This had now been rectified. There had been an increase in uptake in adolescent vaccinations, except for HPV where there had been a small decline in uptake over the last few years. Shingles uptake in those aged 70 years was 35%. A measles elimination action plan had recently been published for 2020/21, which looked at system wide actions to improve uptake and proposed a catch-up programme.

93. In Northern Ireland, there had been a trend of small but continued declines in coverage for all antigens measured at one, two and five years of age. HPV vaccine uptake had increased compared with the preceding year. Shingles uptake had declined compared to the preceding year at 46.5%, action was underway to try and separate the shingles programme from the influenza programme, to try and improve uptake.

94. The Committee agreed that action was required to reverse the trends in coverage. There was no evidence that the declining trends were associated with parental confidence and the declines were likely to be associated with delivery of the programme. PHE and NHSE were working together to try and improve delivery of the programme in England. Work was underway to try and make call/recall more robust, to improve governance and to work more closely with CCGs.

95. The Committee asked that representatives from the four countries present at the February meeting about strategies underway to try and improve coverage.

ACTION: Representative from England, Wales, Scotland and Northern Ireland to present on their strategies to improve uptake.

X. Any other business

Polio vaccination in sewage workers

96. The Advisory Committee on Dangerous Pathogens (ACDP) had written to the Chair on polio vaccination of sewage workers. This was mainly due to concerns about vaccine-derived polio viruses in sewage. PHE indicated that the small potential risk from sewage had been present for many years. The main ask was that sewage workers were up-to-date with their vaccines. PHE proposed updating the 'Green Book' with a general paragraph in the chapter about occupation health assessments including ensuring that people were up to date with their vaccines.

RSV prophylaxis

97. A letter had been received advocating for wider use of Palivizumab®. The Chair noted that there were several RSV vaccines and prophylactics in development. It was noted that data were likely to be limited on the risk of RSV in specific groups, and that the Green Book stated that clinical discretion could be used in the use of Palivizumab®. The Committee considered that an RSV Sub-committee was required to consider evidence on pipeline products, modelling, and to identify evidence gaps, and this Sub-committee could also consider the use of Palivizumab®. A chair for this Sub-committee would be sought from JCVI members.

Prof Andrew Pollard (Chair)
Professor Pollard receives no personal payments from the manufacturers of vaccines He is Director of the Oxford Vaccine Group in the Department of Paediatrics, University of Oxford and has current research funding from the Bill and Melinda Gates Foundation, the National Institute for Health Research, the European Commission, Medical Research Council, Wellcome Trust, Innovate UK, Meningitis Research Foundation, and the Global Alliance for Vaccines and Immunisation. He chairs the scientific advisory group on vaccines for the European Medicines Agency and is a member of WHO's SAGE. Other investigators in the Department conduct research funded by vaccine manufacturers and the Department has received unrestricted educational grant funding for a three-day course on paediatric infectious disease from Gilead, and GSK in June 2019.
Prof Anthony Harnden (Deputy Chair)
Professor Harnden has no registered conflicts of interest.
Dr Peter Elton
Dr Peter Elton has no registered conflicts of interest
Prof Adam Finn
Professor Adam Finn receives no personal payments from the manufacturers of vaccines. Professor Finn undertakes unpaid advisory work for Astellas on a klebsiella-pseudomonas vaccine. Professor Finn's Department receives funding for consultancy work from VBI vaccines on a developmental Hep B vaccine, and Bionet on a developmental pertussis toxin vaccine. The University of Bristol conducts research funded by GSK on meningococcal carriage, by Pfizer on pneumococcal carriage and transmission.
Prof Matt Keeling
Professor Matt Keeling has no registered conflicts of interest.
Prof Wei Shen Lim
Professor Wei Shen Lim's Department has funding from Pfizer for work indirectly related to pneumococcal vaccines.
Prof Jeremy Brown
Professor Brown has received payment for consultancy work from ImmunoBio on a novel pneumococcal vaccine. Professor Brown's Department has undertaken work for Novartis on the effects of monoclonal antibodies on vaccine responses.

Dr Martin Williams
Professor Martin Williams has no registered conflicts of interest. Professor Williams holds a contract for work with Public Health England.
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
Prof Maarten Postma
Professor Postma has received honoraria from SPMSD (health economics) MSD (health economics) and is an advisor to companies on Rotateq and Rotarix vaccines. Professor Postma works for the University of Groningen which receives grants from SPMSD and GSK for work related to influenza vaccines. Professor Postma attends advisory boards unrelated to vaccines or vaccine industry Professor Postma organized a conference which was financially supported by Pfizer relating to Health Economics. Professor Postma works for the University of Groningen which has an external PhD student who is employee at Sanofi Pasteur working on a thesis on high dose influenza vaccine.
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 Health Protection Research Unit at the London School of Hygiene and Tropical Medicine. He receives research funding from the National Institute for Health Research, the Medical Research Council, the Wellcome Trust and Gavi, The Vaccine Alliance, and the Bill & Melinda Gates Foundation.
Dr Maggie Wearmouth
Dr Wearmouth has no registered conflicts of interest

Professor Simon Kroll
Professor Kroll received research funding from Meningitis Now, to investigate carriage of meningococci and non-pathogenic Neisseria in infants. The funding period ended in 2018. He is the Honorary Medical Director of Meningitis Now
Dr Rebecca Cordery
Dr Cordery has no registered conflicts of interest Dr Cordery works for Public Health England
Dr Kevin Brown
Dr Brown has no registered conflicts of interest Dr Brown works for Public Health England
Dr Jillian Johnston (co-opted member)
Dr Jillian Johnston has no registered conflicts of interest
Mrs Anne McGowan (co-opted member)
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.
Dr Lorna Willocks (co-opted member)
Dr Lorna Willocks has no registered conflicts of interest
Ms Julie Yates (co-opted member)
Ms Julie Yates has no registered conflicts of interest