

HPV SUB-COMMITTEE OF THE JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

Minute of the meeting held on Wednesday June 8 2015 10:30 – 16:30

Members

Prof Judith Breuer (Chair)
Dr Kate Cuschieri
Dr Peter Elton
Prof Adam Finn
Dr Richard Gilson

Prof Henry Kitchener
Mrs Pauline MacDonald
Prof Andrew Pollard (JCVI Chair)
Dr Ann Sullivan

Observers

Ms Carolyn Heaney (DH)
Dr Peter Grove (DH)
Dr David Mesher (PHE)
Dr Kohjun Ong (PHE)
Ms Michelle Parkinson (DH)
Prof Julietta Patnick (PHE)

Ms Joanne Yarwood (PHE)
Dr Joshua Pink (University of Warwick)
Dr Karen Powell (PHE)
Dr Vanessa Saliba (PHE)
Mr Geoff Wootton (DH)

Invited observers from Devolved Administrations and MHRA

Dr Claire Cameron (HPS)
Dr Martin Coleman (DHSSNI)

Dr Elizabeth Reaney (DHSSNI)

Dr Richard Roberts (Public Health Wales)
Dr Nicola Steedman (Scottish Government)
Dr David Vardy (Welsh Assembly Government)

Invited Experts and Presenters

Dr Hans Berkhof (VU Univeristy Amsterdam)
Prof Ray Borrow (PHE)
Dr Samik Datta (University of Warwick)

Dr Mark Jit (PHE)

Prof Matt Keeling (University of Warwick)
Prof Margaret Stanley (University of Cambridge)

Secretariat

Mr Jonathan Crofts (PHE)

Mr Andrew Earnshaw (PHE)

Apologies

Dr Phil Bryan (MHRA)
Mrs Emma Burton-Graham (PHE)

Prof John Edmunds
Dr Karen Homer (PHE)
Dr Kevin Pollock (HPS)

Dr Mary Ramsay (PHE)
Dr Andrew Riley (Welsh Assembly Government)
Prof Claire-Anne Siegrist (WHO)
Dr Kate Soldan (PHE)
Prof John Watson Deputy CMO (DH)

I. Welcome

1. The Chair of the HPV Sub-committee welcomed all to the meeting. The Chair reminded members and observers that many of the papers had been provided in confidence, and they should not be shared outside of the meeting.
2. The Chair welcomed Dr Hans Berkhof from VU University Amsterdam Epidemiology & Biostatistics Department who had been invited for his expert view on the modelling work on vaccinating boys.
3. The Chair took declarations of interest from members and informed the Committee that Margaret Stanley had provided consultancy services for all three manufactures of HPV Vaccines (GSK, SPMSD, and Merck) and could be asked questions and asked to give her views but would not be able to contribute to discussions unless specifically directed to do so.
4. The following attending members declared interests in the companies that manufacture and supply the HPV vaccines discussed (Sanofi-Pasteur MSD, Merck and GSK).

Member / Contributor	Action	Interest
Judith Breuer	None	The Member is able to participate in the discussion and to vote
Pauline MacDonald	None	The co-opted Member is able to participate in the discussion
Andrew Pollard	Non-personal, Non-specific GSK	The Member is able to participate in the discussion and to vote
Peter Elton	None	The Member is able to participate in the discussion and to vote
Richard Gilson	Non-personal, specific Sanofi-Pasteur MSD	The Member is able to participate in the discussion but not to vote
Henry Kitchener	Non-personal, specific GSK	The Member is able to participate in the discussion but not to vote
Kate Cuschieri	None	The Member is able to participate in the discussion and to vote
Ann Sullivan	None	The Member is able to participate in the discussion and to vote

II. Minutes of previous meeting

5. The Committee agreed that the minute of the meeting on January 21 was an accurate record.

III. 9 valent vaccine: presentation from manufacturer

6. The Chair welcomed Dr Alex Dos Santos, Medical Director, UK. Dr Sandrine Samson and Dr Lidia Siemaszkiewicz, Medical Affairs Manager, UK from Sanofi Pasteur MSD (SPMSD) to present to the Committee information relating to the 9 valent vaccine Gardasil 9 which has gained licensure in the USA and is shortly expected to gain licence in Europe for a 3 dose schedule (0, 2, 6 months). The Chair reminded the Committee that they had requested information relating to specific subject areas from clinical trials on Gardasil 9 concerning:

- magnitude and persistence of responses to the additional HPV components;
- data on efficacy in the target population adolescent girls;
- information on responses in other age groups/males;
- data on two dose schedules;
- safety information compared to Gardasil;
- interference with the quad serotypes in Gardasil;
- data on concomitant use with other adolescent vaccines
- any independently collated epidemiological evidence.

The Committee had also asked how the immunogenicity of the 9 valent vaccine compared with the quadrivalent vaccine for the 4 original vaccine types after the first dose, and how the remaining 5 vaccine types in the 9 valent vaccine compare with the levels seen for the 4 vaccine types in the quadrivalent vaccine after the first dose.

The Committee considered the presentation by SPMSD and noted that:

- Gardasil 9 contains more adjuvant than the quadrivalent vaccine to maintain the ratio between the antigen virus like particles (VLPs) for each HPV type and adjuvant. Gardasil 9 also has a higher concentration of antigen for the HPV types 6, 16 and 18 compared to that used in the quadrivalent vaccine to compensate for potential immune interference on the original 4 HPV types by the additional 5 HPV types (31, 33, 45, 52, 58) included in the vaccine. Work had been done varying the amount of VLP for each HPV type in Gardasil 9 to elicit a comparable antibody response for the original 4 HPV types in Gardasil 9 to that seen for Gardasil.
- The rationale for choosing the 5 additional high risk types in the vaccine was based on their relative contribution to cervical cancer worldwide. The 7 high risk types in the vaccine account for 90% of cervical cancers worldwide compared to 70% for types 16 and 18 in the quadrivalent vaccine. In the EU this is 89% and 75% respectively.

- The clinical programme of trials for the 9 valent vaccine included 9 studies 7 of which had been used for the submission for the licence for the three dose schedule; efficacy of Gardasil 9 in women compared to Gardasil, immuno-bridging comparing vaccination in women to adolescent girls and adolescent boys, sequential use of Gardasil 9 with Gardasil, concomitant administration with other routine vaccines, immuno-bridging comparing Gardasil 9 to Gardasil in adolescent girls, boys, young men (including men who have sex with men (MSM)) and young women and the gathering of safety data for the 3 dose schedule.
 - Immunogenicity data published in the New England Journal of Medicine showed Gardasil 9 to be non-inferior to Gardasil in 16-26 year old women for the original 4 HPV types showing that the benefit of Gardasil was maintained in Gardasil 9. In the same study efficacy against persistent infection and pre-cancerous lesions for the additional 5 types combined was greater than 95%.
 - Immuno bridging studies had demonstrated Gardasil 9 to be non-inferior when compared between adolescent girls and women with persistence demonstrated up to 3 years so far. Similarly, the immunogenicity of Gardasil 9 was non inferior in adolescent boys compared to women, and in men compared to women. MSM gave a slightly lower immune response compared to other men which was consistent and in line with previous results for Gardasil in MSM. It was noted that the MSM study population were all HIV negative (-ve) and that there was no clear hypothesis for this observation.
 - There was no significant effect on the immunogenicity of Gardasil 9 when used concomitantly with dTap, dT-IPV or dTap-IPV vaccines and no effect on the immunogenicity of the concomitant vaccine used.
 - Compared to Gardasil the overall safety profile of Gardasil 9 was very similar. Although there were more injection site reactions (swelling and erythema) these were not unexpected owing to the increased antigen and adjuvant content of the vaccine.
7. The Committee expressed its disappointment that data on the two dose schedule were not yet available and also that no data were presented on immunogenicity/seroconversion after one dose. Noting that the trial of 2 doses started 2-3 years ago the Committee expected that data on the kinetics of the antibody response would already be available for up to 18 months follow up.
8. The Committee was also concerned that all participants in the 2 dose arm of the trial were to receive a 3rd boosting dose at 36 months and that there would be no long term follow up of immunogenicity or efficacy for two doses of Gardasil 9. The Committee were informed by SPMSD that for Gardasil 9 Immunogenicity would only be followed for two doses up to the intended booster dose and that longer term follow up after two doses was only taking place for the quadrivalent vaccine.

9. The Committee noted that the geometric mean titres (GMT) of antibody elicited for each of the additional 5 HPV types were nearly all lower than those seen for types 18 and 16. However the Committee noted that direct comparison of GMT for each type was not appropriate because each competitive luminex assay used a single monoclonal antibody to one epitope for each VLP HPV type. A direct comparison could only be made measuring total antibody or neutralising antibody or the efficacy in the longer term.
10. The Committee concluded that Gardasil 9 showed promise and that it had no concerns on the three dose schedule of Gardasil 9 for the original 4 HPV types in the vaccine.
11. The Committee agreed, however, that it would need to see persistency data for 2 doses for all the 9 types especially for the 4 original HPV vaccine types, and also in the 3 dose schedule for the non-Gardasil types. The Committee would also like to see sero-conversion data for 1 dose of Gardasil 9 compared to Gardasil as well as antibody levels.
12. The Committee agreed that it was disappointing that SPMSD plan to boost all 2 dose recipients after 36 months and strongly advised that the manufacturer should be looking to measure persistency and effectiveness of the two dose schedule for longer and in the absence of a 3rd boosting dose.

Action: Secretariat to formerly write to SPMSD requesting to see 1 dose and 2 dose data for Gardasil 9 including kinetics up to 18 months, especially for the 4 original HPV vaccine types as soon as it is available, and to strongly recommend that persistency and effectiveness data be measured in the longer term for two doses without a booster at 36 months.

IV. Impact and cost-effectiveness HPV vaccination of MSM (PHE)

13. The Chair reminded the Committee that the initial results of the impact and cost effectiveness assessment by PHE were presented in September 2014 and the Committee had advised JCVI that a targeted programme for MSM in Genito-urinary Medicine (GUM) and HIV clinics was achievable at a realistic cost effective price. JCVI agreed, with the advice and issued interim advice inviting stakeholders to comment on this together with the assumptions used in the modelling assessment. The modelling work had also undergone independent peer review. As a result of the feedback from JCVI, peer review and stakeholders PHE were asked by JCVI in February 2015 to incorporate some modifications to the assessment. PHE had updated their analysis accordingly.
14. The Committee were reminded that the original work presented in September 2014 had looked at scenarios vaccinating HIV positive (+ve) MSM aged 16-25 or 16-40 attending GUM clinics and then widening these groups to include all MSM. The assessment had estimated that at the list price of the vaccine a targeted programme for HIV +ve MSM would be cost effective and that if the

combined price of vaccine plus admin was at a lower but realistic price a programme for all MSM aged 16-40 would also be cost effective. The cost effectiveness was dependent on an admin price based on delivery costs in the schools HPV vaccination programme and that in order to compete against the quadrivalent vaccine the bivalent vaccine would have to be purchased at a price that did not appear realistic.

15. The Committee received a presentation from PHE on the updated assessment on a targeted programme for MSM and noted the following key changes had been made to the base case of the assessment:
 - The uptake in MSM for the 3 dose course had been changed to a much more conservative estimate of 89% for the first dose falling to 69% and 49% for the 2nd and 3rd dose. This estimate was based on a number of studies including surveillance data on the uptake of the Hepatitis B vaccine in MSM in GUM clinics.
 - That instead of assuming all HIV positive MSM (diagnosed and undiagnosed) attend GUM and HIV clinics the model now used an estimate based on a proportion of this population attending GUM and HIV clinics.
 - Anal cancer survival rates had been updated based on more recently published estimates.
 - The model had been recalibrated using more recent data on progression rates to anal cancer and the model was now able to be fitted to both prevalence and incidence of HPV-associated anal cancer.
16. The Committee noted the minor changes that had also been made to the model including updating anal cancer treatment costs, demographic data, the average incidence of warts, using data from the third National Survey of Sexual Attitudes and Lifestyle (Natsal-3) for partnership rates and adjusting the HPV clearance rate in HIV +ve MSM.
17. The assessment also looked at other scenarios from the base case including using a 1.5% discount rate, including laryngeal cancer, a lower or higher vaccine efficacy, lower duration of protection, absence of herd effects (static model), higher completion rates and a two dose schedule.
18. The Committee considered that basing uptake on Hepatitis B uptake might not be representative of MSM wanting a vaccine to prevent genital warts and that there was evidence, based on anonymous sampling, that some undiagnosed HIV positive individuals do attend GUM clinics and do not get tested for HIV.
19. The assessment also looked at scenarios extending the age ranges to 16-45 and 16-74 years old. The Committee noted that Natsal sexual behaviour data becomes sparse for MSM after the age of 40 years and that it is difficult to extrapolate HIV prevalence after the age of 45 years due to a cohort effect. This meant that PHE was less confident in the estimates for extending

vaccination above the age of 40, and especially above the age of 45. In general there was less confidence in scenarios for HIV positive MSM than for all MSM because of uncertainty about the estimates used on the efficacy and duration of protection for the vaccine in HIV +ve MSM and the proportion (diagnosed and undiagnosed) that attend GUM and HIV clinics.

20. The Committee considered the results and noted that qualitatively the results had not changed and therefore the overall conclusions had not changed. At the list price of the vaccine, vaccinating HIV +ve individuals up to the age of 45 was cost effective (within the cost-effectiveness threshold of £20000 per quality adjusted life year (QALY)) though not up to the age of 74. Using the threshold price (combined vaccine and administrative costs) previously calculated for all MSM aged 16-40 it would be cost saving to vaccinate HIV +ve MSM although results were more uncertain for HIV +ve individuals and therefore more speculative. At the same threshold price (previously calculated for all MSM aged 16-40) vaccinating all MSM up to 45 was also within the cost-effectiveness threshold of £20000 per QALY.
21. The Committee noted that the estimated threshold price per dose (including administrative costs) at which a targeted programme would be cost-effective for extending from a programme for HIV +ve MSM aged 16-40 (if this option were a realistic option) to all MSM 16-40 was now higher compared to the original estimate in the previous analyses presented in September 2014. This threshold becomes even higher in a scenario where you exclude the possibility of a programme that can only target HIV +ve MSM (under the assumption that this is not a realistic option) and directly compare vaccinating all MSM aged 16-40 to no vaccination at all.
22. The Committee noted that warts prevention was still a main influencing factor for the targeted programme being cost effective.
23. The Committee noted that the Department of Health (DH) analytical team had investigated the cost of administration for vaccinating in a GUM setting and had concluded that the administrative price used in the assessment was within the range of what DH estimated this to be and was therefore a reasonable price to assume. The DH analytical team considered that vaccinating in a GUM setting should not be a huge excess from an administration point of view if it can dovetail with the activities of the clinic.
24. The Committee concluded that the updated assessment had taken into account the key concerns that had been raised and that no further work was necessary. The Chair summarised the discussions of the Committee concluding that:
- Qualitatively the results of the updated assessment had not changed and that the Committee's original advice was still valid that a targeted programme for all MSM up to the age of 40 would be cost effective at a realistic price for the combined costs of vaccine and administration.

- For reasons of uncertainty the Committee did not advise a programme for HIV+ve MSM only but considered that the age for vaccinating all MSM could be extended to 45 as it did not consider that the sexual behaviour of MSM would change between the age of 40 and 45. Information beyond the age of 45 was more uncertain though a view might be taken about whether to advise that HIV+ve MSM above the age of 45 could also be vaccinated.
 - The advice of the committee was dependent on the vaccine being purchased and delivered at a cost effective price and the main scenario results undergoing an uncertainty analysis such that the JCVI could be confident of the certainty of the most plausible Incremental Cost-Effectiveness Ratio estimate.
25. The Committee noted that the DH would take forward negotiations with local government, following the JCVI's advice, about the commissioning and delivery of a programme and how this should be funded. Central procurement was feasible and the most likely option to keep costs down however there was still some complexity to resolve in negotiating delivery costs.

V. Impact and cost-effectiveness HPV vaccination of adolescent boys

Process

26. The committee were reminded by the JCVI Chair that the results being presented by Warwick University were part of the second opinion modelling process that DH had commissioned. Second opinion modelling was setup by DH to inform, for assurance purposes, those issues under consideration by JCVI that are more complex and warrant a second model. The work by PHE on the main model or first opinion model was still in progress and the Warwick model would be the first results presented to the Committee. The Warwick team would be presenting preliminary results and looking for feedback from the Committee to take the work forward.
27. The Chair invited PHE to give an overview of the modelling work on boys and potential options and noted that:
- The PHE model would be an individual based model that would incorporate both screening and vaccination and would be able to consider a range of scenarios including gender neutral vaccination and switching between vaccines including the incremental benefit of moving to the 9-valent vaccine.
 - PHE had allocated additional resources to the project to help expedite the work.
 - That John Edmunds at the London School of Hygiene and Tropical Medicine was also working on an individual based model for Cancer Research UK looking at inequalities in vaccination and screening. This model was close to completion but the scope of work did not include cost effectiveness analyses. However, PHE could independently use the outputs of the model to conduct cost-effectiveness analyses if needed.

- The original compartmental model used to inform the decision in 2008 could be quickly updated to revisit gender neutral vaccination using the most recent evidence. The Committee had previously agreed, however, based on advice from PHE, that this was not their preferred option.
 - Marc Brisson (from Université Laval) has been looking at comparing published models from around the world running similar scenarios that potentially could also be used to inform the process.
28. The JCVI Chair reminded the Committee that a process had been agreed at previous meetings, which was that the PHE modelling work, which was still in development, was the main study intended to inform the Committee's final deliberation on whether to extend HPV vaccination to adolescent boys. The Warwick work would be used to help inform and contribute to this process and challenge the assumptions in the main model. This process would ensure that that the Committee's conclusions would be as robust as possible. The Committee agreed that it would be important follow the agreed process.
29. The Committee considered that the modelling work would also have to have the capacity to look at more imaginative scenarios of different combinations of doses and vaccine type (bi, quad and 9 valent) in the different groups (girls, boys, MSM) for example one dose in boys and two doses in girls etc. The Committee noted that this would be possible but would involve additional work for the modellers and that the timescales would depend on what was asked.
30. The Committee considered a presentation from Dr Hans Berkoff looking at the direct health effects of vaccinating boys along with girls in the Netherlands that had recently been published in the British Medical Journal. The Committee noted that:
- There is benefit in vaccinating boys and all the models are likely to show this but the outcome of cost effectiveness for HPV is strongly influenced by the rules used for discounting and cost-effectiveness. This is because the costs (of vaccinating) occur in the present but the benefits of cancer prevention is not realised until approximately 50 years later. Vaccinating boys as well as girls is unfavourable in term of cost-effectiveness because the benefits, which are smaller in boys than in girls, are discounted. Also most of the benefit in boys can be achieved through achieving high uptake in a girl's only vaccination programme.
 - Uptake in the Netherlands for the bivalent vaccine for the girls programme is low (60%) compared to that seen in the UK (>85%) partly because in Holland they do not use a school based vaccination programme.
 - Earlier modelling work In the Netherlands showed it is better to increase the uptake in girls rather than vaccinate boys to reduce the overall HPV prevalence in the heterosexual population. However the work had not looked at the issue that vaccinating boys will prevent future cancer in men.

- In the latest study the investigators considered what the direct benefit to males was in terms of cancer prevention if you vaccinated boys and how this was affected by the uptake in girls. The investigators used a relatively simple model with an epidemiological formula and not a natural history model although it did take into account herd effects.
- In heterosexual men the risk of infection is strongly influenced by the uptake in the girls programme while the impact of vaccinating boys will depend on the excess attributable risk in MSM that is caused by HPV.
- The investigators estimated that to prevent one HPV associated cancer in males you would need to vaccinate 795 boys when uptake is 60% in girls and 1735 boys when uptake is 90% in girls. In comparison vaccinating 200 girls is enough to prevent one case of cervical cancer. Therefore vaccinating girls is approximately 4 times more effective in preventing cervical cancer than vaccinating a boy to prevent an HPV associated cancer. However the number of boys you need to vaccinate heavily depends on what proportion of male HPV associated cancers is clustered in MSM and this is not so well understood in Holland.
- Using WHO rules on cost-effectiveness at 60% uptake in girls vaccinating boys in the Netherlands seems economically feasible at approximately 100 Euros a boy.

Modelling update from Warwick University HPV vaccination of adolescent boys

31. The Committee considered a presentation from Warwick University on the preliminary results modelling the impact and cost effectiveness for extending vaccination to adolescent boys. The Committee noted that:
 - Warwick had constructed a susceptible infected susceptible (SIS) stochastic individual based model which included partnership rates for different ages, sex and sexual orientation using data from the National Survey of Sexual Attitudes and Lifestyles (NATSAL) 2 Survey (with plans to include survey 1 & 3).
 - The model assumed individual transmission and recovery rates for each of the 4 strains of HPV (18, 16, 11 and 6), with no immunity from natural infection, which could be updated to include all 9 strains in the 9-valent vaccine if sufficient data are available. By default, vaccine waning was assumed to occur after 20 years.
 - The model had been fitted using a number of data sources including sero-prevalence data, however, fitting the model to the level of infection observed in the 16-18 age group and the low prevalence observed in men had proven to be challenging. Two contradicting pieces of information in the data were the cause of this: transmission data showing a higher rate of transmission from women to men than men to women, and data showing a relatively low prevalence of HPV infection in men.

- The economic part of the model takes the outputs of life histories of infections from the epidemiological model, which are then extrapolated to clinical events for each individual taking into account the attributable fraction for HPV for each associated condition. The model included: cervical (including CIN grades 2 and 3 but not pre-cancers), vaginal, vulval, anal, penile and oropharyngeal cancers, recurrent respiratory papillomatosis (RRP) and anogenital warts. For oropharyngeal cancer, only cancer of the pharynx was included. Costs associated with screening were also included.
- For the attributable fraction for each HPV associated cancer or warts the model used the assumption that both high-risk types (HPV 16 and 18) and both low-risk types (HPV 6 and 11) have the same risk of causing disease from infection.
- The effect of the incidence of HPV infection in a population were modelled for different vaccination strategies taking into account the impact of the current programme since its introduction in 2008 (including the catch up campaign), up to the present and then switching to different scenarios including; stopping the programme, continuing with the girls-only programme, switching to a boys-only programme, or adding a boys programme and varying the uptake in both girls and boys (90/90, 90/70 or 45/45 respectively).
- The model is simulated for 100 years in a population of 50 000 people and then works out the incidence of the different HPV associated diseases under each scenario modelled. Warwick planned to increase the population size to smooth out stochastic variation due to small numbers.
- Warwick are looking to include the option of having an MSM strategy. In the model the MSM population is defined as any person who will have sex with a man in their lifetime which based on NATSAL data was estimated to be 11% of the male population.

32. The Committee noted the preliminary results showed that:

- A programme to vaccinate boys only or girls only would have more or less the same impact but there would be a slightly better impact on cervical cancer with a girls-only programme. The results showed that a lot of the benefit of vaccinating one sex is seen in the other sex but by vaccinating both you get some further impact which is not realised by vaccinating only one sex.
- The overall impact of each strategy evens out in the long term reaching similar levels at equilibrium after 100 years but the decline in disease incidence is achieved faster by vaccinating both boys and girls. Increasing coverage on boys beyond 70% does not have much more benefit.
- The faster decline in incidence of a gender neutral programme brings forward the benefits which are then less influenced by the effect of discounting. The corollary of this is that the cost effectiveness of including boys in the programme will get worse the later it is introduced as the opportunity of achieving benefits earlier is lost.

33. The Committee considered that a time limited programme for boys, providing it was cost effective, might also be an option to consider to bring forward the benefits earlier although the criteria for when to switch off a programme for boys would have to be carefully considered. Any boys programme would also impact on the timescales of a targeted MSM programme as well.
34. The Committee noted that further work was needed by Warwick on a number of issues for which the committee had highlighted its concerns including; considering natural immunity in women from infection for which there was robust evidence, using more data (published) on the prevalence of HPV in males, reconsidering the estimated attributable fraction of HPV associated cancers, especially oropharyngeal cancer (and the upward trend of these cases), incorporating all 9 HPV types for the 9 valent vaccine, and examining an MSM only programme.
35. The Committee noted that Warwick also planned to increase the numbers in the simulation and reduce some of the uncertainty inherent in the model. Warwick would also liaise with PHE over costing data to make sure that those parameters which were non contentious were aligned in the two models. The Committee thanked the Warwick team for their presentation and looked forward to seeing further iterations of the work.

VI. Papers for comment

36. The Committee noted the following papers submitted for comment:

King EM et al. Human papillomavirus DNA in men who have sex with men: type-specific prevalence, risk factors and implications for vaccination strategies. *BJC* (2015), 1–9 | doi: 10.1038/bjc.2015.90

Drolet M et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. *Lancet* [http://dx.doi.org/10.1016/S1473-3099\(14\)71073-4](http://dx.doi.org/10.1016/S1473-3099(14)71073-4)

Blomberg M et al. Dose-related differences in effectiveness of HPV vaccination against genital warts: a nationwide study of 550,000 young girls. *Clin Infect Dis.* (2015) doi: 10.1093/cid/civ364 First published online: May 5, 2015.

Joura E A et al. A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women. *N Engl J Med* 2015;372:711-23. DOI: 10.1056/NEJMoa1405044

VII. AOB

Safety of the HPV Vaccine

37. The Committee reviewed safety information on the HPV vaccine provided by the Medicines and Healthcare products Regulatory Authority (MHRA) (1-2) as well as reports in the media (3-4) and literature (5-13) investigating temporal associations of the HPV vaccine to a range of overlapping syndromes including

Postural Orthostatic Tachycardia Syndrome (POTS). The Committee noted that:

- Suspected adverse reactions (ADRs) reported to the MHRA via the Yellow Card Scheme are not necessarily proven side effects, and cannot be used to compare the safety of different vaccines. The absolute number of ADRs reported to MHRA since 2008 for the HPV vaccine was higher than for other vaccines, but this in itself did not raise specific safety concerns. The overall profile of these reports was very similar to that observed for other vaccines given to adults and adolescents, such as Td-IPV, flu and Hepatitis B (3) and were not unexpected, and the proportion that are serious is less than for another vaccine routinely used in teenagers.
 - The majority of ADRs were not serious, and were in line with previous experience of vaccinating teenagers. The reporting rate in the context of close to 90% uptake in the UK so far gives no specific cause for concern.
 - As with any vaccine or medicine given to large numbers of people, isolated cases of serious events had been reported in temporal association with HPV vaccine in the UK. Among such events six cases of POTS had been reported since the programme started in 2008, a time in which more than 8 million doses of HPV vaccine have been administered and close to 3 million adolescent girls have been vaccinated across the UK.
 - POTS is a chronic health condition associated with an abnormal increase in heart rate after standing up. It is associated with a range of other symptoms that overlap with a number of other conditions such as Chronic Fatigue Syndrome (CFS), Complex Regional Pain Syndrome (CRPS) and fibromyalgia (14-16).
 - The MHRA had published a study which found evidence of no association between HPV vaccine and CFS or fibromyalgia (11); other investigators have found no evidence of an increased risk of a range of autoimmune, neurological, and venous thromboembolic adverse events after the HPV vaccine (5;9).
 - Cases of POTS following HPV vaccine had also been reported in Denmark and other countries, and the literature on such cases was considered (6-8; 12; 13).
 - POTS and other suspected ADRs for the HPV vaccine remain under review by the MHRA and the European regulatory network. At present, a causal association with HPV vaccine has not been established.
38. The Committee noted that since the start of the HPV vaccination programme in 2008 approximately 3 million girls have received the HPV vaccine in the UK. Uptake of the HPV vaccine is high and in the last three years, coverage of the routine programme for the full course has been consistently above 86% (17).
39. The Committee, having considered the information on suspected ADRs which are temporally linked with, but are not necessarily caused by HPV vaccination,

agreed that these were in line with what the Committee would expect from a teenage vaccination programme and there was currently no evidence of a causative link between HPV vaccination and POTS. The Committee concluded that it had no concerns regarding the safety of using the HPV vaccine in adolescent girls.

40. The Committee thanked the MHRA for its work and noted the importance of carefully monitoring vaccine safety to protect the public and to ensure that confidence is maintained in the HPV immunisation programme which is expected to significantly reduce the number of cases of cervical cancer and other HPV associated cancers and save the lives of many women in the years ahead.
41. The Committee agreed that a holding statement should be drafted that could be used reactively to support a combined communications response by Public Health England, NHS England, MHRA and DH in the event of escalating coverage in the national media.

VIII. Next meeting

42. The Committee agreed to meet at suitable time in late 2015 or early 2016 to consider clinical trial data on the two dose schedule for the 9 valent vaccine if it available.

Appendix

Consideration of the Safety of the HPV Vaccine

References

1. MHRA data on adverse reactions reporting following HPV, dTIPV, influenza and hepatitis B vaccinations (May 2015)
2. MHRA data – a complete list of adverse reactions reported following HPV vaccination (May 2015)
3. Article in '[The Independent](#)' – “Thousands of teenage girls enduring debilitating illnesses after routine school cancer vaccination”
4. The 'Toronto Star' - [Public Health Editor](#) and [Publisher](#)'s comments on retraction of the story “A wonder drug's dark side” their website and an [opinion article](#) published in response
5. Arnheim-Dahlström et al (2013) Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. [BMJ 2013;347](#)
6. Blitshteyn (2013) Postural tachycardia syndrome following human papillomavirus vaccination. [Eur J Neurol](#)
7. Brinth et al. (2015) Suspected side effects to the quadrivalent human papilloma vaccine. [Dan Med J 62/4](#)
8. Brinth et al. (2015) Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papillomavirus. Vaccine (article in press)
9. Brotherton (2013) Safety of the quadrivalent human papillomavirus Vaccine: Now well established. [BMJ 2013;347](#)
10. Nishioka et al (2014) Clinical features and preliminary diagnostic criteria of human papillomavirus vaccination associated with neuroimmunopathic syndrome (HANS). International Journal of Rheumatic Diseases 2014; 17 (Suppl. 2): 6–29
11. Donegan et al (2013). Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. Vaccine 31 (2013) 4961– 4967
12. Kinoshita et al (2014) Peripheral Sympathetic Nerve Dysfunction in Adolescent Japanese Girls Following Immunization with the Human Papillomavirus Vaccine. Intern Med 53: 2185-2200
13. Martínez-Lavín (2015) Hypothesis: Human papillomavirus vaccination syndrome small fiber neuropathy and dysautonomia could be its underlying pathogenesis. Clin Rheumatol
14. Jarjour (2013) Postural Tachycardia Syndrome in Children and Adolescents. Semin Pediatr Neurol. 2013 Mar;20(1):18-26
15. Kizilbash et al (2014) Adolescent Fatigue, POTS, and Recovery: A Guide for Clinicians. Curr Probl Pediatr Adolesc Health Care 2014;44:108-133

16. Okamoto et al (2012) Neurohumoral and haemodynamic profile in postural tachycardia and chronic fatigue syndromes. *Clinical Science* (2012) 122, 183–192
17. [Public Health England - Human Papillomavirus \(HPV\) Vaccine Coverage in England, 2008/09 to 2013/14 - A review of the full six years of the three-dose schedule](#)
18. Bosch FX, Manos MM, Munoz N, Sherman M, Jansen AM, Peto J, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International Biological Study on Cervical Cancer (IBSCC) Study Group. *J Natl Cancer Inst* 1995;87:796–802.
19. Schiffman MH, Bauer HM, Hoover RN, Glass AG, Cadell DM, Rush BB, et al. Epidemiologic evidence showing that human papillomavirus infection causes most cervical intraepithelial neoplasia. *J Natl Cancer Inst* 1993;85:958–6

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