JCVI interim position statement on HPV vaccination of men who have sex with men (MSM)

Introduction

1. In 2008 following a detailed review of the cost-effectiveness and impact of HPV vaccination in adolescents, JCVI recommended a universal programme of HPV vaccination in girls aged 12-13 years of age in schools, along with a catch up programme for girls 13 to under 18 years of age. At this time JCVI agreed that the evidence indicated vaccinating boys was unlikely to be cost-effective, as vaccine efficacy was high, and high coverage in girls would provide herd protection for boys, meaning that a programme which included boys would provide little additional benefit.

2. JCVI has kept the HPV vaccination programme under review and in 2012 identified concerns that men who have sex with men (MSM) are a group at high risk for HPV infection and associated disease who receive very little health benefit from the current HPV vaccination programme. JCVI subsequently issued a call for evidence, and indicated a need for modelling of the impact and cost-effectiveness of a targeted programme of vaccinating MSM.

3. Although not the subject of this position statement, the Committee recognises the importance of the on-going assessment of HPV vaccination of adolescent boys. The Committee is disappointed that modelling work on the impact and cost-effectiveness of this programme by PHE is not able to begin until early 2015, due to its dependence on modelling work that will not be completed until then, but JCVI members agree that it would be inadvisable to take shortcuts which could undermine the validity of the results in order to expedite this work. In addition the Committee notes that were a targeted programme for MSM to go ahead, then consideration would need to be given as to whether other groups should have access to HPV vaccination, for example unimmunised women over 17 years of age and non-MSM individuals attending Genito-Urinary Medicine (GUM) clinics. Further data have been requested so that consideration can be given to whether these additional groups might be included in the HPV vaccination programme and so that the Department of Health has an evidence base on which to consider the issue of equity in vaccination.

4. JCVI and the HPV sub-committee have now considered evidence on the impact and cost-effectiveness of a targeted programme of vaccinating MSM. The evidence indicates that a targeted programme undertaken in GUM and HIV clinics could be cost-effective, subject to implementation at a cost-effective price. This statement sets out the key evidence and describes the considerations and interim position of the JCVI in this regard. As with all significant decisions, the JCVI is issuing its interim findings for consultation to ensure that the most appropriate and up-to-date evidence has been used, and that reasonable assumptions have been made where evidence is limited or unavailable. Once the consultation is completed, the JCVI will develop its final advice to the Secretary of State for Health.

Background

Previous deliberations on HPV vaccination programmes

5. JCVI began consideration of HPV vaccination in 2006. JCVI considered all available evidence before development of a recommendation for the introduction of an HPV vaccination programme in the UK, including:
   - vaccine efficacy studies,
   - burden of disease resulting from HPV infection (epidemiology),
   - the expected health benefits of introducing an HPV vaccination programme,
   - whether the programme would be cost effective,
   - attitudinal work, and
   - the suitability of a routine immunisation programme.
6. At the October 2007 meeting JCVI concluded that a universal HPV vaccination programme for girls aged 12 to 13 years would be cost effective. In addition to this, the Committee also recommended a time-limited 'catch up' vaccination of girls aged 13 to 17 years. In July 2008 a full statement on HPV vaccination was issued[1].
7. JCVI did not recommend vaccinating boys at this time as it was considered unlikely to be cost-effective. The Committee considered that high coverage in girls would provide herd protection to boys, and that vaccination of boys would generate little additional benefit to the prevention of cervical cancer, which was the main aim of the programme. Additionally, JCVI agreed that there was insufficient evidence on the protective effects of the vaccine against cancers affecting males such as anal, head and neck cancers. JCVI agreed that when more data became available, high-risk groups such as MSM would be considered.

Review of the existing programme

8. The HPV immunisation programme was introduced in 2008 with girls aged 12-13 years routinely offered a course of three doses of vaccine. A catch-up campaign offered vaccine to girls aged 13 to 17 years of age. The vaccine used routinely from 2008 to September 2012 was the bivalent vaccine, Cervarix®, which provides protection against HPV types 16 and 18. Since September 2012 the quadrivalent vaccine Gardasil® has been used, which in addition to providing protection against HPV types 16 and 18 also provides protection against HPV types 6 and 11 responsible for the majority of cases of genital warts in the UK. Coverage with the complete vaccine course for the routine cohort in the UK has exceeded 80%.
9. Since the programme was introduced evidence has emerged that HPV immunisation is likely to provide protection against a wider range of HPV-related diseases, including anal, penile and oropharyngeal cancers. Questions have subsequently been raised on whether the immunisation programme should now include boys and/or MSM and at the June 2012 JCVI meeting, the committee asked the Health Protection Agency (HPA) to consider modelling work to assess the impact and cost effectiveness of HPV immunisation of MSM. It was acknowledged that this would take some time to complete due to a lack of data on

[1] JCVI statement on human papillomavirus vaccines to protect against cervical cancer

the incidence of HPV in MSM, the prevalence of HPV infections in MSM by age and prevalence in the settings where vaccination could be offered to MSM.

10. At the June 2012 JCVI meeting, the committee also agreed that a call for evidence be issued to ask for information relating to:

    - a two dose HPV vaccination schedule;
    - the impact of the current HPV programme;
    - HPV immunisation of MSM;
    - the impact of HPV immunisation on a wider range of HPV-related diseases; and
    - the potential impact of higher valency vaccines.

11. In October 2013 the committee agreed that consideration of options for vaccinating MSM should be prioritised and agreed that modelling would be required to assess the cost-effectiveness of a targeted programme to vaccinate MSM. The committee also agreed that a HPV sub-committee should be formed to look at all the issues around HPV vaccination under consideration, including vaccination of MSM when attending sexual health services and to report its findings and recommendations back to the JCVI. [2]

12. At the January 2014 HPV Subcommittee meeting the Subcommittee was informed that modelling to inform a decision about vaccinating MSM on attendance at sexual health services was underway and would be completed by the autumn of 2014[3], and so the Subcommittee met again in September 2014 to consider the results of the modelling and cost-effectiveness analyses on vaccinating MSM when attending sexual health services (GUM and HIV clinics)[4]. JCVI considered the findings and advice of the HPV Subcommittee at its October 2014 meeting and advised that an interim statement should be issued and that stakeholders should be invited to comment on the validity of the modelling and cost-effectiveness analyses and the interim advice of the Committee. The Committee also advised, for assurance purposes, that the modelling and cost effectiveness work undergo additional peer review in parallel to the stakeholder consultation.[5]

Impact and Cost-effectiveness analysis

13. JCVI's consideration of a vaccination programme for MSM when attending sexual health services was primarily based on its assessment of a modelling and cost effectiveness study conducted and coordinated by Public Health England in collaboration with University College London (UCL) and the London School of Hygiene and Tropical Medicine[6].

[2] Minute of the JCVI meeting held on 2 October 2013
[3] Minute of the HPV sub-committee held on 20 January 2014
[4] Minute of the HPV sub-committee September 2014
[5] Minute of the JCVI meeting held on 1 October 2014
[6] Jit *et al* (unpublished). The impact and cost-effectiveness of selective HPV vaccination of men who have sex with men via genitourinary medicine clinics: a rapid assessment.

Methodology

14. The modelling and cost effectiveness study considered vaccination of four groups of MSM attending GUM and HIV clinics: HIV positive MSM aged 16-25 years, HIV positive MSM aged 16-40 years, MSM aged 16-25 years and MSM aged 16-40 years. In all scenarios both the quadrivalent and bivalent vaccines were considered and MSM were assumed to be vaccinated with a three dose schedule.

15. Dynamic SIRS models (Susceptible, Immune, Recovered, Susceptible) were used for the study and the modelling considered the impact of vaccination on anal, penile and oropharyngeal cancers, and anogenital warts (AGW). Impact on cancers of the oral cavity and larynx, for which there is not yet strong evidence for a causal link with HPV 16 was not included and noted as a potential (unestimated) additional benefit.

16. Costs and benefits were discounted at 3.5% and JCVI criteria were used for assessing cost-effectiveness. The administrative cost per dose used in the base case was the same as that for the girls' programme which is delivered in schools. In the sensitivity analysis a much higher fee was also explored, based on the national non-mandatory tariff for consultations at GUM clinics. Additionally, in the base case scenario the list prices of the vaccines were used in the model and a threshold price at which the vaccines would be cost effective was also calculated.

Data Sources

17. Data from a number of published and unpublished sources were evaluated in determining the most plausible parameters for the analysis undertaken. The analysis accounted for data on:

    - vaccine efficacy;
    - the proportion of men who are MSM;
    - MSM partner change rates;
    - the proportion of MSM attending GUM clinics;
    - rates of MSM attendance at GUM clinics;
    - HIV prevalence in MSM including estimates of undiagnosed infection;
    - disease progression rates from HPV infection to anal cancer;
    - anal cancer incidence in MSM;
    - the age distribution of all male anal cancers;
    - anal cancer incidence adjusted according to HIV status;
    - age specific incidence of penile and oropharyngeal cancers associated with HPV infection;
    - HPV-related risk for penile and oropharyngeal cancer in MSM, adjusted according to HIV status;
    - the proportion of cancers attributable to HPV 16 and 18 infections;
    - anal cancer survival rates calculated using data for rectal cancer as a proxy;
    - oropharyngeal cancer survival rates adjusted to reflect the better survival rates for HPV-related oropharyngeal cancers;

- costs updated to 2012/13 GBP values;
- treatment costs per episode of AGW in men;
- estimates of quality of life loss/disutility;
- estimates for duration of each episode of care, treatment and recovery time, adjusted for MSM;
- estimates for treatment costs for anal and penile cancers;
- treatment costs for oropharyngeal cancers were calculated relative to the cost of cervical cancer;
- treatment costs for oral cavity and laryngeal cancers based on the costs for treatment of oropharyngeal cancers;
- administration costs based on the cost for the (school-based) HPV immunisation programme for young girls, with a sensitivity analysis assuming higher administration costs based on the proposed national non-mandatory tariff for consultations at GUM clinics.

18. JCVI and the sub-committee agreed that the parameters values used in the analysis were the most plausible based on the available evidence. These values will however be independently peer reviewed according to the standard process for independent review for JCVI. The results of the peer review process will be provided to the HPV sub-committee for consideration, who will in turn report back to JCVI prior to finalisation of the Committee's position.

Considerations of the Committee

19. During its deliberations JCVI noted that where evidence was limited or unavailable that a number of assumptions had been made in parameterising the model. In particular the Committee noted assumptions in the base case scenario that:

- 100% acceptance, uptake and completion of a 3-dose schedule would be achieved in MSM attending GUM clinics;
- lifelong protection against vaccine strains (protection for 20 years in sensitivity analyses);
- duration of protection was the same regardless of HIV status;
- cross-protection against high-risk non-vaccine HPV types had not been considered for either vaccine (due to the limited evidence available regarding the presence and longevity of cross-protection, and because HPV 16 and 18 accounted for a higher proportion of HPV associated non-cervical cancers, than cervical cancers);
- the bivalent vaccine did not provide cross-protection against AGW (given the limited evidence regarding the impact and longevity of cross-protection);
- vaccination would provide protection against future infection in seropositive individuals who had cleared their infection (as demonstrated in vaccination trials in females)

- anal cancer incidence was taken to be higher among GUM attendees compared to non-GUM attendees (MSM) with the risk of HPV related cancer adjusted according to HIV status (anal and other cancers);
- the age and time-dependent reduction in anal cancers due to vaccination had been applied to non-anal cancers (due to limited evidence of the natural history of the non-anal cancers);
- HIV positive individuals would attend GUM clinics more frequently than HIV negative MSM, regardless of whether or not their HIV had been diagnosed, with 17.8% of HIV infected individuals assumed to be undiagnosed.

20. The Committee noted that these assumptions could lead to an over or underestimation of the impact of vaccination, however the HPV sub-committee and JCVI considered that the assumed parameters would, on balance, provide a reasonable indication of the impact of HPV vaccination in MSM vaccinated in GUM clinics.

Uncertainty

21. The Committee identified a number of uncertainties regarding the behaviours of HIV positive MSM, and the impact of vaccination in this group. The data were generally poorer for this group as the numbers were smaller, meaning it was difficult to estimate the risk difference between HIV positive and HIV negative MSM in terms of cancer. The Committee considered that for HIV positive MSM there was a greater uncertainty on duration of protection from HPV vaccination as there was no evidence available.

22. A number of assumptions regarding the clinical course of disease and the sexual mixing of sub-groups of MSM had also been made. However the committee agreed that further parameterisation within the model, and inclusion of additional data of limited quality would only have a small impact on the overall outcomes of the model, and would lead to an increased level of uncertainty with regards to the findings. Lower uptake, within reasonable limits, would have a very limited impact on the cost-effectiveness of the programme. A lower completion rate could, however, have an impact on the cost-effectiveness of the programme, as three doses were likely required to achieve long term protection. This had not been examined in the modelling work undertaken, although the Committee noted that the impact of lower uptake might possibly be balanced out by any increased attendance due to the availability of HPV vaccination.

23. There was little evidence on the levels of uptake which could be expected and there were no data for MSM on the levels of immunity achieved from only two doses of vaccine. However, some studies had shown a high level of willingness to be vaccinated and a small pilot study in north London indicated an 80% uptake of the offer to vaccinate.

Results

24. The Committee noted that the impact on AGW was smaller than the impact on the HPV associated cancers, as the model assumed many MSM had AGW at their first visit to a GUM clinic. However, despite the larger impact on cancer, the benefits of preventing AGW were of importance in the model as they occurred much earlier after vaccination and thus were less impacted by discounting. Because of this much of the net-benefits of a targeted programme were due to the prevention of AGW and the cost-effectiveness of HPV vaccination in MSM was therefore driven to a large extent by the prevention of AGW.

25. At the list price the quadrivalent vaccine was the more cost-effective vaccine in all scenarios and the bivalent vaccine was significantly less cost-effective, because much of the total net health benefits were due to the prevention of AGW. However, if the current standard non-mandatory tariff price for GUM clinics was used as the administration cost (as opposed to an opportunity cost), then no option was cost-effective.

26. Under the criteria used by JCVI, vaccinating HIV positive MSM aged 16 to 25 years was cost-effective at the list price of the vaccine. Vaccinating HIV positive MSM aged 16 to 40 years was also incrementally cost-effective under the base case assumptions. Extending vaccination to all MSM aged 16 to 40 years was not incrementally cost-effective when using the list price of the vaccines. However, vaccination of all MSM aged 16 to 40 years was cost-effective under the criteria used by JCVI at a threshold vaccine price below the list price.

27. JCVI noted that vaccination of older MSM was cost-effective because of on-going HPV acquisition and disease risk in older MSM, the late age at which HIV is acquired among MSM (more become HIV positive after the age of 25) and the fact that HIV positive MSM account for over 50% of the cancers in the absence of vaccination and also have a significant burden of AGW.

Operational issues

28. Whilst the analyses reviewed indicated that a programme could be cost effective, the Committee agreed that key operational and delivery issues would need to be addressed, should such a programme be considered.

29. As sexual health in England is commissioned by Local Authorities (LAs) vaccination programmes undertaken in this setting, primarily Hepatitis B vaccination, were not commissioned or procured centrally. The Committee considered that obtaining the vaccine at a price which was cost-effective for MSM vaccination in GUM and HIV clinics was highly likely to depend on the vaccine being centrally procured.

30. The Committee advised that it would be very important to closely monitor vaccine coverage and completion and the impact of the programme if it is implemented as the outcome would also influence the consideration of a programme for adolescent boys.

Conclusion and advice

31. JCVI chose GUM clinics as the setting to be considered when assessing the impact and cost-effectiveness of a programme for the vaccination of MSM as this was the most accessed sexual health service by MSM for which sufficient quantitative sexual health data could be obtained to inform the modelling and cost effective analyses. Whilst there were a number of uncertainties associated with assumptions made in the analyses reviewed, the Committee agreed that a programme to vaccinate MSM aged 16-40 years should be considered, provided that the programme could be undertaken at a price where administration and vaccine costs combined were cost-effective. Vaccinating all MSM aged 16-40 years attending GUM or HIV clinics was the programme of choice in part because of the greater uncertainty around implementation of a strategy of vaccinating only HIV positive MSM.

32. A targeted programme of vaccinating MSM in GUM and HIV clinics was considered highly likely to prevent HPV associated cancers in MSM. The analysis however indicated that substantial benefit would also be realised from the prevention of AGW, and that cost-effectiveness of a targeted programme was reliant on the prevention of AGW infections in MSM. The Committee therefore considered that any vaccine used for a programme targeting MSM should also provide protection against HPV types 6 and 11 responsible for the majority of cases of AGW in the UK.

33. The Committee has therefore concluded that a programme for the vaccination of MSM aged 16 to 40 years should be implemented in GUM and HIV clinics in the UK using the quadrivalent HPV vaccine, subject to the programme being commissioned and implemented at a cost-effective price.

Additional considerations

34. JCVI has recognised that the mechanisms and arrangements by which a targeted programme of vaccinating MSM in GUM and HIV clinics could be undertaken are complex and would require appropriate commissioning and procurement arrangements to be in place. JCVI therefore further advised that DH should consider options for implementation, in collaboration with Public Health England, NHS England and Local Authorities.

Invitation to stakeholders

35. The consultation concerns JCVIs consideration of the scientific evidence for a programme to vaccinate MSM assessing sexual health services. However, JCVI has also identified potential issues around commissioning and implementation that are still to be resolved concerning arrangements to deliver a cost-effective programme via GUM and HIV clinics. Of note are some unresolved issues around the administrative cost of delivering vaccination via sexual health services and the arrangements for procurement and delivery. Usually the Committee has a clear estimate of the administrative cost for delivering vaccination for a programme under consideration but because of this unprecedented situation JCVI has identified a cost effective threshold that combines the cost of vaccination and administration.

36. Assessment of the potential impact and cost-effectiveness of targeted vaccination of MSM was a priority among the issues in HPV vaccination under consideration by JCVI. The Committee has acknowledged stakeholder concerns that MSM are a group at high risk of HPV infection and subsequent disease as they receive little indirect protection from the highly successful HPV vaccination programme in adolescent girls. JCVI has noted a number of assumptions in the modelling and cost-effectiveness study, including a 100% uptake and completion of a 3-dose course of vaccination and lifelong protection against vaccine strains, as well as various areas of uncertainty owing to scarcity of data around the clinical course of disease and the impact of vaccination in HIV positive MSM. Despite these reservations JCVI has been able to come to an informed decision based on the findings of the modelling and cost-effective work and provide advice on vaccinating MSM in GUM settings. JCVI would now like to invite and consult stakeholders to comment on the validity of the assumptions and findings of the modelling and cost-effectiveness study and the interim advice of the Committee. Comments to JCVI should be sent to JCVI-consultation@phe.gov.uk by no later than January 7 2015.

The Joint Committee on Vaccination and Immunisation

November 2014

Notes

1. The Joint Committee on Vaccination and Immunisation (JCVI) is an independent Departmental Expert Committee and a statutory body constituted for the purpose of advising the Secretary of State on *"The provision of vaccination and immunisation services being facilities for the prevention of illness".*

2. The JCVI's terms of reference as agreed by the UK health departments are - *"To advise UK health departments on immunisations for the prevention of infections and/or disease following due consideration of the evidence on the burden of disease, on vaccine safety and efficacy and on the impact and cost effectiveness of immunisation strategies. To consider and identify factors for the successful and effective implementation of immunisation strategies. To identify important knowledge gaps relating to immunisations or immunisation programmes where further research and/or surveillance should be considered."*