

Impact and cost-effectiveness of selective human papillomavirus vaccination of men who have sex with men

Authors

Allen Lin^{1,2,*}, Koh J. Ong^{3,*}, Peter Hobbelen³, Eleanor King⁴, David Mesher¹, W. John Edmunds¹, Pam Sonnenberg⁴, Richard Gilson⁴, Irenjeet Bains³, Yoon H. Choi³, Clare Tanton⁴, Kate Soldan³, Mark Jit^{1,3}

*contributed equally

¹ Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom

² Department of Systems Biology, Harvard Medical School, Boston, MA 02115, United States of America

³ National Infections Service - Colindale, Public Health England, London NW9 5EQ, United Kingdom

⁴ Research Department of Infection and Population Health, University College London, Gower Street, London WC1E 6BT, United Kingdom

Corresponding author

Mark Jit

National Infections Service – Colindale

Public Health England

61 Colindale Avenue

London NW9 5EQ

United Kingdom

E-mail: mark.jit@phe.gov.uk

Telephone: +44 2083277803

Running title

HPV vaccination for MSM

Key point

Offering human papillomavirus (HPV) vaccination to men who have sex with men up to age 40 years via genitourinary clinics will have a large impact on HPV-related diseases, and is likely to be cost-effective.

Abstract

BACKGROUND: Men who have sex with men (MSM) have a high lifetime risk of anogenital warts and cancers related to infection with human papillomavirus (HPV). They also benefit less from herd protection than heterosexual males in settings with female-only HPV vaccination.

METHODS: We evaluated the potential health impact and cost-effectiveness of offering vaccination to MSM who visit genito-urinary medicine clinics. We used a mathematical model of HPV 6/11/16/18 sexual transmission within an MSM population in England, parameterised with sexual behaviour, GUM attendance, HPV prevalence, HIV prevalence, warts and cancer incidence data. Interventions considered were offering HPV vaccination to either HIV-positive MSM or MSM regardless of HIV status, for age bands 16-25, 16-30, 16-35 and 16-40 years.

RESULTS: Substantial declines in anogenital warts and male HPV-related cancer incidence are projected to occur following an offer of vaccination to MSM. MSM not attending GUM clinics will partially benefit from herd protection. Offering vaccination to HIV-positive MSM up to age 40 is likely to be cost-effective if vaccine procurement and administration costs are below £96.50 a dose. At £48 a dose, offering vaccination to all MSM up to age 40 is likely to be cost-effective.

CONCLUSIONS: Quadrivalent HPV vaccination of MSM via GUM clinics is likely to be an effective and cost-effective way of reducing the burden of HPV-related disease in MSM.

Keywords: human papillomavirus; vaccination; men who have sex with men

Introduction

Human papillomavirus (HPV) infection causes cervical, anal, penile, oropharyngeal and oral cavity cancers as well as anogenital warts [1]. Most high income countries vaccinate girls around 9-14 years old against HPV, but only a few countries (Austria, Australia, the United States and several Canadian provinces) recommend extending vaccination to males (“gender-neutral vaccination”). When female vaccine coverage is high, heterosexual males are largely protected by herd protection and hence vaccinating boys becomes less cost-effective [2]. However, men who have sex with men (MSM) benefit far less from this herd protection, despite bearing a disproportionately high burden of male HPV-related disease [3]. These predictions about herd protection have been confirmed empirically by post-female vaccination data from Australia showing large decreases in warts in heterosexual males but not in MSM [4].

While most economic evaluations of gender-neutral vaccination have only considered heterosexual men, more recent evaluations have incorporated consideration of their impact on MSM [5–7]. Even these evaluations find that extending a female vaccination programme to males would not be cost-effective in settings with high female vaccine coverage unless female vaccine coverage and/or vaccine prices are sufficiently low [7]. However, a selective vaccination programme for MSM may address the inequity in disease burden and vaccine provision, while still potentially being cost-effective. MSM who are unvaccinated prior to same-sex debut may still benefit through herd protection from vaccination of their male partners. Such a strategy must include a mechanism for identifying and reaching MSM (ideally soon after same-sex debut), such as delivery through a clinical setting where MSM self-identify to health professionals.

In England, HPV vaccination has been offered to girls aged 12-13 since September 2008, with uptake exceeding 80%. At these coverage levels, adding boys to girls-only HPV vaccination programme is unlikely to be cost-effective [8]. Genitourinary medicine (GUM) clinics have historically provided a specialised service to MSM and could provide an avenue for a selective programme. However, there is little evidence about the effectiveness and cost-effectiveness of such an approach, since not all MSM attend GUM clinics, and those that do may attend after being exposed to HPV.

To address this gap, we have evaluated the potential health impact and cost-effectiveness of offering vaccination to MSM via GUM clinics, beginning in year 2016, using a model of HPV 6/11/16/18 sexual transmission within an MSM population, and data from these clinics in England.

Methods

Overview

Our analysis consisted of interlinked models of: (i) same-sex HPV 6/11/16/18 transmission within an MSM population as well as the impact of vaccination, (ii) natural history of HPV infection and disease (anogenital warts, anal, penile, oropharyngeal, oral cavity and laryngeal cancer), and (iii) costs and quality adjusted life year (QALY) implications of disease outcomes (see Figure 1). A brief model description is given below and key parameters used are shown in Table 1. Full details including model flow diagrams and equations are in the Supplementary Material.

Modelled population context

The third National Survey of Sexual Attitudes and Lifestyles (Natsal-3) [9] suggests that 33% of MSM attended GUM clinics in the past year and 52% had ever attended [10]. MSM attending GUM clinics are at higher risk of HIV and STI infection [11][12]. Antiretroviral treatment coverage is high (90%) for the 38,432 MSM accessing HIV care [13].

Transmission

Similar to our previous model of heterosexual HPV 6/11/16/18 transmission [14], we use a SIRS (susceptible-infected-recovered-susceptible) structure, except now with same-sex parameters to exclusively model partnerships between MSM aged 10-74. These MSM are further stratified based on their age (in months), risk group (based on partner change rates), HIV status, and whether or not they attend GUM clinics. At each age, they are either not yet same-sex active, same-sex active (and hence susceptible to infection), infected by a particular HPV type or having cleared an infection (and obtain natural immunity). The proportion of men who become same-sex active at each year of age was estimated from Natsal-3 [9], assuming all MSM reach same-sex debut before age 35, capturing 95% of Natsal-3 responses. Age- and risk group-specific same-sex and female partner change rates, and mixing between age groups are informed by the same data. Partnerships include oral-genital, anal-genital and other genital contact, without distinguishing between transmission routes. Projected female HPV prevalence declines and estimated transmission probabilities from previous modelling [14] were used

to calculate infection risk from sex with women amongst MSM. Individuals who clear infections can receive short-term type-specific immunity that can subsequently wane.

Disease natural history

Disease outcomes modelled were anogenital warts (for HPV 6/11) and all male cancers (for HPV 16/18) classified by the International Agency for Research on Cancer (IARC) as having evidence of causation by HPV 16, i.e. cancers of the anus, penis, oropharynx and oral cavity [1]. Laryngeal cancers (where “epidemiological evidence is not conclusive to confirm the role of HPV 16 or 18”) were included in sensitivity analysis.

For warts, we adapted a previous model [14], in which 10%-30% of newly infected individuals develop warts and seek GUM clinic treatment. For anal cancer, we developed a de novo model of HPV 16/18 infection progressing to low- and high-grade anal intraepithelial neoplasia, and finally to cancer. Rates governing transitions between different disease stages were estimated from the literature and by fitting to age-standardised anal cancer incidence in English MSM, and age-specific anal HPV prevalence in 511 MSM attending a London-based GUM clinic (both stratified by HIV status) [15]. Non-anal cancers were dealt with in a simpler way due to limited data on their natural history. For each year following the initiation of MSM vaccination, the proportionate reduction in anal cancer incidence by age, HIV status and HPV type from the pre-vaccination equilibrium predicted by the model was applied to the corresponding incidence of the other cancers. Age-specific incidence of HPV-related cancers was obtained from the Office for National Statistics. Risk of progression to non-anal cancers was assumed to be similar for both HIV-negative MSM and heterosexual men [16], but higher in HIV-positive MSM [17].

Vaccination

We considered a strategy of offering quadrivalent HPV vaccination to either HIV-positive MSM or MSM regardless of HIV status, and to either 16-25, 16-30, 16-35 or 16-40 year olds. Offering vaccination outside this age range was not modelled because of limited GUM clinic attendance data, and in the case of under 16s, confidentiality constraints.

When vaccination is initiated, all MSM in the eligible age range attending GUM clinics are offered vaccination. At subsequent time steps, vaccination is offered only to MSM attending GUM clinics for the first time since the selective vaccination programme was initiated. GUM attendance rates were based

on 2009-2012 clinic returns [18], stratified by known HIV-positive status [19]. Dose completion for the three-dose schedule was based on MSM hepatitis B vaccination completion rate reported by a London hospital [20]; surveys of GUM-attending MSM [15] and sexual health professionals [21] suggest similarly high acceptability for HPV vaccines.

Quadrivalent vaccine efficacy against persistent infection from the naïve-to-relevant type cohort in trials in males was used [22]. We assumed that vaccinees who fail to complete the schedule, receive all doses but fail to be immunised, or lose vaccine protection are not offered revaccination. In the base case, lifelong vaccine protection is assumed based on lack of observed waning in eight years of follow-up for quadrivalent vaccine trials in 9-15 year old boys and girls [23]. Vaccination is assumed to have no effect on clearance or disease progression of HPV infection acquired prior to receiving the first of three doses [24]. However, MSM who clear a prevalent vaccine-type HPV infection subsequent to vaccination are assumed to be protected from subsequent infections of the same type.

Economic analysis

We estimated changes in costs (due to both vaccination and health care for HPV-related diseases) and quality adjusted life years (QALYs) following vaccination. The economic evaluation followed the reference case of the National Institute for Health and Care Excellence [25], as interpreted by the Joint Committee on Vaccination and Immunisation (JCVI)'s Working Group on Uncertainty in Vaccine Evaluation and Procurement [26]. In particular, a health care provider perspective was adopted and health outcomes were measured in QALYs. Costs and benefits were discounted to 3.5% in the base case, and to 1.5% in a sensitivity analysis. Costs were inflated to 2013/14 prices using the Hospital and Community Health Services index [27]. A time horizon of 100 years was used in line with previous analyses of HPV vaccination [8]. We used a cost-effectiveness threshold of £20,000/QALY. Vaccine procurement and administration was assumed to cost either £96.50/dose or £48/dose. We also calculated the threshold price per dose for vaccination to be cost-effective, as the net (discounted) monetary benefit of vaccination (converting QALYs using a conversion factor of £20,000/QALY) divided by the number of doses delivered.

Uncertainty analysis

We constructed 5000 meta-scenarios by altering assumptions governing sexual partnership formation, HPV epidemiology and disease natural history for each HPV type. Each meta-scenario was fitted by

varying transmission probability per partnership to minimise the sum of squared residuals between data and model outcomes by age and HIV status (warts incidence for HPV 6/11 and anal HPV prevalence for HPV 16/18). The 1000 best-fitting meta-scenarios were paired with 1000 sets of parameters drawn using Latin hypercube sampling from the distribution of cost and QALY consequences of HPV-related disease.

In addition to probabilistic sensitivity analyses, we also considered the following alternative scenarios: (i) Low/high vaccine efficacy, based on the lower/upper limits of the confidence interval around efficacy [22], (ii) Vaccine protection wanes completely after a fixed duration of 20 years, (iii) Vaccines protect against laryngeal cancer, (iv) Bivalent instead of quadrivalent vaccination, (v) 1.5% instead of 3.5% discount rate, (vi) 100% three-dose completion rate, (vii) No substantial herd protection, so vaccines only reduce the risk of infection in vaccinees.

Results

Results show rapid declines in warts incidence by 35% (interquartile range 32%-39%) within 5 years of initiating vaccination for 16-40 year old MSM GUM attendees and 15% (12%-18%) if only HIV-positive 16-40 year old MSM are vaccinated (Figure 2). Herd protection is likely to be marked since MSM over a large age range (16-40 years) will receive vaccination in the first year. Declines in cancer take longer, due to the time lag between infection and cancer manifestation. Large cancer incidence reductions (eg. 55% (50%-64%) reduction over 100 years for anal cancer) are eventually expected if all clinic attending MSM aged 16-40 years are offered vaccination. This reduction is smaller (e.g. 40% (36%-45%) over 100 years for anal cancer) if only HIV-positive 16-40 year old MSM are vaccinated (section A11 of Supplementary Material).

With the quadrivalent vaccine costing £96.50/dose, the best option with an incremental cost-effectiveness ratio (ICER) below £20,000/QALY gained would be to vaccinate all HIV-positive MSM 16-40 years (Table 2). If the vaccine costs only £48/dose, vaccination becomes cost saving for this cohort, and could be extended to all MSM 16-40 years.

Multivariate uncertainty analysis suggests this conclusion is robust (section A13 of Supplementary Material). JCVI considers vaccination cost-effective if the most plausible ICER falls below £20,000/QALY gained, and there is no more than a 10% probability that the ICER exceeds £30,000/QALY gained [26]. At a vaccine cost of £48/dose, in our analysis vaccinating all MSM is more cost-effective than the next

best alternative (vaccinating HIV-positive MSM) in 85.4% of scenarios when the threshold is £20,000/QALY gained, and 99.3% of scenarios when the threshold is £30,000/QALY gained. Hence at £48/dose vaccinating 16-40 year old MSM would satisfy the JCVI conditions. One-way sensitivity analyses suggest that cost-effectiveness is most sensitive to uncertainty around vaccine costs, the disutility around warts episodes, as well as the duration and cost of anal cancer treatment (see details in section A12 of the Supplementary Material).

Table 3 shows how the cost-effectiveness of vaccinating all 16-40 year old MSM, compared with vaccinating the next most expensive non-dominated option i.e. HIV-positive 16-40 year old MSM, changes with alternative scenarios about HPV epidemiology and vaccine action. Threshold price per vaccine dose for such an extension of vaccination to be cost-effective is £63 in the base case, ranging from £33 (if vaccine protection lasts only 20 years) to £97 (if discounting at 1.5%).

Using the bivalent vaccine instead of the quadrivalent vaccine is only likely to be the most cost-effective option if the bivalent vaccine is £41 or more cheaper per dose than the quadrivalent vaccine.

Discussion

Quadrivalent HPV vaccination of 16-40 year old MSM attending GUM clinics is cost-effective if the vaccine can be procured and delivered at no more than £63/dose in the base case (£33-£97 across scenario sensitivity analyses). While HPV vaccine tender prices in England are unknown, equivalent prices in high-income countries submitting data to the World Health Organization range from £20.90 to £48.00 [28], while delivery costs of £10/dose may be reasonable [29]. Even with vaccine costs at £96.50/dose, a more limited programme offering vaccination to HIV-positive 16-40 year old MSM would be cost-effective. A nonavalent vaccine at the same price is likely to have a similar cost-effectiveness profile since almost all male HPV-related cancers are caused by HPV 16/18. However, a bivalent vaccine is unlikely to be cost-effective in a selective MSM programme given that it needs to be at least £41/dose cheaper to procure and deliver than the quadrivalent vaccine.

Besides vaccine costs, results are sensitive to uncertainty in the disutility caused by warts or anal cancer, and the cost of treating anal cancer. Warts disutility is especially influential, and is driven particularly by variability not just in the measured quality of life of someone with warts, but also the duration of time spent with warts [30].

The cost-effectiveness of MSM vaccination may be even better than reported due to additional benefits of vaccination not fully captured. First, while we assumed that HIV increases the rate of HPV-related disease progression, we assumed for computational simplicity that HPV has no effect on HIV acquisition, despite some evidence to the contrary [31]. Second, our model was fitted to recent cross-sectional data on sexual behaviour, GUM attendance among MSM, HIV prevalence and cancer incidence. In the future, these data may change, although the direction of change is difficult to predict. However, both anal [32] and oropharyngeal [33] cancer incidence has been increasing, and the increase may be particularly pronounced among HIV-positive MSM due to improved survival in the era of antiretroviral therapy. Third, we only modelled disease occurring in the ages 10-74 years. An estimated 24%, 30%, and 8% of anal, penile and oropharyngeal cancers respectively in 2008-12 in England [34] occur in men aged 75 and older. However, the importance of these cancers to the cost-effectiveness of vaccination is reduced by discounting since vaccination occurs much earlier and because these men have lower life expectancies. Fourth, it is possible that offering HPV vaccination at GUM clinics may increase attendance rates among young MSM. A survey among 16-20 year old MSM in Australia found that 86% would be willing to disclose their sexual orientation to a health care provider in order to receive HPV vaccination if it were free of charge [35]. Such an effect would increase vaccine uptake as well as potentially uptake of other sexual health and health promotion services that may reduce the incidence of other sexually transmitted diseases, albeit at increased costs.

Our modelling has limitations because we model compartments of the MSM population rather than discrete individuals. In particular, we divide the population into three sexual activity tiers, within which individuals have the same number of partners. Thus, we do not separately model rare individuals with very many partners, even compared to the 5% most same-sex active individuals. In addition, we do not vary all parameters in the model, such as those obtained from Natsal-3 or GUMCAD. However, by widely varying other correlated epidemiological and vaccination uptake parameters, we likely capture the uncertainty in outcomes. Furthermore, the data requirements of an individual-based model may not be justified given the sparsity of data on MSM. Lastly, we do not model separate disease risks for diagnosed and undiagnosed HIV-positive MSM.

Only two cost-effectiveness analyses of selective MSM vaccination HPV programmes have been previously conducted, both in the United States [36,37]. Both used static models, and hence did not consider potential herd protection from vaccinating only a proportion of MSM. One study [37] only explored a limited strategy of vaccination as adjunct prevention in HIV-negative MSM following treatment for high-grade anal neoplasia, and concluded that it may be cost-effective. A second study

assumed that all MSM would be vaccinated at a certain age, and found that at a composite vaccination cost of US\$500 (about £100/dose in 2014 GBP) per vaccinated individual, vaccinating MSM up to age 26 was cost-effective at a threshold of US\$50,000 (£30,000 in 2014 GBP) per QALY gained. To our knowledge, our study is the first cost-effectiveness evaluation of selective HPV vaccination for MSM explicitly considering a delivery pathway to reach MSM. It is also the first to use a transmission model, which was critical to identifying the most cost-effective strategy. By doing so, we show that such a strategy may bring substantial population-level benefits even though not all MSM attend GUM clinics.

Our work suggests that MSM HPV vaccination can be delivered in a feasible and cost-effective way in settings where MSM regularly attend specialist sexual health services. While our analysis considered GUM clinics only, the results likely apply to other sexual health service providers able to deliver vaccines attended by MSM with a similar HPV infection risk profile. While we only considered vaccination between the ages of 16-40 due to data limitations, vaccinating younger MSM is highly likely to also be cost-effective, and our analysis does not preclude that vaccinating beyond age 40 could also be cost-effective.

Although GUM clinic-based HPV vaccination for MSM was found to be cost-effective with large impact on disease incidence, the largest reductions in HPV-related disease will only occur through universal vaccination of 12-13 year old boys, since many MSM initiate same-sex activity and hence are at risk of HPV infection before attending such clinics. However, introducing gender-neutral vaccination does not preclude offering vaccination to MSM up to a higher age, particularly since many MSM were not born in England and may be missed by an adolescent programme.

NOTES:

Author contributions

AL and KJO contributed equally to this work. AL, KJO, MJ, KS, PH, EK and DM conceptualised the model and interpreted the results. AL coded and parameterised the model with input from KJO, PH, YHC, MJ and KS. DM, EK, KS, WJE, PS, RG, IB and CT provided and analysed key data sources for the model. KJO, AL and MJ conducted the economic evaluation. AL, KJO and MJ wrote the manuscript with input from all other authors. All authors approved the final version of the manuscript. MJ is the guarantor.

Acknowledgments

We thank Mary Ramsay, Vanessa Saliba, Andrew Earnshaw, Jonathan Crofts and Cath Mercer for helpful comments. We also thank Mona Jeffreys and Rouran Li for sharing unpublished data from their studies. We thank all clinics that report data to the Genitourinary Medicine Clinic Activity Dataset (GUMCAD), Survey of Prevalent HIV Infections Diagnosed (SOPHID) and HIV and AIDS Reporting System (HARS), as well as the GUMCAD/SOPHID/HARS team at Public Health England for collating and validating the data.

Funding

This work was part supported by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Immunisation at the London School of Hygiene and Tropical Medicine in partnership with Public Health England (grant number IS_HPU_1112_100). AL was supported by a British Marshall Scholarship.

Natsal-3 is a collaboration between University College London, the London School of Hygiene and Tropical Medicine, NatCen social research, Public Health England (formerly the Health Protection Agency), and the University of Manchester. The study was supported by grants from the Medical Research Council [G0701757]; and the Wellcome Trust [084840]; with contributions from the Economic and Social Research Council and Department of Health. We thank the study participants and the team of interviewers from NatCen social research who carried out the fieldwork. The Natsal study was approved by the Oxford Research Ethics Committee A [Ref: 10/H0604/27].

Disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR the Department of Health or Public Health England. The funders had no role in study design; in the

collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflicts of interests

WJE's partner works for GlaxoSmithKline; all other authors have no other relationships or activities that could appear to have influenced the submitted work.

Ethics

Ethics approval was not required for this study. The Natsal study was approved by the Oxford Research Ethics Committee A [Ref: 10/H0604/27].

Accepted Manuscript

References

1. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 100B. A Review of Human Carcinogens: Biological Agents. 11-Human Papillomaviruses. 2012. Available at: <http://monographs.iarc.fr/ENG/Monographs/vol100B/>. Accessed 6 September 2016.
2. Seto K, Marra F, Raymakers A, Marra C a. The cost effectiveness of human papillomavirus vaccines: a systematic review. *Drugs* **2012**; 72:715–43.
3. Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. *Lancet Oncol.* **2012**; 13:487–500.
4. Ali H, Donovan B, Wand H, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme : national surveillance data. *Br. Med. J.* **2013**; 346:f2032.
5. Laprise J-F, Drolet M, Boily M-C, et al. Comparing the cost-effectiveness of two- and three-dose schedules of human papillomavirus vaccination: A transmission-dynamic modelling study. *Vaccine* **2014**; 32:5845–53.
6. Burger E a, Sy S, Nygård M, Kristiansen IS, Kim JJ. Prevention of HPV-related cancers in Norway: cost-effectiveness of expanding the HPV vaccination program to include pre-adolescent boys. *PLoS One* **2014**; 9:e89974.
7. Bogaards JA, Wallinga J, Brakenhoff RH, Meijer CJLM, Berkhof J. Direct benefit of vaccinating boys along with girls against oncogenic human papillomavirus: bayesian evidence synthesis. *BMJ* **2015**; 350:h2016.
8. Jit M, Choi YH, Edmunds WJ. Economic evaluation of human papillomavirus vaccination in the United Kingdom. *BMJ* **2008**; 337:a769.
9. Mercer CH, Tanton C, Prah P, et al. Changes in sexual attitudes and lifestyles in Britain through the life course and over time: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). *Lancet* **2013**; 382:1781–94.
10. Mercer CH, Fenton KA, Copas AJ, et al. Increasing prevalence of male homosexual partnerships and practices in Britain 1990-2000: evidence from national probability surveys. *AIDS* **2004**; 18:1453–8.
11. Yin Z, Brown AE, Hughes G, Nardone A, Gill ON, Delpech VC. HIV in the United Kingdom 2014 Report: data to end 2013. 2014. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/401662/2014_PHE_HIV_annual_report_draft_Final_07-01-2015.pdf. Accessed 7 September 2016.

12. Aghaizu A, Wayal S, Nardone A, et al. Sexual behaviours, HIV testing, and the proportion of men at risk of transmitting and acquiring HIV in London, UK, 2000-13: a serial cross-sectional study. *lancet. HIV* **2016**; 3:e431-40.
13. Skingsley A, Kirwan P, Yin Z, Nardone A, Hughes G, Delpech V. HIV new diagnoses, treatment and care in the UK 2015 report: data to end 2014. 2015. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/469405/HIV_new_diagnoses_treatment_and_care_2015_report20102015.pdf. Accessed 7 September 2016.
14. Choi YH, Jit M, Gay N, Cox A, Garnett GP, Edmunds WJ. Transmission dynamic modelling of the impact of human papillomavirus vaccination in the United Kingdom. *Vaccine* **2010**; 28:4091-4102.
15. King EM, Gilson R, Beddows S, et al. Human papillomavirus DNA in men who have sex with men: type-specific prevalence, risk factors and implications for vaccination strategies. *Br. J. Cancer* **2015**; 112:1585-93.
16. Nyitray AG, Carvalho da Silva RJ, Baggio ML, et al. The Prevalence of Genital HPV and Factors Associated With Oncogenic HPV Among Men Having Sex With Men and Men Having Sex With Women and Men: The HIM Study. *Sex. Transm. Dis.* **2011**; 38:932-940.
17. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* **2007**; 370:59-67.
18. Savage EJ, Mohammed H, Leong G, Duffell S, Hughes G. Improving surveillance of sexually transmitted infections using mandatory electronic clinical reporting: the genitourinary medicine clinic activity dataset, England, 2009 to 2013. *Euro Surveill. Bull. Eur. sur les Mal. Transm. = Eur. Commun. Dis. Bull.* **2014**; 19:20981.
19. Brown AE, Gill ON, Delpech VC. HIV treatment as prevention among men who have sex with men in the UK: is transmission controlled by universal access to HIV treatment and care? *HIV Med.* **2013**; 14:563-70.
20. Milne C, Bayley J, Taylor C. A retrospective case note analysis of hepatitis B vaccination prescribing in a genito-urinary clinic setting: what is the role of the fourth vaccine? *HIV Med.* **2014**; 15:154.
21. Nadarzynski T, Smith H, Richardson D, Jones CJ, Llewellyn CD. Human papillomavirus and vaccine-related perceptions among men who have sex with men: a systematic review. *Sex. Transm. Infect.* **2014**; 90:512-23.
22. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. *Lancet* **2011**; 364:401-411.

23. Ferris D, Samakoses R, Block SL, et al. Long-term Study of a Quadrivalent Human Papillomavirus Vaccine. *Pediatrics* **2014**; 134:e657–e665.
24. Hildesheim A, Herrero R, Wacholder S, et al. Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection: a randomized trial. *JAMA* **2007**; 298:743–53.
25. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2013. Available at: <https://www.nice.org.uk/article/pmg9/chapter/foreword>. Accessed 15 January 2016.
26. Joint Committee on Vaccination and Immunisation. Joint Committee on Vaccination and Immunisation - Code of Practice June 2013. 2013. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224864/JCVI_Code_of_Practice_revision_2013_-_final.pdf. Accessed 15 January 2016.
27. Curtis L. Unit Costs of Health & Social Care 2013. Canterbury: Personal Social Services Research Unit, University of Kent at Canterbury, 2013.
28. Herlihy N, Hutubessy R, Jit M. Current global pricing for human papillomavirus vaccines bring the greatest economic benefits to rich countries. *Health Aff.* **2016**; 35:227–234.
29. Joint Committee on Vaccination and Immunisation. Minutes of the meeting on 7 October 2015. 2015. Available at: <https://app.box.com/s/iddfb4ppwkmjtusir2tc/1/2199012147/46319285265/1>. Accessed 29 January 2016.
30. Woodhall SC, Jit M, Soldan K, et al. The impact of genital warts: loss of quality of life and cost of treatment in eight sexual health clinics in the UK. *Sex. Transm. Infect.* **2011**; 87:458–63.
31. Chin-Hong P V, Husnik M, Cranston RD, et al. Anal human papillomavirus infection is associated with HIV acquisition in men who have sex with men. *AIDS* **2009**; 23:1135–42.
32. Grulich AE, Poynten IM, Machalek DA, Jin F, Templeton DJ, Hillman RJ. The epidemiology of anal cancer. *Sex. Health* **2012**; 9:504–8.
33. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. *J. Clin. Oncol.* **2013**; 31:4550–9.
34. Office for National Statistics. ONS: Cancer survival rates, Cancer Survival in England: Patients Diagnosed 2007-2011 and Followed up to 2012. 2013. Available at: <http://www.ons.gov.uk/ons/rel/cancer-unit/cancer-survival/cancer-survival-in-england--patients-diagnosed-2007-2011-and-followed-up-to-2012/stb-cancer-survival-in-england--patients-diagnosed-2007-2011-and-followed-up-to-2012.html>. Accessed 1 December 2015.
35. Zou H, Grulich AE, Cornall AM, et al. How very young men who have sex with men view

- vaccination against human papillomavirus. *Vaccine* **2014**; 32:3936–41.
36. Kim JJ. Targeted human papillomavirus vaccination of men who have sex with men in the USA: a cost-effectiveness modelling analysis. *Lancet. Infect. Dis.* **2010**; 10:845–52.
 37. Deshmukh AA, Chiao EY, Das P, Cantor SB. Clinical effectiveness and cost-effectiveness of quadrivalent human papillomavirus vaccination in HIV-negative men who have sex with men to prevent recurrent high-grade anal intraepithelial neoplasia. *Vaccine* **2014**; 32:6941–7.
 38. Office for National Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2011 and Mid-2012. Newport, United Kingdom: 2012.
 39. Erens B, Phelps A, Clifton S, et al. Methodology of the third British National Survey of Sexual Attitudes and Lifestyles (Natsal-3). *Sex. Transm. Infect.* **2014**; 90:84–9.
 40. Aghaizu A, Brown AE, Nardone A, Gill ON, Delpech VC. HIV in the United Kingdom 2013 Report: data to end 2012. London, United Kingdom: 2013. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/326601/HIV_annual_report_2013.pdf. Accessed 6 September 2016.
 41. Hickson F, Bourne A, Weatherburn P, Reid D, Jessup K, Hammond G. Tactical dangers: Findings from the United Kingdom Gay Men’s Sex Survey 2008. 2010. Available at: <http://sigmaresearch.org.uk/files/report2010b.pdf>. Accessed 7 September 2016.
 42. Hawkins MG, Winder DM, Ball SLR, et al. Detection of specific HPV subtypes responsible for the pathogenesis of condylomata acuminata. *Viol. J.* **2013**; 10:1.
 43. Ball SLR, Winder DM, Vaughan K, et al. Analyses of Human Papillomavirus Genotypes and Viral Loads in Anogenital Warts. **2011**; 1350:1345–1350.
 44. Brown DR, Schroeder JM, Bryan JT, Stoler MH, Fife KH. Detection of multiple human papillomavirus types in Condylomata acuminata lesions from otherwise healthy and immunosuppressed patients. *J Clin Microbiol* **1999**; 37:3316–3322.
 45. Alemany L, Saunier M, Alvarado-Cabrero I, et al. Human papillomavirus DNA prevalence and type distribution in anal carcinomas worldwide. *Int. J. Cancer* **2015**; 136:98–107.
 46. Giuliano A, Lee J, Fulp W, Villa L. Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. *Lancet* **2011**; 377:932–940.
 47. de Pokomandy A, Rouleau D, Ghattas G, et al. Prevalence, clearance, and incidence of anal human papillomavirus infection in HIV-infected men: the HIPVIRG cohort study. *J. Infect. Dis.* **2009**; 199:965–73.
 48. Office for National Statistics. Cancer Registration Statistics, England, 2011. 2011. Available at: <http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2013-06-26>. Accessed 6 September 2016.

49. James RD, Glynne-Jones R, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 × 2 factorial trial. *Lancet. Oncol.* **2013**; 14:516–24.
50. Jeffreys M, Rachet B, McDowell S, Habib AG, Lepage C, Coleman MP. Survival from rectal and anal cancers in England and Wales, 1986–2001. *Eur. J. Cancer* **2006**; 42:1434–40.
51. Office for National Statistics. ONS One- and five-year survival of patients diagnosed in 1991–95 and 1996–99: less common cancers, sex and age, England and Wales. 2005. Available at: https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalenglandandwaleslesscommoncancersbyagegroup/19911999/lesscommoncancersbyagegroup_tcm77-252734.xls. Accessed 6 September 2016.
52. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N. Engl. J. Med.* **2010**; 363:24–35.
53. Arya M, Li R, Pegler K, et al. Long-term trends in incidence, survival and mortality of primary penile cancer in England. *Cancer Causes Control* **2013**; 24:2169–76.
54. Jick H, Hagberg KW. Effectiveness of influenza vaccination in the United kingdom, 1996–2007. *Pharmacotherapy* **2010**; 30:1199–1206.

Figure captions

Figure 1. Model flow diagram showing the four dynamic models of HPV 6/11/16/18 infection in MSM, together with economic models of the cost and quality of life implications of their outcomes.

Figure 2. Proportionate reduction over time in annual cases of (a) anogenital warts and (b) anal cancer following quadrivalent HPV vaccination of MSM attending GUM clinics aged 16-40. Boxes show interquartile range (with the notch as the median), while whiskers indicate the entire range across 1000 meta-scenarios.

Accepted Manuscript

Tables

Table 1. Summary of demographic, epidemiological, sexual behaviour, and clinic attendance parameters used in the models. Shaded boxes represent parameters varied through scenario analysis either before or after fitting.

Parameter	Depends on	Value			Source
Demographics parameters					
Number of 10-year-old boys in England		292,700			[38]
% of male population that is MSM	Age	Peaks at 3.47% at age 35			[39]
Monthly natural mortality rate without HIV	Age	$1.6 \cdot 10^{-5}$ to $5.4 \cdot 10^{-3}$			[38]
Mortality rate ratio in HIV-positives and HIV-negatives		2.18			[11]
% of HIV-positive MSM undiagnosed		22.65%			[40]
HIV prevalence in MSM	Age	Peaks at 12.7% at age 46			[15,40]
		Low activity	Mid activity	High activity	
Monthly HIV force of infection	Activity group, age	Max: $5.3 \cdot 10^{-4}$	1.35 RR vs low	2.37 RR vs low	[18,41]
Median age of sexual debut	Activity group	17	16	15	[39]
Epidemiological parameters					
% of anogenital warts due to HPV-6/11		90%			[42]
% of HPV-6/11-related anogenital warts due to HPV-11		10%, 15% or 25%			[42–44]
% of anal cancers caused by HPV-16/18		69.4%-73.8%			[45]
% of HPV-16/18-related cancers due to HPV-18		1.3%-4.3%			[45]
Partner who governs the probability of HPV transmission per partnership		Either low- or high-activity partner			
HPV vaccine efficacy against HPV-6/11		77.6% (95% CI: 61.4-87.0)			[22]

HPV vaccine efficacy against HPV-16/18		63.7% (95% CI: 44.5-76.2)		[22]
Duration of vaccine-induced immunity		Lifelong or 20 years		
		HIV-negative	HIV-positive	
Duration of HPV natural immunity	HIV	Lifelong, 20, 10, 3 or 0 yrs	Lifelong, 20, 10, 3 or 0 yrs	
HPV clearance rate (cleared episodes/1000 person-months)	HIV	50, 80, 110, 140 or 170	8, 12, 16, 20 or 24	[46,47]
Percentage of HPV-6/11-infections causing anogenital warts	HIV	10%, 20% or 30%	10%, 20% or 30%	[14]
Number of first warts diagnoses at each age	HIV, age	Max: 152	Max: 16	[18]
Prevalence of HPV 16 (ages 18-40)	HIV, age	Mean: 11%	Mean: 33%	[15]
Prevalence of HPV 18 (ages 18-40)	HIV, age	Mean: 4%	Mean: 8%	[15]
Anal cancer incidence (per 100,000 py)	HIV, age	Max: 18.5	Max: 282	[3,48]
Oropharyngeal cancer incidence (per 100,000 py)	HIV, age	Max: 6.7	Max: 12.7	[17,48]
Penile cancer incidence (per 100,000 py)	HIV, age	Max: 2.2	Max: 6.3	[17,48]
Oral cavity cancer incidence (per 100,000 py)	HIV, age	Max: 11.2	Max: 21.9	[17,48]
Laryngeal cancer incidence (per 100,000 py)	HIV, age	Max: 9.3	Max: 24.0	[17,48]
Anal cancer survival	Age	70-91% after 1 year		[34,49,50]
Oropharyngeal cancer survival	Age	57-88% after 1 year		[34,51,52]
Penile cancer survival	Age	77-94% after 1 year		[53]
Oral cavity cancer survival	Age	64-84% after 1 year		[51]
Laryngeal cancer survival	Age	75-90% after 1 year		[54]
Sexual behaviour parameters				
Age group assortativeness in MSM-MSM partnerships		47%		[39]
Age group assortativeness in MSM-female partnerships		40%		[39]

Activity group assortativeness		0.1, 0.5 or 0.9			
HIV assortativeness		0.1, 0.5 or 0.9			
		Low	Mid	High	
% of MSM population in each activity group		80%	15%	5%	[39]
Same-sex partner change rate (per 3 months)	Activity group, age	Max: 0.6	Max: 4.4	Max: 17.1	[39]
Female partner change rates (per year)	Activity group, age	Max: 0.5	Max: 0.06	Max: 0.05	[39]
Clinic attendance parameters					
		Low	Mid	High	
% MSM attending GUM clinics	Activity group	48%	70%	79%	[10,18]
Probability of clinic debut	Age	50% debut by age 21			[18]
		HIV-negative		HIV-positive	
Monthly clinic attendance rate in attenders	HIV status, age	Max: 10%		Max: 15%	[18]
Number of clinic visits per episode of anogenital warts	HIV status	1.16		1.20	[18]
		Dose 1	Dose 2	Dose 3	
Vaccine uptake and completion	Dose	89%	69%	49%	[15][20]

Table 2. Incremental costs, QALYs gained and cost per QALY gained for the different vaccination options. Each strategy is compared with the previous most effective non-dominated strategy. Number of doses, costs and QALYs are discounted at 3.5% per annum.

Vaccination option	Vaccine doses		Incremental costs (£m)		Incremental QALYs gained			Incremental cost (£) per QALY gained	
	Undiscounted	Discounted	£96.50/dose	£48/dose	Due to warts	Due to cancers	Total	£96.50/dose	£48/dose
No vaccination	0	0	-	-	-	-	-	-	-
HIV+ 16-25	65,288	19,100	-0.39 ^a	-1.32 ^a	172	289	461	Cost saving	Cost saving
HIV+ 16-30	126,158	18,700	0.21	-0.69 ^a	96	219	315	682	Cost saving
HIV+ 16-35	183,605	18,800	0.58	-0.34 ^a	61	172	233	2,470	Cost saving
HIV+ 16-40	234,452	18,200	0.83	-0.05	37	124	161	5,160	Cost saving
All 16-25	941,495	207,000	19.3	9.23	194	47	241	80,100 ^b	38,300 ^b
All 16-30	1,172,038	295,000	25.8	11.5	323	312	634	40,600 ^b	18,100 ^b
All 16-35	1,269,048	348,000	29.7	12.9	384	477	861	34,500 ^b	14,900 ^b
All 16-40	1,335,684	395,000	33.4	14.3	423	596	1020	32,800	14,000

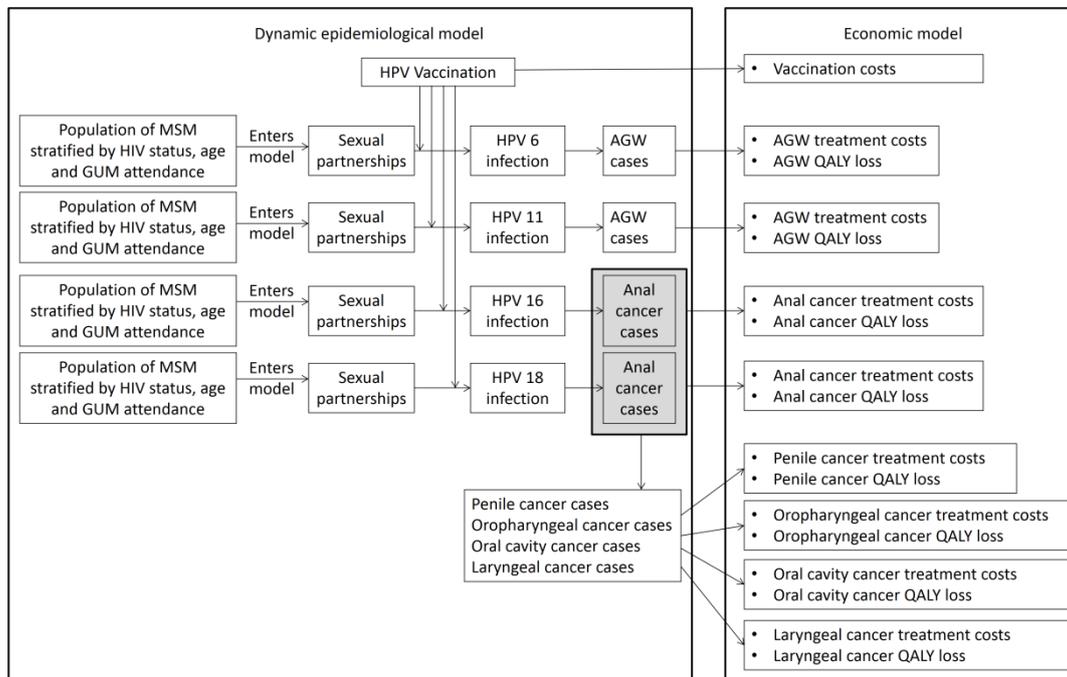
^aStrongly dominated (costs more and is less effective than another strategy)

^bWeakly dominated (costs more and is less effective than a combination of other strategies)

Table 3. Incremental cost-effectiveness ratio and threshold vaccine cost per dose (for procurement and administration) of vaccinating 16-40 year old MSM (compared to the best alternative scenario of vaccinating HIV-positive 16-40 year old MSM) under different assumptions

Scenario	Threshold cost per dose (£)	Cost (£) per QALY gained	
		£96.50/dose	£48/dose
Base case	63	32,800	14,000
1.5% discounting	97	19,800	7,800
Protection against laryngeal cancers	68	30,500	12,800
Vaccine duration of 20 years	33	66,900	31,000
Low (61.4%, 44.5%) vaccine efficacy	50	43,000	19,100
High (87.0%, 76.2%) vaccine efficacy	71	28,900	12,100
No herd effects	35	62,000	28,600
100% dose completion	73	27,800	11,500

Figure 1



Accepted

Figure 2

