HUMAN PAPILLOMAVIRUS EPIDEMIOLOGY IN MEN WHO HAVE SEX WITH MEN: IMPLICATIONS FOR A VACCINE PROGRAMME AT SEXUAL HEALTH CLINICS IN THE UK

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Presented for the degree of Doctor of Philosophy

DECLARATION

I, Eleanor King, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Signature

ABSTRACT

Men who have sex with men (MSM) are at increased risk of human papillomavirus (HPV) infection and related disease. There are two licensed HPV vaccines against the high-risk HPV types, HPV16/18, one of which, the quadrivalent vaccine, additionally targets low-risk HPV types (HPV6/11). MSM will not benefit from the UK's school-based HPV vaccine programme targeting girls. Sexual Health clinics (SHC) are the most feasible setting for vaccinating MSM. This thesis aimed to inform the policy decision on whether to vaccinate MSM attending SHCs in the UK by estimating underlying epidemiological parameters: HPV exposure in the MSM population attending SHCs, expected vaccine coverage and the effect of HPV16 vaccination on anal cancer incidence.

A cross-sectional survey of 522 MSM was conducted at a SHC. Specimens (anal and external genital swabs, urine, oral rinse and serum) were tested for HPV and demographic, behavioural and clinical information was collected (HPV-MSM-MMC study). A static deterministic cohort model was developed of HPV16 infection and anal cancer in SHC-attending MSM.

A substantial burden of HPV infection in MSM could be prevented at SHCs: a third of HPV-MSM-MMC participants were infected with ≥1 quadrivalent-vaccine HPV types yet none with all four. Therefore all had potential to benefit, at least partially, from vaccination. An additional third had evidence of prior exposure (seropositive or history of anogenital warts) to quadrivalent-vaccine types and a final third had no evidence of exposure.

A targeted HPV vaccine programme at SHCs would result in ≥50% coverage of the UK's MSM population. Vaccination at SHCs would efficiently interrupt HPV transmission because SHC-attenders represent MSM at high risk of HPV infection. Vaccination against HPV16 was predicted to substantially reduce anal cancer incidence, even without the effect of herd immunity. This thesis provides strong evidence for HPV vaccine effectiveness using a programme targeting MSM attending SHCs.

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ABBREVIATIONS

AGW	Anogenital Warts
AIDS	Acquired Immunodeficiency Syndrome
AIN	Anal Intra-epithelial Neoplasia
aOR	Adjusted Odds Ratio
ART	Anti-Retroviral Therapy
ASC	Atypical Squamous Cells
ASCUS	Atypical Squamous Cells of Undetermined Significance
ATP	According To Protocol
AUDIT-C	Abbreviated Alcohol Use and Disorders Identification Test
BASSH	British Association for Sexual Health and HIV
bp	Base pairs
CASI	Computer-Assisted Self-Interview
CI	Confidence Interval
CIN	Cervical Intra-epithelial Neoplasia
DNA	Deoxyribose Nucleic Acid
EGL	External Genital Lesions
ELISA	Enzyme-Linked Immunosorbent Assay
EU	ELISA Unit
FOI	Force of Infection
GEE	Generalized Estimating Equation
GMSHS	Gay men's Sexual Health Survey
GP	General practitioner
GUM	Genito-Urinary Medicine
GUMCAD	Genito-Urinary Medicine Clinic Activity Dataset
HAART	Highly Active Anti-Retroviral Therapy
HBV	Hepatitis B Virus
HGAIN	High-grade Anal Intraepithelial Neoplasia
HIV	Human Immunodeficiency Virus
HPA	Health Protection Agency
HPV	Human papillomavirus
HR	Hazard Ratio
HR-HPV	High risk HPV types
HSIL	High-grade Squamous Intraepithelial Lesion
HSV	Herpes Simplex Virus
IARC	International Agency for Research on Cancer
ID	Identification
IgG	Immunoglobulin G

IQR	Inter-Quartile range
ITT	Intention to Treat
JCVI	Joint Committee on Vaccination and Immunisation
LCR	Long Control Region
LGAIN	Low-grade Anal Intraepithelial Neoplasia
LR-HPV	Low risk HPV types
LSIL	Low-grade Squamous Intraepithelial Lesion
MSEW	Men who have sex exclusively with women
MLE	Maximum Likelihood Estimation
MMC	Mortimer Market Centre
MSM	Men who have sex with men
MSMW	Men who have sex with men and women
Natsal	The National Survey of Sexual Attitudes and Lifestyles
NHS	National Health Service
ONS	Office for National Statistics
OR	Odds Ratio
ORF	Open Reading frame
PBS	Phosphate-Buffered Saline
PCR	Polymerase Chain Reaction
PHE	Public Health England
QALY	Quality Adjusted Life Years
QOL	Quality of Life
R_0	Basic Reproduction number
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R_n	Effective reproductive number
RPM	Revolutions Per Minute
RR	Relative Risk
SHAAPT	Sexual Health and HIV Activity Property Type Codes
SHC	Sexual Health Clinic
STI	Sexually Transmitted Infection
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
UCL	University College London
VE	Vaccine Efficacy
VEU	Vaccine Evaluation Unit
VL	Viral Load
VLP	Virus Like Particle

ACKNOWLEDGEMENTS

The work for this thesis was carried out at the Centre for Sexual Health & HIV Research at UCL. I was fortunate to be supported in the thesis by four supervisors and additional advisors at Public Health England (PHE).

This thesis would not have been possible without Pam Sonnenberg, my primary supervisor. I am continually awed and inspired by her ability to focus, multi-task and teach. She has shared her expertise with me in a way that is exciting and rewarding and I have learnt so much from her. Not only has she contributed hours and hours to reading multiple drafts of thesis chapters, demonstrating extraordinary patience, she has also understood the external pressures (and joy) associated with raising a young family and has helped me to balance these with the demands of the PhD. I cannot thank her enough.

I would also like to thank my other supervisors, Richard Gilson, John Edmunds and Mark Jit, and advisors from PHE, Kate Soldan and Simon Beddows. Their combined wisdom and guidance, evidenced by a huge volume of emails containing answered questions and reviewed drafts, has been invaluable. In addition, Richard Gilson was Principal Investigator taking clinical responsibility for the participants of the HPV-MSM-MMC study and assisting with the ethics and R&D approval processes.

At the outset of this PhD, Graham Hart and Richard White gave valuable advice for which I am very grateful. Thanks also to David Mesher at PHE, for the GUMCAD data presented in this PhD and for coordinating lab test results with Kate Soldan; to Simon Beddows and his team, for HPV testing; and to Anne Presanis, for sharing her HIV incidence estimates. I am indebted to Carmel Young, research nurse on the HPV-MSM-MMC study, for her dedication and great humour. Systematic literature searching/screening would never been so much fun without Soonita Oomeer.

At the Centre for Sexual Health & HIV Research I have benefited from friendship, expertise and support. I am particularly grateful to Andrew Copas, for statistical chat, Cath Mercer, for her open-door, questionnaire advice and cupcakes, Fiona Burns, for donating a SNAP survey software licence, Maryam Shahmanesh for tales of the viva, Philip Prah, Nigel Field and Clare Tanton. Then, the PhD troop, those past (passed!) and present. In particular, Vicky Jones, Jesse Mears, Sarah Woodhall, Sonali Wayal, Ibi Fakoya, Sarika Desai and Catherine Aicken who have made this feel like a team enterprise. Thank you.

Participants of the HPV-MSM-MMC study were so enthusiastic and generous with their time in sharing their information. Without them this thesis would not have been possible and I am very grateful to them.

I would like to thank the Medical Research Council and the Centre for Sexual Health & HIV Research for funding this PhD.

Finally, I would like to acknowledge my family and friends who have demonstrated unbelievable generosity, love and support. In particular, Sophie, for helping Leo and Annie grow so happily; Dad, for proof-reading (and for being excellent); Mum, for encouragement; Maggie, for pep-talks and Leo and Annie, for being, so wonderfully, Leo and Annie.

To Mike, captain of bath-time, brewer of tea, buoyancy aid and general life-enhancer: I am more than grateful for everything, far beyond the limits of this page to specify.

1. INTRODUCTION

1.1 BACKGROUND AND RATIONALE

Human papillomaviruses (HPV) are known to cause cancers at several sites as well as warts. The most common HPV-related cancer, and cause of the greatest loss of life and health, is that of the cervix. Other HPV-related cancers, most notably anal cancers and head and neck cancers are less common but of increasing concern[1–4]. Whilst the burden of HPV-related disease in all men is lower than in all women, men who have sex with men (MSM) are at known high risk for HPV-related disease. For example, the odds of anal cancer in MSM is 33 times greater than in men with no history of receptive anal sex[5] and the odds of head and neck cancer are 8.9 times higher in MSM compared to heterosexual men in the US[6]. In addition, in the UK, the incidence of genital warts, the most commonly diagnosed viral sexually transmitted disease, was 163 per 100,000 men in 2008, of which 6% were in MSM[7], yet MSM only represent 2.8% of the UK population and are therefore disproportionately burdened by this disease[8].

Two vaccines against HPV16/18 infection (the most common high-risk HPV types; HR-HPV) are now widely used. The bivalent vaccine (Cervarix®) protects against HPV16/18. The quadrivalent vaccine (Gardasil®) protects against HPV16/18, and the low-risk types HPV6/11 which are responsible for the majority of genital warts[9]. A 9-valent vaccine targeting five additional HR-HPV types[10,11], 31/33/45/52/58, responsible for a further 20% of cervical cancers[12,13], was approved by the US food and drug administration in December 2014 and is expected to be licensed for use in Europe[14–17].

In 2008, the UK introduced an HPV immunisation programme for adolescent girls, primarily as prevention of cervical cancer[18,19], following recommendation from the Joint Committee on Vaccination and Immunisation (JCVI). The JCVI acknowledged a lack of evidence to assess the value of an HPV vaccine programme targeted at MSM (Box 1). Based on findings of a mathematical model, boys were not included in the vaccination programme[19].

Mathematical modelling studies have shown that if boys are vaccinated, as well as girls, the population prevalence of HPV diminishes more quickly but that improving the coverage in girls is more cost-effective than extending vaccination to boys[19,20].

With the current immunisation policy, heterosexual men will gain indirect protection from HPV because their female sexual partners will, as a result of immunisation, be less likely to be infected. The benefit to MSM is expected to be far less and appear more slowly, as their male sexual partners will not have been protected from infection by immunisation. There is some overlap between MSM and heterosexual populations, but it is unclear to what extent indirect protection will, in time, effect any reduction in HPV-related disease amongst MSM. It is likely that MSM will continue to experience high levels of HPV infection and disease while these are declining in the heterosexual population.

BOX 1. EXCERPT FROM THE 2008 JCVI STATEMENT ON HPV VACCINES TO PROTECT AGAINST CERVICAL CANCER

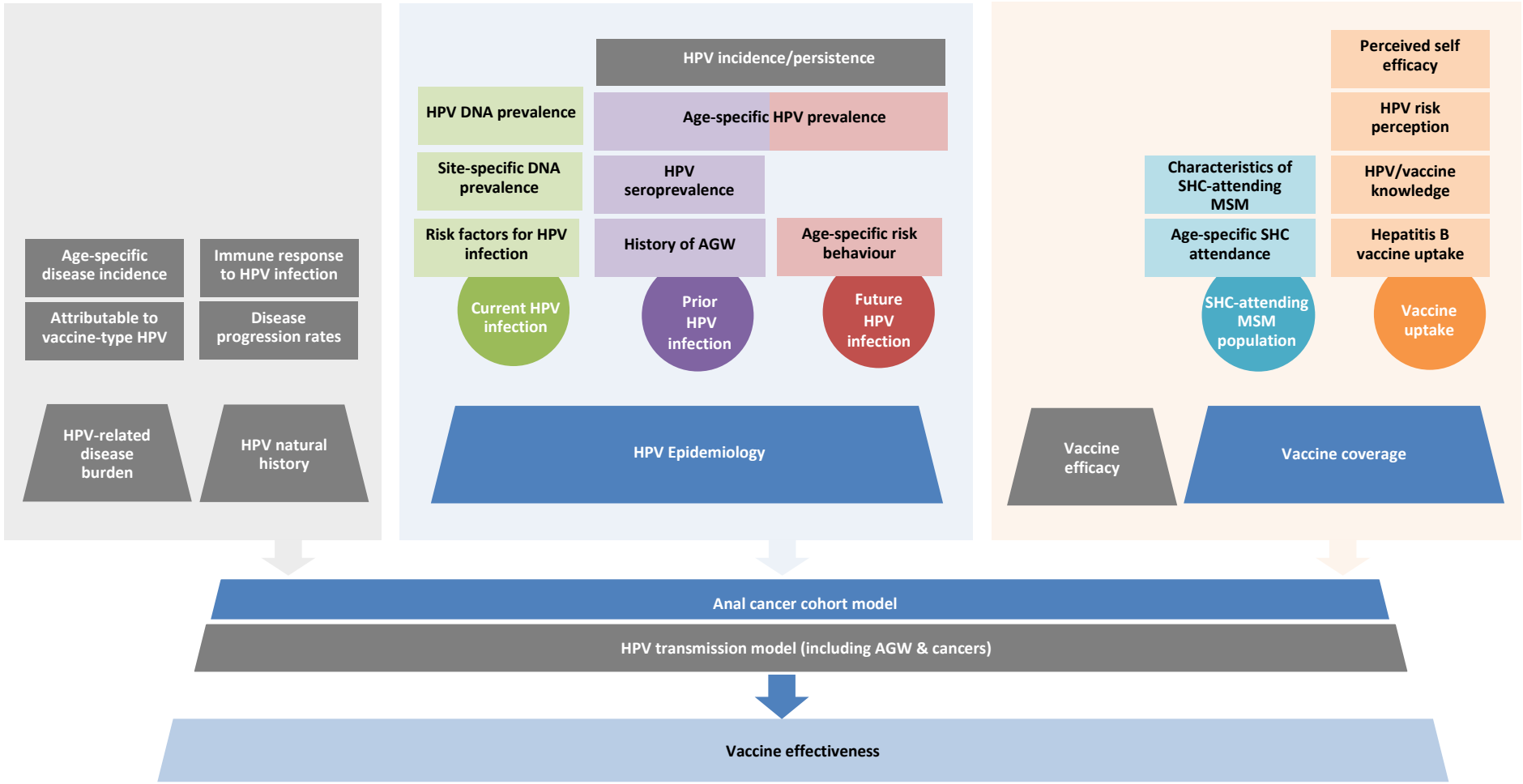
> *"At the time of recommendation, JCVI considered that there was insufficient evidence on the protective effects of the vaccine against cancers affecting males such as anal, and head and neck cancers. When more data becomes available, high-risk groups such as men who have sex with men would be considered."*
>
> *JCVI 2008*

Given the difficulty of identifying MSM at an early stage in their lifetime, for example in a school setting before their sexual debut, the earliest opportunity for a health intervention in this population is likely to be in a sexual health clinic (SHC). Whether this is a suitable service in which to deliver a prophylactic HPV vaccine programme will depend on:

- The proportion of MSM accessing SHCs
- The proportion of MSM at SHCs currently infected with HPV
- The proportion of MSM at SHCs who have prior exposure to HPV and have immunity
- The proportion of MSM at SHCs at risk of HPV exposure
- The proportion of MSM at SHCs who would complete a vaccine course
- The administrative and logistical factors affecting programme delivery

This thesis examines the potential effectiveness of an HPV vaccination programme targeted at MSM attending SHCs by estimating key characteristics of HPV epidemiology and estimates of vaccine coverage in this population. Figure 1 represents the conceptual framework for this thesis and uses colour for concepts that will be estimated as part of this work, for example estimating risk of HPV exposure (current, prior and future), and grey for concepts that will be derived from the literature when synthesising the findings of this thesis.

FIGURE 1. SCHEMATIC REPRESENTATION OF THE CONCEPTUAL FRAMEWORK OF THE THESIS



1.2 RESEARCH QUESTION

Would a targeted HPV vaccine programme for MSM in the UK, delivered in sexual health clinics (SHCs), be likely to be effective?

1.3 AIMS AND OBJECTIVES

The aim of this thesis is to inform the policy decision on whether to vaccinate MSM attending SHCs in the UK

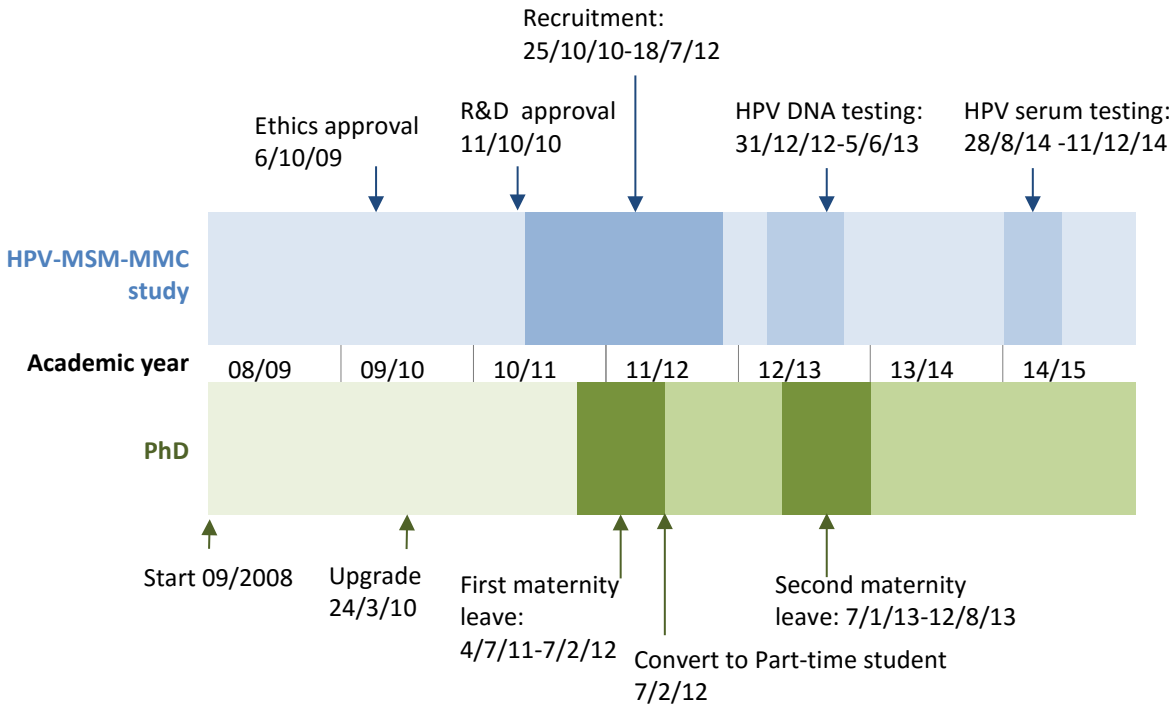
OBJECTIVES

The broad objectives are:

1. To describe the population of MSM attending the Mortimer Market Centre (SHC) in terms of demographics, behaviours and sexually transmitted infections
2. To estimate HPV prevalence and risk factors in MSM who attend SHCs in the UK using different specimen types (anal, external genital, urine and oral)
3. To compare HPV prevalence and risk factors across specimen types
4. To estimate HPV16/18 seroprevalence in MSM who attend SHCs in the UK
5. To estimate anogenital wart (AGW) prevalence in MSM who attend SHCs in the UK
6. To estimate potential vaccine coverage of MSM attending SHCs in the UK
7. To systematically review, appraise and summarise the literature on oral HPV infection in MSM
8. To estimate the effect of a hypothetical targeted HPV vaccine programme for MSM, delivered at SHCs, on HPV16 prevalence and related anal cancer incidence

Specific objectives are listed at the beginning of each results chapter.

FIGURE 2. TIMELINE OF PHD AND HPV IN MSM AT MORTIMER MARKET CENTRE STUDY



1.4 STRUCTURE OF THE THESIS

This thesis is based on an empirical study carried out at the MMC, a sexual health service in central London, among MSM (HPV-MSM-MMC study), and a mathematical modelling study of anal HPV16 infection and anal cancer in SHC-attending MSM. The timeline of the HPV-MSM-MMC study alongside the PhD timeline, including interruptions, is shown in Figure 2.

Chapter 2 summarises the literature on aspects of HPV relevant to this thesis, including the estimates of HPV exposure in MSM available in 2009, at the start of this PhD.

Chapter 3 is a systematic review and meta-analysis of oral HPV infection in MSM up to 2014.

Chapter 4 details the methods used in the HPV-MSM-MMC study, includes descriptive results relating to participant characteristics and behaviour, and addresses the external validity of the study's findings.

Chapter 5 presents the estimates of HPV prevalence and risk factors for HPV DNA detection. The relationship between DNA detection across anatomical sites (anal, external genital, urine and oral) is also explored and risk factors for HPV type-specific concordance at anogenital sites are identified. Findings are put into context with random effects meta-analyses of studies of HPV prevalence in MSM up to mid-2015.

In chapters 6 and 7, prior exposure to HPV infection is estimated, first by measuring seroprevalence of HPV16/18 (chapter 6) and then by measuring the prevalence of AGW (chapter 7).

Chapter 8 explores health service use, HPV knowledge, vaccine attitudes and likelihood of accepting the vaccine, and provides estimates of vaccine uptake in SHC-attending MSM.

Chapter 9 describes a preliminary mathematical modelling study used to inform estimates of vaccine effectiveness against HPV16 and HPV16-related anal cancer in HIV-negative and HIV-positive MSM attending SHCs.

Each chapter's findings are put into context by comparing to estimates from the literature up to 2014.

Chapter 10 extends the context surrounding the research question and discusses the main findings of the PhD and addresses the research question.

1.5 ROLE OF THE CANDIDATE

I received funding for this PhD from the Medical Research Council (MRC DTA). My PhD advisory panel consisted of my primary supervisor, Dr Pam Sonnenberg, my secondary supervisor, Dr Richard Gilson, supervisors of the mathematical modelling study (Professor John Edmunds and Dr Mark Jit) and advisors from Public Health England (PHE; Dr Simon Beddows and Dr Kate Soldan).

HPV-MSM-MMC STUDY

I was involved in the HPV-MSM-MMC study from its conception and was responsible for survey design and development, instrument testing/validation, project management, applications to funders, ethics committee and regulatory bodies, data management, cleaning and analyses and writing the first drafts of publications. I was supported in the study conception by Professor Graham Hart, Dr Pam Sonnenberg and Dr Richard Gilson (RG), and in developing the study protocol and materials by the advisory panel. RG, consultant in genitourinary medicine (GUM), was the principal investigator and he met with the study team regularly to monitor the progress of the study and to discuss problems and solutions, where necessary. He was also involved in the administration and ethics application for the study. While I was on maternity leave, RG was responsible for quality assurance at MMC. The study nurse, Carmel Young, recruited all men to the study, processed blood and oral samples before storing them and shipped all laboratory specimens to PHE. Dr Simon Beddows was responsible for all HPV DNA testing at the Virus Reference Department, PHE, Colindale and Dr Kate Soldan (PHE) organised for Dr Ezra Linley to conduct HPV serology testing at the vaccine evaluation unit, PHE, Manchester. I undertook all the data analyses relating to the HPV-MSM-MMC study in this thesis with statistical support from Dr Andrew Copas and Philip Prah.

ANAL CANCER MODEL

I undertook all the mathematical model development and analyses in this thesis. Dr Richard White and Professor John Edmunds advised on the model set-up at the outset of this PhD. I was supported in decision-making, methodology and interpretation of results in the modelling study by Professor John Edmunds and Dr Mark Jit.

ORAL HPV IN MSM SYSTEMATIC REVIEW AND META-ANALYSIS

I designed and undertook all of the methods in the systematic review and meta-analysis. I was assisted in the interpretation of the random-effects analyses by Dr Andrew Copas, a

senior statistician. Dr Soonita Oomeer, a GUM & HIV speciality trainee registrar, replicated the search strategy, risk of bias assessment and data extraction (in a subset of articles), to validate the findings.

1.6 PUBLICATIONS AND CONFERENCE PRESENTATIONS RESULTING FROM THIS PHD

PUBLICATIONS (APPENDIX VI, PAGE 320)

1. King EM, Gilson R, Beddows S, Soldan K, Panwar K, Young C, Prah P, Jit M Edmunds WJ, Sonnenberg P. 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: 1585–1593. doi:10.1038/bjc.2015.90.

2. King EM, Gilson R, Beddows S, Soldan K, Panwar K, Young C, Prah P, Jit M Edmunds WJ, Sonnenberg P. Oral human papillomavirus (HPV) infection in men who have sex with men: prevalence and lack of anogenital concordance. ***Sex Transm Infect*** 2015;91:284–286. doi: 10.1136/sextrans-2014-051955.

REPORTS

3. King EM, Gilson R, Beddows S, Soldan K, Panwar K, Young C, Prah P, Jit M Edmunds WJ, Sonnenberg P. Human papillomavirus DNA in men who have sex with men: type-specific prevalence, risk factors and implications for vaccination strategies. Submission to the Joint Committee on Vaccination and Immunisation (JCVI), 22 September 2014.

4. Ong KJ, Lin A, Hobbelen P, King EM, Mesher D, Edmunds WJ, Sonnenberg P, Gilson R, Bains I, Soldan K, Jit M. The impact and cost-effectiveness of selective HPV vaccination of men who have sex with men via sexual health clinics: a rapid assessment. Submission to the Joint Committee on Vaccination and Immunisation (JCVI), 22 September 2014.

ARTICLES SUBMITTED TO PEER-REVIEWED JOURNALS

5. King EM, Oomeer S, Gilson R, Copas AJ, Beddows S, Soldan K, Jit M, Edmunds WJ, Sonnenberg P. Oral human papillomavirus infection in men who have sex with men: a systematic review and meta-analysis. ***Cancer Epidemiol Biomarkers Prev***

CONFERENCE PROCEEDINGS

1. King EM, Sonnenberg P, Panwar K, Beddows S, Prah P, Jit M, Soldan K, Edmunds WJ, Gilson R. Prevalence of, and risk factors for, detectable HPV DNA in anogenital swabs and urine of MSM attending a sexual health clinic in London, UK. Poster PH.PP02.41. Poster presentation at the 29th Annual International Papillomavirus Conference, 21–25 August 2014, Seattle, Washington.
2. King EM, Sonnenberg P, Panwar K, Beddows S, Prah P, Jit M, Soldan K, Edmunds WJ, Gilson R. Prevalence of, and risk factors for, detectable HPV DNA in anogenital swabs and urine of MSM attending a sexual health clinic in London, UK: evidence to inform HPV vaccination policy. Poster presentation at the Public Health England Annual Conference 2014, 16–17 September 2014, Warwick University, UK; Poster 202.
3. King EM, Oomeer S, Gilson R, Copas AJ, Beddows S, Soldan K, Jit M, Edmunds WJ, Sonnenberg P. Oral human papillomavirus infection in men who have sex with men: a systematic review and meta-analysis. Abstract: HPV15-0355. Poster presentation at the 30th Annual International Papillomavirus Conference, 17-21 September 2015, Lisbon, Portugal.
4. King EM, Sonnenberg P, Panwar K, Beddows S, Prah P, Jit M, Soldan K, Edmunds WJ, Gilson R. HPV DNA detection in urine, external genital and anal specimens in MSM: concordance between sites, and risk factor comparison. Abstract: HPV15-0352. Poster presentation at the 30th Annual International Papillomavirus Conference, 17-21 September 2015, Lisbon, Portugal.

2. LITERATURE REVIEW

In this chapter, I establish the context of the thesis, combining background information with literature reviews of the epidemiological parameters estimated in this thesis. I adopted this approach in order to reflect the conceptual framework of the thesis (Figure 1, page 20) and the discussion narrative (chapter 10). I have restricted the review to the literature available when developing the research question, up to 2009, and, due to the rapidly accumulating evidence-base during this PhD, have updated these to mid-2015, in the "findings in context" section of each results chapter, and in the discussion.

It starts with a summary of HPV classification and then considers studies that quantify the burden of potentially vaccine-preventable HPV-related disease in MSM. The explanation of HPV natural history, in terms of replication cycle and pathogenesis, links HPV infection to disease. I then review the epidemiology of current HPV infection (DNA detection) in MSM, including age-specific prevalence and risk factors, followed by prior HPV infection, in terms of anti-HPV antibodies and history of AGW. Then I describe the relevance of future risk of infection, estimated from age-specific HPV prevalence and transmission behaviour.

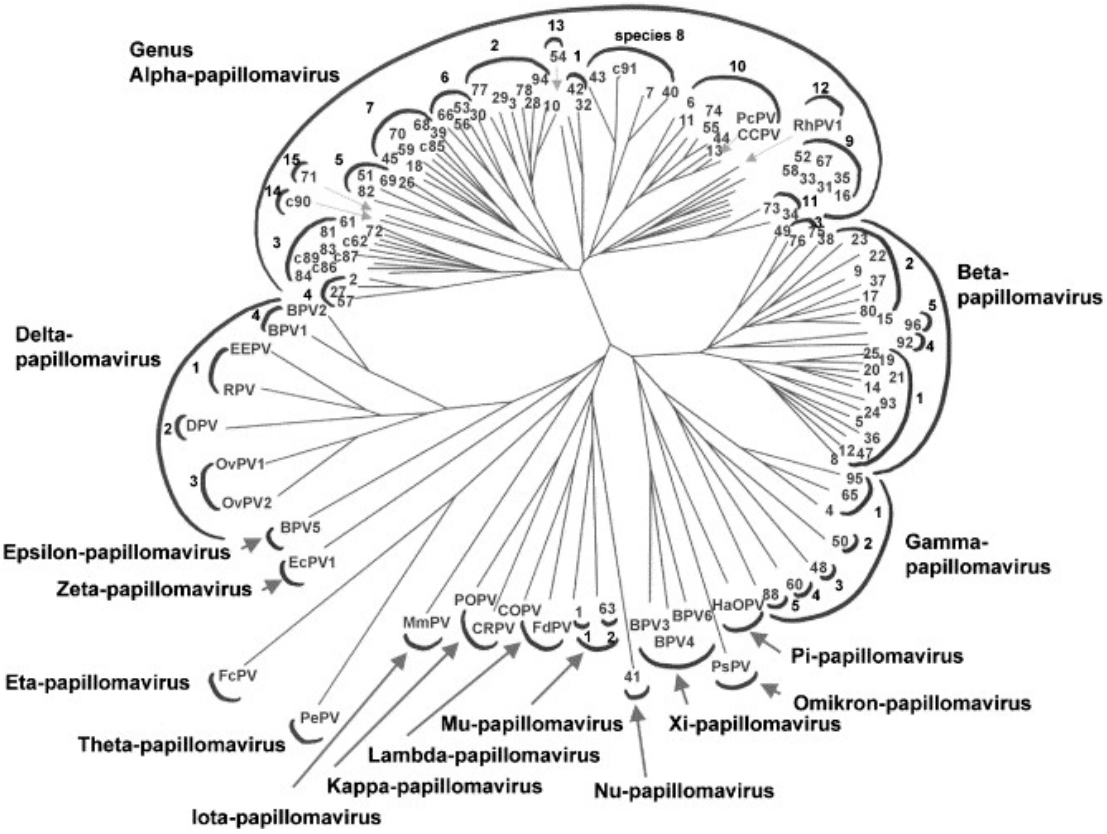
After discussion of HPV infection, I turn to vaccination. First I describe the theory behind interrupting sexually transmitted infections (STIs) through vaccination. I then describe the HPV vaccines and review vaccine efficacy studies. There were no estimates of vaccine efficacy in men at the outset of this PhD, and these important data are reviewed in detail in the thesis discussion, so in this chapter I review efficacy estimates in women, available in 2009. I then describe issues relating to MSM and age at vaccination. Finally, I discuss potential vaccine coverage in the target MSM population and summarise findings from cost-effectiveness analyses available in 2009.

2.1 CLASSIFICATION OF HUMAN PAPILLOMAVIRUSES

Human papillomaviruses belong to the *Papovaviridae* family which is characterised by virus structure and genome organisation. The structure consists of a non-enveloped icosahedral capsid composed of two proteins (the major coat protein, L1; and the minor protein, L2) containing circular double-stranded DNA associated with cellular histones. Of the eight open reading frames (ORF) within the genome, the L1 is the most conserved and is used for

taxonomy. Genera share less than 60% nucleotide sequence identity in the L1 ORF and species share 60-70%. Within species, types share 71-89%, subtypes 90-97% and variants 98%[21]. So far, over 100 types of HPV that infect humans have been identified[22], some of which are displayed in Figure 3.

FIGURE 3. A CLADOGRAM TO SHOW THE EVOLUTIONARY RELATIONSHIP AND CLASSIFICATION OF PAPILLOMAVIRUSES.



Based on the complete L1 ORF of 96 HPV types and 22 animal papillomavirus types. Source: de Villiers *et al*[21].

HPV types are differentially equipped to infect cells, evade immune responses, replicate within, and transmit from, specific host tissue sites. For example, HPV16 is sexually transmitted, infects mucosal surfaces such as the mouth, oesophagus and cervix and can lead to cancer. This work focuses on sexually transmitted HPV types, within the genus alpha-papillomaviruses, that are tropic to mucosal surfaces of the genital and upper digestive tracts of men. Of alpha-papillomaviruses, those that cause warts or respiratory papillomatosis, HPV6 and HPV11, are referred to as low-risk (LR-HPV), those that are associated with malignancies, notably HPV16/18/31/33/35/39/45/51/52/56/58/59/68, are referred to as high risk (HR-HPV) and those possibly associated with malignancies,

HPV26/53/66/70/73/82, are referred to as possible HR-HPV[10,11]. Possible HR-HPV suggests that these types might not be oncogenic, however, given their phylogenetic proximity to other HR-HPV types, it is expected that they would be re-classified as HR-HPV once sufficient data have accumulated to detect this association.

2.2 SEXUALLY TRANSMITTED HPV

HPV transmission depends on skin-to-skin contact and there is strong evidence for sexual transmission, weaker evidence for mouth-to-mouth transmission and inconclusive evidence for fomite or auto-inoculation. Different sex practices involve different anatomical sites with distinct local epithelial environments. For example, the cervix and the anal canal have transformation zones, which are particularly sensitive to HPV infection compared to the keratinised skin of the penis. These differences are reflected in the epidemiology of HPV infection and disease at different anatomical sites.

2.3 HPV-RELATED DISEASE IN MEN AND MSM

HPV-related disease in men includes LR-HPV-related AGW and recurrent respiratory papillomatosis and HR-HPV-related oropharyngeal, penile and anal cancers. Human immunodeficiency virus (HIV) infection is a risk factor for HPV infection, as described on page 42, and MSM are at increased risk of HIV infection, as well as numerous other STIs, compared to men who have sex exclusively with women (MSEW)[23]. Therefore, where possible, the estimates of HPV-related disease outcomes are stratified by HIV status in this review. Furthermore, there appears to be an HIV-independent risk of HPV-related disease in MSM because HIV-negative MSM are at greater risk compared to HIV-negative MSEW.

MSM IN BRITAIN

The National Surveys of Sexual Attitudes and Lifestyles (Natsal) collect population-level data about sexual behaviour in Britain. In 2009, two of these stratified probability sample surveys of the general population had been completed, the first in 1990-1991 (Natsal-1) and the second (Natsal-2) between 1999 and 2001[24]. Table 1 shows the proportion of the British male population reporting same-sex behaviour. In 1990, the proportion of men, aged 16-44, reporting having genital contact with another man in the last five years was 1.5% and in 2000 it was 2.8%[8].

TABLE 1. PROPORTION OF THE BRITISH MALE POPULATION, AGED 16-44, REPORTING SAME-SEX BEHAVIOUR

	Natsal-1 (1990) % (95% CI)	Natsal-2 (2000) % (95% CI)
Homosexual experience ever: any experiences with men-did not necessarily lead to genital contact	6.0 (5.4–6.7)	8.4 (7.6–9.3)
Oral or anal sex, or any other genital contact, with a man ever	3.6 (3.1–4.2)	5.4 (4.8–6.1)
Genital contact with another man in the last 5 years	1.5 (1.2–1.9)	2.8 (2.3–3.3)

Abbreviations: CI= confidence interval, Natsal= National Surveys of Sexual Attitudes and Lifestyles

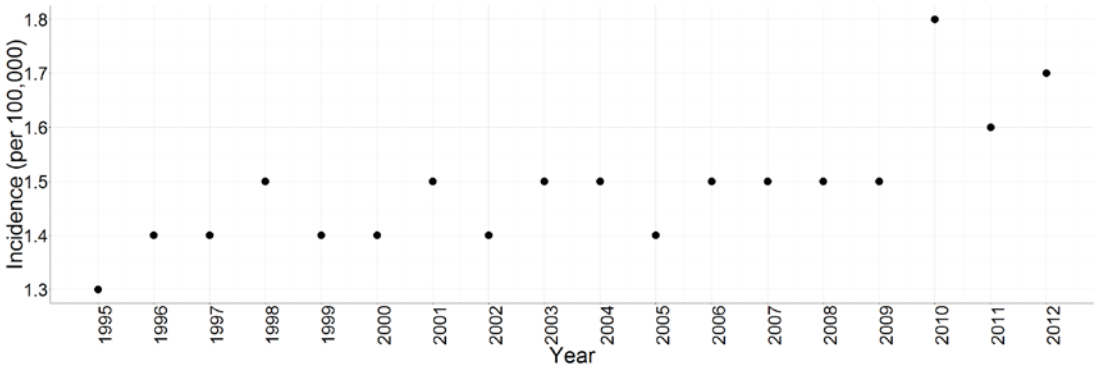
ANOGENITAL WARTS

Overall in men in England in 2009 the incidence of diagnosed episodes of AGW was 163 per 100,000 person years. In 2009, the number of episodes in MSM attending SHC clinics in England was 2,592, representing 6% of all male AGW episodes recorded in SHCs, of which 1,010 (39%) were in MSM residing in London. Incidence was not calculated in MSM due to the uncertainty in the size of the denominator[25]. In women, over 90% of genital warts were associated with HPV types 6 and 11[26].

ANAL CANCER

Anal cancer is rare in men in the UK, with a cancer registry estimate in 2008 of 1.5 per 100,000 person years[27], but is increasing (Figure 4), perhaps due to changes in sexual behaviour[27–29].

FIGURE 4. DIRECTLY AGE-STANDARDISED RATES[a] OF NEWLY DIAGNOSED CASES OF ANAL CANCER PER 100,000 MEN IN ENGLAND 1995-2012[b]

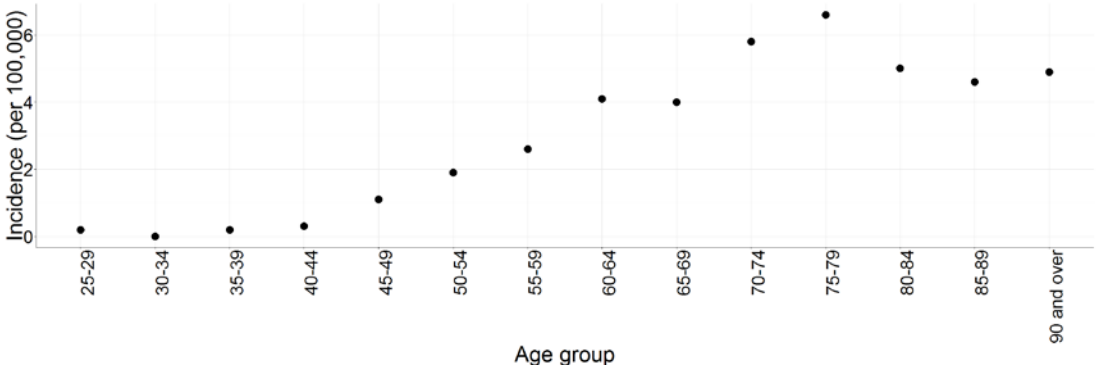


[a]Standardised to the new European Standard Population 2013. [b]Cancers registered before February 2014.

Cancer registries do not collect data on sexual identity or behaviour so determining the risk associated with same-sex sexual behaviour in men compared to exclusively heterosexual

sex is complex. The age-specific rates of anal cancer in men in England (Figure 5) show that cancer is diagnosed in later life, probably resulting from slow disease progression rates.

FIGURE 5. AGE-SPECIFIC RATES OF NEWLY DIAGNOSED CASES OF ANAL CANCER PER 100,000 MEN IN ENGLAND IN 2012[a]



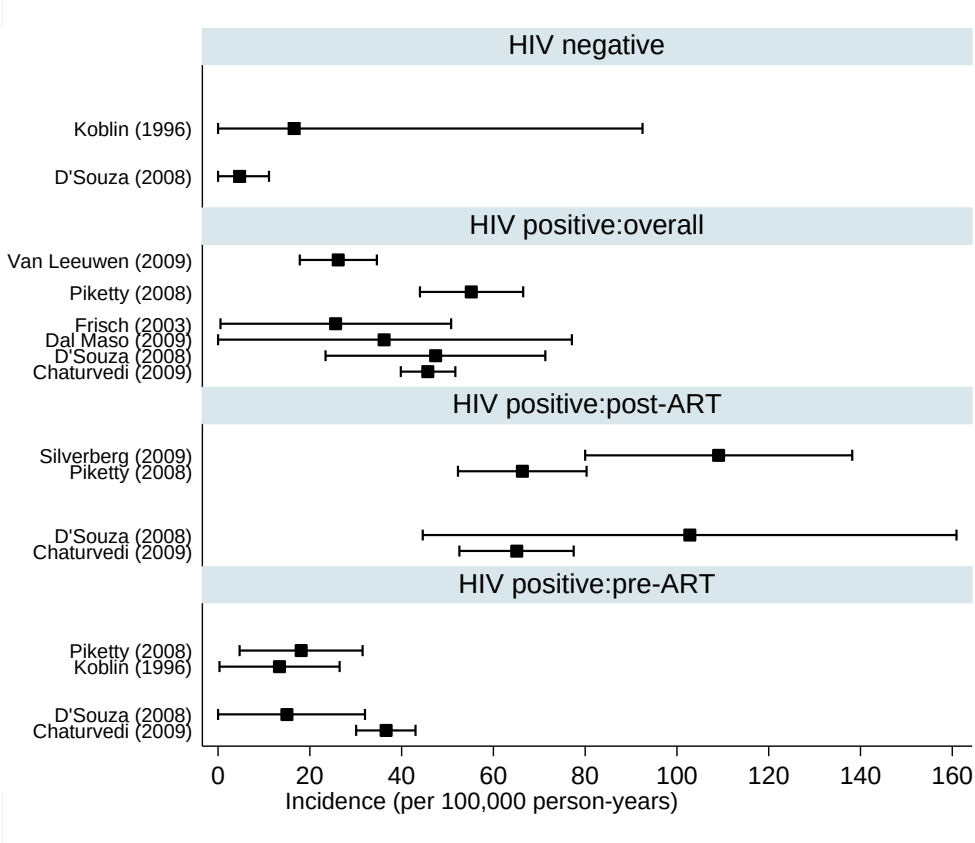
[a]Cancers registered before February 2014. Due to fewer than 20 reported cases in the younger age groups, there is low reliability in the younger estimates.

See page 42, for an explanation of different estimates in MSM by HIV treatment status.

At Chelsea and Westminster hospital, London, in 40,126 patients-years of follow-up of their HIV cohort, there were 26 cases of anal cancer and 25 of these were in MSM. The incidence before the introduction of antiretroviral therapy (ART) in 1996 was 35 per 100,000 patient-years (1984-1995; 95% CI: 15-72) compared to 92 per 100,000 patient-years (95% CI: 52-149) in the post-ART era (1996-2003). Having compared these estimates to those expected in a gender- and age-matched population in England in the same time-frame, these estimates were 67 and 176 times higher in the pre- and post-ART eras, respectively, compared with the general population[30].

Figure 6 shows international studies that have estimated anal cancer incidence in MSM populations. The majority of estimates are from the US. Men in registered homosexual partnerships in Denmark between 1989 and 1997 had 31 times the risk of diagnosed anal cancer compared to the expected incidence from the overall male population[31]. It has been estimated that 77-88% of anal cancer is related to HPV[32,33]. Evidence that the risk of anal cancer is greater in MSM[31] suggests that they are also more susceptible, because of risk behaviour, to other HPV-related outcomes.

FIGURE 6. ANAL CANCER INCIDENCE ESTIMATES, WITH 95% CONFIDENCE INTERVALS, IN INTERNATIONAL MSM POPULATIONS[a], ACCORDING TO HIV STATUS AND COMBINED ANTIRETROVIRAL THERAPY ERA.



Abbreviations: HIV=human immunodeficiency virus, post-ART= post combined anti-retroviral therapy era (1996-2009), pre-ART=pre-combined ART era (before 1996), US=United States of America. [a]in studies conducted before 2009 in Australia, Denmark, France, Italy and the US. Koblin (1996)[34], D'Souza(2008)[35], Van Leeuwen (2009)[36], Piketty (2008)[37], Frisch (2003)[31], Dal Maso (2009)[38], Chaturvedi (2009)[39], Silverberg (2009)[40].

PENILE CANCER

Like anal cancer, cancer of the penis is rare in the UK, with a similar incidence for men of 2.0 per 100,000 person years in 2008[27], but the proportion estimated to be HPV-related is lower at 50%[41]. The overall preventable disease burden in men is therefore less than for anal cancer.

OROPHARYNGEAL CANCER

HPV is associated with oropharyngeal cancers[10]. The tonsils and base of tongue (anatomical sites within the oropharynx) have HPV-susceptible reticulated epithelium at the base of crypts within the stratified squamous epithelium of lymphatic tissue. In men in the UK in 2008, the incidence of cancers of the lip, oral cavity and pharynx was 16.8 per 100,000 person years. Incidence of male tonsillar cancer was 2.7 per 100,000 person years and of

male base-of-tongue cancer was 1.5 per 100,000 person years[27]. The proportion of oropharyngeal cancers attributed to HPV varied by region and by time period, rising (in Europe) from 35% in cohorts recruited before 2000 to 59% in cohorts recruited between 2000 and 2004 and 73% between 2005 and 2009[42]. While it is known that approximately 25% of head and neck cancers and 45-90% of oropharyngeal cancers are associated with HPV infection[43,44], it is uncertain what the rate of disease progression is in those with HPV infection, or what co-factors may be involved.

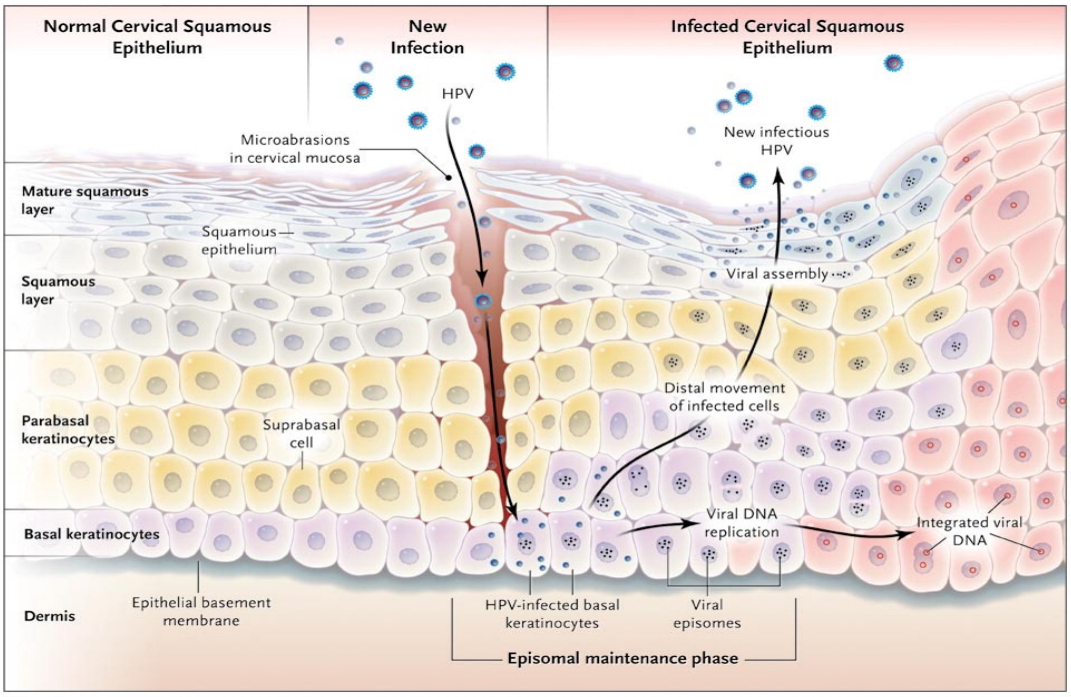
2.4 HUMAN PAPILLOMAVIRUS REPLICATION AND NATURAL HISTORY

HPV-related disease epidemiology does not correspond directly to the underlying pattern of HPV infection because the majority of HPV infections are not pathogenic and are transient, and, in those with persistent infections, the development of cancer takes many years.

The course of HPV infection depends on both the host immune response and viral factors, especially HPV immune evasion capabilities, including the replication cycle, and pathogenesis. Viral pathogenesis and replication are controlled by the eight genes of the viral genome which are grouped into early (E1-E2; E4-E7), late (L1 and L2; capsid proteins) and the LCR. E1 and E2 genes encode the viral replication proteins and E6 and E7 are the viral oncogenes.

Current understanding of the natural history of anal HR-HPV infection is assumed to be similar to that of the cervix, which has been studied in detail. Sexually transmitted HR-HPV is thought to infect keratinocytes at the basal layer of the stratified epithelium at sites of micro-abrasion as shown in Figure 7. Once infected (Figure 8.), either silent infections develop, where viral replication is inhibited and not associated with pathogenicity, or new viral particles are synthesised and released from the upper epithelial layers. Viral synthesis occurs in both productive infections and cervical intra-epithelial neoplasia grade 1 (CIN1). Viral synthesis is associated with ordered viral gene expression and completion of viral replication. Progression to high-grade CIN (CIN2/3) develops with de-regulated gene expression, and progression to cancer is associated with persistence of high-grade CIN (HG-CIN), viral genome integration and deregulated oncogene expression. Regression as well as progression between disease states occurs. Nonetheless, the majority of infections resolve naturally, either completely or resulting in viral latency[45]. Anal lesions are defined similarly to the cervix and termed as anal intra-epithelial neoplasia (AIN).

FIGURE 7. HR-HPV ENTRY INTO BASAL LAYER OF STRATIFIED MUCOSAL EPITHELIUM

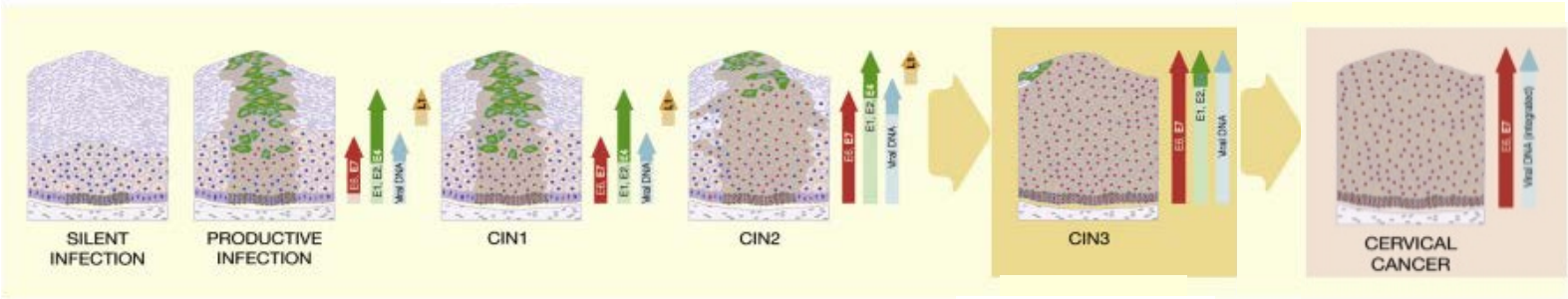


Source: Kahn (2009)[46]

The viral replication cycle is linked to the differentiation of the keratinocyte. During cell division, minimal replication occurs with approximately 50-100 viral copies per cell and then, during cell differentiation, ordered gene expression is triggered, resulting in thousands of viral copies per cell. For a variety of reasons, including the absence of cytolysis, HPV replication does not result in inflammation. Therefore the innate immune response is not triggered and the adaptive immune response is ineffectively primed, permitting HPV infections to persist[47].

Intra-epithelial neoplasia is diagnosed using histology and is graded according to the depth of lesion invasion into the epithelium and the severity of the dysplasia. Using cytology, the Bethesda system classifies squamous cell abnormalities into four categories: atypical squamous cells (ASC), squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intra-epithelial lesion (HSIL). HSIL is the equivalent of AIN2 or AIN3, and LSIL of AIN1[48].

FIGURE 8. CERVICAL HR-HPV INFECTION



Cells in cycle are indicated by the presence of red nuclei. Cells expressing E4 are shown in green, while those expressing L1 are shown in yellow. The brown shading identifies all the cells (differentiated and un-differentiated) that contain viral genomes. Source: Doorbar et al[45].

2.5 PREVALENCE OF HPV INFECTION IN MSM

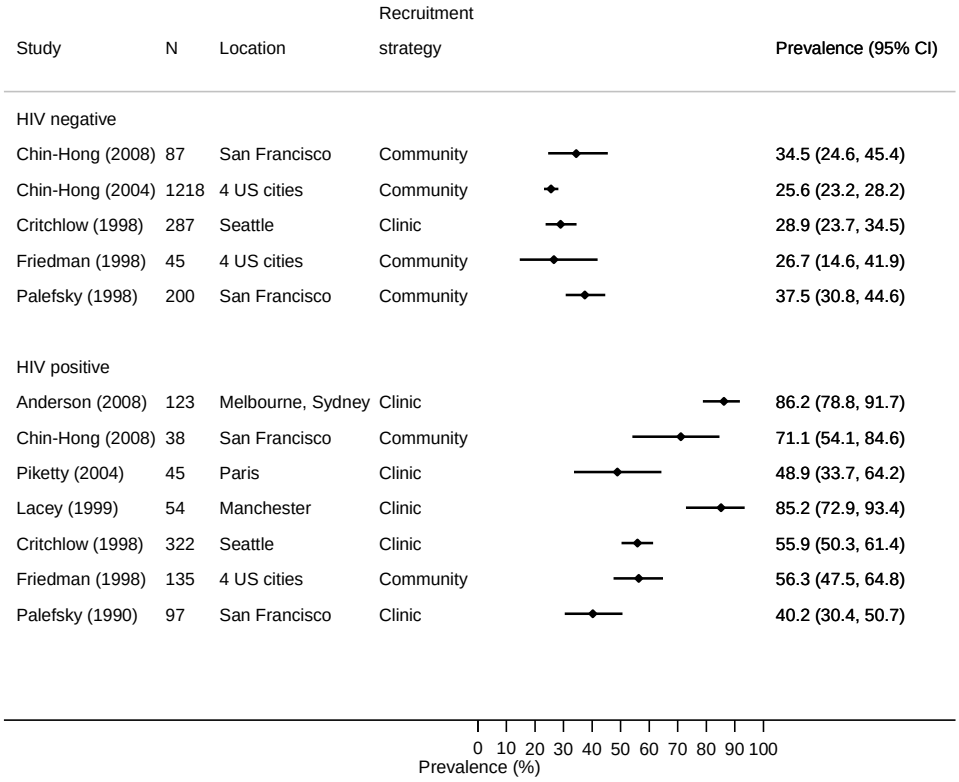
HPV DNA detection by polymerase chain reaction (PCR) is indicative of HPV infection but detection of mRNA would indicate ongoing viral replication, suggestive of active infections that may persist and progress to disease and are probably more clinically relevant[49–51]. All studies estimating the prevalence of HPV infection in MSM have used HPV DNA detection by hybrid capture or PCR and in this thesis, as in the wider literature, HPV DNA detection is used interchangeably with HPV infection.

HIV infection is a risk factor for HPV infection, as described on page 42, so HPV prevalence estimates in this review are stratified by HIV status.

PREVALENCE OF ANAL HPV INFECTION

Studies estimating the crude prevalence of anal HPV infection in MSM up to 2009 are displayed for HR-HPV in Figure 9, for HPV16 in Figure 10, for LR-HPV in Figure 11 and for HPV6 infection in Figure 12. Estimates were not age-standardised. As shown in Figure 9, all five studies measuring the prevalence of at least one HR-HPV type in HIV-negative MSM were performed in the US and only one of these recruited participants in a clinic setting (the acquired immunodeficiency disease syndrome (AIDS) Prevention Project of the Seattle-King County Department of Public Health)[52]. There was variability in the classification of HR-HPV types, especially before 2009, which would have contributed to the differences in estimates between studies[10,53]. A quarter to a third of HIV-negative MSM (range: 26-38%) had at least one detectable HR-HPV type in the anal canal. Chin-Hong *et al.* conducted the largest study in 1218 HIV-negative MSM, the EXPLORE study, and estimated HR-HPV prevalence at 25%[54]. The prevalence of HR-HPV in the anus was generally higher in HIV-positive MSM populations ranging from 40 to 86 percent.

FIGURE 9. STUDIES MEASURING THE ANAL CANAL PREVALENCE OF HR-HPV IN HIV-NEGATIVE AND HIV-POSITIVE MSM POPULATIONS BEFORE 2009.

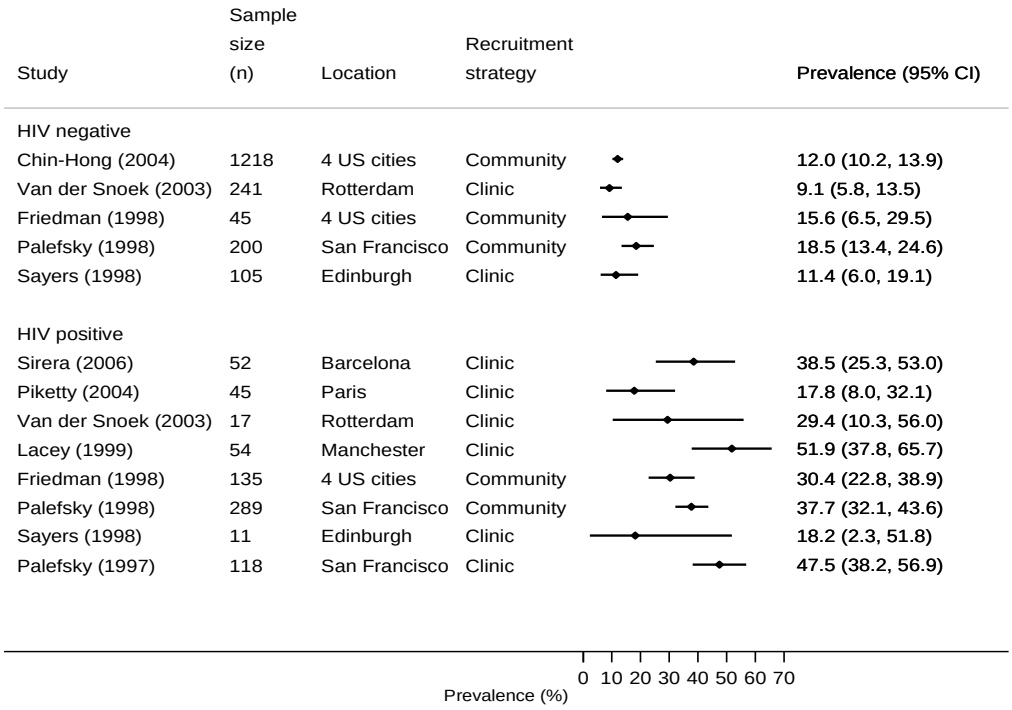


Abbreviations: N= sample size. Chin-Hong (2008)[55], Chin-Hong (2004)[54], Critchlow (1998)[52], Friedman (1998)[56], Palefsky (1998)[57], Anderson (2008), Piketty (2004)[58], Lacey (1999)[59], Sayers (1998)[60], Palefsky (1990)[61].

Figure 10 shows that there were two studies measuring anal HPV16 prevalence in HIV-negative MSM in SHC settings, both in Europe, in 105 MSM in Edinburgh (prevalence=11%) and 241 in Rotterdam (prevalence=9%).

There were more studies of anal HPV16 prevalence in HIV-positive MSM populations. Of the five studies in European clinics, two were in the UK: Edinburgh (n=11)[60] and Manchester (n=54)[59]. Heterogeneity between studies is introduced not only from underlying differences in the population, such as socio-cultural influences on sexual behaviour, or sexual network properties, but also from measurement differences such as sampling method, storage conditions or laboratory assays.

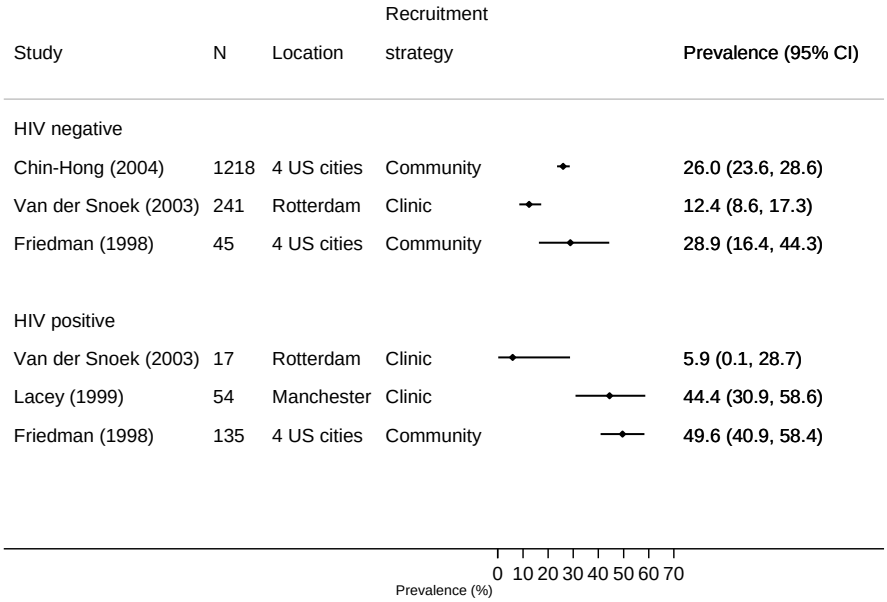
FIGURE 10. STUDIES MEASURING THE ANAL CANAL PREVALENCE OF HPV16 IN MSM POPULATIONS, BY HIV STATUS, BEFORE 2009



Chin-Hong (2004)[54], Van der Snoek (2003)[62], Friedman (1998)[56], Palefsky (1998)[57], Sayers (1998)[60], Sirera (2006)[63], Piketty (2004)[58] Lacey (1999)[59], Palefsky (1997)[64].

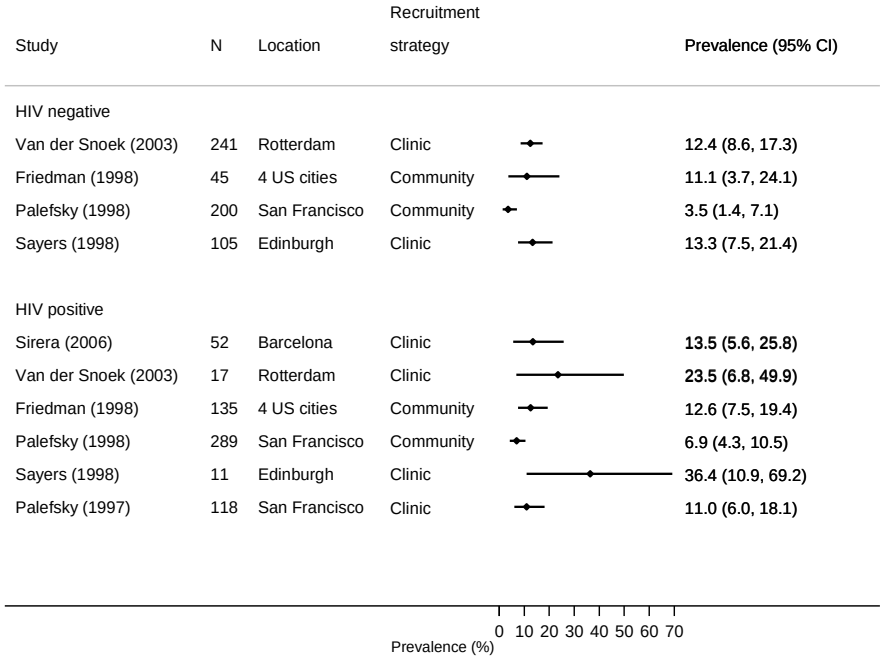
Figure 11 shows the four studies measuring anal LR-HPV prevalence in MSM. Varied classification of LR-HPV types limits the comparison of estimates between studies so Figure 12 displays the estimates from the six studies measuring HPV6 prevalence, of which four recruited from clinic settings. Having stratified estimates by HIV status, four estimates were in HIV-negative (range 4-13%) and six in HIV-positive populations (range 7-36%). Compared to estimates for HPV16 and HR-HPV prevalence, for LR-HPV and HPV6, prevalence did not appear to differ, to the same extent, by HIV status. This pattern was repeated for estimates of HPV11 prevalence, ranging from 3-13% for HIV-negative and 5-27% for HIV-positive MSM.

FIGURE 11. STUDIES MEASURING THE ANAL CANAL PREVALENCE OF LR-HPV IN POPULATIONS OF MSM BEFORE 2009



Abbreviations: N= sample size. LR-HPV definitions: Chin-Hong (2004)[54] =HPV6/11/53/54/55/66/pap155/pap291, Van der Snoek (2003)[62]=HPV6/11, Friedman (1998)[56]=HPV6/11/40/53/54/55/66/pap155/pap291, Lacey (1999)[59]=HPV6/11.

FIGURE 12. STUDIES MEASURING ANAL HPV6 PREVALENCE IN POPULATIONS OF MSM BEFORE 2009



Abbreviations: N= sample size. Van der Snoek (2003)[62], Friedman (1998)[56], Palefsky (1998)[57], Sayers (1998)[60], Sirera (2006)[63], Palefsky (1997)[64]

PREVALENCE AT OTHER ANATOMICAL SITES

The three studies measuring the prevalence of HPV infection at other anatomical sites in MSM populations, before 2009, are presented in Table 2. There were no studies in MSM attending SHCs in the UK. Other studies have compared HPV prevalence at different anatomical sites in non-MSM populations[63,65–67]. Van der Snoek *et al,* conducted a study in Rotterdam, and found that in HIV-positive men, HPV16 was the most frequently detected type (2/17) in penile specimens and in HIV-negative men HPV6 was the most frequently detected type (12/241). Penile HR-HPV prevalence was 3/17 and 19/241 in HIV-positive and HIV-negative MSM, respectively[62].

TABLE 2. STUDIES ESTIMATING HPV PREVALENCE AT EXTRA-ANAL ANATOMICAL SITES IN MSM POPULATIONS

Author (year)	Population	Sample size by HIV status	Penile prevalence % (95% CI)	Oral prevalence % (95% CI)
Van der Snoek (2003)[62]	STI clinic and gay bars/saunas, Rotterdam, The Netherlands	17 HIV+ve 241 HIV-ve	23 (7-50) 16 (11-21)	
Sirera (2006)[63]	HIV clinic, Barcelona, Spain	52 HIV+ve	38 (25–53)	33 (20–47)
Coutlée (1997)[68]	STI/Gasteroenterology clinic, Canada	177 unknown HIV		15 (10-21)

AGREEMENT IN HPV DETECTION BETWEEN ANATOMICAL SITES

Characterising the relationship between HPV infection at different anatomical sites is helpful to understand HPV natural history, to estimate transmission efficiency of specific sexual acts and to explain HPV and related cancer epidemiology.

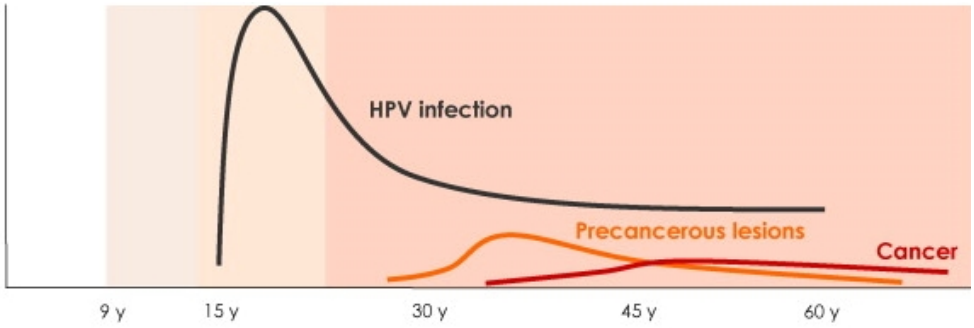
Few studies had examined the relative detection of type-specific HPV between sites. In Spain, penile HPV infection was related to oral HPV infection (OR, 2.7; 95% CI, 1.0–7.7)[63]. However, in 30 men with anogenital HPV-associated lesions, in São Paulo, Brazil, of whom three were homosexual, none had HPV detected at oral mucosa[69].

As a marker for the sensitivity of DNA detection at each anatomical site, the quantity of viral DNA can be measured using real-time PCR and compared across sites. In men in the US, real-time PCR detected the most HPV16 genomes per cell in the penile shaft specimen followed by the anal, peri-anal, coronal sulcus/glans penis, scrotum, semen and urethral specimens[70].

AGE-SPECIFIC PREVALENCE OF HPV INFECTION

Aggregate HPV prevalence is useful for predicting population-level risk but age-specific prevalence provides additional information that is necessary to decide when to vaccinate. The cervical prevalence of HPV rapidly rises in mid-adolescence, corresponding to sexual debut, peaks in late adolescence and declines thereafter (Figure 13)[71].

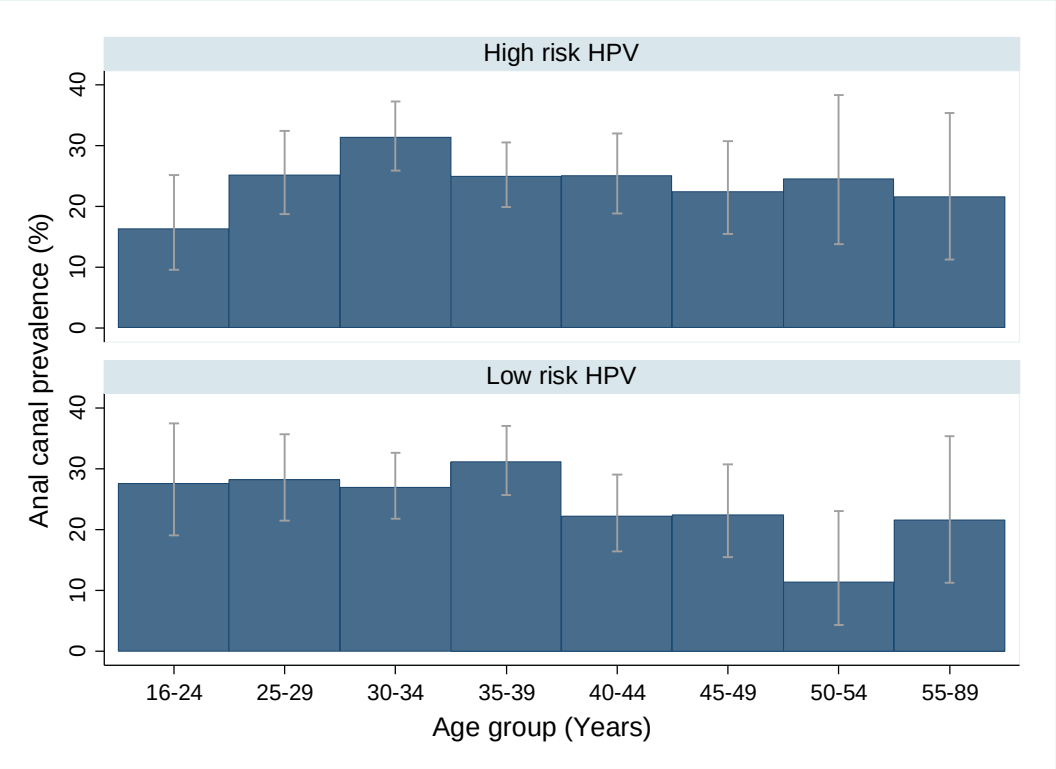
FIGURE 13. AGE RELATIONSHIP OF HPV-RELATED CERVICAL DISEASE



Source: Garland et al[71].

The age-specific anal canal prevalence of HPV was examined in the EXPLORE study of 1218 HIV-negative MSM in the US (Figure 14)[54]. There was no statistically significant age relationship with anal HPV infection (overall, HR-HPV or LR-HPV) or with anal lesions (overall, high grade or low grade). Unlike at the cervix[71], there was no peak in prevalence in the study age range (18-70 years) nor was there a decline in prevalence by age. The majority of men in the EXPLORE study were older than 40 so identifying any age-association in younger men, where prevention is likely to be most beneficial, was limited by sample size.

FIGURE 14. ANAL HPV INFECTION, BY AGE GROUP, IN HIV-NEGATIVE MSM PARTICIPATING IN THE EXPLORE STUDY.



Adapted from Chin-Hong *et al* (2008) to include confidence intervals that were determined using the binomial exact method. HR-HPV types were defined as HPV16/18/31/33/35/39/45/51/52/56/58/59/68/73 and LR-HPV types were defined as HPV6/11/53/54/55/66/Pap 155/Pap 291[54]. NB. The EXPLORE study definition of HR-HPV differs from that used in this thesis (Box 5, page 92)

RISK FACTORS FOR HPV INFECTION AND DISEASE

Factors that have been identified as risk factors for HPV infection in MSM are displayed in Table 3. HIV infection is associated with widespread disruption of the innate and adaptive immune responses, including depletion of CD4+ T cells which are required for effective cell-mediated immunity (CMI)[72]. This impairment to the CMI response might contribute to HIV-associated increased susceptibility to HPV infection, reactivation from latency or duration of infection. Immunosuppression, in combination with increased STI transmission behaviours, would explain the higher HPV prevalence estimates in HIV-positive MSM (Figure 9, page 37) and increased likelihood of HPV disease progression. For example, Palefsky *et al* found that a larger proportion of HIV-positive MSM, who were free of baseline anal HPV-related disease, were found to develop AIN, compared with HIV-negative MSM[73].

A marker for severity of HIV-associated immunosuppression is the CD4 T cell count; the number of T cells expressing the cell surface glycoprotein CD4 per cubic millimetre of

blood. A marker for HIV replication is the number of HIV RNA copies per millilitre of blood. ART has evolved in efficacy over the last 25 years to restore CD4 cell counts and reduce viral replication so that viral load can become undetectable. HPV infection is more likely at reduced CD4 counts yet, following population-level immune reconstitution (ART era), anal cancer rates are still increasing (Figure 6). This is because HIV-positive populations on therapy have increased life expectancy and therefore increased time at risk of HPV-related cancer development, in later life, when the majority of HPV-related cancers are diagnosed (Figure 5). Furthermore, whilst CD4 T cell numbers are restored with ART, the complex balance of functionally different T cells and the associated cytokine cocktail is not regained so there remains immune function impairment in treated HIV-positive populations.

Other factors that increase susceptibility to HPV-related disease include immunosuppressive therapy in transplant recipients[74,75], oestrogen levels[76]; smoking[77]; injected drug use; age; coinfection with *Chlamydia trachomatis*[78] or herpes simplex virus (HSV)[79]; anal receptive intercourse in men; and constant irritation or chronic inflammation of the anus[80–83]. Factors that have been identified in MSM are displayed in Table 3.

TABLE 3. RISK FACTORS FOR HPV INFECTION IN MSM IDENTIFIED IN STUDIES PUBLISHED UP TO 2009

Risk factor	HIV status[a]	Association (95% CI)	Ref.
Behaviours			
Medium/high Lifetime level (frequency and time period) of receptive anal sex compared to no receptive anal sex	-	RR=1.5 (1.1-2.1)	57
> 500 lifetime partners compared to <50	-	OR=2.22 (1.01-4.87)	84
> 30 partners in the last 6 months compared to <6	-	aOR=2.3 (1.5-3.6)	54
Receptive anal intercourse in the last 6 months	-	aOR=2.0 (1.5-2.8)	54
Versatile compared to insertive preference during anal sex	-	OR=2.09(1.09-2.01)	84
Lifetime rectal drug use in HIV-negative MSM	-	RR=1.4 (1.1-1.7)	57
Sexually Transmitted Infections			
HIV-positive	N/A	RR=1.5 (1.4-1.7)	57
Chlamydia infection of the anus in last 12 months	-	OR 3.06 (0.83-11.35)	84
Seropositivity for HSV-2	-	OR 1.86 (1.01-3.45)	84
Clinical			
Anal bleeding in the last 12 months	+	OR=8.36 (1.05-66)	84
Lifetime history of genital warts	-	OR 3.26 (1.45-7.33)	84
Lifetime history of rectal discharge	-	aOR 3.00 (1.30-6.81) RR=1.3 (1.0-1.7)	57

[a]HIV status of the population in which the association was found. Abbreviations: ref.=reference number, -=HIV-negative, +=HIV-positive, -/+=Both HIV-negative and HIV-positive. HSV=herpes simplex virus, RR=relative risk, OR=Odds ratio, aOR=adjusted OR, HR=Hazard Ratio, 95% CI= 95% confidence interval, N/A=Not Applicable

2.6 CUMULATIVE EXPOSURE TO HPV

Prevalence is a measure of the proportion of infected individuals at one point in time. It does not convey information about the dynamics of the infection that are important for estimating cumulative risk of HPV exposure. Prevalence is a function of incidence, the rate of occurrence of new infections, and duration of infection (prevalence=incidence x duration). Age-specific HPV type-specific incidence and clearance rates could be estimated in longitudinal studies but in 2009 these studies had not been conducted in MSM.

The utility of age-specific HPV prevalence for estimating periods of high incidence was demonstrated in women, where maximum incidence occurs in late adolescence (Figure 13). In MSM, where no age-relationship has been defined, other measures of cumulative risk, such as age-specific seroprevalence and history of AGWs, precancerous lesions or cancer, are useful. Each measure has its own limitations so combining these measurements provides the best estimate of age-specific likelihood of prior exposure to HPV.

2.7 HPV SEROPREVALENCE

Seropositivity is a specific but insensitive marker of prior exposure because seroconversion does not always follow natural infection and duration of antibody persistence is variable. In a population of young heterosexual male students in Seattle less than 36 percent seroconverted within two years of HPV infection and seroconversion was associated with genital site of infection and smoking[85]. Questions remain as to the clinical relevance of seropositivity: are infection-induced antibodies effective against re-infection and are they involved in clearance? Seroconversion is not necessary for viral clearance and antibody concentrations are several times lower than those induced by vaccination[86,87]. Furthermore the distribution of duration of infection-induced serum antibodies is not well characterised which limits the use of seropositivity as a direct marker of cumulative exposure.

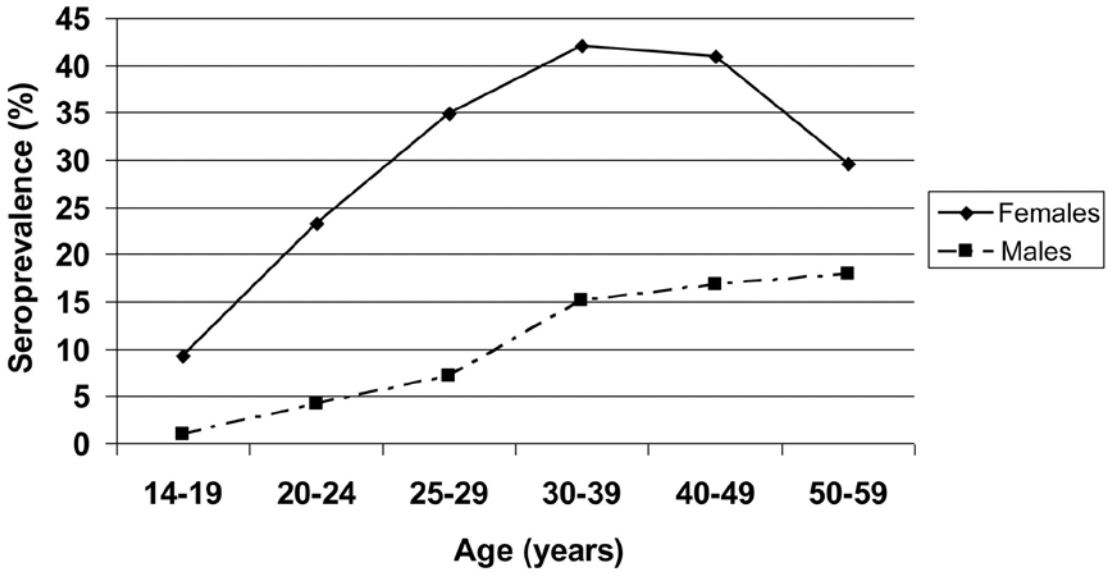
Laboratory tests of seropositivity involve binding of antibodies to virus-like particles (VLPs) detected in a variety of ways such as traditional enzyme-linked immunosorbent assay (ELISA) or competitive Luminex assays. Each assay has its own sensitivity for antibody detection and calibration for antibody quantification.

Seroprevalence had been estimated in one population of MSM, recruited between 1989 and 1995 to an AIDS prevention study from a clinic in Seattle[88]. Less than half of HIV-negative MSM were seropositive for HPV16 (48%; 95% CI 37-58) or HPV6 (41%; 95% CI 31-51) with similar estimates in HIV-positive MSM (HPV16=42%; HPV6=32%). The presence of AGW, a history of gonococcal urethritis and detectable anal HPV6 DNA were associated with HPV6 antibody detection. In contrast, HPV16 seropositivity was associated with being older than 35 years, reporting more than 50 lifetime partners and intravenous drug use. Notably, HIV status, anal HPV16 DNA detection and anal squamous intraepithelial lesions (low or high grade) were not associated with seropositivity[88].

AGE-SPECIFIC SEROPREVALENCE

Men in the National Health and Nutrition Examination Survey (NHANES), between 2003–2004, representing the US population, had a lower seroprevalence, of any quadrivalent-vaccine type, than women (Figure 15) and far lower than MSM in Seattle (as above) with overall estimates of 6% for HPV6, 2% for HPV11, 5% for HPV16, and 2% for HPV18. Seroprevalence was significantly associated with age with men aged 50-59 having a 13-fold risk of seropositivity for any quadrivalent type compared to men aged 14-19 years[89].

FIGURE 15. SEROPREVALENCE OF ANY QUADRIVALENT HPV TYPE, AMONG MALES AND FEMALES, BY AGE GROUP, IN THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY 2003–2004.



Source: Markowitz *et al* (2009)[89]. Quadrivalent vaccine types=HPV6/11/16/18. National Health and Nutrition Examination Survey (NHANES) is a population-based survey in the US.

2.8 AGE-SPECIFIC AGW PREVALENCE

A diagnosis of AGW is a useful marker for exposure to LR-HPV types because AGW development is more likely following HPV infection and occurs sooner than HPV-related cancer development. In England, the genitourinary medicine clinic activity dataset (GUMCAD) routinely collects data on AGWs episodes diagnosed at SHCs, including MSM status, age, and clinic[90]. Of the 2,592 AGW episodes diagnosed in MSM attending SHCs in England in 2009, 8% were in 15-19 year olds, 25% in 20-24 year olds, 33% in 25-34 year olds and 34% in MSM older than 34 years[25]. At a population-level, there is potential for selection bias if not all AGWs episodes are diagnosed or recorded by health services.

2.9 FUTURE RISK OF INFECTION

Although age-specific HPV DNA prevalence, seroprevalence and AGW history can inform estimates of future risk of HPV infection, prevalence at older ages might also be due to increased duration of HPV infection or antibodies resulting from changes in host immunity over time. Age-specific estimates of STI transmission behaviour, such as condomless anal sex, offer an alternative, as proxy measures for risk of infection, in the absence of any studies directly measuring HPV incidence in MSM in 2009.

It is possible that in MSM, like in women, STI transmission declines with age. For example, in the GMSHS, conducted in community venues and SHCs in London in 1996, 66/356 (19%) of MSM younger than 25 years, 220/1149 (19%) of MSM aged 25-34 and 84/612 (14%) of men older than 34 years reported condomless sex with a partner of unknown or discordant HIV status in the last year[91].

2.10 EPIDEMIC THEORY AND VACCINATION

The basic reproduction number, R_0, is defined as the expected number of secondary cases produced by a single, typical, infection in a susceptible population. For STIs, R_0 can be calculated by multiplying the average transmission probability per partnership (β) by the number of partnerships per unit of time (c) by the duration of infectiousness (D)[92].

The basic reproduction number is not applicable to the HPV epidemic in MSM, where a proportion of the population are infectious, a proportion immune (assuming that there is effective natural immunity) and a proportion susceptible. In such a mature epidemic, the number of new cases arising from an infectious person is represented by the effective reproduction number (R_n) which is calculated by multiplying R_0 by the

proportion of the population that is susceptible. Vaccination reduces the proportion of the population that is susceptible, by "removing" them if they develop effective vaccine-induced immunity, and therefore further reduces R_n.

R_n is a useful epidemic parameter for predicting the course of an epidemic because when this is above one an epidemic will occur, when below one an epidemic cannot be sustained and at unity it will persist so becoming endemic. This threshold property can be manipulated to determine the critical proportion of the population that must be immune to eliminate transmission, the herd immunity threshold, which is calculated as one minus the reciprocal of R_0. Vaccine coverage above the herd immunity threshold will result in elimination of transmission and below the threshold will result in the reduction of R_n but not elimination.

This theory is based on population average estimates of β, c and D. In reality, however, MSM populations are heterogeneous in terms of β because different sexual acts are associated with different transmission risks and both partnership duration and frequency of sexual acts within partnerships are variable. Furthermore, there is a highly skewed and wide distribution of partner change rates with some individuals reporting monogamy and others numerous overlapping partnerships, and rates are not constant for the same individual over time. In HPV infection, there is also heterogeneity in D: estimates of clearance rates are type-specific and persistent infections, with a unique D, represent a distinct infection type from transient infections[93].

Heterogeneity results in a different R_n in each sub-population contributing differentially to the overall R_n. Targeting constrained intervention resources at sub-populations with a high R_n, such as MSM attending SHCs, compared to sub-populations with low STI transmission behaviours (low R_n), or spreading resources throughout the entire population, will maximise the reduction of average R_n. This explains the concept of a "core group", one which disproportionately influences the spread of disease by virtue of its higher R_n, often attributed to higher rates of partner change (c)[92].

SEXUAL NETWORKS

Calculations of R_0 and R_n rely on the assumption that individuals acquire sexual partners at random (mass action principle) which does not reflect reality where a set of complex factors play a role in sexual selection. Social network theory can estimate an individual's

importance in a network which is proportional to the extent the network would be interrupted if they were removed. Graph theory can quantify numerous network properties such as clustering and connectedness, and percolation theory allows estimation of the spread of infection through a network and so can dynamically predict the size of an epidemic. This is relevant to vaccination because an individual's network position puts them at risk of acquiring and transmitting an infection which may not be discernible from their individual risk behaviour. Immunising individuals at important network positions will be the most efficient way of disrupting the spread of infection and reducing both individual and population-level risk of HPV infection[94].

2.11 HPV VACCINES

See discussion, page 238, for review of vaccine efficacy literature 2009-present

In 2009, there were two licensed vaccines in the UK: the bivalent vaccine (Cervarix®) protecting against HPV16/18 and the quadrivalent vaccine (Gardasil®) protecting against HPV16/18, and the low-risk types HPV6/11. Gardasil® was indicated for use in women aged 9-26 and Cervarix® in women aged 10-25. Neither had yet been evaluated for use in men.

MODE OF ACTION, TARGETED TYPES

Vaccines contain VLPs that are made up of genetically engineered L1 proteins conferring type-specific humoral immunity when injected intramuscularly. Vaccine-induced HPV type-specific neutralising antibodies are thought to prevent the virus from entering human cells but not from attaching to the cell surface. The bivalent vaccine induces antibodies specific to HPV16 and 18 and the quadrivalent induces antibodies to HPV6, 11, 16 and 18.

RANDOMISED CONTROLLED VACCINE TRIALS IN WOMEN

Vaccine efficacy is estimated in randomised double-blinded controlled trials. For HR-HPV, it is not feasible to estimate the efficacy against cancer, because of slow progression rates, so efficacy was estimated against HPV infection and cancer precursors. At the outset of this PhD, vaccine efficacy estimates were only available in populations of young women with no detectable history of HPV infection. The phase III trials for the bivalent and quadrivalent vaccines showed continued efficacy above 90%

against CIN2/3 in the per protocol arm for 6.4 years (Cervarix®) and 5 years (Gardasil®)[95] with no safety concerns[96].

2.12 TIMING OF HPV VACCINATION

As shown in Figure 13, in order to prevent HPV infection in women it is critical to vaccinate prior to the increase in HPV incidence. Previous exposure to HPV might reduce the vaccine benefit if effective natural immunity is generated so that there would be no additional benefit from vaccination or if previous exposure or increasing age reduces immunogenicity of the vaccine. Furthermore, women already infected when vaccinated do not clear these infections more readily and may still develop disease so intervening before infection is the optimal strategy for prevention[97,98].

Early vaccination of MSM has feasibility issues. Targeting adolescent boys by sexual identity, perhaps in schools or university societies, would be difficult and inefficient for a variety of socio-cultural reasons. MSM attending SHCs are engaged with healthcare but, by definition, having engaged in sex with men, may have been exposed to HPV already.

There is also likely to be heterogeneity of sexual behaviour and HPV prevalence between MSM sub-populations, especially across cultural settings (including place) and between those accessing sexual health services and those who do not.

There is no evidence that vaccines have any therapeutic effect on current HPV infections, in that they do not increase the rate of viral clearance or lesion regression[97,99–101]. A determinant of vaccine effectiveness of MSM at SHCs is what proportion are infected, or have already experienced HPV, by the time (age at which) they attend a SHC.

In 2008, a school-based HPV vaccination programme, targeting girls aged 12-13 years, using the bivalent vaccine, was introduced. Gender-neutral vaccination was considered to be too expensive given the expected indirect benefits for boys/men resulting from female vaccination: men would be having sex with vaccinated women, who would not be infected, so would not be at risk[19]. MSM, on the other hand, would not benefit, to the same extent, from this herd immunity despite being disproportionately affected by HPV-related disease.

2.13 POTENTIAL VACCINE COVERAGE

Interrupting HPV transmission in MSM in the UK by vaccinating MSM who attend SHCs will be optimised if all MSM attend SHCs, opt to receive the vaccine, and complete the vaccine course.

MSM AND SEXUAL HEALTH SERVICE USE

There is inconsistency in the definition of MSM throughout the UK's sexual health clinics. British Association for Sexual Health and HIV (BASSH) guidelines recommend asking about sexual behaviour in the last three months which may offer more standardisation of this population[102]. In 2007, 63,181 episodes of care at SHCs were recorded for MSM and 45,748 HIV tests were offered. In 2008, 70,146 episodes of care at SHCs were recorded for MSM[7] and a proportion of these represent repeat attendances. In the Natsal-2 (2000) survey, 27% of men who reported having sex with another man in the last year had attended a SHC in the last five years [8].

The results of the Gay Men's Sexual Health Survey (GMSHS) carried out annually in London suggest that men selected from pubs, clubs and bars in 2000 were more likely to attend a SHC than those in the general population[103]. In addition, men in the GMSHS who attended a SHC were more likely to have had ten or more sexual partners, had an HIV test or an STI diagnosis than those who had not attended a SHC. In Natsal-2, MSM attending a SHC were more likely to be unemployed, of black ethnicity, and to have ten or more sexual partners than those in the general population[104].

VACCINE UPTAKE

Predictors of vaccine uptake

MSM who perceive themselves to be at risk of HPV infection, believe in the efficacy of the vaccine (outcome expectancies) and in their ability to receive the vaccine and complete the course (perceived self-efficacy) are more likely to intend to receive the vaccine. Behavioural intention is the first stage in the process of health behaviour change[105].

Hepatitis B virus vaccine in sexual health clinics

In 2001 in the UK, the National Strategy for Sexual Health and HIV (Department of Health) recommended that all MSM should be offered hepatitis B virus (HBV) vaccination at their first attendance at a SHC[106]. The HPV vaccines have similar dosing schedules to the HBV vaccine with either a course with injections at 0, 1 and 6 months

or 0, 2, and 6 months. Uptake data from the HBV programme are likely to reflect the anticipated uptake of any vaccination programme with the HPV vaccine.

The effectiveness of this policy has been monitored by the UK's Health Protection Agency (HPA; from 2013 part of Public Health England; PHE) using the HepB3 survey. In 2006, 92% of eligible MSM accepted the 1st dose of the vaccine course but only 38% of eligible MSM received the 3rd dose[107].

2.14 HPV VACCINE COST-EFFECTIVENESS STUDIES IN MEN IN THE UK

In the UK, two dynamic cost-effectiveness modelling studies had been performed of HPV vaccination of girls by 2009, and both showed this strategy was likely to be cost-effective[19,108]. One model also assessed the impact of vaccinating 12 year-old boys on AGWs and cervical cancer and found that extending vaccination to boys slightly reduced the incidence of cervical cancer and AGWs, particularly when vaccine protection was short-lived, but was unlikely to be cost-effective because there were few additional benefits given the high expected effectiveness that would be achieved with high vaccine coverage of girls (80%)[19].

BOX 2. SUMMARY OF RELEVANT KNOWLEDGE BASE AT THE OUTSET OF THIS PHD

HPV-related disease burden in MSM:

- HPV-related disease in MSM includes anogenital warts, anogenital cancers and head and neck cancers
- Anal cancer incidence in HIV-negative MSM is higher than in HIV-negative MSEW and increasing
- Anal cancer incidence is higher in HIV-positive MSM compared to HIV-negative MSM, especially in the ART era

HPV-epidemiology in MSM:

- Few studies on HPV infection in SHC populations of MSM
- Few studies on HPV infection in MSM in Europe
- Little known on anatomical site-specific prevalence
- Few studies estimating age-specific prevalence of HPV infection in MSM
- No longitudinal studies of HPV infection in MSM
- Only one study estimating seroprevalence in MSM
- No studies estimating age-specific seroprevalence in MSM

HPV vaccine efficacy:

- Had not been demonstrated in men
- Had only been demonstrated against HPV infection and cervical disease endpoints
- Uncertainty whether vaccine prevents re-infection or confers cross-protection
- No studies in previously-exposed or immune-impaired (e.g. HIV-positive) populations

HPV vaccine estimates of cost-effectiveness in UK:

- Mathematical modelling studies suggest that gender-neutral HPV vaccine programmes in schools would not be cost-effective while coverage in girls is high

3. ORAL HUMAN PAPILLOMAVIRUS INFECTION IN MEN WHO HAVE SEX WITH MEN: A SYSTEMATIC REVIEW AND META-ANALYSIS

In this chapter I describe the objectives, methods and results of a systematic review of oral HPV DNA detection in MSM. Analyses include a meta-analysis and meta-regression of oral HPV prevalence and a meta-analysis of the association of same-sex sexual behaviour in men and oral HPV infection. I also summarise risk factors for oral HPV infection in men and MSM, review oral incidence and clearance rates and summarise findings on oral-anogenital concordance.

3.1 OBJECTIVES

1. To conduct a meta-analysis of the prevalence of oral HPV infection in MSM (HPV16, quadrivalent-vaccine type HPV, HR-HPV and any HPV).
2. To explore heterogeneity of oral HPV prevalence using meta-regression.
3. To conduct a meta-analysis of the association of HPV infection in MSM compared to MSEW.
4. To review incidence and clearance rates for oral HPV infection.
5. To review risk factors for oral HPV prevalence, incidence and persistence.
6. To review the relationship of oral and anogenital infection.

3.2 METHODS

A systematic review was performed of studies measuring HPV DNA prevalence, incidence and/or persistence in the oral cavity of MSM. Studies were included in HIV-negative and HIV-positive populations, published in English, where an MSM-specific estimate was available in at least five MSM. Case-control studies and studies in clinical case series (e.g. transplant recipients, oral lesions), which might have introduced additional heterogeneity to prevalence estimates, were excluded.

For oral HPV prevalence estimates, conference abstracts that were superseded by journal articles were excluded and baseline estimates were selected from multiple estimates in longitudinal studies.

Databases were searched on 20th October 2014 using the search terms mouth/oral /oropharangeal, HPV/ papillomavirus /papillomaviridae and man/ men /boy$/ adult /male$ /MSM/ "men who have sex with men"/ gay$ /homosexual$ /bisexual$. Medline was searched via PubMed and Medline, Embase and psycINFO using the Ovid platform (Version: OvidSP_UI03.13.01.101, SourceID 63482) using the search strategy in Box 3. Reference lists of included articles were also reviewed to validate the search strategy.

BOX 3. SEARCH TERMS AND STRATEGY FOR MEDLINE/EMBASE/PSYCHINFO VIA THE OVID PLATFORM AND PUBMED

Ovid platform search strategy	1. ((mouth or oral or oropharangeal) and (HPV or papillomavirus or papillomaviridae) and (man or men or boy$ or adult or male$ or MSM or "men who have sex with men" or gay$ or homosexual$ or bisexual$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. limit 1 to english language 3. remove duplicates from 2
Pubmed user query	((("mouth"[MeSH Terms] OR "mouth"[All Fields]) OR ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) OR oropharangeal[All Fields]) AND (HPV[All Fields] OR ("papillomaviridae"[MeSH Terms] OR "papillomaviridae"[All Fields] OR "papillomavirus"[All Fields]) OR ("papillomaviridae"[MeSH Terms] OR "papillomaviridae"[All Fields]))) AND (("men"[MeSH Terms] OR "men"[All Fields] OR "man"[All Fields]) OR ("men"[MeSH Terms] OR "men"[All Fields]) OR boy$[All Fields] OR ("adult"[MeSH Terms] OR "adult"[All Fields]) OR ("male"[MeSH Terms] OR "male"[All Fields]) or MSM or “men who have sex with men” or “gay$” or “homosexual$” or “bisexual$”) AND English[lang]

STUDY SELECTION

All screening and study selection methods were performed independently by Eleanor King (EK) and Soonita Oomeer (SO) and discrepancies were resolved by consensus. Publications were screened via the title, then, if not enough detail was available, via the abstract, and then the full text. Where data were not stratified by sex and sexual orientation, and both variables were reported in the publication (not conference abstract), the corresponding

author was contacted, via emails (initial and three week follow-up), for additional data. If there was no response the publication was excluded. Additional stratified data were obtained from four of the six authors contacted for this purpose.

DATA EXTRACTION

All data extraction was performed by EK using a data extraction form. An independent reviewer (SO) checked and validated a random 50% of articles. Independent data extraction is based on good practice, as outlined in the PRISMA guidelines, although the proportion of papers extracted that needs validation is not specified[109]. Discrepancies would have been agreed by consensus but none were identified. Data extracted, where available, are detailed in Box 4.

BOX 4. DATA EXTRACTED FROM STUDIES, OVERALL AND FOR EACH ANALYSIS

All studies:

Author name, year of publication, median age and range (years), study location, source of recruitment, HIV status, specimen collection method and HPV DNA detection/genotyping assay(s)

Studies included in the summary HPV prevalence estimation:

Number of MSM in the sample and those with any HPV DNA detected, any high risk HPV types, and low risk HPV types and, individually, the number with HPV16, HPV18, HPV6, and HPV11.

Studies examining risk factors for oral HPV DNA:

Statistically significant ($p<0.05$) risk factors in univariate analyses, factors included in multivariate models, and factors that were statistically significant in multivariate models

Studies included in meta-analysis of oral HPV prevalence in MSM compared to MSEW:

The number of MSM and the number of MSEW with and without HPV

Little variation was found in the authors' definition for HR-HPV and LR-HPV and this was used in the meta-analysis. Substantial variation was found in HPV detection/genotyping assays (Table 4). Definitions of MSM varied according to what was available in each publication and were based on either reported behaviours (any sex with men) or sexual orientation. Median age was used to reduce the impact of skewness on the summary statistic for the age distribution. Where median age (for MSM strata, by HIV status) was not available, authors were contacted. If there was no response the mean age was used. Median age estimates were obtained from nine of the 11 authors contacted.

ASSESSMENT OF RISK OF BIAS

For studies included in the HPV prevalence estimation and risk factors for current HPV DNA detection the STROBE checklist (which examines selection and information bias) was used, for items to be included in reports of observational studies[110]. A count of checklist items was used as a marker for risk of bias in each study. Low risk of bias was assigned if at least 20 items were identified, medium if 15 to 19, and high if fewer than 15. Strobe count was explored as a potential source of heterogeneity using meta-regression.

STATISTICAL ANALYSIS

HPV DNA prevalence in MSM was determined as the percentage with detectable DNA in the total number of samples that were tested and adequate for PCR. For consistency, Clopper-Pearson 95% confidence intervals (CI) were calculated for each study, superseding the published intervals. The true population prevalence was not expected to be equal in all studies due to heterogeneity in study populations, specimen collection, and testing, so random effects meta-analysis was used to calculate a pooled estimate with a 95% confidence interval. Heterogeneity was quantified using the I^2 statistic.

A random effects meta-regression was performed to examine the effect of HIV status, recruitment source (sexual health clinic [SHC], HIV clinic, community), oral specimen collection method (rinse/gargle alone or combination, other without rinse/gargle), STROBE count, and median age of participants on prevalence of HPV DNA and HR-HPV DNA. Age and HIV were included *a priori* in a multivariate meta-regression model and other variables significant in univariate analyses. P values were obtained by comparing the multiparameter

Wald test statistic to the appropriate F distribution with Knapp-Hartung modification to standard errors.

Odds ratios (OR) were calculated to represent the effect of male same-sex activity on oral HPV prevalence within each study, and random-effects meta-analysis was used to calculate a pooled OR and 95% CI. Small study bias was considered by examining a funnel plot of the inverse of the standard error and the OR.

Estimates of incidence and clearance rates were standardised to the same unit (per 1000 person-months), and these rates were approximately calculated if they were not presented but sufficient information was reported. For example if median duration of infection was given, in months, an exponential rate was assumed and the rate of clearance was calculated as the inverse of median duration of infection multiplied by 1000. 95% CIs were calculated for these rates using the Poisson exact method. Given the heterogeneity introduced by different approximate methods of estimation, a meta-analysis was not performed on these data.

All meta-analyses were conducted using either the metareg, metaprop[111] or metan functions downloadable from the Boston College Statistical Software Components (SSC) archive and used with Stata 13.1.

TABLE 4. CHARACTERISTICS OF THE STUDIES, AND THEIR PARTICIPANTS, DESCRIBING ORAL HPV PREVALENCE, INCIDENCE, CLEARANCE RATE, RISK FACTORS AND ANOGENITAL CONCORDANCE IN MSM.

					Laboratory assays							Number of MSM		
Study/ publication	**Ana.[a]**	**risk of bias [b]**	**Study location**	**Oral spec.[c]**	**DNA extraction**	**PCR amplification**	**Genotyping**	**HR-HPV def.[d]**	**Med. Age (years)**	**Recruit.**	**HIV[e]**	**MSM**	**Any HPV det.**	**HR-HPV det.**
Human papillomavirus in men (HIM)														
Kreimer (2011)[112]	r		Mexico,		Robotic MDx Media kit		HPV Linear Array Genotyping	n/a			U	130	4	
Kreimer (2013)[113]	p, i/c	low	Brazil, USA	rin/g	(Qiagen)		test (Roche)	n/a	32	com/ clin	U	147	7	2
HIV & HPV in MSM (H2M)														
Mooij (2013)[114]	p,r	low	Amsterdam	rin/g	MagNA Pure LC Total Nucleic Acid Isolation Kit (Roche)	DNA Enzyme Immuno Assay (HPV DEIA, Labo Bio-medical Products)	HPV LiPA25 (Labo Bio-medical products)	A	37.6		-	453	125	40
									45.6		+	314	178	78
Mooij (2014)[115]	i/c							A	38	com/ clin	-	413		
									47		+	276		
Van Rijn (2014)[116]; relationship to seropositivity								D	46		-	441		
									38		+	306		
Multicenter AIDS Cohort Study (MACS)								C		com				
Beachler (2012)[117]	p,r	low	Baltimore, Chicago, Pittsburgh	rin/g	magnetic bead automated platform (QIAsymphonySP, Qiagen)		PGMY09/11 & reverse blot hybridisation				-	173	48	29
											+	192	86	44
Can Ruti HIV-positive Men cohort (CARH-MEN)								B		HIV clin				
Videla (2013)[118]	p, i/c	low	Spain	cytob/g	Qiamp Viral DNA kit (Qiagen)		IVD-CE *F*-HPV typing (Molgentix)		40		+	458	71	
Darwich (2014)[119]	i/c													
Melbourne SHC cohort study								B		STI clin				
Read (2012)[120]	p,r	low	Australia	tampon- & rin/g &swab	MagNA Pure LC Total Nucleic Acid Isolation Kit (Roche)	PGMY09/11 &PCR-ELISA detection protocol	HPV Linear Array Genotyping test (Roche)		33		-	251	18	5
									37		+	249	47	20
Ong (2014)[121]	i/c		Australia	rin/g				mean=52			+	173		
Human papillomavirus infection in adolescent men who have sex with men (HYPER)														
Zou (2014)[122]	p	low	Australia	rin/g	VERSANT kPCR Molecular System SP (Siemens) or MagNA Pure 96 (Roche)	PGMY09/11 &PCR-ELISA detection protocol	HPV Linear Array Genotyping test (Roche)	n/a	19	com	-	200	4	

TABLE 4. CHARACTERISTICS OF THE STUDIES, AND THEIR PARTICIPANTS, DESCRIBING ORAL HPV PREVALENCE, INCIDENCE, CLEARANCE RATE, RISK FACTORS AND ANOGENITAL CONCORDANCE IN MSM. CONTINUED.

					Laboratory assays							Number of MSM		
Study/ publication	Ana.[a]	risk of bias [b]	Study location	Oral spec.[c]	DNA extraction	PCR amplification	Genotyping	HR-HPV def.[d]	Med. Age (years)	Recruit.	HIV[e]	MSM	Any HPV det.	HR-HPV det.
Other														
Beachler (2013)[123]	i/c		Baltimore, US	rin/g	Puregene DNA purification kit (Gentra systems)	PGMY09/11 & reverse blot hybridisation		C	46		+	69		
Parisi (2011)[124]	p	medium	Italy	swab	QIAamp DNA mini kit (Qiagen) & ExoSAP-IT (USB corp.)	MY09/MY11 primers followed by GP5+/GP6+ if negative	sequencing and analysis in NCBI BLAST	C	42	HIV clin	+	134	27	2
Sirera (2006)[63]	p,r	high	Spain	cytob	F-HPV Typing Kit (Molgentix, BCN, Spain)	multiplex F-HPV PCR with a set of 15 fluorescently labeled primers	Capillary electrophoresis on ABI 3,130 XL genetic analyzer and GeneMapper 4.0 Software (Applied Biosystems, CA).	B	mean =42	HIV clin	+	52	17	
Del Mistro (2012)[125]	p,r	high	Italy	saliva	proteinase K/phenol/chloroform	MY09/MY11 primers followed by nested biotinylated GP5+/GP6+ if negative	direct sequencing or reverse line Blot using Consensus High Risk HPV genotyping kit (Qiagen)	A	40.3	HIV clin	+	38	16	7
Colon-López (2014)[126]	p,r	low	Puerto Rico	rin/g	DNA purification from buccal cell protocol from Gentra PureGene kit (Qiagen)	INNO-LiPA HPV Genotyping Extra Amp	INNO-LiPA HPV genotyping Extra assay (Innogenetics)	n/a	mean =38.5	STI clin	U	57	11	
Gaester (2014)[127]	p,r	high	Sao Paulo	rin	Illustra Tissue and Cells GenomicPrep Mini Spin Kit (Easton Turnpike)	MY09/MY11 primers &g gel electrophoresis	Papillomastrip, based on reverse blot technique(Operon Immune & molecular diagnostics)	n/a	43	HIV clin	+	127	10	
Ong (2014)[121]	p	high	Australia	rin/g & rin/g after brushing & toothb	MagNA Pure 96 isolation and purification systmen (Roche)	PGMY09/11 &PCR-ELISA detection protocol	HPV Linear Array Genotyping test (Roche) or SPF10-LiPA 25 assay version	B	52	STI clin	+	173	45	26

TABLE 4. CHARACTERISTICS OF THE STUDIES, AND THEIR PARTICIPANTS, DESCRIBING ORAL HPV PREVALENCE, INCIDENCE, CLEARANCE RATE, RISK FACTORS AND ANOGENITAL CONCORDANCE IN MSM. CONTINUED.

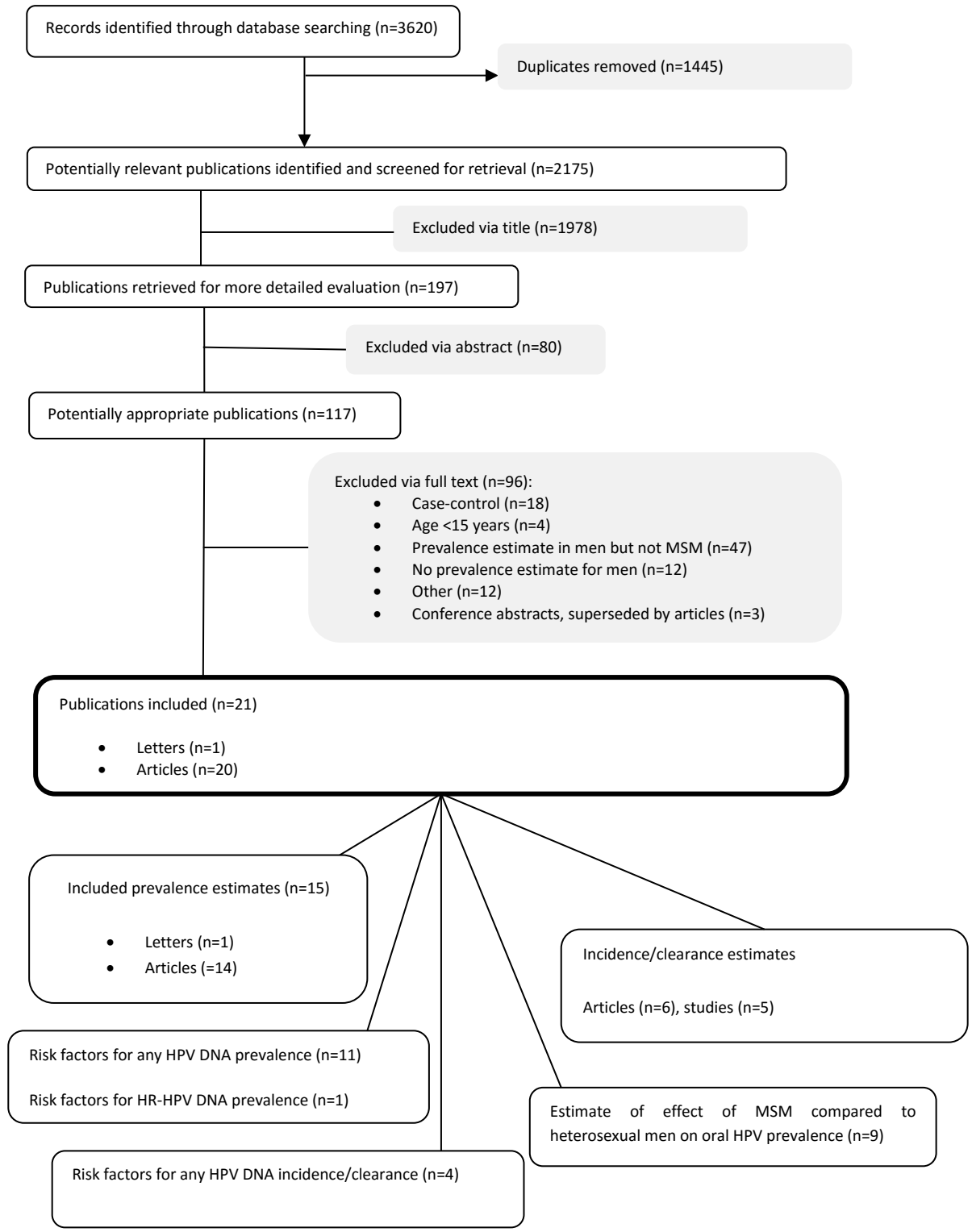
					Laboratory assays							Number of MSM		
Study/ publication	Ana.[a]	risk of bias [b]	Study location	Oral spec.[c]	DNA extraction	PCR amplification	Genotyping	HR-HPV def.[d]	Med. Age (years)	Recruit.	HIV[e]	MSM	Any HPV det.	HR-HPV det.
Coutlée (1997)[68]	p,r	low	Canada	cytob	Lysed with Tween 20 and NP-40	MY09/MY11 primers, spotting onto nylon membranes, HPV generic probe labelled with ^{32}P-deoxynucleotides	type-specific oligonucleotide probes end-labelled with ^{32}P-ATP	n/a	40	STI / gastro-enterocli n	U	177	26	
D'Souza (2014)[128]	p,r	low	Baltimore, US	rin/g	magnetic bead-based automated QIASymphony SP (Qiagen)	PGM09/11 followed by reverse line blot hybridisation	HPV Linear Array Genotyping test (Roche)	C	22	STI clin	U	21	1	0
Antonsson (2014)[129]	p,r	medium	Brisbane, Australia	rin/g	QIAamp DNA mini kit (Qiagen) QIAGEN supplementary protocol for isolation of DNA	GP5+/GP6+ agarose gel; Agencourt AMPure PCR purification kit	Sequencing followed by BLAST database	n/a	22	uni	U	15	1	
Cameron (2005)[130]			Louisiana, US	saliva	Qiagen DNA extraction kit (extracted for saliva cellular pellets)	PGMY09/11				HIV clin	+			

Abbreviations: SHC=sexual health clinic, HYPER= human papillomavirus infection in adolescent men who have sex with men, [a]Ana=analysis: publications included in prevalence study meta-analysis (p), risk factor analysis (r), incidence/clearance rates (ic).Oral spec[c]=oral specimen type:rin=rinse, g=gargle, cytob=cytobrush, toothb=toothbrush [d]HR-HPV def=definition: HPV16/18/31/33/35/39/45/51/52/56/58/59= A; with additional/68=B; with additional /68/73=C. HPV16/18/31/33/45/52/58=D. Med age=median age. Recruit=recruitment strategy, com=community, clin=clinic, uni=university, gasteroentero=gasteroenterology [e] HIV status: +=HIV-positive; -=HIV-negative; U=unknown. Det.=detection.

3.3 RESULTS

2175 articles were identified and 1978 excluded based on information in the title. A further 80 were excluded based on information in the abstract and a further 96 having retrieved the full text (Figure 16). 20 articles were included and one letter representing 17 different studies. Details of the studies, including methods, risk of bias, number of MSM recruited and number with HPV detected are shown in Table 4.

FIGURE 16. FLOW DIAGRAM OF SCREENING AND SELECTION PROCESS

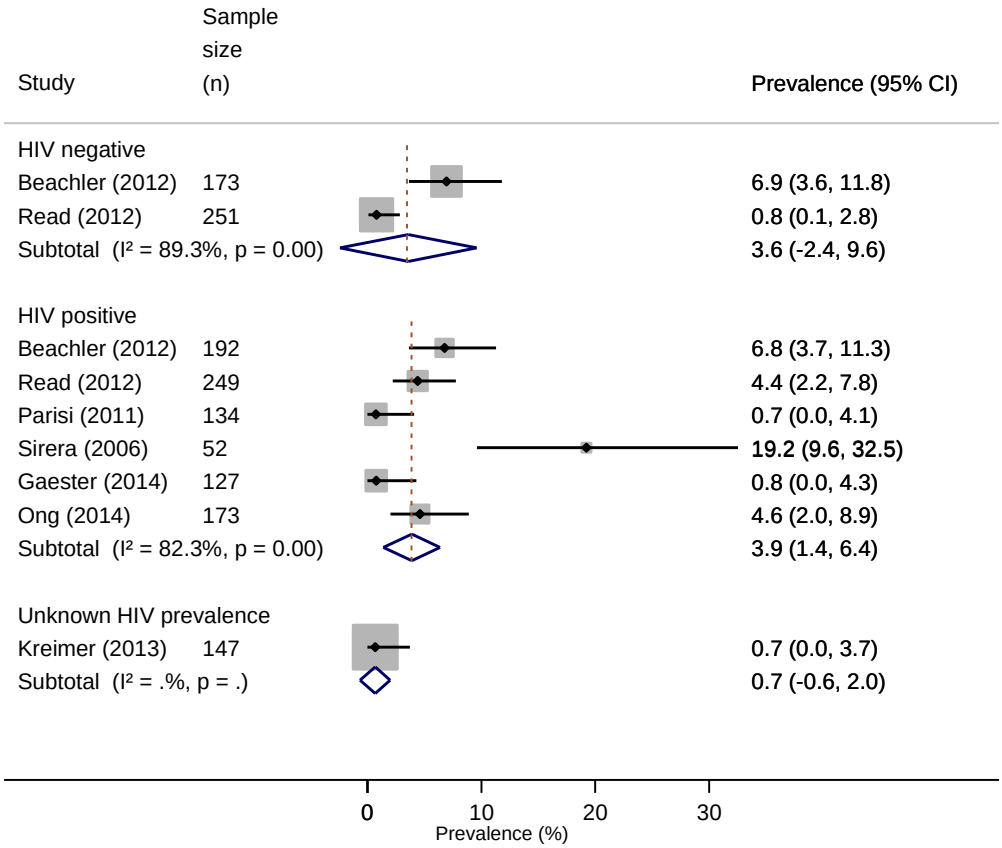


ORAL HPV DNA PREVALENCE

For oral HPV DNA prevalence, 16 studies were included. Estimates of HPV16 prevalence, were available from ten studies, for any quadrivalent-vaccine type from four studies [113,114,120,127], for HR-HPV from 11 studies[68,113,126,128,129] and for any HPV DNA prevalence estimates were available from five studies that included 1228 HIV-negative MSM[114,117,120,122,131], nine studies that included 1737 HIV-positive MSM[63,114,117,118,120,121,124,125,127], and five studies that included 417 MSM with unknown HIV status.

Figure 17 shows that the random-effects pooled prevalence of HPV16 was 3.6% (95% CI -2.4-9.6) in HIV-negative and 3.9% (95% CI 1.4-6.4) in HIV-positive MSM. High heterogeneity was seen across studies in both HIV groups (I^2= 80% and 82%, respectively).

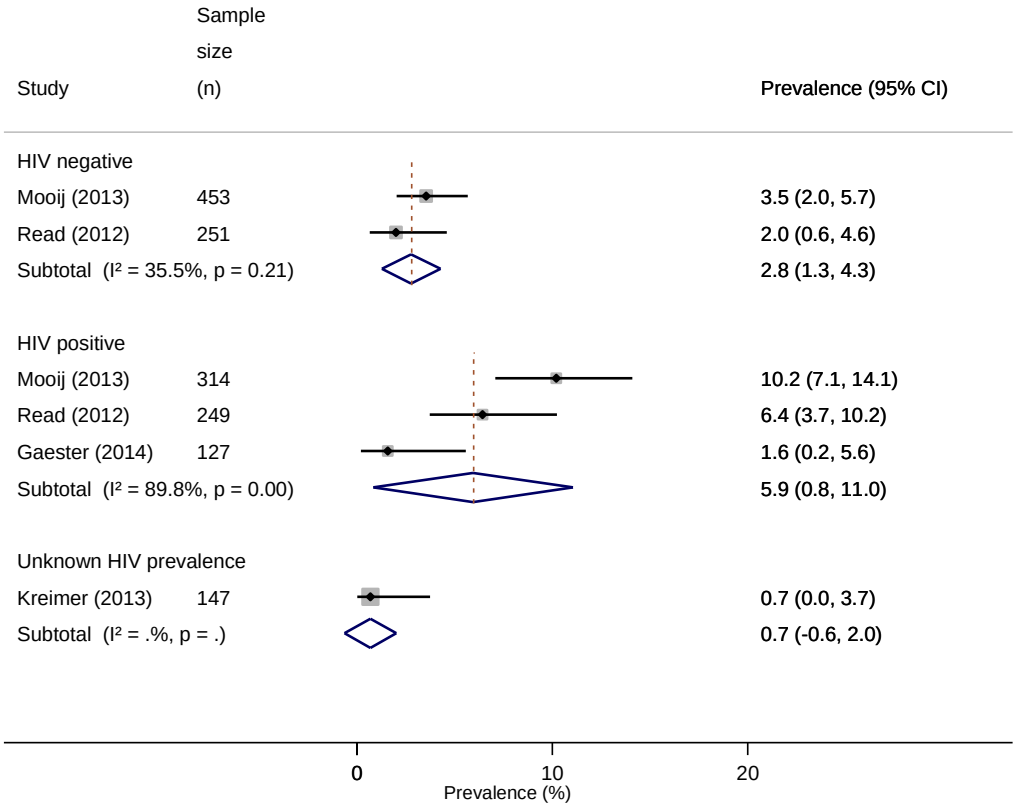
FIGURE 17. RANDOM-EFFECTS ANALYSES OF STUDIES ESTIMATING ORAL HPV16 PREVALENCE IN MSM.



Weights are from random effects analyses. Abbreviations: HPV= Human papillomavirus, MSM=Men who have sex with men, HIV=Human immunodeficiency virus. Beachler (2012)[117], Read (2012)[120], Parisi (2011)[124], Sirera (2006)[63], Gaester (2014)[127], Ong (2014)[121] and Kreimer (2013)[113].

Only three studies measured HPV18, HPV11 and HPV6 prevalence, all in HIV-positive MSM[63,124,127]. Only one of these detected HPV18 in 2/52 MSM (3.8% 95% CI 0.5-13.2)[63] and two studies detected HPV11 DNA (2/52 and 1/134)[63,124]. All three studies detected HPV6 (2/52, 1/134, 1/127), with a pooled estimate of 1.1% (95% CI -0.0-2.3%) and low heterogeneity between these three estimates (I^2= 0%, p=0.48). Figure 18 shows the four studies measuring the prevalence of any quadrivalent-vaccine type HPV detection. The pooled prevalence was 2.8% (95% CI 1.3-4.3%) in HIV-negative MSM and 5.9% (95% CI 0.8-11.0%) in HIV-positive MSM.

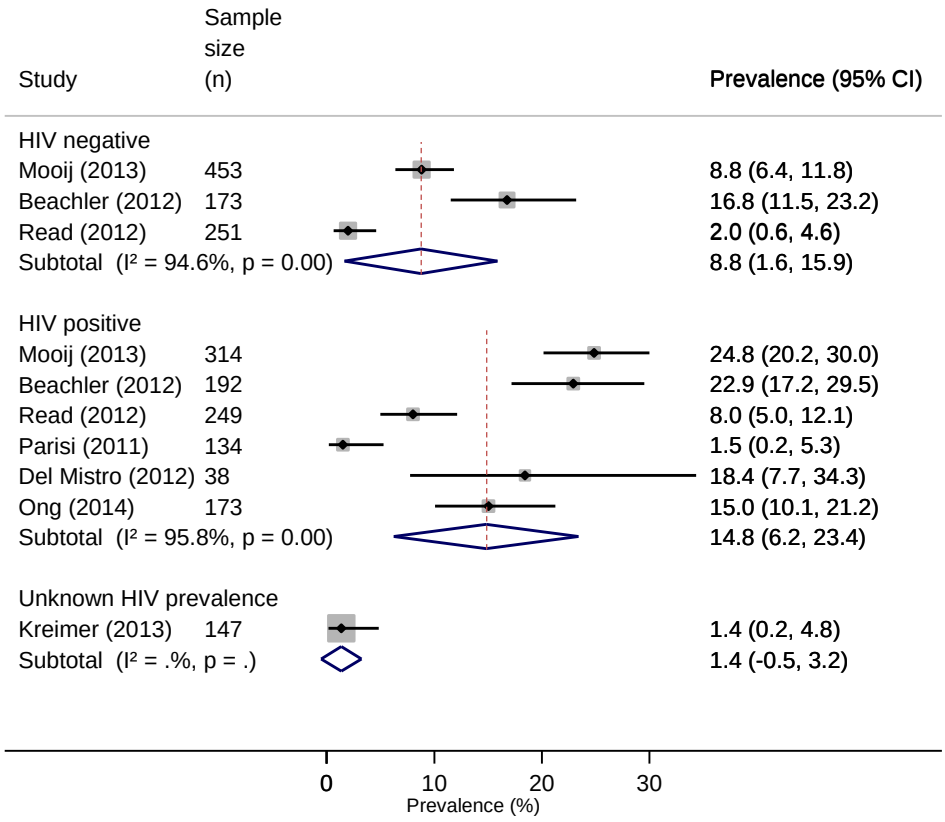
FIGURE 18. RANDOM-EFFECTS ANALYSES OF STUDIES ESTIMATING ORAL QUADRIVALENT-VACCINE TYPE HPV PREVALENCE IN MSM.



Weights are from random effects analyses. Abbreviations: HPV= Human papillomavirus, MSM=Men who have sex with men, HIV=Human immunodeficiency virus. Mooij (2013)[114], Read (2012)[120], Gaester (2014)[127] and Kreimer (2013)[113].

Figure 19 shows that the random-effects pooled prevalence of HR-HPV was 8.0% (95% CI 2.7-13.3%) in HIV-negative MSM and 14.8% (95% CI 6.2-23.4%) in HIV-positive MSM (I^2= 92% and 96%, respectively).

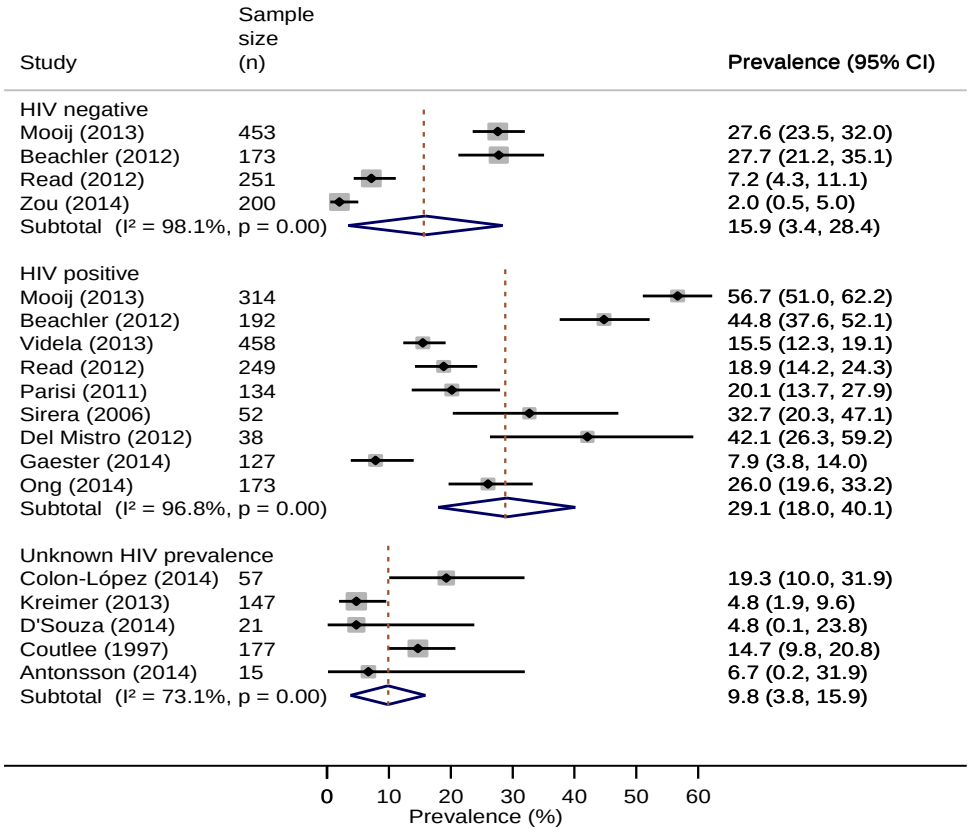
FIGURE 19. RANDOM-EFFECTS ANALYSES OF STUDIES ESTIMATING ORAL HR-HPV PREVALENCE IN MSM.



Weights are from random effects analyses. Abbreviations: HPV= Human papillomavirus, MSM=Men who have sex with men, HIV=Human immunodeficiency virus. Mooij (2013)[114], Beachler (2012)[117], Read (2012)[120], Parisi (2011)[124], Del Mistro (2012)[125], Ong (2014)[121] and Kreimer (2013)[113].

Figure 20 shows that the pooled prevalence of any HPV was 15.9% (95% CI 3.4-28.4%) in HIV-negative and 29.1% (95% CI 18.0-40.1%) in HIV-positive MSM (I^2= 98% and 97%, respectively).

FIGURE 20. RANDOM-EFFECTS ANALYSES OF STUDIES ESTIMATING ORAL HPV (ANY TYPE) PREVALENCE IN MSM.



Weights are from random effects analyses. Abbreviations: HPV= Human papillomavirus, MSM=Men who have sex with men, HIV=Human immunodeficiency virus. Mooij (2013)[114], Beachler (2012)[117], Read (2012)[120], Zou (2014)[122], Videla (2013)[118], Parisi (2011)[124], Sirera(2006)[63], Del Mistro (2012)[125], Gaester (2014)[127], Ong (2014)[121], Colon-López (2014) [126], Kreimer (2013)[113], D'Souza (2014)[128], Coutlée (1997)[68] and Antonsson (2014)[129].

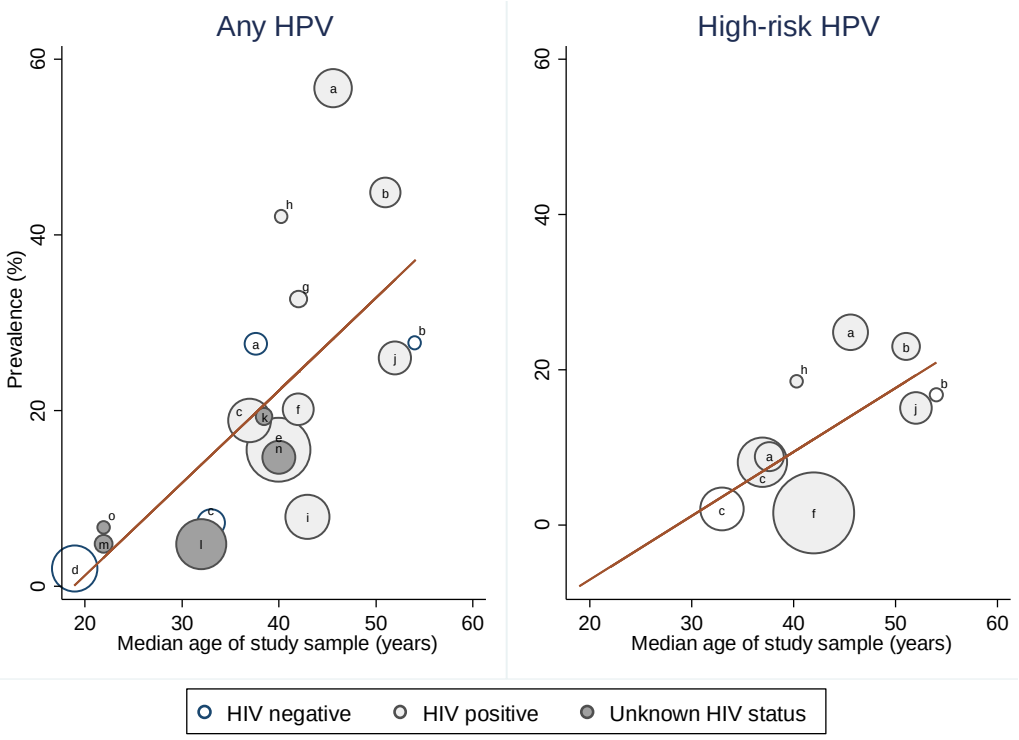
The number of included studies was too low (<10 per stratum) to perform meta-regression stratified by HIV status. As single covariates, HIV status (adjusted R^2=21%, p=0.07), source of recruitment (adjusted R^2=-5%, p=0.56), mode of sample collection (adjusted R^2=-3%, p=0.44), and STROBE count (adjusted R^2=-6%, p=0.85) were not significant contributors to the heterogeneity of any HPV prevalence estimates (Table 5). Heterogeneity in any HPV and HR-HPV prevalence estimates was, in part (45% and 54%, respectively), explained by median age of study participants (p<0.01 and p=0.01, respectively) (Figure 21) but this effect was not significant for HPV16. After adjusting for HIV status, the effect of age remained a significant source of heterogeneity in any HPV prevalence estimates.

TABLE 5. META-REGRESSION OF ORAL HPV PREVALENCE IN MSM AND STUDY-RELATED FACTORS

		UNIVARIATE					MULTIVARIATE				
		Coeff	**T^2**	**Residual I^2 (%)**	**Adjusted R^2 (%)**	**p value**	**Coeff**	**T^2**	**Residual I^2 (%)**	**Adjusted R^2 (%)**	**p value**
HPV16	**Multivariate model**							9	81	-12	0.68
	HIV infection		13	84	-61	0.76					0.99
	No	ref					ref				
	Yes	0.80				0.84	0.09				
	Unknown	-2.84				0.62	-0.49				
	Median Age of study (years)	0.23	3	75	57	0.12	0.23				0.36
	Recruitment source		13	85	-67	0.94					
	HIV clinic	ref									
	STI clinic	-0.16									
	Community	1.18									
	Oral specimen collection										
	Not rinse/gargle	ref	12	83	-50	0.69					
	Rinse/gargle	-1.69									
	STROBE count	-0.07	11	83	-40	0.81					
HR-HPV	**Multivariate model**							47	93	37	0.15
	HIV infection		72	96	3	0.35					0.83
	No	ref					ref				
	Yes	5.73					2.94				
	unknown	-7.60					-0.97				
	Median Age of study (years)	0.82	34	92	54	0.01	0.73				0.09
	Recruitment source		81	96	-9	0.58					
	HIV clinic	ref									
	STI clinic	-0.16									
	community	6.30									
	Oral specimen collection		79	95	-7	0.63					
	Not rinse/gargle	ref									
	rinse/gargle	3.87									
	STROBE count	-0.10	84	96	-13	0.89					
Any HPV	**Multivariate model**							132	94	41	0.02
	HIV infection		177	96	21	0.07					0.57
	No	ref					ref				
	Yes	12.98					6.04				
	unknown	-5.92					-2.26				
	Median Age of study (years)	1.06	122	94	45	<0.01	0.84				0.03
	Recruitment source		236	98	-5	0.56					
	HIV clinic	ref									
	STI clinic	-7.51									
	community	1.78									
	Oral specimen collection		231	97	-3	0.44					
	Not rinse/gargle	ref									
	rinse/gargle	-7.19									
	STROBE count	0.16	237	97	-6	0.85					

Abbreviations: Coeff=coefficient, T^2=tau-squared (between study variance), Not rinse/gargle= oral specimen collection method did not involve a rinse/garge; STROBE= STrengthening the Reporting of OBservational studies in Epidemiology.

FIGURE 21. META-REGRESSION OF MEDIAN AGE OF STUDY POPULATION ON STUDY ESTIMATE FOR ORAL HPV DNA PREVALENCE



Bubbles are weighted in size by inverse of within-study variance. References: a=Mooij (2013)[114], b=Beachler (2012)[117], c=Read (2012)[120], d=Zou (2014)[122], e=Videla (2013)[118], f=Parisi (2011)[124], g=Sirera (2006)[63], h=Del Mistro (2012)[125], i=Gaester (2014)[127], j=Ong (2014)[121], k=Colon-López (2014)[126], l=Kreimer (2013)[113], m=D'Souza (2014)[128], n=Coutlée (1997)[68], o=Antonsson (2014).

RISK FACTORS FOR ORAL HPV DNA DETECTION

Twelve studies that examined risk factors for oral HPV DNA detection, and stated the number of MSM in the population, were analysed (Figure 16). With the exception of Mooij *et al* who examined factors associated with HR-HPV[114], all studies explored factors associated with any HPV. Table 6 shows that the two studies within MSM populations[114,120] identified HIV infection, age (only HIV-negative MSM in Mooij *et al*) , smoking (only HIV-positive MSM in Mooij *et al*), and number of sex partners (only HIV-negative MSM in Mooij *et al*) as risk factors. These were similar to the risk factors identified in studies that had, in addition to MSM, MSEW participants[63,112,118,123,125–127] and/or female participants[117,123,125].

The meta-analysis showed no evidence that MSM were at higher risk of oral HPV DNA detection compared to MSEW (Figure 22). All nine studies measuring oral HPV in both MSM and MSEW were included. With MSEW as the reference group, meta-analysis resulted in a pooled OR of 1.07 (95% CI 0.65-1.74; p=0.80), I^2=51.7%, heterogeneity p=0.04. There was little difference in effect size in the four studies in HIV-positive populations compared to the five with unknown HIV status. No studies in HIV-negative populations presented appropriate data to examine this effect. Excluding estimates from studies with a high risk of bias reduced the heterogeneity (I^2) to 38.4% (heterogeneity p=0.15) and gave a pooled OR of 1.05 (95% CI 0.65-1.68; p=0.85). There were too few studies to formally test for small study bias.

TABLE 6. STUDIES EXAMINING RISK FACTORS FOR ORAL HPV DNA DETECTION IN POPULATIONS THAT INCLUDE MSM

				DEMOGRAPHIC					LIFESTYLE					SEXUAL BEHAVIOUR								STIs				HIV					
Study	**Risk of bias**	**HIV**	**Population**	**Place**	**Sex**	**Age**	**Education level**	**Sexuality or same-sex behaviour**	**Teeth brushing**	**Smoking**	**Use of poppers**	**Cannabis**	**Alcohol**	**Current partner**	**Number of partners**	**Ejaculation during oral sex**	**Condom use**	**Oral sex on woman**	**Oral sex**	**Rimming**	**Receptive anal sex**	**Warts**	**History of STI**	**Penile HPV infection**	**Human herpes virus 8 shedding**	**HIV status**	**Time since HIV diagnosis**	**CD4 nadir**	**Current CD4**	**HIV load**	**HAART use**
Read (2012)[120]	Low	U	MSM			◆			❖	❖					❖	◆						❖				❖					
		+/-				❖																				❖					
Mooij (2013)[114, *]	Low	-	MSM			❖					◆				◆					◆	◆										
		+								◆	◆																				
Videla (2013)[118]	Low	+	♂																			❖					❖	❖			◆
Kreimer (2011)[112]	Medium	U	♂							❖																					
Colon-López (2014)[126]	Medium	U	♂			◆				❖		◆			❖											◆					
Sirera (2006)[63]	High	+	♂																					◆							
Gaester (2014)[127]	High	+	♂					◆		❖							◆		◆												
Del Mistro (2012)[125]	High	+	♀ and ♂																						◆						
Coutlée (1997)[68]	Low	U	♀ and ♂					◆							◆				◆				❖			❖					
D'Souza (2014)[128]	Low	U	♀ and ♂		❖									❖	❖			❖	❖												
Antonsson (2014)[129]	Medium	U	♀ and ♂		◆										◆											◆					
		+/-																								◆					
Beachler (2012)[117]	Low	-	♀ and ♂			◆				◆					❖					❖											
		+					❖			❖					❖													◆	❖	◆		

*All studies examined risk factors for any HPV except for Mooij (2013) which examined risk factors for HR-HPV.

Key:

◆ : Significant (p<0·05) in univariate analyses

❖ : Significant in multivariate analyses

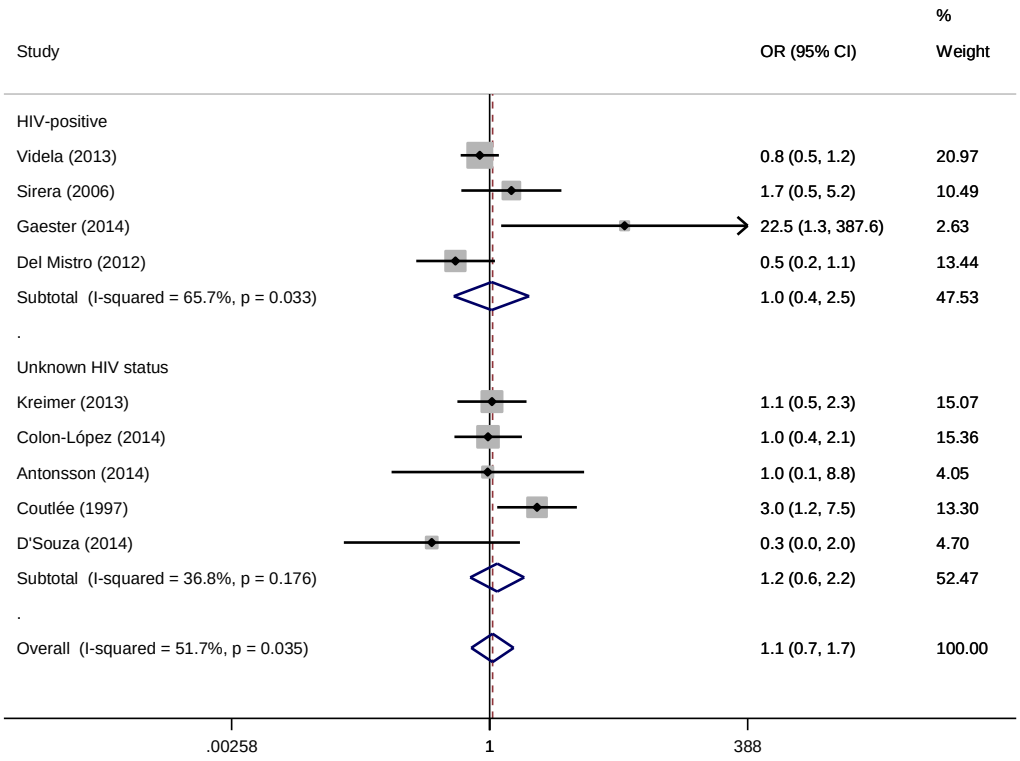
: Covariate in multivariate analyses

U : Unknown HIV status

\- : HIV negative

\+ : HIV positive

FIGURE 22. STUDIES EXAMINING THE EFFECT OF HAVING SEX WITH MEN (AND WOMEN) COMPARED TO HAVING SEX EXCLUSIVELY WITH WOMEN ON THE PREVALENCE OF ORAL HPV



Weights are from random effects meta-analysis. Videla (2013)[118] , Sirera(2006)[63], Gaester (2014)[127], Del Mistro (2012)[125], Kreimer (2013)[113], Colon-López (2014)[126], Antonsson (2014)[129], Coutlée (1997)[68] and D'Souza (2014)[128].

ORAL HPV DNA INCIDENCE AND CLEARANCE RATES

HPV DNA incidence and clearance rates were examined in five longitudinal studies (Table 7). There was inconsistency in the reporting of rates, due to variability in study design, particularly visit schedule and follow-up period. Incidence of oral HPV in MSM ranged from four to 38 per 1000-person months. Men who also had sex with women had higher oral HPV incidence than men who exclusively had sex with men in the two studies where comparison was possible[113,123] but there was no difference in the probability of persistent infections[123]. In the study where direct comparison of HIV-positive and HIV-negative MSM was possible, incidence was more than three times higher in HIV-positive MSM[115].

Definitions of cleared HPV infection differed by study (single undetectable following a detectable or two consecutive undetectable following a detectable). In some studies only incident infections were 'at risk' for clearance, and clearance rate was reported in various

ways, eg median duration of infection, percentage with persistent infection at six months, and number of incident infections clearing in 1000 person-months. However, clearance rate (range: 12-900/1000 person-months) was generally higher than acquisition rate, and in one study, stratified by HIV infection, clearance rate was lower in HIV-positive MSM[115].

Risk factors for oral HPV acquisition and persistence are described, but were not formally examined, due to the low number of longitudinal studies. In MSM, Mooij *et al* found HIV infection increased the risk of oral HPV acquisition[115] but no other risk factors were identified in MSM populations. In populations that included both MSM and non-MSM (and women[123]), living in Mexico compared to USA[113], smoking[113], divorced/separated/widowed marital status[113], increasing education level[113], history of rimming[123], bisexuality[113], and female gender[123] were identified as risk factors for increased oral HPV incidence. Oral HPV persistence was associated with increased time since HIV diagnosis[118,132] and with prevalent compared to incident HPV infections[123].

TABLE 7. INCIDENCE AND CLEARANCE ESTIMATES OF ORAL HPV DNA IN MSM

Study	Oral sampling interval (monthly)	Length of follow-up (months)	HIV status	Population	Sample size	Per 1000 person-months (95% CI)					
						INCIDENCE			CLEARANCE		
						Any HPV	HR-HPV	HPV16	Any HPV	HR-HPV	HPV16
Mooij (2014)[115]	3-6	6	-	MSM	413		7 (4-11)			115 (76-168)	54 (11-162)
			+	MSM	276		24 (17-32)			86 (59-120)	107 (49-203)
Videla (2013)[118]/ Darwich (2014)[119]	12	median=24 IQR=12-36	+	MSM	333	5 (4-7)		1 (0-2)	16 (11-23)		19 (9-34)
Ong (2014)[132]	36	36	+	MSM	249	4 (3-6)	3 (2-4)		12 (7-20)	15 (7-27)	15 (4-32)
Beachler (2013)[123]	6	median=18.2 IQR=6.2-24.0 max=31.6	+	MSM	69	31 (NE-NE)			750 (733-767); 900 (866-935)*		
				MSEW	168	38 (NE-NE)					
Kreimer (2013)[113]	6	median=12.7 IQR=12.1-14.7 range=0.3-37.2	U	MSEM	54	4 (1-12)	3 (0-10)		175 (NE-NE)*+	175 (NE-NE)*+	
				MSMW	93	14 (8-23)	5 (2-11)		129 (NE-153)*+	153 (NE-192)*+	
				MSEW	1392	5 (4-6)	2 (2-3)		154 (102-161)*+	159 (NE-167)*+	137 (NE-159)*+

HIV status: +=HIV-positive; -=HIV-negative; U=unknown *Clearance from incident infections only [+]Calculated from median duration of infection. Abbreviations: MSM=Men who have sex with men, MSEW=Men who have sex exclusively with women, MSEM=Men who have sex exclusively with men, MSMW=Men who have sex with both men and women NE= Not possible to estimate

CONCORDANCE BETWEEN ORAL AND ANOGENITAL HPV INFECTION

Four studies[116,120,124,131] presented data on HPV type-specific concordance at oral and anogenital sites, but only two in MSM where samples were taken at the same time: concordance was not found in 151 HIV-negative oral-anogenital pairs across 21 tested types[131] nor in 166 HIV-positive MSM across 25 tested types[124]. In MSEW HIV-positive men, Videla *et al.* found that 2/191 (1%) had HPV16 detected in the anal brushing, penile swab, and oral brushing[118].

Concurrent HPV detection, without details of HPV type, at oral and anogenital sites in MSM was presented in two studies[63,118]. Videla *et al.* found that 65/458 (14%) MSM had concurrent oral and anal HPV infection and 30/457 (7%) had concurrent oral and penile[118]. Sirera *et al.* showed that penile HPV infection was related to oral HPV infection (OR 2·7; 95% CI 1·0-7·7) and that two or three site (penile, anal, oral) concordance of any HPV was 48%[63]. A further three studies were identified in which oral and anogenital samples had been tested for HPV but concordance estimates were not presented[113,122,123].

3.4 KEY FINDINGS

The pooled estimate from this meta-analysis for HIV-negative MSM (any HPV=16%; HPV16=2%) was half that for HIV-positive MSM (any HPV=29%; HPV16=4%), although the contribution of HIV status to heterogeneity in oral HPV prevalence across studies was of borderline statistical significance (p=0.07). Furthermore, HIV status was consistently found to be a risk factor for oral HPV infection in cross-sectional studies[114,117,120,126] and oral HPV incidence was three-fold higher in HIV-positive MSM than HIV-negative MSM in the only study where comparison was possible[115].

A positive correlation between median age of study participants and oral prevalence was shown, which partly explained heterogeneity between study estimates, and may be modified by HIV status. No within-study associations between age and oral HPV were found in studies of HIV-positive MSM, but four studies including HIV-negative MSM did find a statistically significant association with age[114,117,120,126] (only one in multivariate)[114] and another found a non-significant trend[112]. This may suggest that oral HPV infection is independent of age in HIV-positive MSM but increases with age in HIV-negative MSM. However the HIV-positive MSM populations studied were generally older than HIV-negative populations so there was potential to conceal an age-association in younger HIV-positive MSM.

Although it appears that participants with unknown HIV status have lower prevalence than either the HIV-positive or HIV-negative groups (Figures 17-20), this is likely to be an artefact of the one study that contributed data to the unknown HIV prevalence estimates. Kreimer *et al.* (2013) reported low oral HPV prevalence for all types among HIM study participants compared to studies in both HIV-negative MSM and HIV-positive MSM (Figures 17-20)[113]. The HIM study samples from populations in three countries (Mexico, Brazil, US) using a variety of methods that differ across countries, including military recruits, universities and advertisements. Men were compensated if included. Among the inclusion criteria for the HIM study were no reported history of HIV/AIDS (HIV tests were not performed) and no history of AGW diagnosis[133]. The generalisability of estimates from the HIM study is therefore complex and the low estimates of oral HPV prevalence may reflect the effects of participant selection into the study.

There was no evidence from this analysis that MSM are more at risk of oral HPV infection than MSEW (although varying definition of MSM between studies and lack of data in HIV-negative MSM limits this conclusion).

Women may play a role in oral HPV transmission in MSM: in one study[113] compared to MSEW, oral HPV acquisition was higher in men who have sex with men and women, but not men having sex exclusively with men; in another study MSEW, but not MSM, were more at risk compared to women[113,123]. Perhaps the transmission probability from female genital mucosa to oral is higher than the probability from penile to oral.

Clearance rates were greater than incidence in all five longitudinal studies. The clearance rate applies only to MSM infected with HPV (10-30% of the MSM population) and incidence to the susceptible portion (70-90% of MSM, assuming no natural immunity) so that, all other things equal, in the total population the number of new infections will eventually equal the number of cleared infections and the prevalence will stabilise.

3.5 FINDINGS IN CONTEXT

A global systematic review of oral HPV infection in healthy men and women was performed in 2010 which estimated the prevalence of oral HPV as 4.6% and 4.4% for men and women, respectively[134]. Oral HPV prevalence estimates in MSM from this meta-analysis were three to six times higher.

There has been no meta-analysis of the incidence and clearance rates of oral HPV infection, nor for risk factors for oral HPV acquisition.

Using pooled data collected by the international head and neck cancer epidemiology consortium, a history of same-sex sexual contact in men was shown to be strongly associated with cancers at the base of the tongue but not with other oral cancers[6].

3.6 STRENGTHS AND LIMITATIONS

The strengths of this study include the high inter-rater agreement in study selection and data extraction and the exploration of reasons for heterogeneity in prevalence estimates including risk of bias. Yet there remain several limitations. The extreme heterogeneity between prevalence estimates was not explained so pooled estimates should be used with

caution. Approximation methods were used to estimate incidence and clearance rates and standardise them across studies; this, undoubtedly, introduced uncertainty into the estimates and so precluded meta-analysis. Although not designed for measuring risk of bias in meta-analyses, the STROBE checklist was used, which was not ideal for assessing the quality of study designs. It was not possible to include data from four potentially eligible studies[135–138].

4. HPV-MSM-MMC STUDY: OVERVIEW OF METHODS AND DESCRIPTION OF STUDY PARTICIPANTS

In this chapter, I describe the cross-sectional study of HPV in MSM attending a sexual health clinic in London. The methods in this chapter are referred to in subsequent chapters, each addressing specific objectives and presenting results. Here, I first summarise the study and its aims, then describe the data collection, data management, specimen collection/storage/transportation/testing, statistical methods and challenges to study implementation. Finally, I describe participant demographic and behavioural characteristics and consider potential participation bias and external validity.

4.1 AIMS OF THE HPV-MSM-MMC STUDY

1. Estimate the size of sub-populations composing the overall SHC-attending MSM population that are likely to have differential response to or benefit from the HPV vaccine
2. Estimate risk of future infection with HPV in SHC-attending MSM
3. Estimate potential vaccine coverage, via SHCs, in MSM in the UK

4.2 OBJECTIVES ADDRESSED IN CHAPTER 4

- To describe study design, data management, laboratory and statistical methods
- To describe non-participation and missing data
- To describe key characteristics of study participants, including HIV prevalence, and the age-association of STI transmission risk behaviours
- To compare study participants to other MSM populations
- To discuss potential participation bias and external validity introduced as a result of study design

4.3 METHODS

SUMMARY

522 MSM attending the Mortimer Market Centre (MMC) between October 2010 and July 2012, aged 16 to 40 years inclusive, were consented to participate in this cross-sectional study. Participants completed a computer-assisted self-interview (CASI) questionnaire covering demographics, sexual behaviour, history of STIs (including AGWs and HIV), knowledge of HPV, attitudes to HPV vaccination and health service use. Biological specimens (anal, external genital, urine and oral) were collected and tested for HPV DNA. Blood was also collected and serum was tested for the presence of antibodies specific to HPV16 and HPV18. STI diagnoses and HIV test history were extracted from the clinic database using Sexual Health and HIV Activity Property Type (SHAAPT) codes[139].

STUDY SETTING

The study was conducted at MMC, Camden, London, one of the largest outpatient clinics for general sexual health problems in Europe, with approximately 80,000 patient attendances per year. Of the men attending the clinic, approximately half are MSM. At MMC, there is a separate clinic for HIV-positive patients, but it is common for HIV-positive patients, both registered at MMC or elsewhere, to use the sexual health clinic for other STI-related services.

Patients attend MMC for a variety of STI-related reasons, including asymptomatic screens and HIV tests. While we do not have data on reasons MSM attend this particular clinic, these are likely to be similar to those reported in the *Maximising STI control in local populations* survey, which was conducted in 2009[140]. In 109 MSM attending the three London clinics 42.3% attended because they reported symptoms; 9.6% because their partners had symptoms; 37.5% for an asymptomatic screen and 34.6% because they wanted an HIV test. Participants could report multiple reasons for attending.

For HIV-positive MSM attending the sexual health clinic at MMC, HIV-related clinical data, including immunological and viral markers and prescription history, were not available. However, in the UK in 2010/11, MSM were less likely than heterosexual men to receive a late HIV diagnosis (<350 CD4 cell per µl). MSM were likely to be linked to HIV care (over 90%

had received a CD4 count within three months of diagnosis) and to have received ART within a year of their diagnosis[141]. The majority of HIV-positive MSM attending SHCs in the UK are therefore likely to have suppressed HIV infection.

STUDY POPULATION

Men were eligible for this study, and were approached consecutively, if they attended MMC during the recruitment period; were aged between 16 and 40 years inclusive; reported anal or oral sex with another man in the last 5 years; were able to understand the consent process and questionnaire in English; and had not participated in the study already.

These eligibility criteria were devised so it was possible to compare this study to other UK studies; to capture the population most likely to be targeted for HPV vaccination; to address the effect of age on HPV infection and for practical reasons.

Using the same definition as that used in Natsal, this study defined an MSM risk population (anal or oral sex with another man in the last five years) that moderated between men who are at very low risk of acquiring STIs, for example having had one same-sex experience in their lifetime, and those MSM at higher risk who had had sex with another man in the last three months[8]. Adhering to the Natsal definition facilitated comparison of MSM attending SHCs to MSM in the general population.

It was hypothesised that younger men, with less lifetime exposure to HPV, would be more likely to be HPV-naïve and would gain more benefit from the prophylactic vaccine so young MSM were targeted by the age eligibility criterion. Due to ethical considerations the lower age limit was 16 years. A distribution of age was required, in order to examine the association of age and HPV prevalence and risk of HPV acquisition, but the upper age limit was 40 years to avoid oversampling older men.

Men who were not able to understand the CASI questionnaire in English were not eligible for the study. This was assessed by the researcher. This exclusion was necessary for the following reasons:

- It was not feasible (within time and finance constraints) to translate and validate all the study materials into all of the possible languages encountered at MMC.

- It was hypothesised that only a small proportion (estimated to be 10%) of the MSM attending the clinic would be excluded because of language and/or literacy.
- Reporting bias: if some respondents were to answer the questionnaire via translator and the rest of the participants to answer via CASI, there was a risk of distortion of data due to social desirability bias.

SAMPLE SIZE CALCULATIONS

In 2009, the expected MSM population prevalence ($\hat{p}$) of anal HR-HPV ranged from 26-96% (Figure 9) and of HPV16 ranged from 9-52% (Figure 10). The single required accuracy formula (Equation 1) was used to calculate that more than 384 MSM were required to measure prevalence in the sample within 5% (a =0.05) of 52%.

Assuming that the majority of MSM attending MMC are HIV-negative, 17% was considered a reasonable estimate for HPV16 prevalence. With an estimate for HPV16 prevalence of 17%, a sample size of 532 men would provide 80% power (μ=0.84) to detect a difference between two equally sized subgroups (e.g. age groups) at the 5% significance level if the true prevalence in the subgroups is 12% (π_1) and 21% (π_2), i.e. a relative risk of 1.75 (Equation 2).

For HR-HPV, a sample of 532 men would provide more than 90% power to detect a relative risk of 1.75 between two equally sized subgroups if the true prevalence in those subgroups was 42% and 24%, at the 5% significance level, and the overall prevalence was 33%.

EQUATION 1. SINGLE REQUIRED ACCURACY FORMULA

$$n \geq \left(\frac{1.96}{a}\right)^2 \times \hat{p}(1-\hat{p})$$

EQUATION 2. COMPARISON OF TWO PROPORTIONS

$$n \geq \frac{\mu\sqrt{(1-\pi_1) + \pi_2(1-\pi_2)} + 1.96\sqrt{2\bar{\pi}\,(1-\bar{\pi})}}{(\pi_1-\pi_2)^2}$$

Where π_1 = prevalence in sub-group 1, π_2 = prevalence in sub-group 2, $\bar{\pi} = \frac{\pi_1 + \pi_2}{2}$ = mean prevalence and μ = the value obtained from standard normal distribution at the percentile corresponding to the chosen level of power

DATA COLLECTION

Patient identification and recruitment

The method of recruitment was designed so as to ensure patient confidentiality. Patient consent and questionnaire completion took place in a clinic room designated for study use. Clinic staff identified eligible potential participants and referred them to the study nurse based in the clinic. The study nurse discussed the study with the patient, checked eligibility for the study, gave them the patient information sheet to read and, if appropriate, witnessed them consenting to the study.

Study procedures

The study nurse performed both the routine National Health Service (NHS) and the study procedures in one visit as this was more time efficient for the participant. After consenting, the participant completed a CASI questionnaire and then study specimens were taken at the same time as the routine clinic tests. Five specimens were obtained from each participant: urine, one external genital swab, one intra-anal swab, one oral rinse/gargle and 6ml of blood.

Questionnaire development and validation

Key principles informing the development of the questionnaire

In order to maximise the quality, completeness and validity of the survey data, it was necessary to consider which variables to measure, how to phrase questions, how to order questions, how many questions to include, the respondent's understanding of how to respond to questions and how to facilitate the recollection of the fact relating to the question[142,143].

Measurement objectives

In addition to risk factors that were identified in previous studies (Table 3, page 43), other basic demographic information, sexual behaviour, history of STIs (including AGWs) and markers for intention to accept the HPV vaccine were measured..

Research variables

Both Natsal and the GMSHS have been validated through extensive development, cognitive interviewing, piloting and/or use in the field. Where possible, questions in the HPV-MSM-

MMC survey were phrased in the same way as in other surveys, such as Natsal and GMSHS, in order to confer validity of tested questions to this survey, and to ensure external validity of the work.

Use of alcohol was measured using the abbreviated alcohol use and disorders identification test (AUDIT-C) that has been validated for screening for high-risk drinking in primary care[144,145].

Based on the importance of use of health services, perceived risk, outcome expectancies and perceived self-efficacy as predictors of vaccine uptake[105], data were captured relating to perceived risk of HPV acquisition and the likelihood of both being offered (use of health services) and accepting (perceived self-efficacy) the HPV vaccination if a targeted programme existed. There were nine true or false items designed to assess existing knowledge about HPV. Questions were devised to address risk perception, outcome expectancies/belief in efficacy and perceived self-efficacy. It was considered that the patient information sheet contained sufficient detail to answer these questions correctly.

There were 62 questions in the survey some of which were made up of multiple items. There were a total of 101 items in the survey. The questionnaire is included in this thesis as Appendix I.

Interview method

CASI was used in this study for several reasons. Firstly, the questionnaire format and questions were identical for each respondent. This consistency helped to diminish measurement error that might have resulted in reporting bias if, for example, in a face-to-face interview different men were asked questions with a different tone or by different clinicians. For example, it is known that people (especially women) tend to report more information to female interviewers[146].

Secondly, respondents were not concerned with the reaction of the interviewer to their responses. This anonymity helped to diminish social desirability bias where responses are amended in order to appear more favourable to others. For example, respondents may have felt that health care professionals would not have approved of high frequency of partner change and accordingly reduced their estimate of number of partners in the last

month. With CASI, social desirability bias can be significantly reduced, especially if there are no personal identifiers (e.g. name, place of work etc) on the questionnaire, which results in CASI measuring higher risk sexual behaviour (e.g. more sexual partners, more unprotected intercourse) than clinician interview[146].

Additionally, a well-designed questionnaire can use skipping and auto-completion of items to reduce the completion time and response error compared to a pen-and-paper questionnaire. These features, as well as the question consistency and reduction in social desirability bias, result in more complete data than face-to-face interviews. This is important because item non-response can introduce bias to survey data if those who do not answer a particular question are systematically more or less likely to report that behaviour than those who do answer the question[147]. For this reason and to maximise the statistical power in the analyses, it is important to minimise non-response. CASI is also generally acceptable to respondents when measuring sexual behaviour and requires no data entry therefore reducing transcription errors[148].

Description of survey instrument

Any potential ambiguity in the meaning of questions or terms was minimised by questionnaire testing and use of previously validated questions. Mapping the response to the questionnaire was simplified by using mutually-exclusive and collectively-exhaustive multiple choice or open-ended fields with the units specified (e.g. years). For open-ended questions, the field type (i.e. numeric or string) was assigned during questionnaire development so that potential completion errors were mitigated. The survey was designed and delivered in SNAP 10 survey software.

The questionnaire was designed to take approximately ten minutes to complete with variability due to routing. Ten minutes was deemed a suitable length of time to ask participants to spend on the questionnaire without interfering with their routine NHS visit. It was not considered so long that patients would be put off participating nor would it affect item completion due to fatigue. It did provide enough time to answer the 101-item questionnaire. The range of questionnaire items was 44-99 due to routing.

Questions relating to a similar topic were grouped into sections. To facilitate fact recall, logical groupings were made, such as a set of behaviours within the same time-frame. Sections and questions were ordered to begin with less sensitive items, to ease the participant into the questionnaire format, which then gained focus. To maximise consistency and continued relevance, some items were ordered to allow for routing.

The questionnaire tone mirrored that which would be used in the clinic for taking a sexual history. Thus, for example, the phrase 'insertive anal sex' was used rather than the colloquial term 'fucking' that has been used in other sexual behaviour surveys of gay men in the UK. Young people in focus groups in 1998 in the UK generally preferred health professionals to use formal rather than vernacular terms[149]. Signposting and guidance were included to aid understanding and patience. For example, the series of questions relating to the three most recent partners was preceded with comments explaining which partners were eligible to be included and stating that "it will be helpful for you to think of them now".

Questionnaire testing

The survey was pre-tested and piloted to assess its acceptability and validity. First it was reviewed by experienced researchers in the field of sexual behaviour surveys (Dr Catherine Mercer & PS) and their comments were incorporated. Then it was tested on a sexual health clinician (RG) and colleagues in the centre for sexual health & HIV research, particularly those who had designed their own behaviour surveys.

The survey, the patient information sheet and the informed consent form were piloted on ten MSM who met the study's eligibility criteria at MMC. Half of these men completed the survey without interruption so that the completion time could be monitored followed by a discussion of any ambiguities. The rest "thought aloud" and asked questions as they went along. The questionnaire was edited between each interview and piloting continued until no new issues were revealed. A summary of the findings from the pilot survey are in Appendix II.

SEXUALLY TRANSMITTED INFECTIONS, INCLUDING HIV

All SHAAPT codes reported within 30 days of the study visit were retrieved and assumed to represent a diagnosis made at study visit. HIV test history was recorded from beginning of clinical records up to 30 days after the visit. Gonorrhoea, chlamydia, herpes simplex virus (HSV) and syphilis infections were reported individually. All remaining STIs (hepatitis A, HBV, hepatitis C, chancroid, lymphogranuloma venereum, Donovanosis, trichomoniasis, scabies, pediculosis pubis, molluscum contagiosum, epididymitis, balanitis, candidosis and other conditions requiring treatment) were collapsed into the 'other' category.

The electronic patient records, of participants who attended the clinic because they thought they had an episode of AGW but did not receive a related SHAAPT code, were accessed to explore this discrepancy.

DATA MANAGEMENT

Anonymisation, data-linking

Enrolment Log

MMC uses stickers in patient notes that are attached to forms and laboratory specimens. The stickers are printed with the clinic's patient identification (ID) number, the date of birth and the patient's name. Participants in the study were assigned a study ID number ranging from 4000 to 4531. Bar-coded labels were used in the study as shown in Figure 23. The study ID number was encoded (bar code 39) so that the samples arriving at the laboratory could be identified using a scanner. The clinic sticker and the study ID number were both listed on the study's enrolment log which was also maintained as an excel spreadsheet.

FIGURE 23. STUDY-SPECIFIC BARCODE LABELS

Informed consent form

The other written linking of study participant to the patient was the study's consent form. This listed both the participant's study ID number and the patient's name. The participant signed three copies of the consent form. One was placed in the medical notes, one was kept in the study's site file and the other was given to the participant.

Merging datasets

Figure 24 displays the process of merging datasets. Study ID numbers were used to identify participants' questionnaire responses and study laboratory samples. STI diagnoses were retrieved from the NHS records for all patients in the clinic during the study period. These were identifiable by name and clinic ID. The questionnaire responses were merged with the HPV test results using the study ID. The STI diagnoses were merged with the electronic enrolment log using clinic ID and date of visit. The clinic ID was deleted from the resulting dataset. The STI diagnoses were then merged with the questionnaire responses and HPV results using the study ID.

QUALITY ASSURANCE & CONTROL

Instructions were written and tested for all study procedures: the laboratory protocol and the specimen collection and processing manual. The enrolment log and survey data were regularly checked for anomalies and there were frequent meetings with the study nurse to discuss study processes. The PHE laboratory checked samples for leakage and appearance when they received them. Any problems were reported back to the research nurse and study co-ordinator. Recruitment rate was monitored regularly by updating an electronic participant tracker. This tracker gave estimated date of end of recruitment and also allowed for the monitoring of the age profile of the sample. Data checks were performed for eligibility, consistency between answers and consistency between answers and STI diagnoses.

ETHICAL CONSIDERATIONS

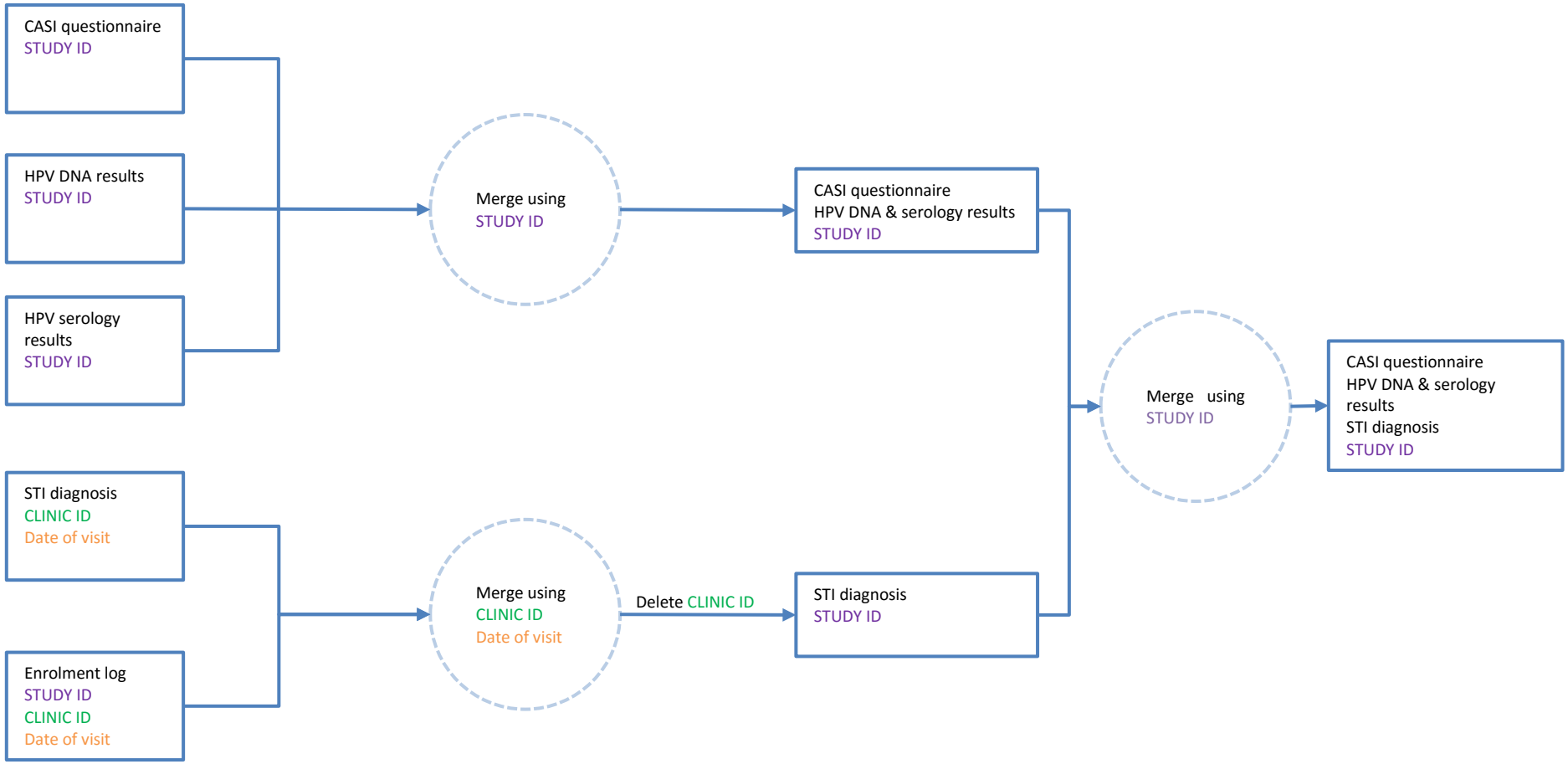
The questionnaire collected personal sensitive information such as income, smoking, drinking and sexual behaviour. Confidentiality of the participant was addressed so that social desirability bias was minimised and privacy was respected. The participant completed the questionnaire in a closed clinic room while the study nurse labelled the biological specimen tubes. The study nurse was not in a position to see the computer screen but was available to answer any questions about the survey. All of the questions were optional as it was decided that having the participant feel that they could opt out and were volunteering information outweighed the negative impact of item non-completion.

Routine clinic visit tests, diagnoses and reporting were unaffected by participation in the study. Participants were not informed of the results of their HPV tests. Not only is the HPV assay not validated for clinical use, but also, there is currently no clinical intervention for a participant who receives a positive HPV test. All laboratory tests were performed together, at the end of the study. HPV infection is often transient, lasting approximately one year[150]. Men who participated at the beginning of the enrolment period might have cleared their infections spontaneously by the time their samples were tested so the results would no longer be relevant.

ETHICAL APPROVAL

We gained ethical approval for the study from the Camden and Islington Research Ethics Committee on 6th October 2009 (REC reference number: 09/H0722/71) and received research and development approval from the North Central London Research Consortium on 7th October 2010 (R&D ref: CSP 30296). The ethics committee and R&D office were informed of the closure of the study on 8th August 2012.

FIGURE 24. MERGING DATASETS



BIOLOGICAL SPECIMENS

Collection and transportation

A first-void urine sample was collected and refrigerated at 4°C until transportation. The anal and the external genital specimens were obtained using a sterile plastic shaft flocked swab that was pre-soaked in sterile saline (one each). The anal swab was inserted 3cm into the anal canal and rotated 360° applying gentle pressure to the walls of the canal. The external genital specimen was obtained by rubbing the following areas with the swab:

1. Glans penis/coronal sulcus
2. Penile shaft including the prepuce (if present)
3. Scrotum
4. Perianal area

Both swabs were inserted into their own Copan Universal Transport Medium (UTM-RT) ™ collection vial and stored at 4°C until they were transported.

Delays, due to the additional logistical requirements for on-site oral sample processing, resulted in oral specimens only being collected in the latter five months of the recruitment period (7th March 2012 onwards). The oral specimen involved a 30-second gargle/rinse with 15ml of Scope® mouthwash according to a published protocol[112]. Oral samples were refrigerated immediately and processed the same day. To process, the rinse was centrifuged at 3200 RPM for 15 min at 4°C and, after the supernatant was discarded, the pellet was resuspended in 20 ml of cold PBS (4°C). The centrifugation/resuspension was repeated twice and the final pellet was resuspended in 1.2 ml of PBS with repeat pipetting and vortexing to ensure a homogeneous sample.

Urine and swabs were transported with a cold pack within 48 hours of collection and oral specimens were transported on dry ice at the end of the study (22nd October 2012) to the virus reference department, PHE, Colindale.

A blood sample was collected using gold-topped BD vacutainer SST II Advance tubes. The BD instructions were followed to separate the plasma from the serum. Two aliquots of serum were stored at -20°C. These samples were shipped on dry ice to the VEU, Public Health Laboratory, Manchester.

LABORATORY METHODS

HPV DNA extraction, amplification, detection, genotyping

On arrival at the Colindale laboratory, urine specimens (1ml) were centrifuged (13 000 rpm for 20 min) and the pellet resuspended in 300µl sterile phosphate buffered saline prior to storage at -80°C. Swab specimens were vortexed to agitate the material from the swab into the buffer and aliquots of 300µl were stored at -80°C. At the end of the study (timeline, page 22), specimens were removed for batch processing wherein all available specimens from each individual were processed for DNA extraction and HPV testing in the same run.

Thawed aliquots were lysed with 40µl Qiagen Protease and 265µl Qiagen buffer then nucleic acid was extracted on a BioRobot Universal platform using QIAamp®DNA Blood BioRobot® MDx kit (Qiagen Limited, Crawley, West Sussex, UK). Ten microlitres of the 100µl elution were used for PCR amplification using the in-house single-round multiplex PCR, with modified GP5+ and GP6+ primers, targeting the L1 gene, and type-specific infections were resolved using a genotyping assay based on the Bio-Plex® (Luminex xMAP®, Bio-Rad Laboratories, Hemel Hempstead, Hertfordshire, UK) platform[151]. Specimen integrity was established by incorporating a control PCR targeting the human pyruvate dehydrogenase gene.

Real-time PCR on anal and external genital samples

In order to quantify cellular and HPV DNA, real-time PCR was performed on anal and external sample pairs in which both samples had detectable HPV16 in the genotyping assay. PCR primers and probes targeting HPV E6 and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) were optimized for the ABI 7500 Fast PCR machine (Applied Biosystems) using Platinum UDG Supermix (Life Technologies). The original aliquot (300uL) was eluted from extraction into 100uL and 10% (10uL) was used for typing. Therefore the viral copies per reaction can be converted to copies per ml by multiplying by 33.333. Viral load (VL) was calculated as HPV copies per cell (c/c) as determined by dividing the number of viral copies per reaction by the half the number of GAPDH copies per reaction. A positive control of pooled HPV16, HPV18, HPV31 and HPV45 DNA from a mixture of samples demonstrated good reproducibility[152]. Samples positive for HPV16 by genotyping assay but negative via

real-time PCR, were assumed to result from differences in assay sensitivity, and were censored at five copies per reaction for calculation purposes.

LCR sequencing of HPV16 in anal and external samples

To explore whether same genotype concordance was reliably the same variant and the proportion of mixed variant infections, sequencing of the variable LCR was performed in external and anal samples with detectable HPV16: an 1187 base-pair (bp) fragment encompassing the entire LCR and a portion of the E6 ORF was sequenced to identify intra-type variants. HPV16 samples were amplified in a single 1329 bp fragment with primers 16-F101 and 16-R20. Template amplification was performed in a 25µL reaction mix containing Kapa HiFi HotStart ReadyMix (Kapa Biosystems), 5pmol of each primer and 5µL of template DNA sample under the indicated cycling conditions on a PTC-200 thermal cycler (MS research). The resulting PCR product was evaluated for its molecular weight using a DNA mass ladder (Invitrogen) and GelAnalyzer software (www.gelanalyzer.com) and sequenced using 5pmol of each indicated sequencing primer[153].

Classification of HPV genotypes

Box 5 shows the oncogenic risk classification of HPV genotypes as used in all analyses from the HPV-MSM-MMC study.

BOX 5. ONCOGENIC RISK AND VACCINE-PREVENTABLE CLASSIFICATION OF HPV GENOTYPES

Bivalent vaccine types	16/18
Quadrivalent vaccine types	6/11/16/18
9-valent vaccine types	6/11/16/18/31/33/45/52/58
HR-HPV types	16/18/31/33/35/39/45/51/52/56/58/59/68
LR-HPV types	6/11
Possible HR-HPV types	26/53/66/70/73/82

HPV antibody detection

Serum was tested for Immunoglobulin G (IgG) to HPV types 16 and 18 using a type-specific ELISA that has been validated against a pseudovirion-based neutralization assay in post-vaccination samples from women[154]. Briefly, VLP16 and VLP18, purified from recombinant baculovirus were pre-coated onto separate 96-well microtitre plates for between 60 and 120 hours at 4°C. Following blocking to prevent non-specific binding, test, positive control and standard serum were added to VLP16 and VLP18 plates, double diluted and incubated for 60 minutes at room temperature. The microtitre plates were then washed. Specific bound antibody was detected using horseradish peroxidise mouse anti-human conjugate and developed with a specific chromogenic substrate. Optical density was determined at 450nm with a 620nm reference. Quantitative results were calculated from the standard and expressed in arbitrary ELISA units per millilitre (EU/mL). The lower limit of the assay at the VEU was 19 and 18 EU/mL for HPV16 and HPV18, respectively, with values below this classed as seronegative.

STATISTICAL METHODS

Data cleaning and categorising

Eligibility, range and consistency checks were performed on the survey dataset. Categorical variables were cross-tabulated to identify inconsistencies between answers which were corrected or recoded as missing, as appropriate. Distributions of continuous variables were explored for consideration as predictors in regression models and checked for outliers using histograms. If approximately normally distributed, or potentially transformed into a normal distribution, we used all data for continuous variables in regression models. Continuous variables that were highly skewed, and could not be transformed, were collapsed by recoding as categorical variables with meaningful cut-offs whilst maintaining sufficient numbers within each group for analyses.

Statistical standards in HPV in MSM study

All statistical analyses were conducted using STATA v13.1 and, unless otherwise specified, a p value of <0.05 was considered statistically significant. CIs around estimates of proportions (prevalence estimates) were determined at 95% using the Clopper-Pearson (exact) method. During multivariate model analyses, the Wald test (instead of the likelihood ratio test) was performed to assess the statistical significance of individual predictor variables on the

outcome. A non-parametric test for trend, based on the Wilcoxon rank-sum test, was used to assess the existence of a trend across ordered categories for variables with at least three categories. Not all tables display missing data for each variable but this can be calculated from totals. Missing data were not imputed and complete case analyses were performed. Odds ratios (OR) are reported for univariate analyses, and adjusted ORs for multivariate logistic regression models.

Participant characteristics and missing data

Results on pages 99-100

The frequency of collected and tested biological samples and completed questionnaire items was summarised. A comparison was made between MSM who declined to participate and participants. The mean age was compared between the two groups using a t test. The difference in the proportion of those that were new patients between the two groups was tested using the χ^2 test. The difference in mean age and proportion of new patients across the reasons for not participating were tested using one-way ANOVA and χ^2 tests. The proportion of missing data for each questionnaire item was determined as the number of men who were asked the question who did not provide a response.

Results in this chapter, page 104

In participants, demographic and behavioural variables were categorised and frequency was summarised. For continuous variables the median and inter-quartile range (IQR) was reported. Age at first sex was compared between HIV-negative and HIV-positive populations using the t test. To explore the potential for future HPV acquisition at any age, the effect of age on sexual behaviour was examined. Firstly, the association of number of sexual partners and age was explored both by logistic regression (≤ 30 compared to >30 lifetime partners) and linear regression (number of partners in the last year). Then, a categorical age variable (18-30 compared to 31-40 years) was used in logistic regression with other categorical behavioural variables.

External validation

Results in this chapter, page 109

External comparisons of the study population were made with the MSM aged 16-40 attending MMC and other STI clinics in England in 2011 (Genitourinary Medicine Clinic Activity Dataset; GUMCADv2[139]), MSM in the general population 2010-2012 who reported attending an STI clinic in the last 5 years (Natsal-3[155]), and MSM who participated in the GMSHS in London's pubs and clubs in 2011[156]. Variables explored, where available, were

age, ethnicity, lifetime partners and anal partners (in total and without a condom) in the last year.

HPV PREVALENCE AND RISK FACTORS

HPV prevalence

HPV DNA prevalence was estimated by HPV type, HIV status, specimen type and age. Estimates were made of the number of men with detectable HPV DNA out of the number of men with an adequate sample for HPV testing. Anogenital HPV DNA prevalence was defined as the proportion of participants with detectable HPV DNA in ≥1 of the three anogenital specimen types (anal swab, external genital swab or urine) in participants with ≥1 specimen type that was adequate for HPV testing. HIV status was determined from both questionnaire data (self-reported) and clinical records at MMC.

Results in chapter 5, page 117

Risk factors for HPV

Univariate logistic regression was used to explore the age-relationship with HPV infection detected at ≥1 anogenital site (any type, HPV16/18, any of the quadrivalent-vaccine types, any 9-valent vaccine types, any HR-HPV, and HPV6/11) with age as a continuous predictor variable.

The effect of demographic and behavioural risk factors was examined on the detection of HR-HPV DNA at each anatomical site. Age-adjusted logistic regression models were fitted to all the data allowing multiple outcomes from individuals by HPV type (rather than collapsing the HR-HPV variable) using the generalised equation estimation (GEE) method assuming an exchangeable working correlation (i.e the same correlation between pairs of HPV types; an unstructured correlation matrix failed to converge)[157]. Variables were considered significant if $p<0.05$ using the Wald test.

Results in chapter 5, Page 125 and appendix IV, Appendix table 4 and Appendix table 5, page 303

Demographic and behavioural risk factors for quadrivalent-vaccine types were also assessed using age-adjusted logistic regression having collapsed the quadrivalent-vaccine type variable so that each participant contributed a single outcome.

ANALYSES OF SPECIMEN AGREEMENT ON HPV DNA DETECTION

Results in chapter 5,

Page 122

The occurrence of joint detection of HPV at two or more anatomical sites was quantified by estimating prevalence of each 9-valent vaccine type by sample combination and using agreement, concordance and kappa estimates and the McNemar test, as described in Box 6. Agreement was used to describe the proportion of MSM that are either negative or positive at both sites for HPV detection ($(a+d)/N$). Concordance was used for the proportion of MSM who have the same HPV DNA detected at both sites in MSM (a/N). Expected concordance, due to chance, was estimated as the type-specific prevalence at anatomical site A multiplied by that prevalence at site B. Confidence intervals around the kappa estimates were determined using an analytical method. Kappas were summarised across multiple HPV types by calculating the weighted average of the kappas, where for each kappa the weight is proportional to 1 minus the expected agreement, and 95% CIs were generated using bootstrapping (1000 replications)[158]. For all joint detection measures, within the compared sites, MSM were included if each specimen type was adequate for HPV testing.

BOX 6. CALCULATIONS OF AGREEMENT, CONCORDANCE, KAPPA AND THE MCNEMAR TEST STATISTIC FOR MEASURING THE RELATIONSHIP BETWEEN DETECTING HPV AT ONE SITE COMPARED TO ANOTHER

		Site B +ve	Site B -ve	Total
Site A	+ve	a	b	$a+b$
	-ve	c	d	$c+d$
				N

$$Agreement = \frac{(a+d)}{N}$$

$$Random\ agreement = \frac{(a+b)(a+c)+(c+d)(b+d)}{N}$$

$$Concordance = \frac{a}{N}$$

$$Concordance\ due\ to\ chance = \frac{(a+b)}{N} \times \frac{(a+c)}{N}$$

$$Kappa = \frac{agreement - random\ agreement}{1 - random\ agreement}$$

$$McNemar's\ test\ statistic = \chi^2 = \frac{(b-c)^2}{b+c}$$

Results on page 136

The distributions of number of cells per reaction, number of HPV16 copies per reaction and number of HPV16 copies per cell (VL) were compared between anal and external swabs using kernel density plots, medians and IQRs and differences were formally tested using the matched-pairs signed-ranks test.

Results on page 138 and appendix IV, Appendix table 6, page 309

The effect of demographic and behavioural risk factors on the odds of detectable HR-HPV at two or more anogenital sites (concordance) was compared to no infection and to anogenital single infection. Age-adjusted logistic regression models were fitted using the generalised equation estimation method as on page 95.

Serology analyses

Results in chapter 6, page 153

The association of age and HPV-IgG detection was explored by HIV status using logistic regression with age first as a continuous and then as a categorical independent variable. In MSM with detectable IgG for HPV16 and/or HPV18, an analysis of the relationship between IgG titre and age was performed using linear regression.

Results on pages 156-169

Risk factors for detectable HPV16-IgG were explored first using univariate logistic regression, or Fisher's exact test if any cell of the contingency table contained fewer than five MSM, and then using multivariate logistic regression having adjusted for age and number of lifetime partners *a priori* and stratified by HIV status. This was repeated for HPV18-IgG.

HPV6/11, AGWS AND STI ANALYSES

Results in chapter 7, pages 174-191

History of AGW was derived from two data items: reporting ever having had an AGW diagnosis and receiving a SHAAPT code for AGW within 30 days of the visit (hereafter, diagnosis at visit). Sensitivity and specificity of a suspected AGW episode was estimated using a diagnosis of AGW at visit as the gold standard. Demographic, behavioural and biological variables (anogenital HPV6/11 and HPV16/18 DNA, anti-HPV16 /18 and STIs) were examined for association with AGWs using logistic regression or the Fisher's exact test (where cells had an expected frequency of five or fewer). Unadjusted ORs and aORs, adjusting for age and number of lifetime partners, are presented. Correlation was examined between age and age of most recent partner using Pearson's r: r=0 indicates no correlation,

r=1 indicates a perfect positive linear relationship and r=-1 indicates a perfect negative linear relationship.

HEALTH-SEEKING BEHAVIOUR, VACCINE ATTITUDES AND HPV KNOWLEDGE

The association of anogenital HPV DNA (6/11 and 16/18), HPV16/18 antibodies and AGWs with the mean age at first attending a SHC in the UK were explored using t tests. The prevalence of anogenital HPV, HPV serum antibodies and AGWs were estimated in the sub-group of MSM attending a SHC for the first time.

Results in chapter 8, pages 196-199

The history of health service use in SHC-attending MSM was described and factors that affect MSM's intentions to receive vaccines were assessed. Health service use, HPV knowledge and STI risk perception, by quadrivalent HPV type status, were explored to identify potential opportunities and barriers for delivery of vaccination.

Results on page 199

To explore the open-ended reasons for or against perceived likelihood of accepting the HPV vaccine, answers were grouped. Each answer was assessed and, if it did not fit into existing groups, either a new group was created, or the definition of an existing group was amended so it became inclusive.

Results on page 201

Random-effects meta-analyses

In chapters 5 and 6, random-effects meta-analyses were performed on chapter estimates and other HPV prevalence estimates from studies published up to mid-2015 using methods described in chapter 3, page 56. Studies for these 'findings in context' sections were not identified systematically.

Strengths and limitations of the HPV-MSM-MMC study

Recruitment

It was beneficial to run the study at MMC because the large patient population enhanced recruitment and the entire research team were in the same building. This facilitated trouble-shooting and motivating the clinic researchers. However, the recruitment rate was slower than predicted and was hindered by only having one study nurse working on the study, who was not able to be present during all of the clinic opening hours.

In the clinic, it was difficult to identify the broader risk group of MSM that had had sex with another man in the last five years and men were usually recruited using the operational

definition at MMC: anal or oral sex with another man in the last three months. The study population was therefore a higher risk subset of the targeted population.

Data

Eleven surveys that were completed in October 2011 and four surveys completed in February 2012 were lost during the transfer from the study's CASI tablet computer to the main UCL server and on three occasions the CASI survey failed to save the data.

There was a period in which the study's screening log was not completed. The log was completed from the start of recruitment (25th October 2010) until 31st October 2011 and then restarted on 14th February 2012 until the end of recruitment (18th July 2012). There was therefore missing data on the participation rate between 1st November 2011 and 13th February 2012, three and a half months of the 20-month recruitment period.

4.4 RESULTS

PARTICIPATION RATE

A total of 522 men participated in the study. Of 413 eligible men who were approached when the screening log was active 341 (82.6%) consented to participate in the study. Men who participated were slightly older (mean = 29.7 years; 95% CI 29.1-30.3) than men who did not agree to participate (mean = 28.2; 95% CI 26.8-29.6; p=0.05) and were 1.8 (95% CI 1.0-3.3) times more likely to be a new patient at the clinic (p=0.04). Across the reasons listed for not participating in Table 8, there was no difference in the mean age (F=1.13 p=0.35) or the proportion who were new patients in the clinic (χ^2 with 5 df=4.76, p=0.45).

TABLE 8. REASONS FOR NOT PARTICIPATING IN THE HPV-MSM-MMC STUDY

Reason for not participating (multiple responses were permitted)	**n (%)**	**Mean age (years)**	**New patients n (%)**
Time	30 (39.0)	28.4	5 (16.7)
Declined for other reasons e.g depressed/eye infection	17 (22.1)	30.7	2 (11.8)
English language not sufficient	14 (18.2)	27.1	4 (28.6)
Anxious/upset	9 (11.7)	25.7	4 (44.4)
Extra tests	4 (5.2)	26.8	1 (25.0)
No reason given	3 (3.9)	27.7	1 (33.3)

RESPONSE RATE

The flowchart in Figure 26 shows the available data in the study. All 522 men who participated in the study completed the questionnaire. Some men declined to give specific samples. The resulting number of samples available for analyses were: 512 anal and stored blood samples (98.1%); 521 external genital swabs (99.8%) and 182 oral samples (97.9% of the 186 men offered the oral sample). Overall, the questionnaire took between five and 15 minutes to complete and it was generally completed in seven to ten minutes.

MISSING DATA

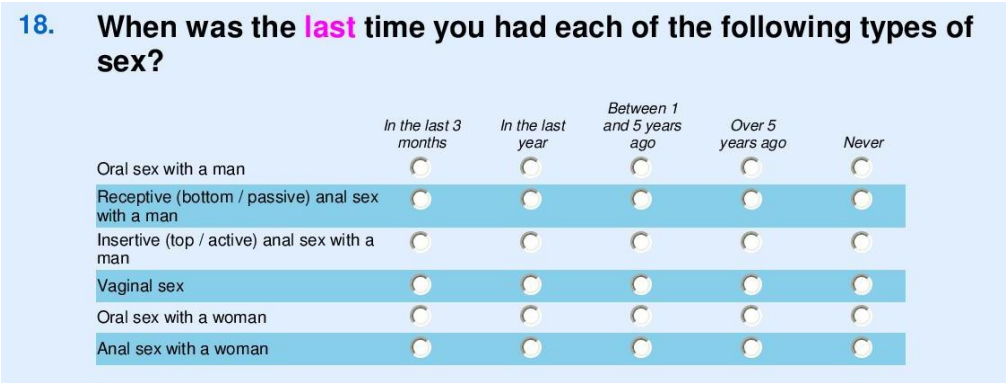
Missing surveys

Eighteen (3.5%) questionnaires were not available for analysis (see page 99). The analyses were carried out on the 504 completed surveys.

Item non-completion

Most of the sample (98.0%) completed more than 46 of the 55 items that were asked to all participants. Table 9 lists the items that had more than 5% non-response. A fifth of the sample did not complete the three items asking about sex with a woman that were part of question 18 (Figure 25). Nearly two thirds of the sample did not give a reason for their intention to accept the HPV vaccine. This item was not missing at random as men who were less likely to accept the vaccine would be more likely to give a reason. All men were asked whether they had told their general practitioner (GP) their sexual orientation and 5.6% did not respond. This was question 52 of 62 so was near the end of the survey. There were three participants with more than 47 of the 101 questionnaire items (maximum including routed questions) missing. One of these men was described as “manic” by the research nurse and unable to sit down for long. There is no information as to why the other two men did not complete the questionnaire fully. The data from all three men were included in the analyses.

FIGURE 25. SCREENSHOT OF QUESTION 18 FROM THE CASI QUESTIONNAIRE



18. When was the last time you had each of the following types of sex?

	In the last 3 months	*In the last year*	*Between 1 and 5 years ago*	*Over 5 years ago*	*Never*
Oral sex with a man	○	○	○	○	○
Receptive (bottom / passive) anal sex with a man	○	○	○	○	○
Insertive (top / active) anal sex with a man	○	○	○	○	○
Vaginal sex	○	○	○	○	○
Oral sex with a woman	○	○	○	○	○
Anal sex with a woman	○	○	○	○	○

FIGURE 26. FLOWCHART OF NUMBER OF MSM WITH AVAILABLE DATA AND BIOLOGICAL SPECIMENS

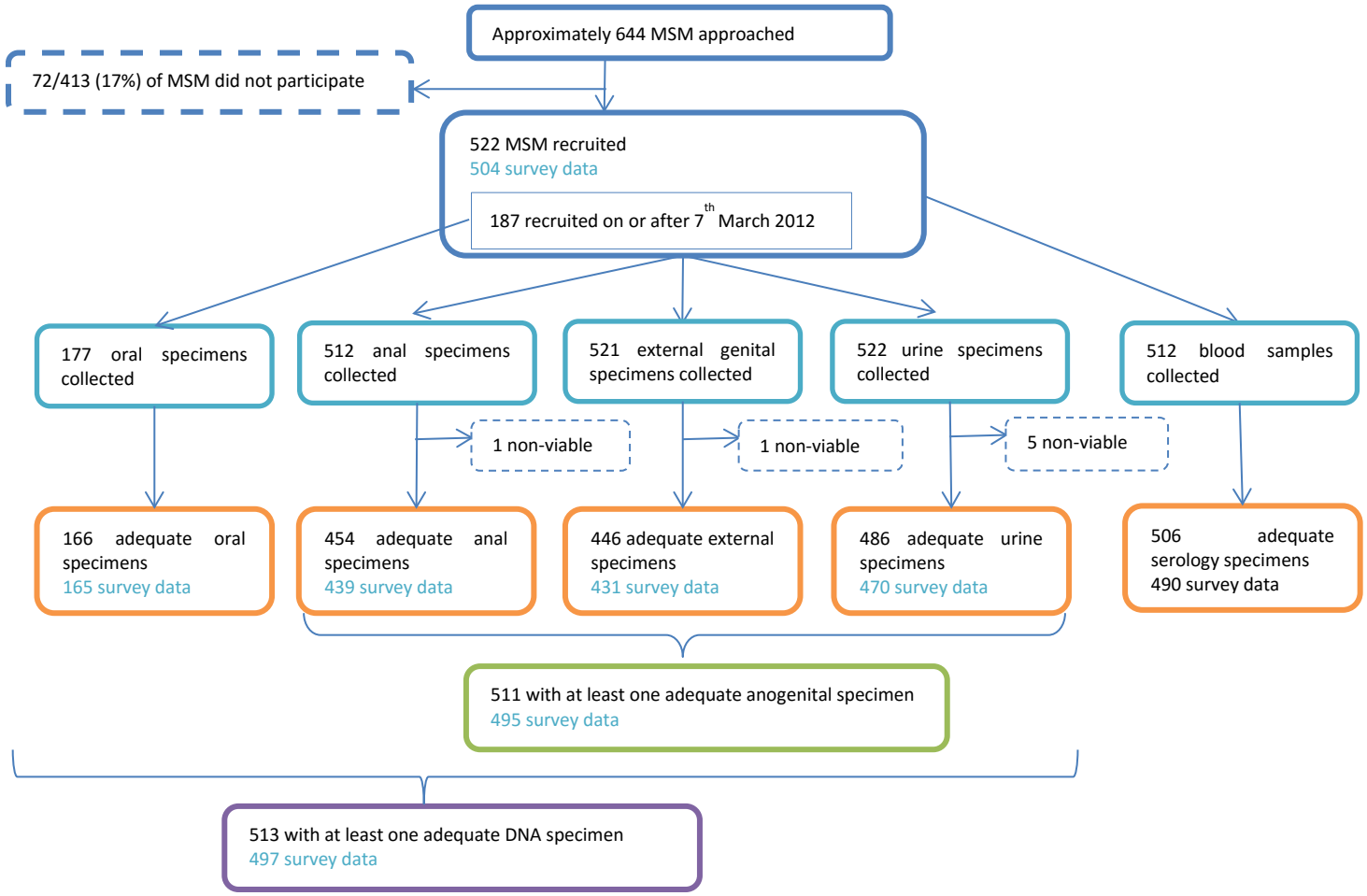


TABLE 9. LIST OF VARIABLES WITH MORE THAN FIVE PERCENT OF MISSING DATA, DUE TO NON-COMPLETION

Question	Number of non-responders/ Number of men asked question (%)
When was the last time you had:	
Vaginal sex	110/504 (21.9)
Oral sex with a woman	107/504 (21.2)
Anal sex with a woman	109/504 (21.6)
Please give reason below (Follow up to question: The HPV vaccine course is 3 injections in a 6 month period. If you were offered the HPV vaccine in this clinic, how likely would you be to accept it?)	324/504 (64.3)
Please specify (Follow to response "Mixed/Other" from the ethnic group categories)	7/58 (12.1)
In the last year, with how many men have you only had oral sex	40/494 (8.1)
When you had anal sex without a condom in the last year, were you…always insertive, always receptive, versatile, mostly insertive, mostly receptive?	36/326 (11.0)
Age of partner 3	24/460 (5.2)
How certain are you of their age? Partner 3	33/460 (7.2)
Is this a regular (main) or a casual partner?	
Partner 2	27/483 (5.6)
Partner 3	37/460 (8.0)
How many partners do you think this partner has had in the last year? Partner 3	26/460 (5.7)
How certain are you about the number of partners they have had?	
Partner 1	30/502 (6.0)
Partner 2	37/483 (7.7)
Partner 3	44/460 (9.6)
When was the last time you had sex with this partner? (number)	
Partner 1	43/502 (8.6)
Partner 2	53/483 (11.0)
Partner 3	63/460 (13.7)
When was the last time you had sex with this partner? Partner 3 (unit)	29/460 (6.3)
When was the first time you had sex with this partner? (number)	
Partner 1	46/502 (9.2)
Partner 2	56/483 (11.6)
Partner 3	65/460 (14.1)
When was the first time you had sex with this partner? Partner 3 (unit)	31/460 (6.7)
What was the result of this [HIV] test?	27/475 (5.7)
Please specify [Follows response to: Where did you last receive a DIAGNOSIS of genital or anal warts? "Other" category]	1/5 (20.0)
Where did you last receive TREATMENT for genital or anal warts?	13/145 (9.0)
Please specify [Follows response to: Where did you last receive TREATMENT for genital or anal warts? "Other" category]	1/9 (11.1)
Have you told your GP your sexual orientation?	28/503 (5.6)
Please specify [Follows response to: Where were you vaccinated? "Other" category]	4/35 (11.4)

Non-viable or missing samples

Ten participants declined the anal swab, and ten a blood sample, so 512 of each were collected. One participant declined the external genital swab so 521 were collected and 10/187 declined the oral specimen so 177 were collected (Figure 26). On arrival at the laboratory, five urine samples were non-viable, two having leaked and three having evidence of fungal growth. In addition, one anal and one external swab (from the same participant) had both leaked and could not be processed.

PARTICIPANT CHARACTERISTICS

Table 10 shows the services that were delivered to HPV-MSM-MMC participants at the study visit and is indicative of the breakdown of the sample in terms of reported behaviour and symptoms because specific symptoms would prompt specific investigations. For example, microscopy is recommended for MSM reporting symptoms and the sampling site relates to whether receptive or insertive behaviours were reported**.**

TABLE 10. SERVICES PROVIDED TO HPV-MSM-MMC PARTICIPANTS AT THE STUDY VISIT, DETERMINED FROM SEXUAL HEALTH AND HIV ACTIVITY PROPERTY TYPES (SHAAPT) CODES.

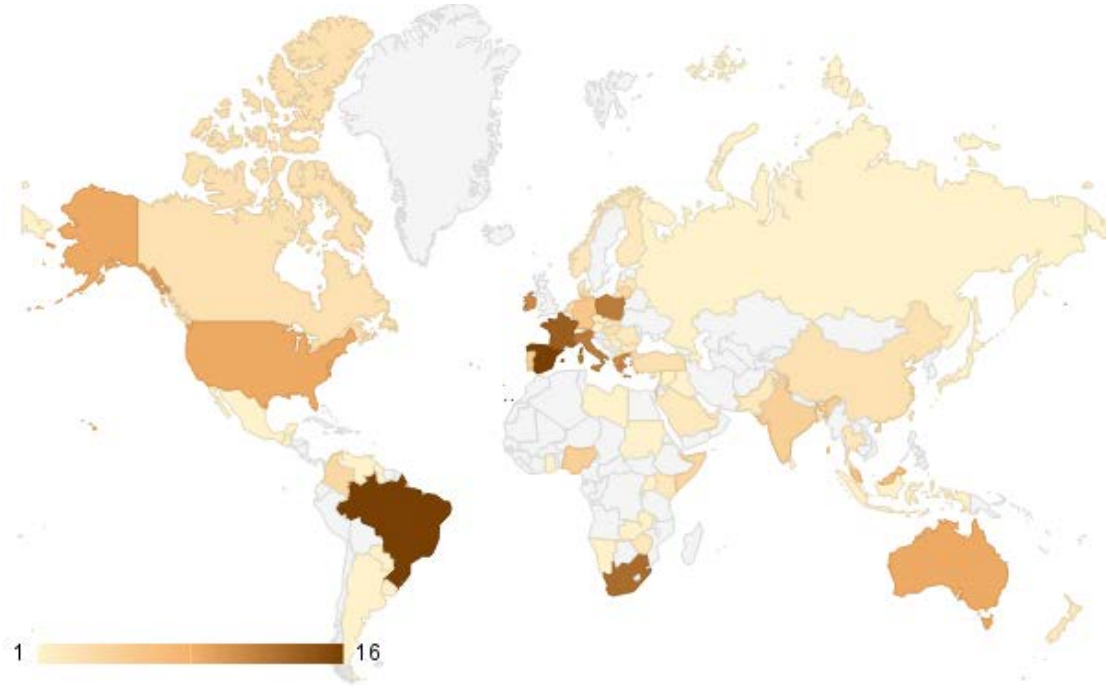
	N=522	
	No.	%
Chlamydia, gonorrhoea, syphilis & HIV tests (full screen)	327	62.6
Chlamydia, gonorrhoea and syphilis tests	30	5.8
Chlamydia and gonorrhoea tests	19	3.6
HSV test	18	3.5
Hepatitis (A/ B/ C) tests	97	18.6
Tested for gonorrhoea or syphilis using microscopy	47	9.0
Genital, pharyngeal and rectal tests for chlamydia and gonorrhoea	246	47.1
Referred via partner notification	25	4.8
Hepatitis B vaccine dose	36	6.9
HIV-related care	2	0.4
Post-exposure prophylaxis	7	1.3

Participants could receive more than one SHAAPT code, relating to the visit.

Table 11. shows demographic and lifestyle characteristics of study participants. The median age was 30 years (IQR 25-35), with 17 participants (3.3%) younger than 21. Nearly half (237; 47.0%) were born in the UK and another 193 men (38.3%) had lived in the UK for at least three years. Figure 27 shows that countries in Europe as well as Brazil and South Africa were the most frequently reported countries of birth in 256 MSM who were born outside the UK.

The majority of participants (382/501; 76.3%) were of white ethnicity and 91.5% identified as gay/homosexual. Most participants were employed (79.0%), with at least three years of education post-16 (68.3%). Two-thirds (328/498; 65.9%) reported higher risk drinking behaviour (identified using AUDIT-C, score ≥5), 17/498 (3.6%) hazardous and harmful drinking (AUDIT score 8–15) and a third (29.4%) were current smokers. A third (28.9%) of participants were circumcised, 28/522 (5.4%) had been diagnosed as HIV-positive and 28/503 (5.6%) reported never having had an HIV test.

FIGURE 27. WORLD MAP SHOWING THE FREQUENCY OF COUNTRY OF BIRTH OF 256 PARTICIPANTS WHO WERE NOT BORN IN THE UK



11/267 participants did not answer the question asking for country of birth.

TABLE 11. SELECTED DEMOGRAPHIC AND LIFESTYLE CHARACTERISTICS OF PARTICIPANTS IN THE HPV-MSM-MMC STUDY

	N=522*	
	No.	%
Age group		
18-20	17	3.3
21-25	119	23.3
26-30	127	24.9
31-35	140	27.4
36-40	108	21.1

	N=504*	
Ethnicity		
White	382	76.3
Black	31	6.2
Asian & SE Asian	36	7.2
Mixed/Other	52	10.4
Born in the UK		
No	267	53.0
Yes	237	47.0

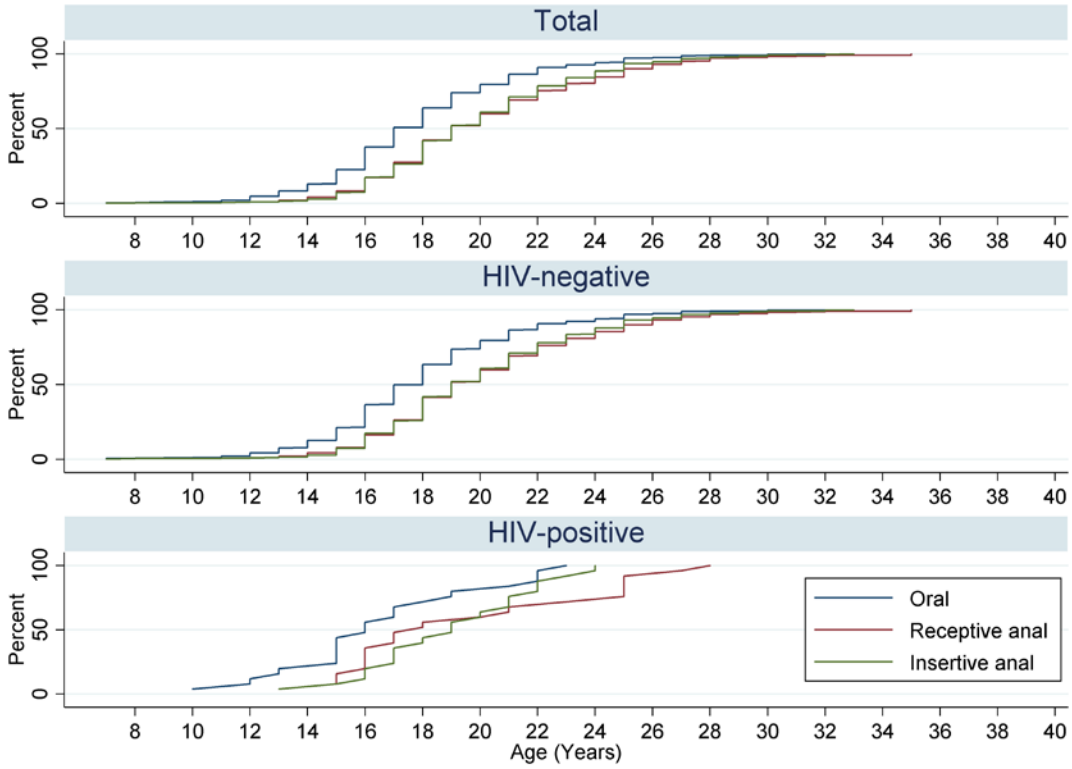
	N=504*	
	No.	%
Currently smoke cigarettes		
No	355	70.6
Yes	148	29.4
Alcohol use disorders identification test- AUDIT-C		
No risk drinking	170	34.1
Risk drinking	328	65.9
Currently employed		
No	106	21.0
Yes	398	79.0
Years of education since age 16		
None	13	2.6
Up to 2 years	62	12.3
3 years or more	344	68.3
Still in education	85	16.9
Sexual orientation		
Gay/homosexual	460	91.5
Bisexual	43	8.6

*Total numbers vary for each question due to missing items: survey questions that were not asked (due to routing) or not answered.

SEXUAL BEHAVIOUR

Table 12 displays selected sexual behaviours of study participants. The majority of men (51.2%) reported first receptive anal sex between 16-20 years old. The median age at first oral, insertive anal, and receptive anal sex with a man was 18 (IQR 16-20), 19 (IQR 17-22), and 19 (IQR 17-23), respectively. HIV-positive MSM had first oral sex earlier (median=16 years) compared with HIV-negative MSM (median=18; p=0.04) but there was no difference in age at first anal sex (receptive or insertive) by HIV status (Figure 28).

FIGURE 28. CUMULATIVE PERCENTAGE OF MSM ATTENDING MMC WHO HAD EXPERIENCED SEX WITH MEN BY AGE



Two thirds of men (66.2%) had had more than 30 lifetime male sex (anal or oral) partners and only six men (1.2%) had had fewer than three lifetime partners. Of those who had an anal sex partner in the last year, 295/472 (62.5%) had sex with at least one partner without a condom. For each year increase in age, the odds of having more than 30 lifetime partners increased by 14.1% (95% CI 10.0-18.4) but there was no association between age and the number of partners, new partners, or partners without a condom in the last year. For example, the median number of male anal partners in the last year was six (IQR 3-15) in men aged 18-30 and eight (IQR 3-20) in men aged 31-40. Younger men, aged 18-30, were more likely to have had receptive anal sex in the last year than older men (86% vs 77%; OR 1.8; 95 %CI 1.1-2.9). The proportion of men who had sex without a condom in the last year was higher among younger men (66% vs 58%; OR 1.4 95% CI 0.9-2.0) but this was not statistically significant.

TABLE 12. SELECTED SEXUAL BEHAVIOURS OF PARTICIPANTS IN THE HPV-MSM-MMC STUDY

Number of partners	N=504*	
	No.	%
Total lifetime male partners oral and anal		
Fewer than 20	99	19.7
21-30	71	14.1
31-100	170	33.8
101-500	163	32.4
Number of anal sex partners in the last year		
0	1	0.2
1-4	179	37.6
5-10	136	28.6
11-30	113	23.7
More than 30	47	9.9
Number of new anal sex partners in the last year		
0	23	4.9
1-4	205	43.4
5-10	120	25.4
11-30	86	18.2
More than 30	38	8.1
Number of condom-less sex partners in the last year		
0	178	37.6
1-4	232	49.1
5-10	40	8.5
11-30	16	3.4
More than 30	7	1.5
Number of exclusively oral sex partners in the last year		
0	48	10.6
1-4	158	34.8
5-10	148	32.6
11-30	69	15.2
More than 30	31	6.8

Other sexual behaviours	N=504*	
	No.	%
Age at first insertive anal sex (years)		
Up to 15	34	7.4
16-20	245	53.5
21-25	145	31.7
26-39	34	7.4
Age at first oral sex with man (years)		
Up to 15	105	21.2
16-20	274	55.4
21-25	98	19.8
26-39	18	3.6
Age at first receptive anal sex (years)		
Up to 15	36	7.8
16-20	235	51.2
21-25	141	30.7
26-39	47	10.2
Oral sex with man in the last year		
Yes	494	99.2
No	4	0.8
Receptive anal sex in the last year		
Yes	403	81.7
No	90	18.3
Insertive anal sex (man) last year		
Yes	435	89.9
No	49	10.1
Position during condom-less sex in last year		
Insertive	76	26.2
Receptive	46	15.9
Versatile	168	57.9
Use of drugs in anus/rectum ever		
No	454	90.1
Yes	50	9.9
Concurrency between any of 3 most recent partners		
No	224	44.4
Yes	280	55.6

*Total numbers vary for each question due to missing items: survey questions that were not asked (due to routing) or not answered. Position/role during oral sex was not collected

EXTERNAL COMPARISONS OF STUDY POPULATION

HPV-MSM-MMC participants broadly mirrored that of MSM attending MMC during the recruitment period, in terms of age and ethnicity, but were slightly younger (Table 13). MSM attending other SHCs in England in 2010-2011 were younger and less ethnically diverse. Participants had more lifetime partners than MSM who had attended a SHC in the last five years in the Natsal-3 survey (British population in 2010-2012). Within Natsal-3, MSM who had attended a SHC had more lifetime partners than those who had not. For example, 93% of HPV-MSM-MMC participants reported >10 lifetime partners, compared to 78% of MSM who had attended a SHC in Natsal-3, and to 25% of MSM who had not attended. (Natsal-3 team, personal communication). MSM participating in the GMSHS, recruiting from London social venues in 2011, had slightly fewer male anal partners in the last year and appeared to be less likely to have had anal sex in the last year than participants in the HPV-MSM-MMC study, although this was not formally tested[156].

TABLE 13. COMPARISON OF DEMOGRAPHIC AND SEXUAL BEHAVIOUR DISTRIBUTIONS BETWEEN HPV-MSM-MMC PARTICIPANTS AND OTHER BRITISH MSM POPULATIONS.

	HPV in MSM study population		MSM aged 16-40 (GUMCAD. V2), attending during 2010-2011:				MSM, aged 16-40, in the general British population 2010-2012 (Natsal-3): at least one male sexual partner (genital contact) in past 5 years				MSM (aged 18-40) in GMSHS 2011	
			MMC 2010-2011		SHCs in England		MSM attending a SHC in the last 5-years		MSM not attending a SHC in the last 5-years			
Total (N)	522		4,376		63,597		43		49		902	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Age (years)												
18-20	17	3.3	124	2.8	5,237	8.2	5	10.6	14	28.2	47	5.2
21-25	121	23.2	728	16.6	15,279	24.0	9	21.8	10	20.3	184	20.4
26-30	133	25.5	1,144	26.1	16,580	26.1	13	31.0	17	34.4	264	29.3
31-35	142	27.2	1,182	27.0	14,029	22.1	11	24.9	3	7.0	228	25.3
36-40	109	20.9	1,198	27.4	12,472	19.6	5	11.8	5	10.2	179	19.8
Ethnicity												
White	382	75.8	3,236	74.0	50,007	78.6	42	92.7	46	98.0	711	78.9
Black	31	6.2	231	5.3	2,531	4.0	0	0.0	0	0.0	32	3.6
Asian & SE Asian	36	7.1	333	7.6	3,629	5.7	0	4.1	2	0.0	71	7.9
Mixed Other	52	10.3	411	9.4	3,994	6.3	1	3.2	2	2.0	87	9.7
Not known / not stated	3	0.6	165	3.8	3,436	5.4	0	0.0	0	0.0	n/a	n/a

TABLE 13. COMPARISON OF DEMOGRAPHIC AND SEXUAL BEHAVIOUR DISTRIBUTIONS BETWEEN HPV-MSM-MMC PARTICIPANTS AND OTHER BRITISH MSM POPULATIONS. CONTINUED.

	HPV in MSM study population		MSM aged 16-40 (GUMCAD. V2), attending during 2010-2011:		MSM, aged 16-40, in the general British population 2010-2012 (Natsal-3): at least one male sexual partner (genital contact) in past 5 years				MSM (aged 18-40) in GMSHS 2011	
			MMC 2010-2011	SHCs in England	MSM attending a SHC in the last 5-years		MSM not attending a SHC in the last 5-years			
Lifetime number of same-sex partners										
0 - 1	3	0.6	Behavioural data not collected in GUMCAD v2		0	0.9	12	24.4	n/a	n/a
2 - 4	15	3.0			7	16.7	17	35.2	n/a	n/a
5 - 9	17	3.4			4	9.3	9	18.3	n/a	n/a
10+		93.1			32	35.7	11	22.2	n/a	n/a
10-20	64	12.7			13	0.9	4	8.8	n/a	n/a
21-30	71	14.1			4	16.7	3	5.3	n/a	n/a
31-100	170	33.8			11	9.3	1	1.6	n/a	n/a
>100	163	32.4			4	8.7	3	6.5	n/a	n/a
Anal sex in the last year										
No	17	3.4			8	18.6	22	43.8	95	11.6
Yes	482	96.6			35	81.4	28	56.2	721	88.6
Number of anal partners without condom in last year (of those who report having had anal sex in the last year)										
0	178	37.6			0	0.0	0	0.0	286	42.3
1	128	27.1			14	72.9	11	63.1	228	33.7
2-4	104	22.0			4	20.3	5	27.7	120	17.7
5-10	40	8.5			0	0.0	2	9.2	25	3.7
>10	23	4.9			1	6.9	0	0.0	18	2.7

4.5 KEY FINDINGS

The estimated participation rate in the HPV-MSM-MMC study was high at 81% and surveys were generally well completed with samples collected.

Despite aiming to capture young MSM, there were few participants younger than 21. Participants were generally well-educated, alcohol drinkers with a high level of smoking and STI transmission behaviours. HIV prevalence (HIV positive diagnosis) was 5%. Rates of partner change and prevalence of HPV did not decline with age

4.6 FINDINGS IN CONTEXT

The MSM in this study reported high levels of sexual risk behaviour compared to MSM in the general population in the UK and MSM attending pubs and clubs in London. Smoking levels were similar (29% of participants) to men, aged 25-34, in the general population (30% of men[159]) and hazardous and harmful drinking was higher at 49% compared to 32% in men in England in 2004[160].

4.7 STRENGTHS AND LIMITATIONS

Participation bias

There was a difference in the age and likelihood of being a first-time attendee between MSM participating in and declining from the study but this was not based on complete data. In contrast, when comparing to the MSM who attended MMC during the recruitment period, the age difference was reversed and did not appear to be significant.

More MSM reported a language barrier to participation (18% of reasons reported) than was anticipated during study design. It is possible that reasons for not participating in the study would correlate with not being offered or accepting the HPV vaccine since translators would be required before consenting to vaccination and clinicians might avoid offering the vaccine to men who are excessively emotional or upset. This might result in a upwards bias in estimating vaccine intentions (chapter 8, page 201).

Non-response bias

A fifth of participants did not reply to the three items relating to sex with women. Although there may be other reasons for not replying to these items, it seems likely that participants did not feel that this question was relevant to them because they did not have sex with

women. Therefore, in the following results chapters, sex with women variables had missing items recoded as 'never' and sensitivity analyses were performed to examine the effect of recoding (results not shown).

Additionally, there is some evidence of response fatigue. In the series of questions relating to the three most recent partners, each additional partner had a higher proportion of non-response than its precedent. Furthermore, more questions at the end of the survey had more than five percent missing than those at the beginning.

5. HPV-MSM-MMC STUDY: HPV PREVALENCE, SPECIMEN AGREEMENT AND RISK FACTORS

In this chapter, I present the primary results from the HPV-MSM-MMC study: HPV DNA prevalence and risk factors for HPV DNA detection. I first present HPV prevalence estimates and type distribution across specimen types. Then I report the age-specific HPV prevalence (for any HPV type, HR-HPV and vaccine-preventable HPV types) and risk factors for the detection of quadrivalent-vaccine types in anogenital specimens of any type. I then report risk factors for HR-HPV detection in each specimen type.

I then turn to quantifying the relationship between HPV DNA detection and site, first reporting the contribution to vaccine-type prevalence from each specimen type, then formally estimating agreement and concordance for HPV detection between sites. I then focus on HPV16 in the anal and external genital swabs, comparing viral load and LCR variation. I report on risk factors that I identified for anogenital type-specific HPV concordance.

I then put the findings from this chapter into context by reviewing the literature up to mid-2015, including random-effects meta-analyses. Finally I discuss potential bias within the study that should be considered when interpreting the findings presented in this chapter.

5.1 OBJECTIVES

1. To estimate the prevalence of detectable DNA of HPV, HR-HPV, vaccine-preventable HPV and individual HPV types by HIV status and specimen type in SHC-attending MSM in the UK
2. To describe the relative HPV type distribution by specimen type
3. To explore the association between HPV prevalence and age
4. To identify associations between quadrivalent-vaccine type DNA detection and socio-demographic and behavioural variables at any anogenital site
5. To identify associations between HR-HPV DNA detection and socio-demographic and behavioural variables at each anatomical site

6. To quantify the relationship between HPV DNA detection at different sites
7. To compare HPV16 viral load and HPV16 variants in the anal and external specimens
8. To identify associations between socio-demographic and behavioural variables and HR-HPV DNA detection at two or more (concordant) anogenital sites
9. To discuss biases to be considered when interpreting the findings from this chapter

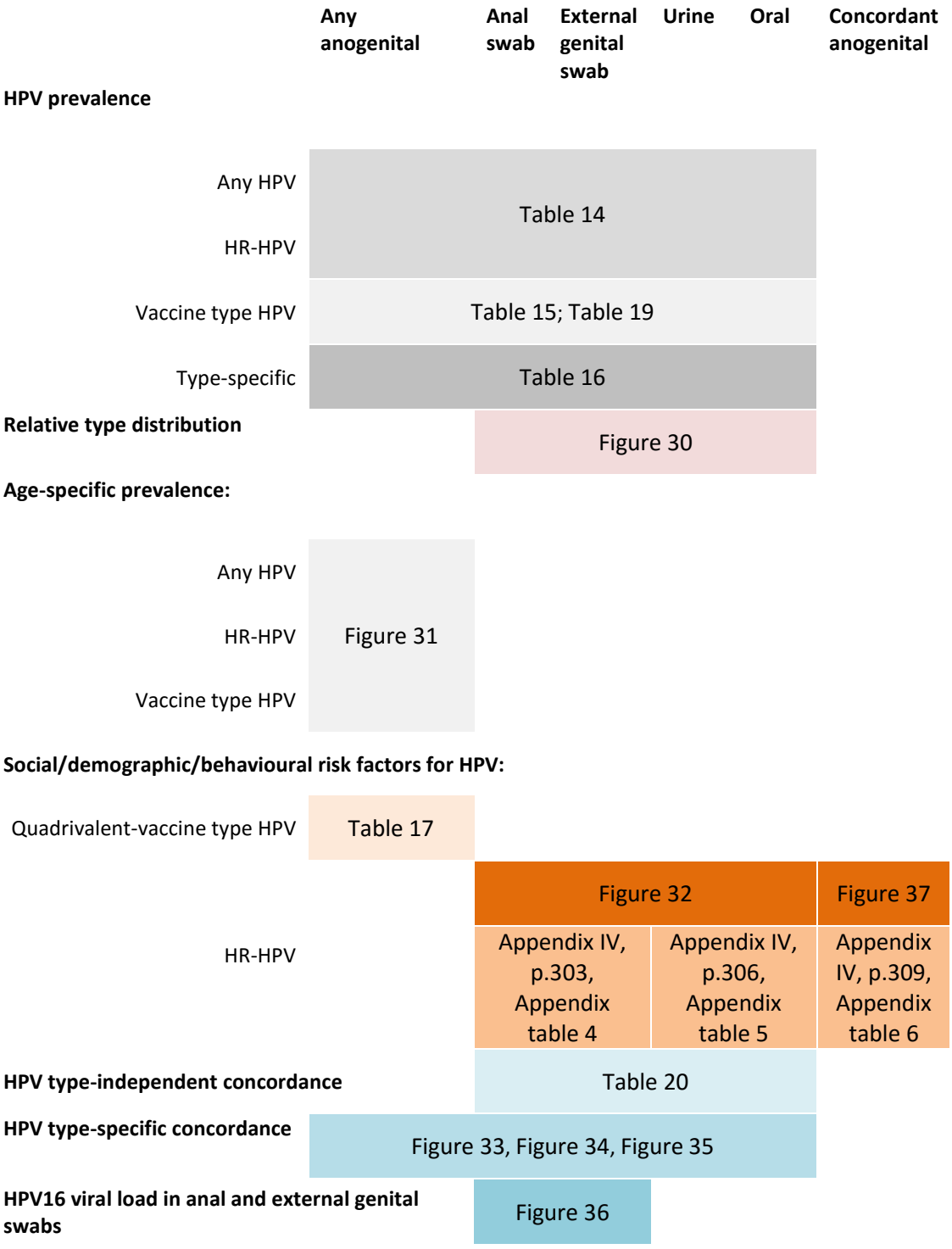
METHODS

The methods used to meet these objectives have been described in chapter 4. In particular, the collection, processing and testing of laboratory specimens are described on pages 90-93 and statistical methods are described on pages 93-97.

5.2 RESULTS

Of 522 MSM participating in this study, at least one sample that was adequate for PCR was available for 513 MSM and at least one anogenital sample in 511 MSM. Data from the CASI survey were available for 497 of these MSM. Figure 26, in chapter 4 (page 102), shows that the number of adequate samples for anal, external, urine and oral was 454, 446, 486 and 166, respectively. The median age of these 513 MSM was 30 (IQR: 25-35). Figure 29 summarises the results presented in this chapter.

FIGURE 29. SUMMARY OF RESULTS TABLES AND FIGURES RELATING TO OBJECTIVES IN CHAPTER 5



HPV PREVALENCE

HPV and HR-HPV prevalence

Table 14 shows the prevalence of HPV DNA in different specimen types. The highest HPV DNA prevalence of 65.9% (95% CI 61.3-70.2) was found in the anal swab which was similar to the external genital swab (63.9%; 95% CI 59.3-68.4). HPV DNA prevalence was also similar in the oral cavity (12.7%; 95% CI 8.0-18.7) and urine (11.1%; 95% CI 8.5-14.2). This pattern was repeated for HR-HPV DNA with estimates of 40.5%, 38.8%, 5.1% and 5.4% for anal, external, urine and oral, respectively.

At any anogenital site, the overall prevalence of HPV was 72.2% (95% CI 68.2-75.9). The prevalence was 71.1% (95% CI 66.8-75.1) in HIV-negative MSM and 92.6% (95% CI 75.7-99.1) in HIV-positive MSM (χ^2=5.90, p=0.02). The prevalence of detectable HR-HPV types was 47.2% (95% CI 42.9-51.5) overall, 45.7% (95% CI 41.2-50.2) in HIV-negative MSM and 74.1% (95% CI 53.7-88.9) in HIV-positive MSM (χ^2=8.28, p<0.01).

Of the 13 HIV-positive MSM with an oral specimen adequate for HPV testing, none had HPV detected using the universal PCR probe. In HIV-negative MSM (n=151), the oral prevalence of any HPV was 13.7% (95%CI 8.7-20.2) and HR-HPV was 5.9% (95% CI 2.7-10.9).

Vaccine-preventable HPV prevalence

Table 15 shows that at any anogenital site, at least one quadrivalent-vaccine type (HPV6/11/16/18) was detected in 166/511 (32.5%) of participants; 18.4% (95% CI 15.3-22.0) had a bivalent-vaccine type(s) (HPV16/18); 71 (13.9%) had anogenital HPV 16/18 without HPV6/11; and 72 (14.1%) had HPV6/11 without HPV16/18. Table 15 shows that 1.4% of participants, with an adequate anogenital sample, had both bivalent types, none had all four quadrivalent types and 0.4% had more than three 9-valent vaccine types detected in anogenital specimens. In oral specimens (n=166), four (2.4%) had at least one quadrivalent type (one with both HPV6 and HPV18).

For HIV-negative MSM (n=484), the prevalence of any bivalent, quadrivalent and 9-valent vaccine-preventable HPV types at any anogenital site was 17.4% (95% CI 14.1-21.0), 31.0% (95% CI 26.9-35.3) and 43.8% (95% CI 39.3-48.4), respectively. For HIV-positive MSM (n=27)

bivalent type prevalence was 37% (95% CI 19-58), quadrivalent-vaccine type prevalence was 59% (95% CI 39-78) and 9-valent vaccine type prevalence was 74% (95% CI 54-89).

HPV type-specific prevalence

Table 16 shows that the most commonly detected HPV types were 16, 11 and 6 with anogenital prevalence estimates of 13.5% (95% CI 10.8-16.8), 11.5% (95% CI 9.0-14.6) and 9.4% (95% CI 7.1-12.3), respectively.

For HIV-negative MSM the anogenital prevalence estimate for HPV6 was 9.7% (95% CI 7.2-12.7), for HPV11 it was 10.7% (95% CI 8.1-13.8), for HPV16 it was 12.6% (95% CI 9.8-15.9) and for HPV18 it was 6.0% (95% CI 4.0-8.5). For HIV-positive MSM the prevalence estimates for HPV6, HPV11, HPV16 and HPV18 were 3.7% (95% CI 0.9-19.0), 25.9% (95% CI 11.1-46.3), 29.6% (95% CI 13.8-50.2) and 11.1% (95% CI 2.4-29.2), respectively.

TABLE 14. PREVALENCE OF HPV DNA IN DIFFERENT SPECIMEN TYPES

	Anogenital								Oral	
	Anal	N=454	External	N=446	Urine	N=486	≥1 Anogenital[a, b]	N=511		N=166
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Any bivalent HPV vaccine types (16/18)	16.1	(12.8-19.8)	13.7	(10.6-17.2)	1.9	(0.9-3.5)	18.4	(15.1-22.0)	1.2	(0.1-4.3)
Any quadrivalent HPV vaccine types (6/11/16/18)	29.1	(24.9-33.5)	24.0	(20.1-28.2)	3.3	(1.9-5.3)	32.5	(28.6-36.7)	2.4	(0.7-6.1)
HPV16/18 and HPV6/11	2.4	(1.2-4.3)	1.8	(0.8-3.5)	0.0	(0.0-0.1)	4.5	(2.9-6.7)	0.6	(0.02-3.3)
HPV16/18 not HPV6/11	13.7	(10.6-17.2)	11.9	(9.0-15.3)	1.9	(0.9-3.5)	13.9	(11.0-17.2)	0.6	(0.02-3.3)
HPV6/11 not HPV16/18	13.0	(10.0-16.4)	10.3	(7.7-13.5)	1.4	(0.6-2.9)	14.1	(11.1-17.4)	1.2	(0.1-4.3)
Any 9-valent HPV vaccine types (6/11/16/18/31/33/45/52/58)	40.1	(35.5-44.8)	36.1	(31.6-40.7)	5.3	(3.5-7.7)	45.4	(41.0-49.8)	4.2	(1.7-8.5)
High risk HPV types (HR-HPV)[d]	40.5	(36.0-45.2)	38.8	(34.2-43.5)	5.1	(3.4-7.5)	47.2	(42.8-51.6)	5.4	(2.5-10.0)
Multiple HR types[d] (2 or more)	11.5	(8.7-14.7)	9.4	(6.9-12.5)	0.4	(0.0-1.5)	17.4	(14.2-21.0)	0.0	(0.0-2.2)
Any HPV type[c]	65.9	(61.3-70.2)	63.9	(59.3-68.4)	11.1	(8.5-14.2)	72.2	(68.1-76.1)	12.7	(8.0-18.7)
Multiple types (2 or more)	20.9	(17.3-25.0)	19.3	(15.7-23.3)	1.0	(0.3-2.4)	29.2	(25.3-33.3)	0.6	(0.0-3.3)

[a]27/511 were HIV-positive MSM in whom: 10 had any bivalent types, 16 any quadrivalent types, 20 any 9-valent types, 20 HR-HPV, 11 multiple HR types, 25 had detectable HPV and 16 had multiple HPV types. [b]HPV detected at anus (via swab) or external genitalia including penis (via swab) or urine. If any of the 3 sample types were adequate for DNA detection then included in the denominator. [c]Reacted to the universal probe for HPV DNA. [d]HR-HPV classified according to International agency for research on cancer (IARC) monograph carcinogenic or probably carcinogenic[10,11].

TABLE 15. NUMBER OF VACCINE-PREVENTABLE HPV TYPES DETECTED IN DIFFERENT SPECIMENS

HPV type	Anal swab		External genital swab		Urine		≥1 Anogenital[a]		Oral	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Number of bivalent vaccine HPV types (16/18)										
0	385	84.8	385	86.3	477	98.2	417	81.6	175	98.9
1	69	15.2	59	13.2	9	1.9	87	17.0	2	1.1
2	0	0.0	2	0.5	0	0.0	7	1.4	0	0.0
Number of quadrivalent vaccine HPV types (6/11/16/18)										
0	322	70.9	339	76	470	96.7	345	67.5	173	97.7
1	112	24.7	89	20	15	3.1	128	25.1	3	1.7
2	20	4.4	17	3.8	1	0.2	34	6.7	1	0.6
3	0	0.0	1	0.2	0	0.0	4	0.8	0	0.0
4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Number of 9-valent vaccine HPV types(6/11/16/18/31/33/45/52/58)										
0	272	59.9	285	63.9	460	94.7	279	54.6	170	96.1
1	144	31.7	124	27.8	24	4.9	157	30.7	6	3.3
2	30	6.6	33	7.4	2	0.4	59	11.6	1	0.6
3	7	1.5	4	0.9	0	0.0	14	2.7	0	0.0
4	1	0.2	0	0.0	0	0.0	1	0.2	0	0.0
5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
6	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0
7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Total adequate samples	454		446		486		511		177	

[a]HPV detected at anus (via swab) or external genitalia including penis (via swab) or urine. If any of the 3 sample types were adequate for DNA detection then included in the denominator.

TABLE 16. HPV TYPE-SPECIFIC PREVALENCE IN DIFFERENT SPECIMEN TYPES

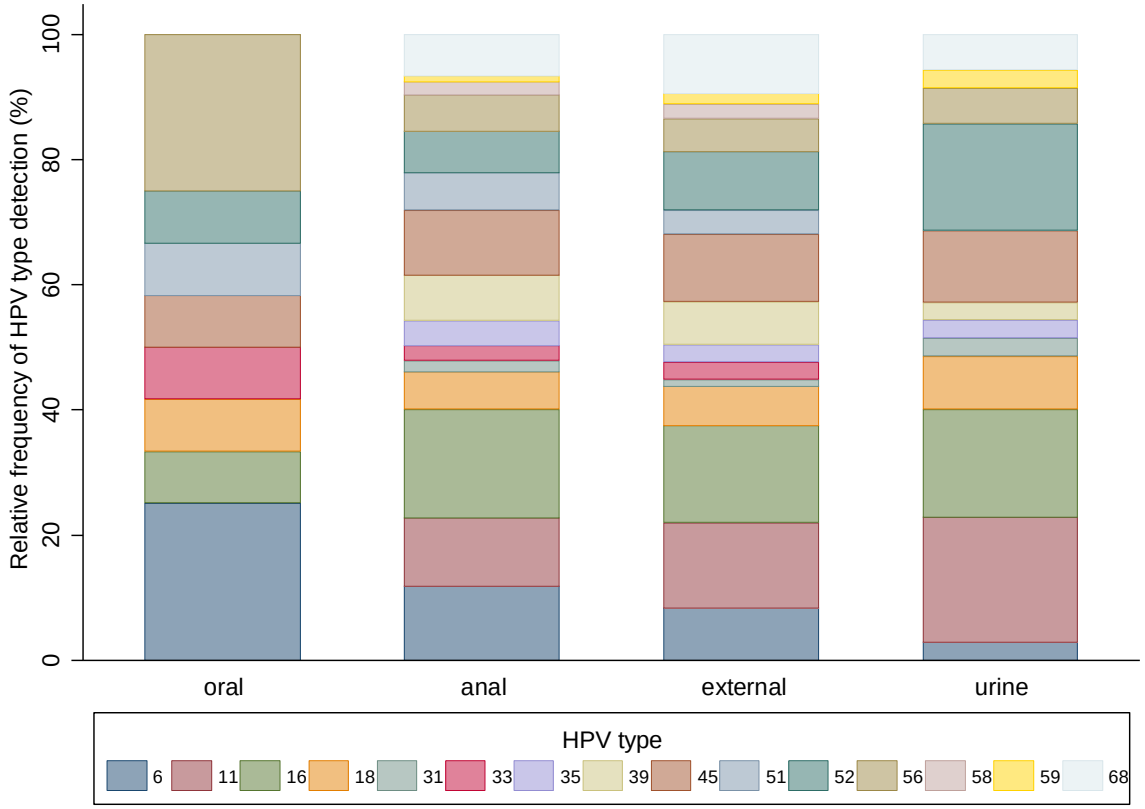
HPV type	Anogenital								Oral	
	Anal	N=454	External	N=446	Urine	N=486	≥1 Anogenital[a, b]	N=511		N=166
16	12.6	(9.6-16.0)	10.1	(7.5-13.3)	1.2	(0.5-2.7)	13.5	(10.7-16.8)	0.6	(0.0-3.3)
18	4.4	(2.7-6.7)	4.0	(2.4-6.3)	0.6	(0.1-1.8)	6.3	(4.3-8.7)	0.6	(0.0-3.3)
31	1.3	(0.5-2.9)	0.7	(0.1-2.0)	0.2	(0.0-1.1)	1.6	(0.7-3.1)	0.0	(0.0-2.2)
33	1.8	(0.8-3.4)	1.8	(0.8-3.5)	0.0	(0.0-0.8)	2.5	(1.4-4.3)	0.6	(0.0-3.3)
35	2.9	(1.5-4.8)	1.8	(0.8-3.5)	0.2	(0.0-1.1)	3.3	(1.9-5.3)	0.0	(0.0-2.2)
39	5.3	(3.4-7.8)	4.5	(2.8-6.8)	0.2	(0.0-1.1)	5.9	(4.0-8.3)	0.0	(0.0-2.2)
45	7.5	(5.2-10.3)	7.0	(4.8-9.7)	0.8	(0.2-2.1)	9.0	(6.7-11.8)	0.6	(0.0-3.3)
51	4.4	(2.7-6.7)	2.5	(1.2-4.4)	0.0	(0.0-0.8)	4.7	(3.0-6.9)	0.6	(0.0-3.3)
52	4.8	(3.1-7.2)	6.1	(4.0-8.7)	1.2	(0.5-2.7)	7.8	(5.7-10.5)	0.6	(0.0-3.3)
56	4.2	(2.5-6.5)	3.4	(1.9-5.5)	0.4	(0.0-1.5)	5.5	(3.7-7.8)	1.8	(0.4-5.2)
58	1.5	(0.6-3.2)	1.6	(0.6-3.2)	0.0	(0.0-0.8)	2.3	(1.2-4.1)	0.0	(0.0-2.2)
59	0.7	(0.1-1.9)	1.1	(0.4-2.6)	0.2	(0.0-1.1)	1.0	(0.3-2.3)	0.0	(0.0-2.2)
68	4.8	(3.1-7.2)	6.1	(4.0-8.7)	0.4	(0.0-1.5)	7.8	(5.7-10.5)	0.0	(0.0-2.2)
Possibly high risk HPV types	9.9	(7.3-13.0)	10.8	(8.0-14.0)	1.2	(0.5-2.7)	14.1	(11.3-17.4)	0.0	(0.0-2.2)
26	1.1	(0.4-2.6)	1.1	(0.4-2.6)	0.2	(0.0-1.1)	1.6	(0.7-3.1)	0.0	(0.0-2.2)
53	3.7	(2.2-5.9)	3.4	(1.9-5.5)	0.4	(0.0-1.5)	5.7	(3.8-8.0)	0.0	(0.0-2.2)
66	0.7	(0.1-1.9)	0.0	(0.0-0.8)	0.0	(0.0-0.8)	0.6	(0.1-1.7)	0.0	(0.0-2.2)
70	2.6	(1.4-4.6)	2.0	(0.9-3.8)	0.0	(0.0-0.8)	2.7	(1.5-4.6)	0.0	(0.0-2.2)
73	2.9	(1.5-4.8)	4.9	(3.1-7.4)	0.6	(0.1-1.8)	4.9	(3.2-7.1)	0.0	(0.0-2.2)
82	0.0	(0.0-0.8)	0.0	(0.0-0.8)	0.0	(0.0-0.8)	0.0	(0.0-0.7)	0.0	(0.0-2.2)
Low risk HPV types										
6 and/or 11	15.4	(12.2-19.1)	12.1	(9.2-15.5)	1.4	(0.6-2.9)	18.6	(15.3-22.2)	1.8	(0.4-5.2)
6	8.6	(6.2-11.6)	5.4	(3.5-7.9)	0.2	(0.0-1.1)	9.4	(7.0-12.3)	1.8	(0.4-5.2)
11	7.9	(5.6-10.8)	8.7	(6.3-11.8)	1.4	(0.6-2.9)	11.5	(8.9-14.6)	0.0	(0.0-2.2)

[a]27/511 were HIV-positive MSM in whom: 8 had detectable HPV6/11.[b]HPV detected at anus (via swab) or external genitalia including penis (via swab) or urine. If any of the 3 sample types were adequate for DNA detection then included in the denominator.

RELATIVE TYPE DISTRIBUTION ACROSS SITES

Figure 30 shows the relative contribution of each HPV type to overall genotyped HPV prevalence at each anatomical site. Each HPV type detected is treated independently; in multiple-type infections each HPV type contributes to the denominator. At all sites, the quadrivalent-vaccine types represented approximately 50% of the genotyped HPV detected. There was less diversity in the types detected at the oral site compared to the anogenital sites. At the oral site HPV6 and HPV56 were the most common types and HPV11 was not detected. The anogenital sites had similar HPV type distribution, particularly the anal and external sites. In GEE models, there was no interaction between anatomical site of HPV infection and type of HPV infection for HPV6/11/16/18 ($p=0.41$) or for all of the 21 HPV types tested ($p=0.93$).

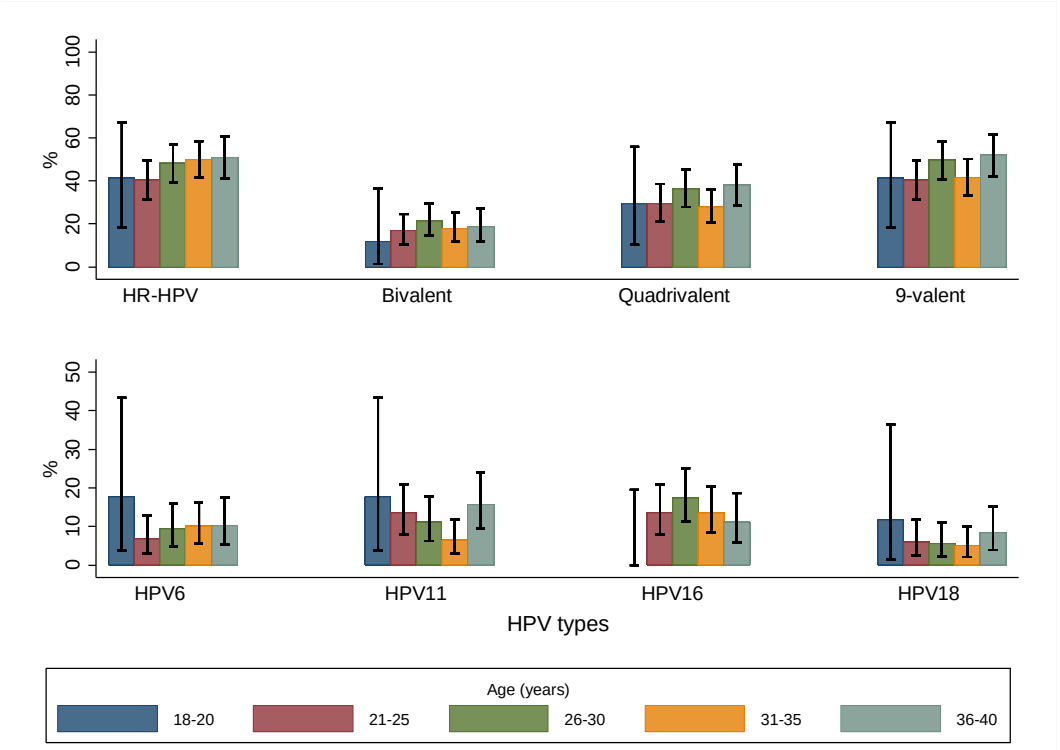
FIGURE 30.THE RELATIVE DISTRIBUTION OF HPV TYPES DETECTED AT DIFFERENT ANATOMICAL SITES



AGE-SPECIFIC HPV PREVALENCE

Figure 31 shows age-specific prevalence of HPV at any anogenital site. For any HPV type, and modelling age as a continuous variable (from 18 to 40 years), there was a 4.7% (95% CI 1.2-8.4) increase in the odds of an HPV infection per year. The effect was not significant when examining age as a categorical variable, except in the nonparametric test for trend ($p<0.01$), but confidence intervals are wide, and there were few participants in the youngest category in particular (17 in 18-20). There was no significant association between age and HR-HPV, bivalent, quadrivalent or 9-valent vaccine type detection, considered separately.

FIGURE 31. HPV PREVALENCE IN ANY ANOGENITAL SAMPLE BY AGE



NB. Y axis scales differ between upper and lower panels. In 511 participants of the HPV-MSM-MMC study with at least one anogenital specimen that was adequate for HPV testing. Data for this figure are displayed in Appendix III, page 300.

SOCIAL, DEMOGRAPHIC AND BEHAVIOURAL RISK FACTORS FOR QUADRIVALENT-VACCINE TYPE HPV DNA DETECTION AT ANY ANOGENITAL SITE

Table 17 and Table 18 show the association of socio-demographic and sexual behavioural variables with anogenital quadrivalent-vaccine type DNA detection. Table 18 shows that, at any anogenital site, detection of any quadrivalent-vaccine types was associated with number of lifetime anal or oral sex partners (aOR=2.6 in those with >100 compared to ≤20 partners), an HIV positive diagnosis (aOR=3.2; 95% CI 1.5-7.1) and rectal drug use (aOR=2.0; 95% CI 1.1-3.6). In MSM with fewer than 30 lifetime male partners, the mean number of partners was lower (16.6 partners) in those without quadrivalent-vaccine types than those with detectable quadrivalent HPV (mean=19.8; t=-2.1; p=0.04). Between one and 30 lifetime partners (n=166), the odds of having a detectable quadrivalent-vaccine type increased by 5% per partner (aOR=1.05; 95% CI 1.01-1.10). There were no other statistically significant associations between quadrivalent-vaccine type infection and demographic, health or behavioural variables, after adjusting for age.

TABLE 17. ASSOCIATION OF SOCIO-DEMOGRAPHIC FACTORS FOR QUADRIVALENT-VACCINE TYPE DETECTION AT ANY ANOGENITAL SITE

	Total	HPV6/11/16/18 prevalence				
	N[a]	n	%	Age-adjusted OR[b]	95% CI	p value
Demographic						
Age group						
18-20	17	5	29.4	0.68	(0.22-2.07)	0.38
21-25	119	35	29.4	0.68	(0.39-1.18)	
26-30	127	46	36.2	0.93	(0.55-1.58)	
31-35	140	39	27.9	0.63	(0.37-1.08)	
36-40	108	41	38.0	1	-	
Ethnicity						
White	377	120	31.8	1	-	0.59
Black	30	11	36.7	1.24	(0.57-2.68)	
Asian & SE Asian	28	8	28.6	0.78	(0.35-1.72)	
Mixed/Other	57	21	36.8	1.39	(0.76-2.55)	
Born in the UK						
No	263	86	32.7	1	-	0.86
Yes	232	74	31.9	0.97	(0.66-1.41)	
Currently employed						
No	105	32	30.5	1	-	0.73
Yes	390	128	32.8	1.09	(0.66-1.41)	
Years of education since age 16						
None	13	3	23.1	0.61	(0.16-2.25)	0.93
Up to 2 years	58	19	32.8	1.01	(0.55-1.83)	
3 years or more	340	112	32.9	1	-	
Still in education	84	26	31.0	0.96	(0.55-1.67)	
Sexual orientation						
Gay/homosexual	452	149	33.0	1	-	0.39
Bisexual	42	11	26.2	0.73	(0.36-1.50)	
Health						
Self-rated general health						
Very good	253	87	34.4	1	-	0.20
Good	216	70	32.4	0.92	(0.63-1.36)	
Fair	21	3	14.3	0.32	(0.09-1.13)	
Bad	4	0	0.0	1	(1.00-1.00)	
Circumcised						
No	349	111	31.8	1	-	0.66
Yes	142	48	33.8	1.10	(0.72-1.66)	
Diagnosis of HIV						
No	484	150	31.0	1	-	<0.01
Yes	27	16	59.3	3.21	(1.45-7.08)	
Smoking, alcohol and substance use						
Currently smoke cigarettes						
No	349	118	33.8	1	-	0.31
Yes	145	42	29.0	0.80	(0.53-1.23)	
Higher risk drinking (AUDIT-C)						
No	167	53	31.7	1	-	0.89
Yes	322	104	32.3	1.03	(0.69-1.53)	
Use of drugs in anus/rectum ever						
No	446	137	30.7	1	-	0.03
Yes	49	23	46.9	1.98	(1.09-3.60)	

[a]Total numbers vary for each question due to missing items. For survey questions the total including missing items is 495. For age the total is 511. [b]Age is modelled continuously in adjusted models. Odds ratios presented for age group are unadjusted.

TABLE 18. ASSOCIATION OF SEXUAL BEHAVIOURS WITH QUADRIVALENT-VACCINE TYPES DETECTION AT ANY ANOGENITAL SITE.

	Total	HPV6/11/16/18 prevalence				
	N[a]	n	%	Age-adjusted OR[b]	95% CI	p value
Number of sex partners						
Number of lifetime male partners (oral and anal sex)						
Fewer than 20	94	20	21.3	1	-	0.03
21-30	73	24	32.9	1.86	(0.92-3.74)	
31-100	168	53	31.6	1.78	(0.96-3.29)	
101-500	159	63	39.6	2.56	(1.37-4.78)	
Number of anal sex partners in the last year						
0	1	1	100.0	omitted		0.10
1-4	176	45	25.6	1	-	
5-10	135	43	31.9	1.36	(0.83-2.23)	
11-30	109	38	34.9	1.55	(0.92-2.61)	
More than 30	46	20	43.5	2.23	(1.14-4.33)	
Number of new anal sex partners in the last year						
0	22	7	31.8	1.15	(0.45-2.97)	0.43
1-4	202	58	28.7	1	-	
5-10	119	35	29.4	1.03	(0.63-1.70)	
11-30	82	30	36.6	1.42	(0.83-2.45)	
More than 30	38	16	42.1	1.80	(0.88-3.68)	
Number of anal sex partners without a condom in the last year						
0	174	44	25.3	0.64	(0.41-1.00)	0.22
1-4	228	78	34.2	1	-	
5-10	40	16	40.0	1.26	(0.63-2.52)	
11-30	15	6	40.0	1.29	(0.44-3.76)	
More than 30	7	2	28.6	0.76	(0.14-4.00)	
Age at first sex						
Age at first oral sex with man (years)						
Up to 15	101	34	33.7	1	-	0.57
16-20	270	89	33.0	0.95	(0.59-1.55)	
21-25	98	26	26.5	0.67	(0.36-1.26)	
26-39	17	6	35.3	0.98	(0.33-2.96)	
Age at first receptive anal sex (years)						
Up to 15	34	11	32.4	1	-	0.50
16-20	232	77	33.2	1.04	(0.48-2.24)	
21-25	140	42	30.0	0.89	(0.39-2.02)	
26-39	47	20	42.6	1.53	(0.58-4.02)	
Age at first insertive anal sex (years)						
Up to 15	34	11	32.4	1	-	0.56
16-20	238	84	35.3	1.13	(0.53-2.44)	
21-25	145	43	29.7	0.84	(0.37-1.89)	
26-39	33	13	39.4	1.24	(0.44-3.50)	

TABLE 18. ASSOCIATION OF SEXUAL BEHAVIOURS WITH QUADRIVALENT-VACCINE TYPES DETECTION AT ANY ANOGENITAL SITE. CONTINUED

	Total	HPV6/11/16/18 prevalence				
	N[a]	n	%	Age-adjusted OR[b]	95% CI	p value
Sexual behaviour in the last year						
Receptive anal sex in last year						
No	89	22	24.7	1	-	0.08
Yes	397	134	33.8	1.60	(0.94-2.71)	
Insertive anal sex in last year						
No	49	17	34.7	1	-	0.79
Yes	426	140	32.9	0.92	(0.49-1.71)	
Position when having anal sex without condom in last year						
Insertive	75	19	25.3	1	-	0.07
Receptive	46	15	32.6	1.47	(0.65-3.32)	
Versatile	164	66	40.2	2.01	(1.10-3.70)	
Condom use with most recent partner (incl oral)						
Always	237	71	30.0	1	-	0.10
Sometimes	103	29	28.2	0.92	(0.55-1.54)	
Never	151	59	39.1	1.50	(0.98-2.31)	
Still having sex with most recent partner						
No	231	66	28.6	1	-	0.08
Yes	260	94	36.2	1.41	(0.96-2.07)	
Last sex with most recent partner						
Up to 30 days ago	393	133	33.8	1	-	0.11
31-90 days ago	28	4	14.3	0.33	(0.11-0.96)	
90-365 days ago	29	8	27.6	0.76	(0.33-1.76)	
Relationship type with most recent partner						
Regular	242	83	34.3	1	-	0.33
Casual	236	71	30.1	0.83	(0.56-1.21)	
Concurrency between any of 3 most recent partners						
No	220	66	30.0	1	-	0.34
Yes	275	94	34.2	1.20	(0.82-1.76)	

[a]Total numbers vary for each question due to missing items: survey questions that were not asked (due to routing) or not answered. For survey questions the total including missing items is 495. For STI diagnoses at visit the total is 511. [b]Age is modelled continuously in adjusted models.

SOCIAL, DEMOGRAPHIC AND BEHAVIOURAL RISK FACTORS FOR HR-HPV DNA DETECTION ACROSS ANATOMICAL SITES

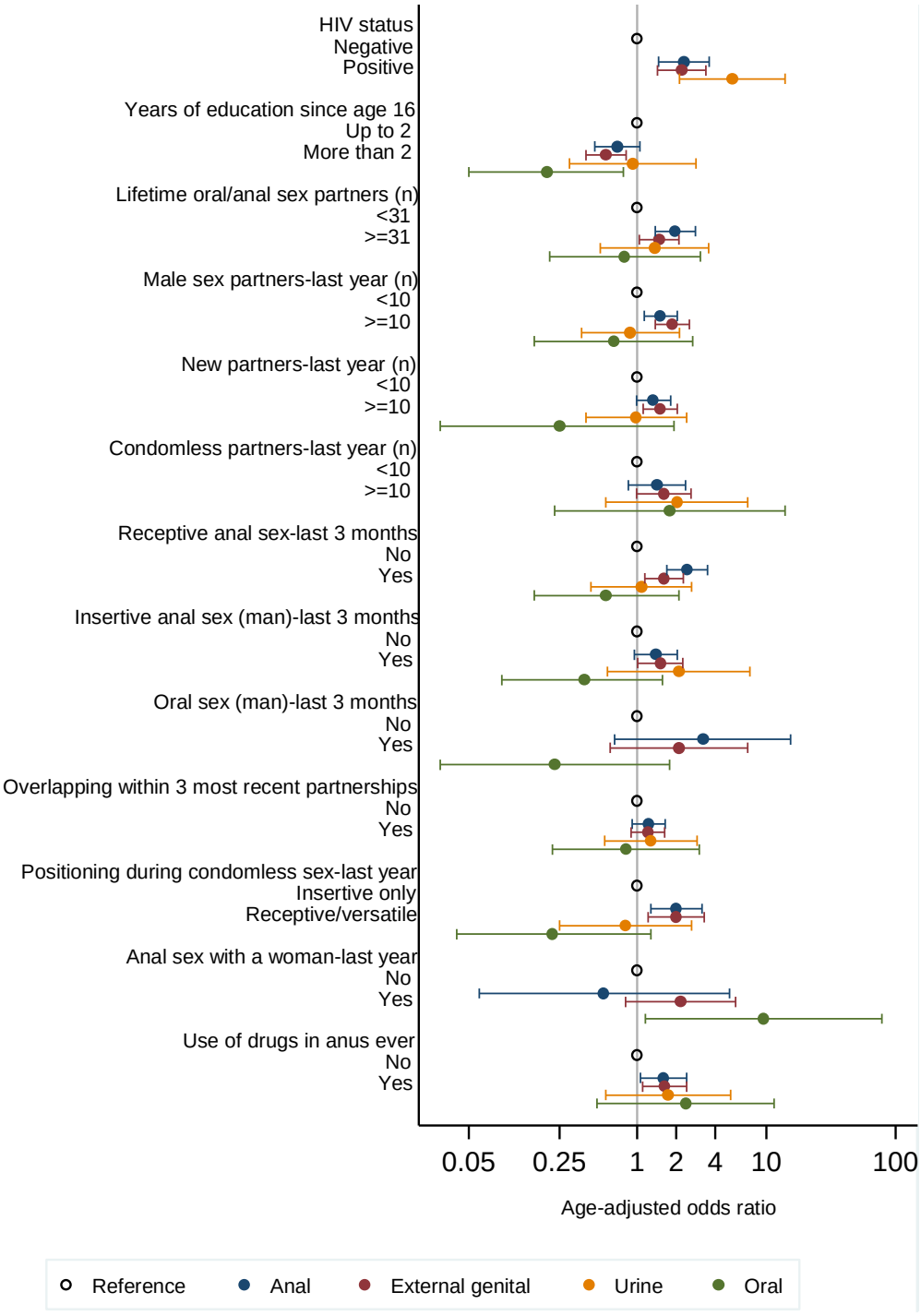
A total of ten socio-demographic and 21 sexual behaviour variables were examined for their association with HR-HPV DNA detection at each site and are displayed in Appendix table 4 and Appendix table 5 in Appendix IV. Categorical variables that were statistically associated with HR-HPV DNA detection at any site are shown in Figure 32. There was no association between age and HR-HPV detection at any site. An HIV positive diagnosis was associated with increased HR-HPV prevalence at all anogenital sites (anal aOR=2.29; 95% CI 1.46-3.60; external aOR=2.20; 95% CI 1.43-3.39; urine aOR=5.42; 95% CI 2.11-13.90).

Comparison of risk factors for HR-HPV at anal and external genital sites

Figure 32 and appendix IV (Appendix table 4) compare risk factors for HR-HPV detection in the two swabs. HR-HPV detection in the anal and the external genital swab had a similar risk profile. More than 30 lifetime partners increased the odds of HR-HPV detection in both the anal (aOR=1.97; 95% CI 1.38-2.82) and the external (aOR=1.48; 95% CI 1.04-2.10) swabs. Having had receptive anal sex in the last three months increased the odds of HR-HPV detection at both the anal (aOR=2.43; 95% CI 1.70-3.49) and external (aOR=1.61; 95% CI 1.14-2.27) swabs. Compared to insertive anal sex, when having sex without a condom in the last year, receptive or versatile positioning increased the odds of HR-HPV detection at both the anal (aOR=2.00; 95% CI 1.27-3.16) and external (aOR=2.00; 95% CI 1.21-3.29) swabs. Having ever used drugs in the anus was also associated with HR-HPV at both sites (anal aOR=1.60; 95% CI 1.06-2.41; external aOR=1.63; 95% CI 1.10-2.41).

Reporting insertive anal sex with a man in the last three months increased the odds of HR-HPV detection in the external swab (aOR=1.52 95% CI 1.01-2.26) but not at other sites.

FIGURE 32. A FOREST PLOT SHOWING THE CATEGORICAL VARIABLES THAT WERE STATISTICALLY ASSOCIATED (P<0.05) WITH DETECTION OF HR-HPV DNA IN AT LEAST ONE SPECIMEN TYPE



Logistic regression models fitted using GEE. Wald test P values. No HIV-positive participants were positive for oral HR-HPV and no men reporting anal sex in the last year with a woman were positive for HR-HPV in urine so odds ratios were not calculated.

Risk factors for HR-HPV in oral and urine specimens

The numbers of HR-HPV positive MSM were low for both urine and oral specimens (Appendix table 5). However some statistically significant associations were revealed for oral HR-HPV detection and these were shared with detection at the external swab. Fewer years of education (0-2 years) since the age of 16 compared to at least three years increased the odds of HR-HPV detection at the oral site (aOR=4.96; 95% CI 1.28-19.25) and at the external site (aOR=1.74; CI 1.21-2.50). HIV was the only statistically significant risk factor for HR-HPV DNA detection in urine (aOR=5.42; 95% CI 2.11-13.90).

COMPARING SPECIMEN TYPES FOR THE DETECTION OF HPV DNA

Table 19 shows the prevalence of vaccine-preventable HPV types by specimen type in 511 MSM with an adequate anogenital specimen. 132 men (29.1%) had at least one detectable quadrivalent-vaccine type in the anal canal. A further 28 men had quadrivalent-vaccine types detected in the external genital swab so that the prevalence in these two samples was 32.1%. Although only 16 men (3.3%) had detectable quadrivalent types in their urine, six of these infections were additional to the 160 detected in the two swabs.

TABLE 19. INCREMENTAL CONTRIBUTION TO PREVALENCE OF VACCINE-PREVENTABLE HPV FROM EACH ANOGENITAL SPECIMEN TYPE IN MSM

HPV type	Anal swab		External genital swab		Anal or external genital swab		Urine		Any anogenital specimen	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
16	57	12.6	45	10.1	66	13.3	6	1.2	69	13.5
18	20	4.4	18	4.0	30	6.0	3	0.6	32	6.3
16 and 18	4	0.9	2	0.5	7*	1.4	0	0.0	7	1.4
16 or 18	69	15.2	59	13.2	82	16.5	9	1.9	87	17
6	39	8.6	24	5.4	48	9.6	1	0.2	48	9.4
11	36	7.9	39	8.7	58	11.7	7	1.4	59	11.5
6 and 11	5	1.1	9	2.0	12	2.4	1	0.2	12	2.4
6 or 11	65	14.3	45	10.1	82	16.5	6	1.2	83	16.2
16 or 18 or 6 or 11	132	29.1	107	24.0	160	32.1	16	3.3	166	32.5
31 or 33 or 45 or 52 or 58	74	16.3	70	15.7	103	20.7	11	2.3	110	21.5
16 or 18 or 6 or 11 or 31 or 33 or 45 or 52 or 58	182	40.1	161	36.1	224	45.0	26	5.4	232	45.4
Total adequate samples	454		446		498		486		511	

*For rows measuring the frequency of both HPV types (HPV16&18 or HPV6&11), when combining specimen types, men were included in the numerator if one type was detected in one specimen (e.g anal) and the other type detected in another specimen (e.g. external) so that it is possible for the total to be greater than the sum of its parts.

Agreement of HPV DNA detection between sites

HPV type-independent agreement and concordance

The agreement for HPV type-independent detection, using the universal PCR probe, in the anal and external genital swabs was 76% (K = 0.45; 95% CI 0.36 - 0.54). Concordance between the swabs was 222/402 (55%) which was higher than that expected by chance (42%). HPV concordance was 41/423 (9.7%) for urine/external, 36/431 (8.4%) for urine/anal, 9/138 (6.5%) for oral/anal and 8/148 (5.4%) for oral/external.

See Statistical Methods, Box 6, page 96 for definitions of agreement, concordance and kappa.

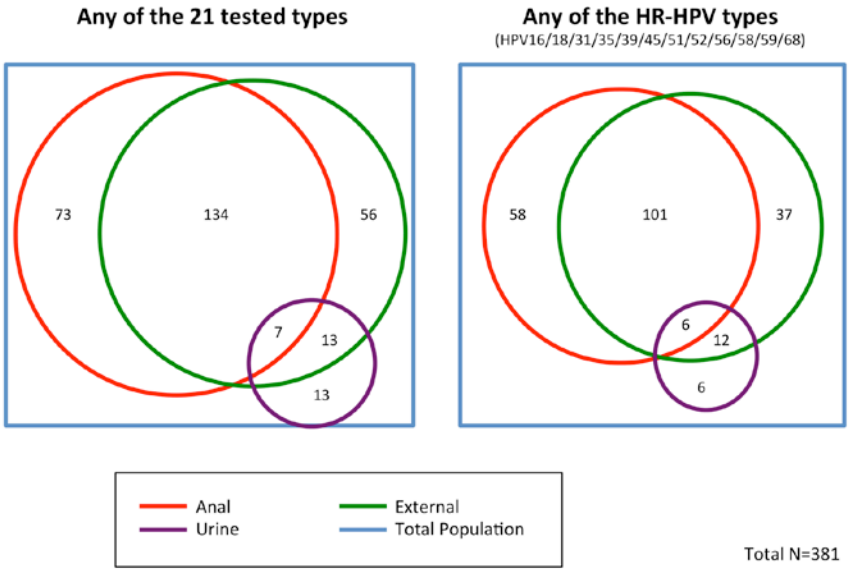
TABLE 20. HPV TYPE-INDEPENDENT CONCORDANCE ACROSS SPECIMEN PAIRS

Specimen pair	a/N	Percentage concordance	Expected concordance (%)
Anal/external genital	222/402	55.2	45.4
urine/external genital	41/423	9.7	7.8
urine/anal	36/431	8.4	7.6
oral/anal	9/138	6.5	7.6
oral/external genital	8/148	5.4	7.3

HPV type-specific agreement and concordance

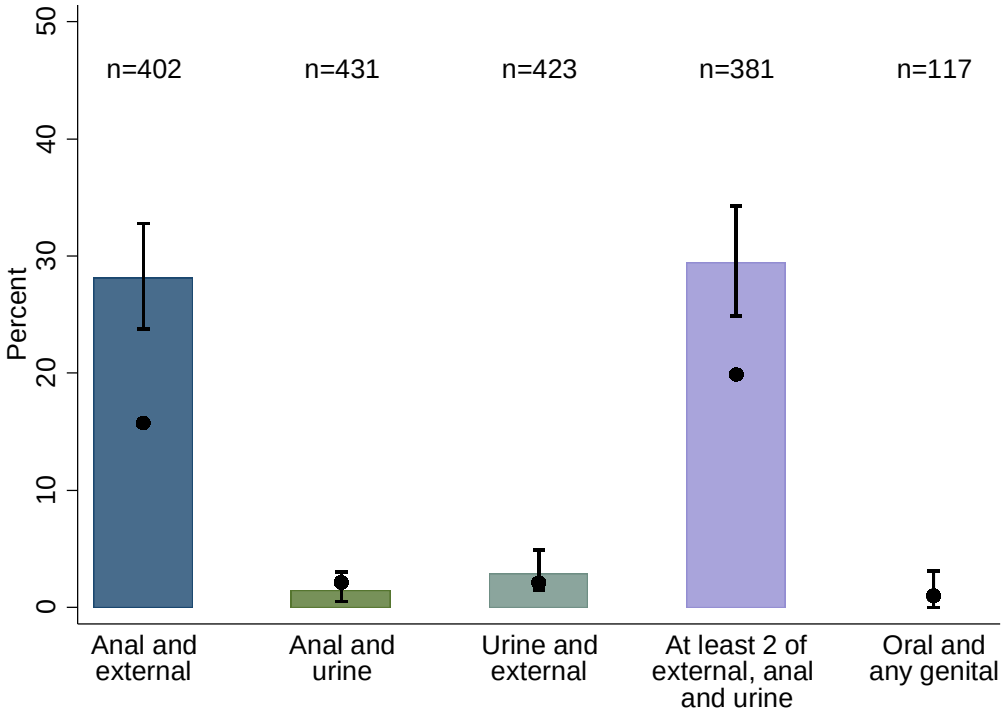
The frequency of HPV detection and agreement across anogenital sites is displayed in Figure 33. Pooled kappa for type-specific agreement for all 21 tested types for anal/external anal/urine and anal/oral agreement was 0.50 (95% CI 0.45-0.55), 0.03 (95% CI 0.00 - 0.07) and 0.11 (95% CI 0.07 - 0.16), respectively. Figure 34 shows that HR-HPV type-specific anogenital concordance was 29.4% (95% CI 24.9-34.2) compared to that expected by chance of 19.9%.

FIGURE 33. NUMBER OF MSM WITH A SPECIFIC GENOTYPE OF HPV DNA (ALL 21 TESTED TYPES AND 13 HR-HPV TYPES) DETECTED AT ONE OR MORE SITES IF ALL THREE SPECIMENS WERE ADEQUATE FOR PCR (N=381).



Circle size represents frequency

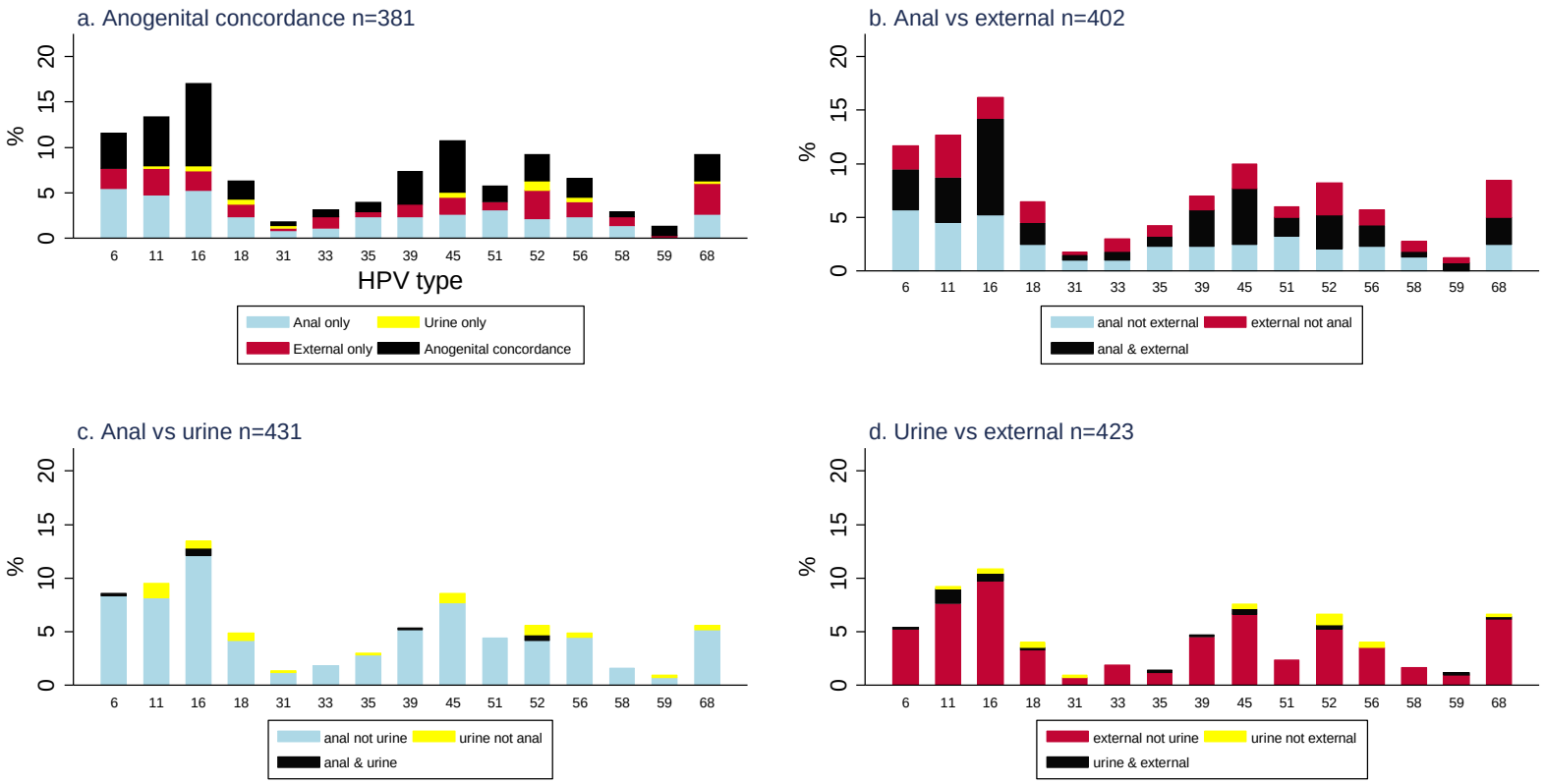
FIGURE 34. A BAR-CHART DISPLAYING HR-HPV TYPE-SPECIFIC CONCORDANCE (%) ACROSS ANATOMICAL SITES.



Percent of men with same HR-HPV type (HPV16,18,31,33,35,39,45,51,52,56,58,59 or 68) in both specimens in men with both specimens adequate for HPV testing. Filled circles represent percentage concordance expected by chance.

Figure 35 shows the prevalence of HR-HPV and types 6/11 (LR-HPV) across specimen type pairs. There was no oral/anogenital type-specific concordance. There was higher anal/external concordance, especially for HPV16 (9.0%) and HPV45 (5.2%). Type-specific prevalence in urine was low, yet there was anogenital/urine concordance for some HPV types especially HPV6 (0.25%), HPV16 (1.26%) and HPV52 (1.51%).

FIGURE 35. HR-HPV AND HPV6/11 TYPE-SPECIFIC HPV DNA DETECTION: CONCORDANCE AND DISCORDANCE ACROSS ANOGENITAL SPECIMEN TYPES



External=external genital swab. Anogenital concordance: at least two or three sites exhibit concordance. Denominator=both/all three samples in comparison were adequate for PCR. Possible HR-HPV types not shown.

DNA quantification in anal and external swabs

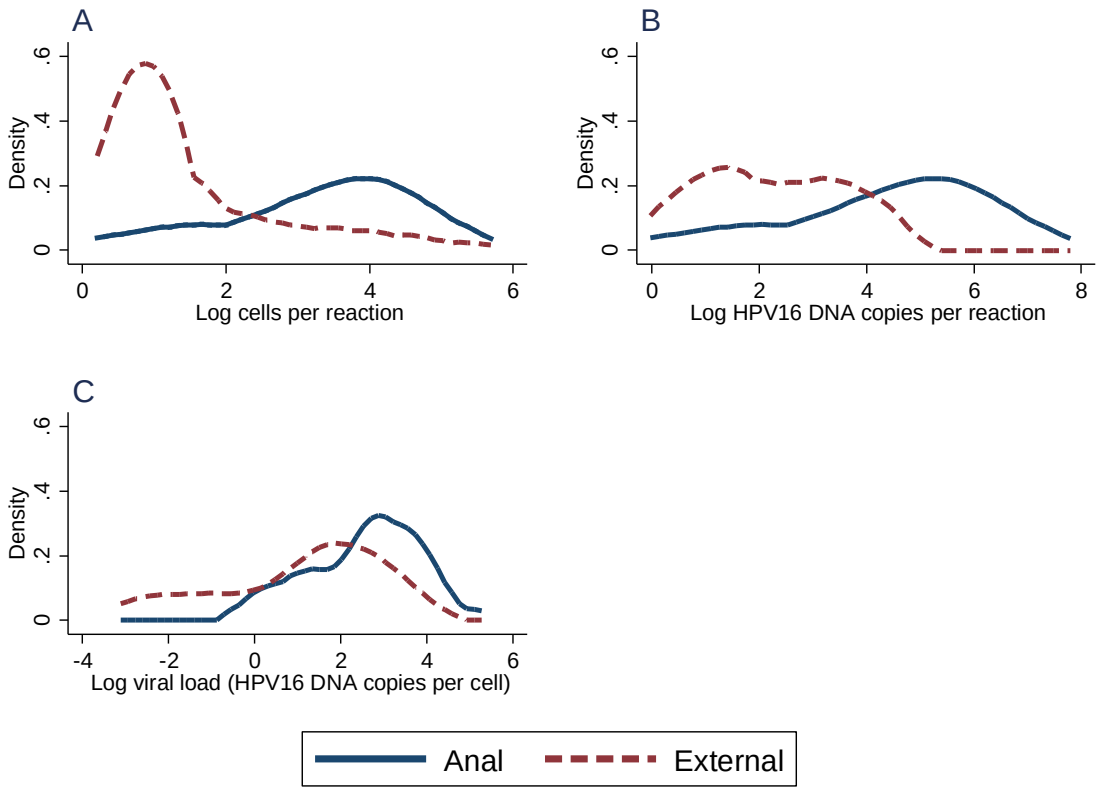
HPV16 was detected in 65/402 MSM in either the anal or external swab. HPV16 was detected only in the anal swab in 21/65 (32%); the external swab only in 8/65 (12%); and in both swabs in 36/65 (55%). Agreement was 92.8% (K = 0.67; 95% CI 0.56 - 0.78) and anal samples were significantly more likely to detect HPV16 than external samples (OR=2.63; 95% CI 1.12-6.85)

Figure 36 shows that there were significantly more cells in the anal swab (median 636; IQR 49-2,984 cells per reaction) than the external genital swab (median 9; IQR 5-76; z=2.46; p=0.01) and HPV16 DNA copies per reaction were higher in the anal (median 55,642; IQR 1,893-642,028) than the external genital (median 152; IQR 8-4,047; z=4.93; p<0.01). Quantification of cellular and viral DNA was possible in both swabs in 14/36 concordant pairs and viral load (VL) was higher in the anal (median 952; IQR 80-2,771) compared to the external genital swab (median 48; IQR 1-220); a 7.7-fold difference in VL (IQR 2.1-637.6; z=2.61; p<0.01).

Sequencing of the LCR

Due to low HPV16 DNA copy number (especially in external samples), sequencing of the variable LCR was only possible in 10/36 concordant pairs and another 10/36 anal samples. There were 2/10 (20%) pairs that had different sequences in the paired samples and 1/20 of anal samples had a mixed variant infection.

FIGURE 36. KERNAL DENSITY PLOTS SHOWING THE DIFFERENCES IN CELL COUNTS, VIRAL DNA AND VIRAL LOAD BETWEEN ANAL AND EXTERNAL SWABS



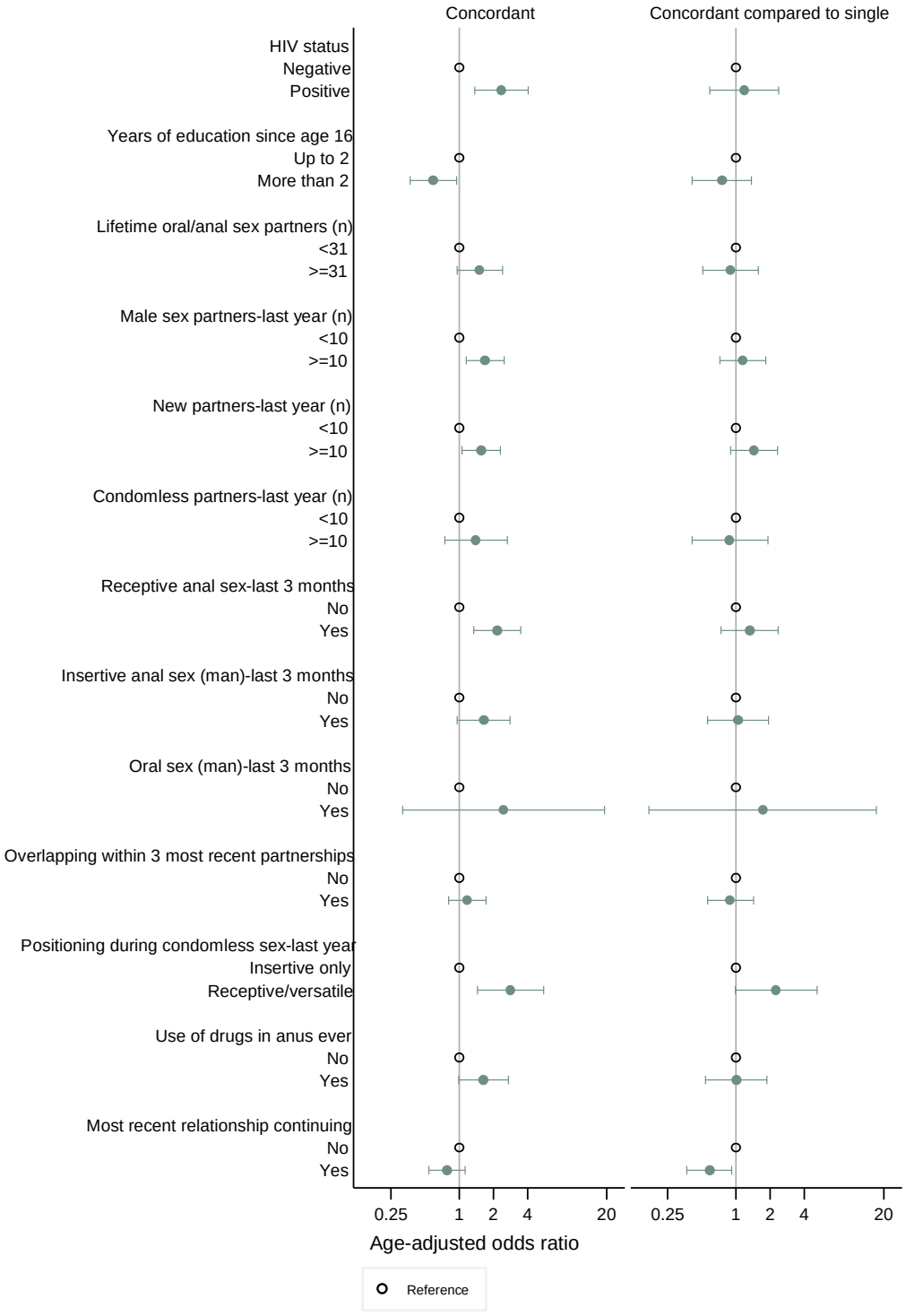
C. restricted to pairs in which both swabs had detectable GADPH and HPV16 DNA

Risk factors for anogenital concordant infections

Appendix IV (Appendix table 6, page 309) shows the factors assessed for their association with anogenital concordant HR-HPV infections compared to not having a concordant infection (i.e HR-HPV infection at a single anogenital site or HPV negative) and to an HR-HPV infection at a single anogenital site. The risk profile, shown in Figure 37, for concordant anogenital infections was similar to those at anal and external sites. HR-HPV type-specific concordant infections at anogenital sites were associated with at least ten male anal sex partners in the last year (aOR=1.69; 95% CI 1.15-2.49), at least ten new anal sex partners in the last year (aOR=1.56; 95% CI 1.06-2.30) receptive anal sex in the last three months (aOR=2.17; 95% CI 1.35-3.49) and receptive anal sex, compared to insertive sex, when having sex without a condom in the last year (aOR=2.84; 95% CI 1.45-5.57).

Compared to a single infection, concordant anogenital HR-HPV infections were associated with reporting that the most recent relationship had ended (aOR=1.82; 95% CI 1.14-2.94).

FIGURE 37. SELECTED RISK FACTORS FOR HR-HPV TYPE-SPECIFIC CONCORDANCE AT ANOGENITAL SITES



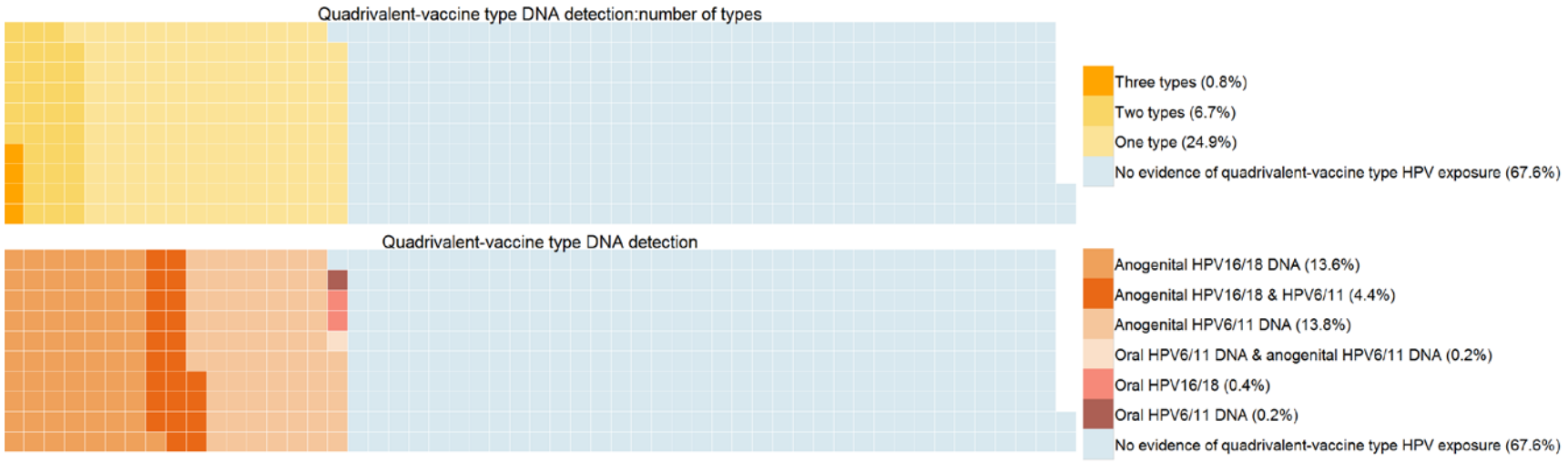
5.3 KEY FINDINGS

Figure 38 simplifies data from Table 14 and Table 15 to show that two thirds (67.6%) of HPV-MSM-MMC participants did not have any of the quadrivalent-vaccine types detected in anogenital specimens. A quarter had one type, 6.7% had two or three types and none had all four quadrivalent types detected. The prevalence of any HPV infection increased with age but no significant associations were detected when grouped HR-HPV, bivalent, quadrivalent or 9-valent vaccine-preventable HPV types were considered. There was no statistically significant association between detectable quadrivalent-vaccine type HPV or HR-HPV and age at first sex (Table 17 and Appendix table 4).

Figure 39 shows the contribution of each anogenital site towards the overall anogenital prevalence of HPV16/18 and HPV6/11. The strongest agreement for HPV detection was between the anal and external swabs but with a pooled kappa was 0.50 was suggestive of only moderate agreement, and LCR sequencing revealed that some HPV16 positive pairs resulted from different variants. Furthermore, the two swabs had risk factors in common for HPV DNA detection. More cellular and viral DNA was harvested from anal swabs than external swabs and there was also higher viral load in the anal swabs.

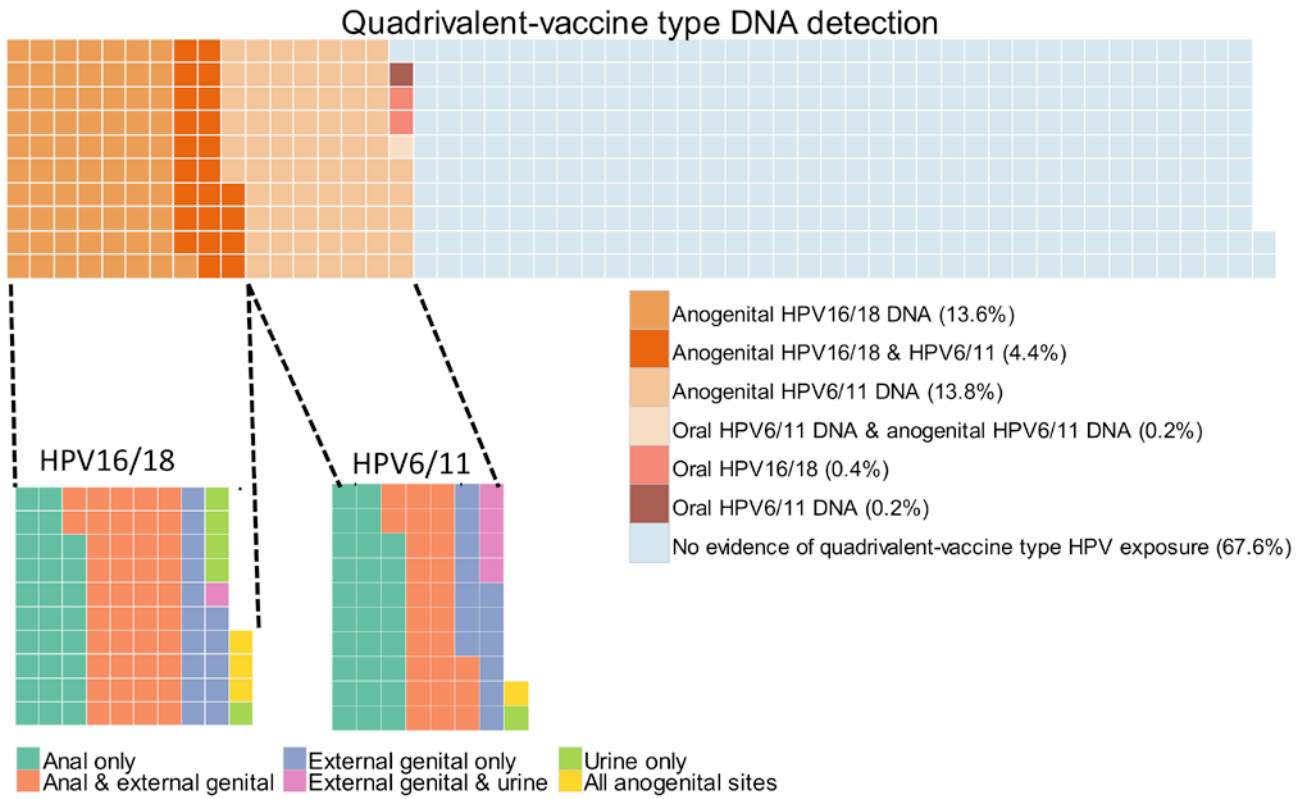
Urine was a poor marker for anogenital infection in MSM swabs. The lack of anogenital concordance with oral HPV infection might be attributed to the low prevalence of oral HPV DNA detection yet despite similarly low prevalence in urine there was some concordance between urine and anogenital swabs. MSM with concordant anogenital HR-HPV infections were more likely to report their most recent relationship having ended than MSM with HR-HPV at a single site.

FIGURE 38. DISTRIBUTION OF QUADRIVALENT-VACCINE TYPE HPV DNA DETECTION AT ANOGENITAL AND ORAL SITES IN 522 MSM ATTENDING MMC



1 square= 1 participant. Upper panel displays the number of quadrivalent-vaccine HPV types detected across all specimens tested for DNA (oral, anal, external genital and urine) and is adapted from Table 15. Lower panel displays results that are adapted from Table 14 by including all participants (n= 522) in the denominator (not just MSM who have specimens adequate for HPV testing). HPVa/b= HPV type a and/or HPV type b. NB. Only a sub-sample (n=166) tested for oral HPV.

FIGURE 39. THE CONTRIBUTION OF EACH ANOGENITAL SAMPLE TO HPV6/11/16/18 PREVALENCE



1 square= 1 participant. This figure expands on the lower panel of Figure 38 to show the breakdown of detectable quadrivalent-vaccine type DNA by specimen. Results are adapted from Table 19 by including all participants (n= 522) in the denominator (not just MSM who have specimens adequate for HPV testing) NB. only a sub-sample (n=166) tested for oral HPV.

5.4 FINDINGS IN CONTEXT

Methods for meta-analysis in chapter 3, page 56

Figure 40 shows the HPV16 prevalence estimate for the HPV-MSM-MMC study highlighted in the results of a random-effects meta-analysis of estimates of HPV16 infection in the anal canal of HIV-negative MSM up to mid-2015. There was high heterogeneity between estimates from 18 studies and the pooled estimate was 12.4% (95% CI 10.5-14.2%). The pooled estimate from the seven studies in Europe was 12.5% (95% CI 10.5-14.4), had low heterogeneity (I^2=32%) that was compatible with that expected by chance (p=0.18), and all European studies recruited from SHCs.

In HIV-positive MSM, as shown in Figure 41, studies conducted in the US or Canada appear to have a higher prevalence than in other regions with overlapping confidence intervals. The random-effects pooled prevalence of HPV16 in HIV-positive MSM was estimated at 28.6% (95% CI 25.3-31.8).

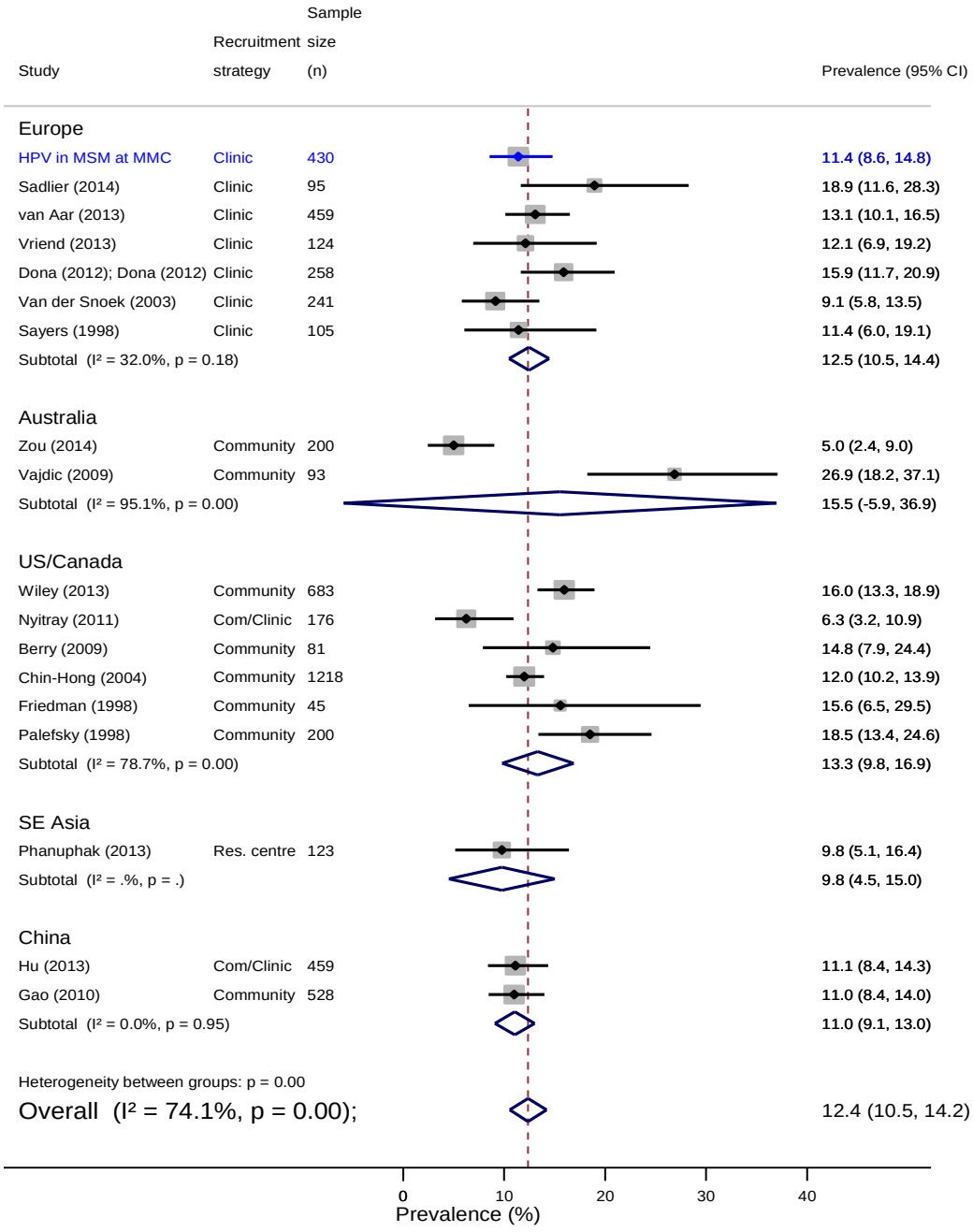
The random-effects pooled estimate of HPV6 prevalence was 12.5% and 19.4% for HIV-negative and HIV-positive MSM, respectively (Figure 42).

There are no studies with directly comparable estimates for prevalence at the external genital swab because this is a composite of penile, scrotum and perianal sites. Two studies in HIV-negative MSM estimating penile HPV prevalence were both in young populations: in Melbourne, Australia, with a median age of 19, penile HPV16 prevalence was 1.5% (95% CI 0.3-4.3)[122], and it was 3.2% (95% CI 1.9-4.9) in the MSM vaccine trial population, described on page 238 (median age= 22 years)[161]. These studies also detected perianal HPV16 in 4.6% (95% CI 2.1-8.5) of young MSM in Melbourne and 6.0% (95% CI 4.2-8.2) of MSM vaccine trial participants. HPV16 prevalence at the scrotum in vaccine trial participants was estimated as 2.2% (95% CI 2.2-3.7%). Therefore, despite the potential for double-counting, total perianal and penile HPV16 prevalence was lower in younger MSM in Sydney (6.1%) than in participants of the HPV-MSM-MMC study (10.1%).

In the MMC population, 29% were circumcised which may protect HIV-positive MSM from HR-HPV infection of the penis[162].

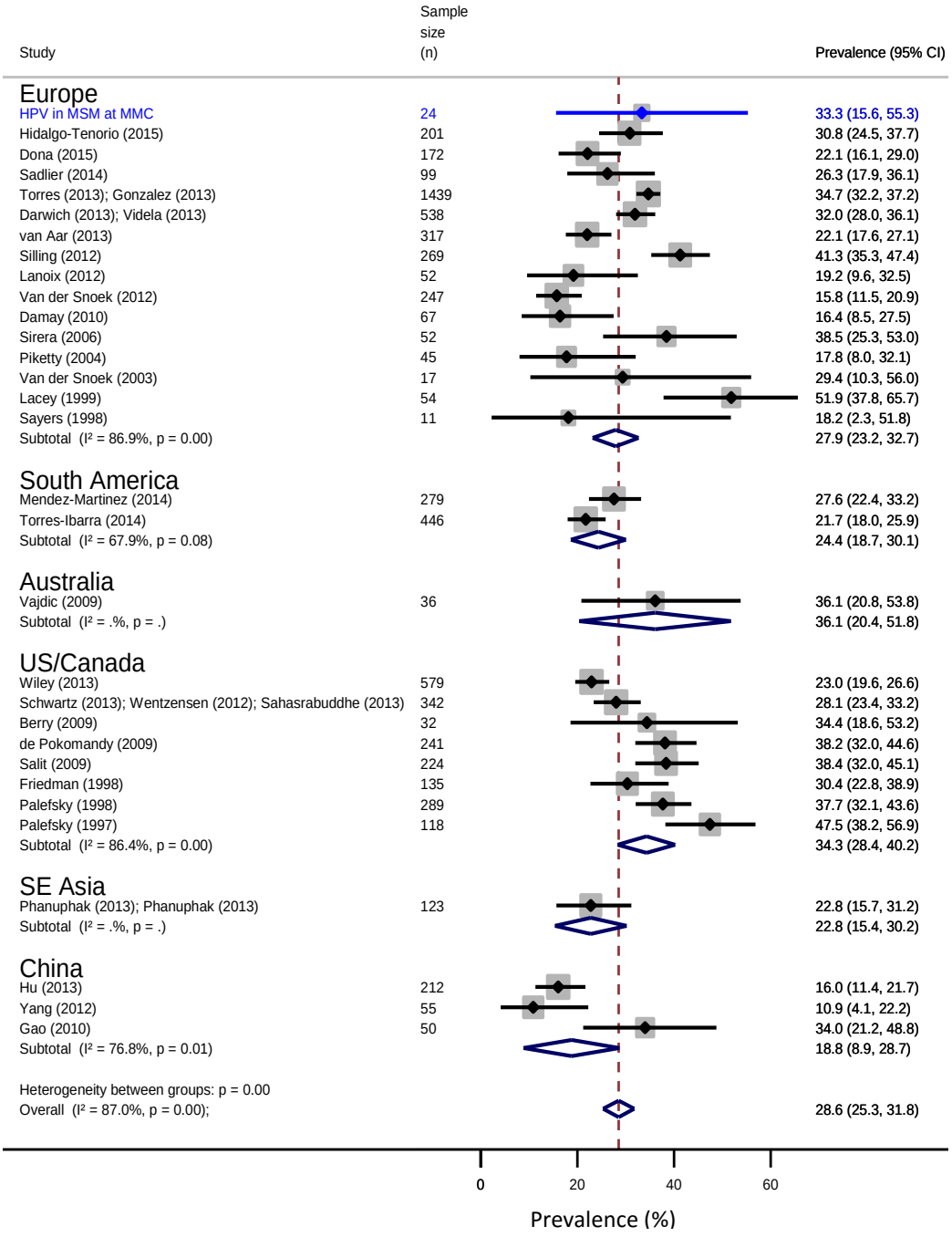
The estimate of oral HR-HPV prevalence for the HPV-MSM-MMC study of 5.4% (95% CI 2.5-10.0) was higher than that of the global estimate in healthy men and women (3.5%; 95% 3.0-4.1) yet the confidence intervals overlap[134]. In the large HPV in men (HIM) study, with predominantly heterosexual male participants in Mexico, Brazil and the US, the prevalence was 1.3%[112]. The estimate in this chapter lies within the range of estimates for HIV-negative MSM[120,123,163]. Figure 43 shows that updating the random-effects meta-analysis of prevalence of oral HPV16 infection from chapter 3, to include the estimate from this chapter, decreases the heterogeneity (I^2=89% to I^2=80%) and has negligible impact on the magnitude of the pooled estimate (3.6% to 1.9%). Likewise Figure 44 shows the result of including the findings from this chapter on the pooled estimate of oral HR-HPV prevalence (8.8% to 8.0%; I^2=95% to I^2=92%). As in the HPV-MSM-MMC study data, Kreimer *et al* found increasing educational level was associated with incident oral HPV infection, which they attributed to increased sexual mixing in educational environments[113]. Kreimer *et al* and Beachler *et al,* found that bisexual or heterosexual men had greater risk of incident oral HPV infection compared to homosexual MSM[113,123].

FIGURE 40. RANDOM-EFFECTS META-ANALYSIS OF STUDIES ESTIMATING ANAL HPV16 PREVALENCE IN HIV-NEGATIVE MSM



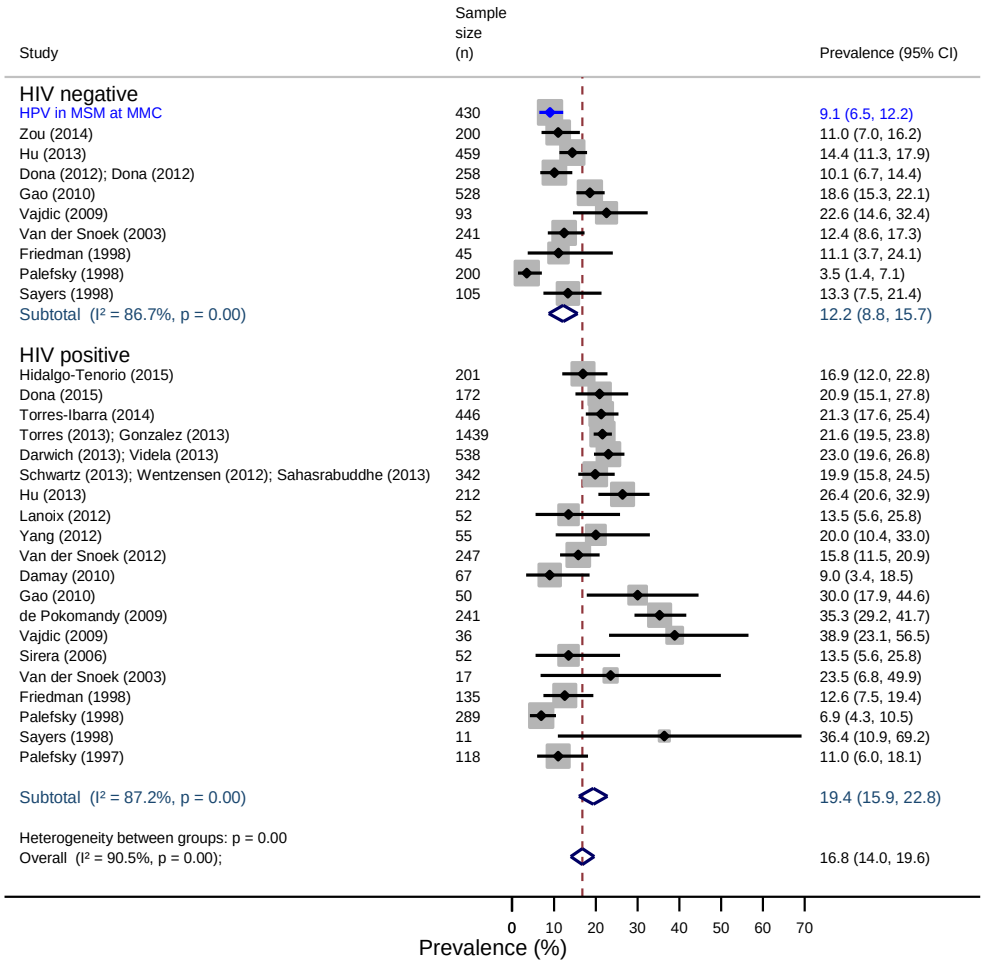
Abbreviations: Com=community, Res.=research, US= United States of America, SE=South East. Sadlier (2014)[164], Van Aar (2013)[165], Vriend (2013)[166], Doná (2012)[167,168], Van der Snoek (2003)[62], Sayers (1998)[60], Zou (2014)[122], Vajdic (2009)[84], Wiley (2013)[169], Nyitray (2011)[170], Berry (2009)[171], Chin-Hong (2008)[55], Friedman (1998)[56], Palefsky (1998)[57], Phanuphak (2013)[50,172], Hu (2013)[173], Gao (2010)[174].

FIGURE 41. RANDOM-EFFECTS META-ANALYSIS OF STUDIES ESTIMATING ANAL HPV16 PREVALENCE IN HIV-POSITIVE MSM, BY REGION



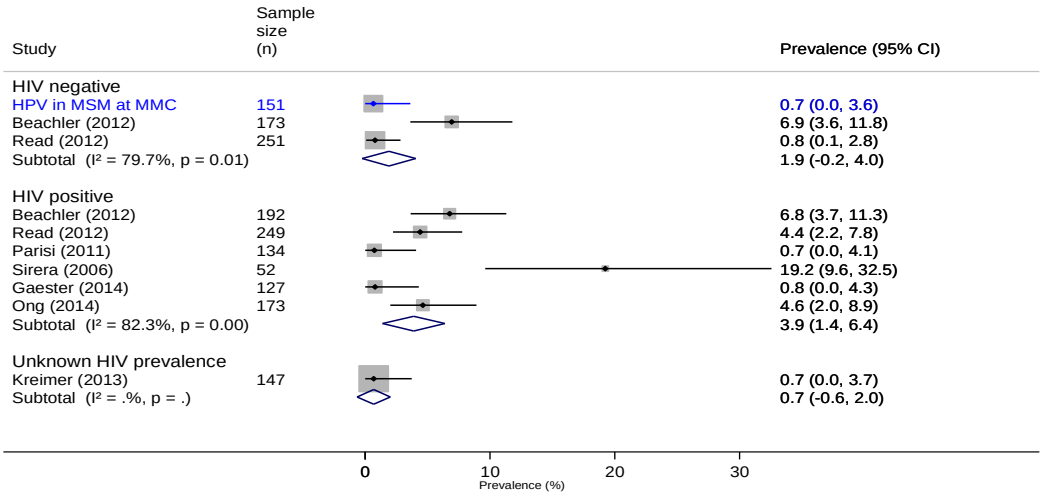
Hidalgo-Tenorio (2015)[175], Donà (2015)[176], Sadlier (2014)[164], Torres (2013)[177], González (2013)[178], Darwich (2013)[179], Videla (2013)[118], Van Aar (2013)[165], Silling (2012)[51], Lanoix (2012)[180], Van der Snoek (2012)[181], Damay (2010)[182], Sirera (2006)[63], Piketty (2004)[58], Van der Snoek (2003)[62], Lacey (1999)[59], Sayers (1998)[60], Mendez-Martinez (2014)[183], Torres-Ibarra (2014)[184], Vajdic (2009)[84], Wiley (2013)[169], Schwartz (2013)[185], Wenzensen (2012)[186], Sahasrabuddhe (2013)[187], Berry (2009)[171], de Pokomandy (2009)[93], Salit (2009)[188], Friedman (1998)[56], Palefsky (1998)[57], Palefsky (1997)[64], Phanuphak (2013)[50,172], Hu (2013)[173], Yang (2012)[189], Gao (2010[174]

FIGURE 42. RANDOM-EFFECTS META-ANALYSIS OF STUDIES ESTIMATING ANAL HPV6 PREVALENCE IN MSM POPULATIONS, BY HIV STATUS



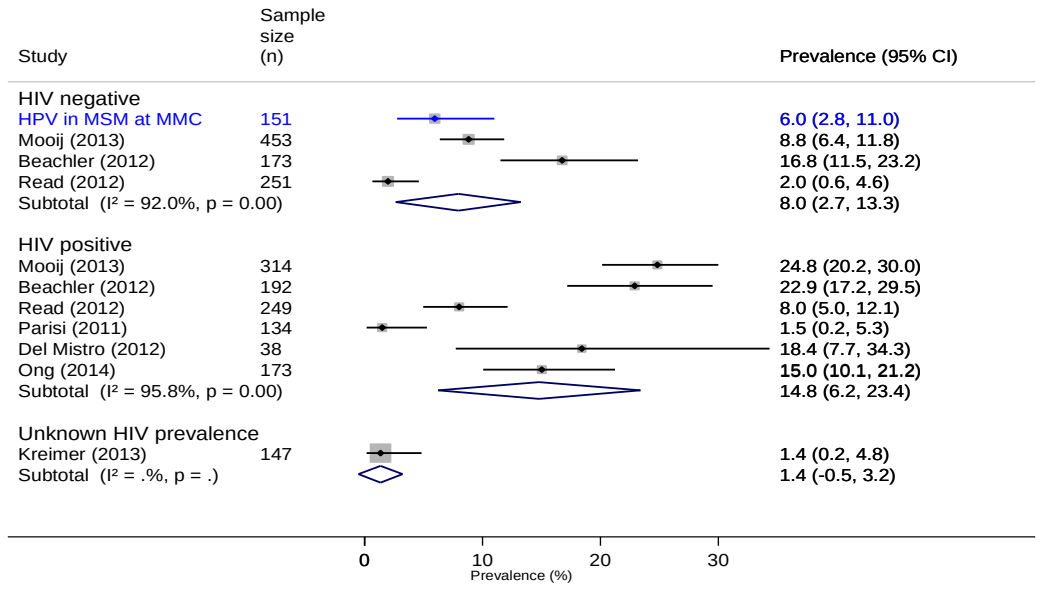
Zou (2014)[122], Hu (2013)[173], Doná (2012)[167,168], Gao (2010)[174], Vajdic (2009)[84], Van der Snoek (2003)[190], Friedman (1998)[56], Palefsky (1998), Sayers (1998)[60], Hidalgo-Tenorio (2015)[175], Doná (2015)[176], Torres-Ibarra (2014)[184], Torres (2013)[177], Gonzalez (2013)[178], Darwich (2013)[179], Videla (2013)[118], Schwartz (2013)[185], Wentzensen (2012)[186], Sahasrabuddhe (2013)[187], Hu (2013)[173], Lanoix (2012)[180], Yang (2012)[189], Van der Snoek (2012)[181], Damay (2010)[182], Gao (2010)[174], de Pokomandy (2009)[93], Sirera (2006)[63], Palefsky (1997)[64]

FIGURE 43. RANDOM-EFFECTS META-ANALYSIS OF STUDIES ESTIMATING ORAL HPV16 PREVALENCE IN MSM POPULATIONS, BY HIV STATUS



This figure updates the analysis in chapter 3, Figure 17, page 63 to include results from the HPV-MSM-MMC study. Weights are from random effects analyses. Beachler (2012)[117], Read (2012)[120], Parisi (2011)[124], Sirera (2006)[63], Gaester (2014)[127], Ong (2014)[121] and Kreimer (2013)[113].

FIGURE 44. RANDOM-EFFECTS META-ANALYSIS OF STUDIES ESTIMATING ORAL HR-HPV PREVALENCE IN MSM POPULATIONS, BY HIV STATUS



This figure updates the analysis in chapter 3, Figure 19, page 65 to include results from the HPV-MSM-MMC study. Weights are from random effects analyses. Mooij (2013)[114], Beachler (2012)[117], Read (2012)[120], Parisi (2011)[124], Del Mistro (2012)[125], Ong (2014)[121] and Kreimer (2013)[113].

The relative detection of HPV DNA between anatomical sites in the same man has been studied [63,65,66,118,124,191,192], but there are few studies in MSM collecting both anal and penile specimens [165,170,179,190,193,194], and fewer still reporting on type-specific concordance.

In MSM in Amsterdam, infections at one anatomical site were detected more often than infections at multiple (at least two) anatomical sites. The prevalence of HPV type-specific concordant (at least two of anal/penile/oral) HR-HPV (HPV16/18/31/33/45/52/58) infections was 14% in HIV-positive and 10% in HIV-negative MSM[116].

Recently, Zou *et al* demonstrated that the incidence of anal HR-HPV DNA detection is over four times higher than penile[195]. That the anal sample is the most sensitive for HPV DNA detection in MSM has been found in several studies[116,118] but in heterosexual men, the penile swab was the most sensitive[65].

The lack of concordance between oral and anogenital specimens was also found in HIV-positive men reported by Videla *et al* (predominantly MSM)[118] and Parisi *et al*[124]. However Edelstein *et al* found that 15/17 men (predominantly heterosexual) had the same type detected at oral and anogenital sites[196].

The lack of a significant association between circumcision status and external genital HPV detection (aOR 1.10, 95% CI 0.72-1.66), may be due to limited power. However, this was in contrast to the protective effect reported from international studies in men having sex with women[197]. There are inconsistent findings for the effect of circumcision status on HPV infection in MSM[162,198,199].

5.5 STRENGTHS AND LIMITATIONS

In a cross-sectional study design, the clinical relevance of HPV detection and the temporal relationship between exposure variables and HPV infection cannot be determined and infections of longer duration are more likely to be detected. Additionally, not all men were tested for HIV at the clinic visit so there is potential for undiagnosed HIV. This potential misclassification would overestimate HPV prevalence in HIV-negative MSM. The sensitivity for the detection of HPV DNA in urine is lower than genital swabs[200] and low HPV prevalence was observed in this specimen type.

The direct comparison across sites of factors associated with HR-HPV was hampered because there was considerably reduced power for the detection of risk factors in the oral and urine compared to the external and anal specimens. Furthermore, for anal and external genital swabs, where the prevalence of HR-HPV was approximately 40%, and for quadrivalent-vaccine types, at approximately 30%, the odds ratio considerably overestimates the relative risk. Therefore the ORs in this chapter should be interpreted as the ratio of HR-HPV odds given the exposure status and not as relative risk.

Where the same risk factor was significantly associated with HPV detection (either quadrivalent or HR-HPV) at multiple sites, the likelihood of this being due to chance is reduced. Since many risk factor analyses were performed in this chapter, those factors that were statistically significant at only one site may well have arisen by chance.

These type-specific estimates are subject to 'masking', where the predominant type is detected in multiple type infection overshadowing other types. This is of relevance if comparing the prevalence estimates in this chapter to post-vaccine prevalence estimates, where non-vaccine types may appear to increase as they are 'unmasked' by removal of the vaccine types.

Testing all samples for HPV of each man in the same run reduced the effect of batch discrepancies when comparing between specimen sites. True differences in prevalence cannot be distinguished from differences in HPV testing specificity and sensitivity or DNA stability across specimens in this study. The relative detection of HPV between sites reported in this chapter would either support underlying differences in HPV tissue-tropism and epidemiology or differential specificity/sensitivity at different anatomical sites.

Oral samples are particularly sensitive to sub-optimal DNA extraction methods[201]. Although oral rinse/gargle sampling is the optimal method for HPV detection, sensitivity is improved by combining with other sampling methods[202]. The oral prevalence estimates might therefore be biased downwards and increased oral-anogenital concordance would be expected with higher oral prevalence.

Perianal sampling using the external swab introduced the potential for contamination from the anal canal site. This potential bias would result in artificially high estimates of agreement between the swabs. Due to funding constraints, swabs could not be collected separately for each of the external genital sites.

6. HPV-MSM-MMC STUDY: HPV SEROLOGY

In this chapter, I present the results from testing the serum for immunoglobulin (Ig) G (antibodies) specific to HPV16 and HPV18. I first present the prevalence of detectable IgG (seropositivity) in MSM; overall and by age. I then examine the antibody titre with respect to age and examine the associations of demographic and behavioural factors with HPV seropositivity. In addition, I report on the relationship between HPV seropositivity and HPV DNA detection. Finally, I put the chapter's findings into context, comparing to those in the literature up to mid-2015.

6.1 OBJECTIVES

1. To estimate the seroprevalence of HPV16 and HPV18 in MSM attending MMC
2. To estimate the age-specific seroprevalence in MSM
3. To describe the relationship between IgG titres and age
4. To explore demographic and behavioural risk factors for seropositivity in MSM
5. To describe the association between HPV DNA detection and seropositivity
6. To discuss biases to be considered when interpreting the findings from this chapter

6.2 METHODS

Methods used to meet the objectives are described in chapter 4. In particular, serology testing is described on page 93 and statistical methods on page 97.

6.3 RESULTS

Of the 522 participants in the study, 512 gave a blood sample and 506 had a sample that was adequate for serological tests (Figure 26, page 102). Of these 506 MSM, 496 also had an anogenital sample that was adequate for DNA testing. The median age of the 506 MSM was 30 (IQR 25-35), 26/506 (5.1%; 95% CI 3.4-7.4) were diagnosed HIV-positive and there were no differences in other demographic and behavioural characteristics from those reported in chapter 4, page 104.

SEROPREVALENCE

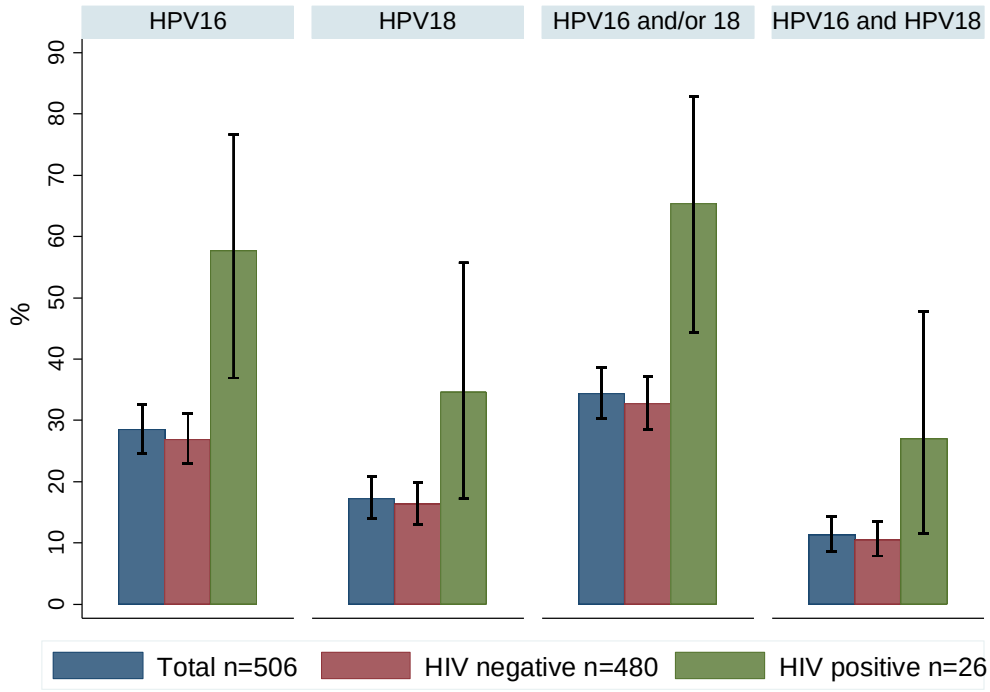
Seroprevalence by HIV status is displayed in Table 21 and Figure 45. Approximately two-thirds of participants had no detectable antibodies to the bivalent-vaccine types. Seroprevalence was higher in MSM diagnosed HIV-positive compared to HIV-negative.

TABLE 21. HPV SEROPREVALENCE IN 506 MSM WITH SERUM SAMPLES ADEQUATE FOR TESTING

HPV type	N	%	95% CI
Anti-HPV16	144	28.5	(24.6-32.6)
HIV-negative	129	26.9	(23.0-31.1)
HIV-positive	15	57.7	(36.9-76.6)
Anti-HPV18	87	17.2	(14.0-20.8)
HIV-negative	78	16.3	(13.1-19.9)
HIV-positive	9	34.6	(17.2-55.7)
Anti-HPV16 **or** anti-HPV18	117	23.1	(19.5-27.0)
HIV-negative	107	22.3	(18.6-26.3)
HIV-positive	10	38.5	(20.2-59.4)
Anti-HPV16 **and** anti-HPV18	57	11.3	(8.6-14.3)
HIV-negative	50	10.4	(7.8-13.5)
HIV-positive	7	26.9	(11.6-47.8)

A total of 506 MSM were included in the denominator: 480 HIV-negative and 26 HIV-positive MSM. Data are displayed graphically in Figure 45.

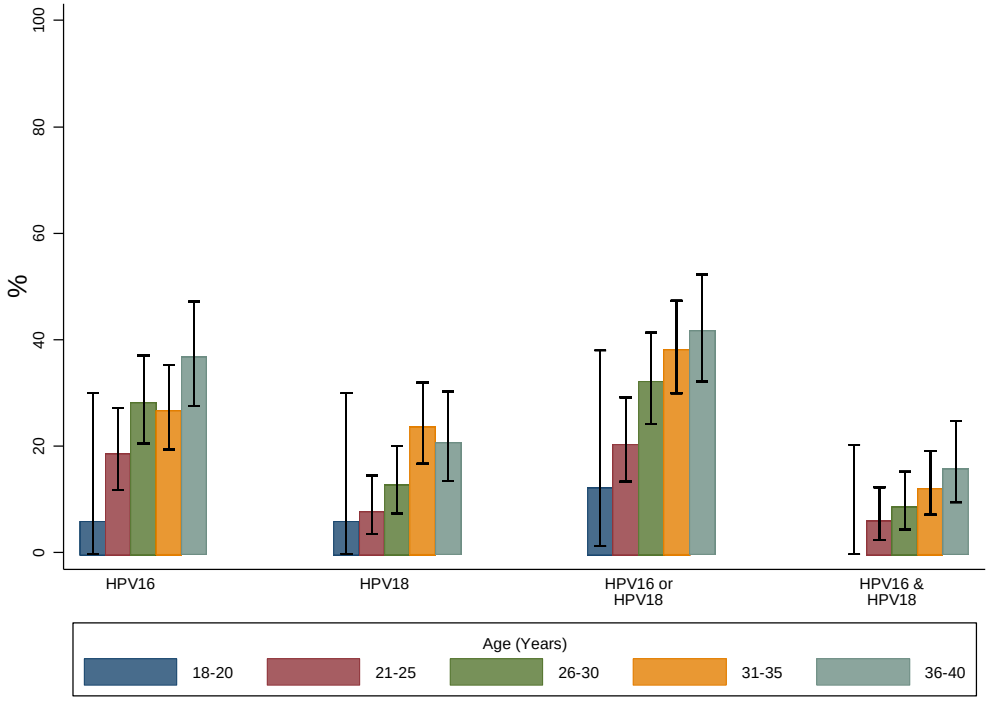
FIGURE 45. BAR CHART REPRESENTING HPV SEROPREVALENCE IN 506 MSM



AGE-SPECIFIC SEROPREVALENCE

Figure 46 demonstrates that in HIV-negative MSM there was a significant relationship between seroprevalence and age for anti-HPV16 (OR=1.07 per year; 95% CI 1.03-1.11) and anti-HPV18 (OR per year=1.08; 95% CI 1.03-1.12). In HIV-positive MSM (n=26) there were wide confidence intervals and there was no statistically significant association (HPV16 OR per year=1.03 (95% CI 0.89-1.20); HPV18 OR per year=0.95 (95% CI 0.81-1.11)).

FIGURE 46. AGE-SPECIFIC HPV SEROPREVALENCE IN 480 HIV-NEGATIVE MSM

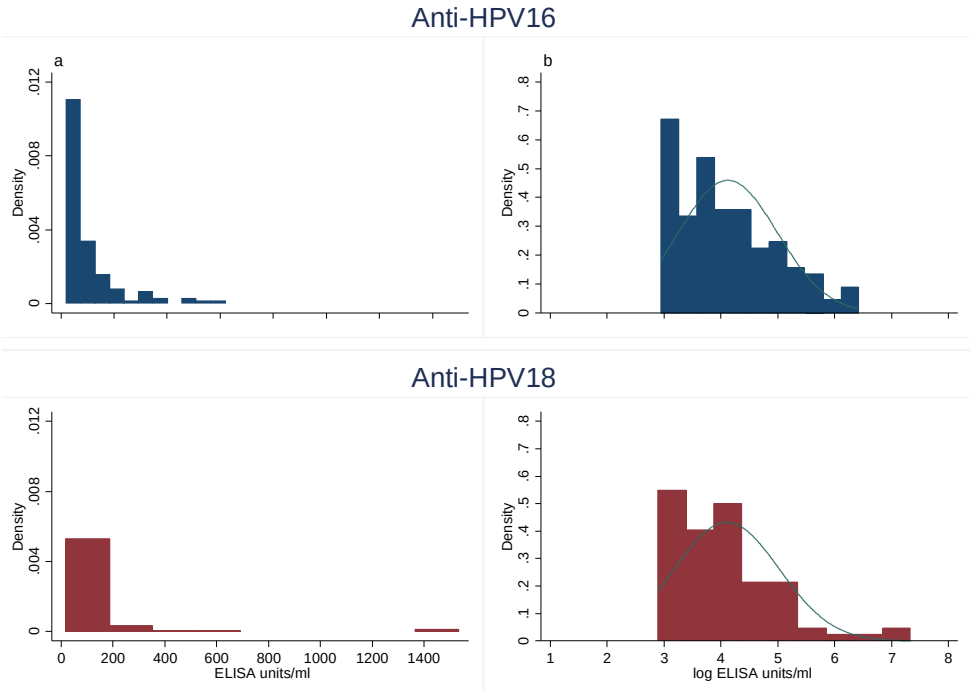


Data for this figure and by HIV status, are displayed in Appendix III, Appendix table 2, page 301.

ANTIBODY TITRES

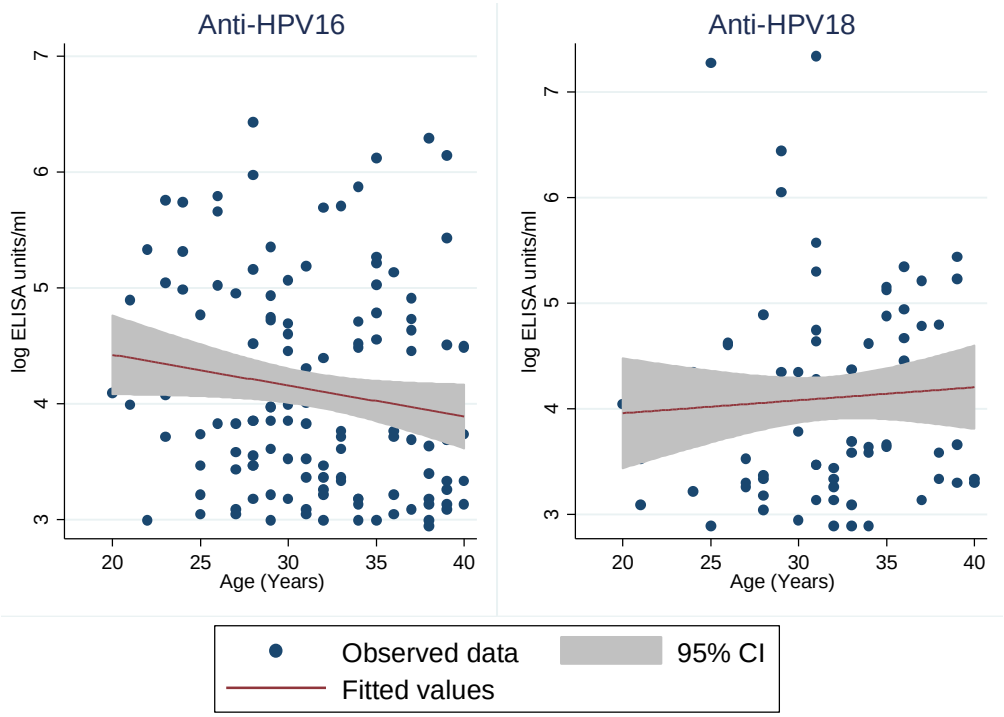
Figure 47, panel a, shows that the distributions of antibody titres in MSM seropositive for anti-HPV16 and anti-HPV18 were highly negatively skewed. Having log transformed these distributions, to improve their normality (panel b), there was no association between anti-HPV16 titre or anti-HPV18 titre (ELISA Units/ml) with age in seropositive MSM. Despite the residuals not being normally distributed, an assumption underlying the t test in ordinary linear regression, the plots of the fitted model to the observed data support the finding that age does not predict anti-HPV titre (Figure 48). Furthermore, there were no differences in the mean log titre across age groups for anti-HPV16 ($F(4, 136)=1.18$, $p=0.32$) or anti-HPV18 ($F(4, 80)=0.18$, $p=0.95$).

FIGURE 47. HISTOGRAMS SHOWING THE DISTRIBUTIONS AND LOG-TRANSFORMED DISTRIBUTIONS OF ANTI-HPV16 TITRES IN 144 HPV16 SEROPOSITIVE MSM AND ANTI-HPV18 TITRES IN 87 HPV18 SEROPOSITIVE MSM.



Panels a and b represent histograms of the distributions and the log-transformed distributions of anti-HPV titres, respectively.

FIGURE 48. LINEAR REGRESSION MODELS OF AGE AND ANTI-HPV TITRES IN HPV SEROPOSITIVE MSM



RISK FACTORS FOR BIVALENT-VACCINE HPV TYPE SEROPOSITIVITY IN MSM

Table 22 and Table 23 show the socio-demographic and behavioural factors that were assessed for their association with HPV16 and, separately, for HPV18 in univariate analyses. Age, HIV status (HPV16 OR=3.71; 95% CI 1.66-8.29; HPV18 OR=2.73; 95% CI 1.17-6.34), at least ten anal partners (altogether and new) in the last year, increasing number of lifetime partners (HPV16 p-trend <0.01; HPV18 p-trend <0.01), having had receptive anal sex in the last three months (HPV16 OR=3.26; 95% CI 1.98-5.36; HPV18 OR=2.20; 95% CI 1.24-3.90), having ever used drugs anally (HPV16 OR=2.16; 95% CI 1.18-3.97; HPV18 OR=2.75; 95% CI 1.43-5.29) and overlapping of any of the three most recent partners (HPV16 OR=1.56; 95% CI 1.04-2.33; HPV18 OR=1.78; 95% CI 1.08-2.91) were statistically significantly associated with both HPV16 and HPV18 seropositivity.

In addition, HPV16 seropositivity was associated with having at least ten anal partners without a condom in the last year (OR=2.88; 95% CI 1.35-6.16), position during condomless receptive anal sex in the last year and age of most recent partner (OR per year=1.04; 95% CI 1.01-1.06). There were no factors independently associated with HPV18 seropositivity.

TABLE 22. UNIVARIATE ANALYSES OF SOCIO-DEMOGRAPHIC, AND HIV STATUS, RISK FACTORS FOR HPV16 AND, SEPARATELY, FOR HPV18 ANTIBODY DETECTION.

	HPV16					HPV18				
Risk factor	Seronegative n (%)	Seropositive n (%)	OR	95% CI	P	Seronegative n (%)	Seropositive n (%)	OR	95% CI	p
Each additional year in age			1.06	(1.03-1.10)	<0.01			1.07	(1.02-1.11)	<0.01
Ethnic group										
White	268 (72.0)	104 (28.0)	1	-	0.68	307 (82.5)	65 (17.5)	1	-	0.89
Black	45 (68.2)	21 (31.8)	1.20	(0.68-2.12)		56 (84.8)	10 (15.2)	0.84	(0.41-1.74)	
Asian & SE Asian	37 (75.5)	12 (24.5)	0.84	(0.42-1.67)		41 (83.7)	8 (16.3)	0.92	(0.41-2.06)	
Born in the UK										
No	185 (70.9)	76 (29.1)	1	-	0.62	220 (84.3)	41 (15.7)	1	-	0.37
Yes	167 (72.9)	62 (27.1)	0.90	(0.61-1.34)		186 (81.2)	43 (18.8)	1.24	(0.78-1.99)	
Currently smoke										
No	248 (72.3)	95 (27.7)	1	-	0.69	286 (83.4)	57 (16.6)	1	-	0.62
Yes	103 (70.5)	43 (29.5)	1.09	(0.71-1.67)		119 (81.5)	27 (18.5)	1.14	(0.69-1.89)	
Increasing or higher risk alcohol drinking (AUDIT-C)										
No	117 (70.9)	48 (29.1)	1	-	0.71	136 (82.4)	29 (17.6)	1	-	0.91
Yes	232 (72.5)	88 (27.5)	0.92	(0.61-1.40)		265 (82.8)	55 (17.2)	0.97	(0.59-1.60)	
Currently employed										
No	80 (75.5)	26 (24.5)	1	-	0.35	91 (85.8)	15 (14.2)	1	-	0.36
Yes	272 (70.8)	112 (29.2)	1.27	(0.77-2.08)		315 (82.0)	69 (18.0)	1.33	(0.73-2.43)	
Years of education post-16										
None	9 (69.2)	4 (30.8)	1	-	0.13*	11 (84.6)	2 (15.4)	1	-	0.40*
Up to 2 years	45 (72.6)	17 (27.4)	0.85	(0.23-3.13)		51 (82.3)	11 (17.7)	1.19	(0.23-6.12)	
3 years or more	230 (69.3)	102 (30.7)	1	(0.30-3.32)		270 (81.3)	62 (18.7)	1.26	(0.27-5.84)	
Still in education	68 (81.9)	15 (18.1)	0.50	(0.13-1.83)		74 (89.2)	9 (10.8)	0.67	(0.13-3.51)	
Sexual orientation										
Gay/homosexual	316 (70.9)	130 (29.1)	1	-	0.15	369 (82.7)	77 (17.3)	1	-	0.87
Bisexual	35 (81.4)	8 (18.6)	0.56	(0.25-1.23)		36 (83.7)	7 (16.3)	0.93	(0.40-2.17)	
Circumcised										
No	252 (72.8)	94 (27.2)	1	-	0.43	291 (84.1)	55 (15.9)	1	-	0.20
Yes	97 (69.3)	43 (30.7)	1.19	(0.77-1.83)		111 (79.3)	29 (20.7)	1.38	(0.84-2.28)	
HIV positive diagnosis										
No	351 (73.1)	129 (26.9)	1	-	<0.01	402 (83.8)	78 (16.3)	1	-	0.02
Yes	11 (42.3)	15 (57.7)	3.71	(1.66-8.29)		17 (65.4)	9 (34.6)	2.73	(1.17-6.34)	

Seronegative : IgG antibodies were not detected in the serum; Seropositive : IgG antibodies were detected in the serum. *P value from Fisher's exact test

TABLE 23. UNIVARIATE ANALYSES OF SEXUAL BEHAVIOUR RISK FACTORS FOR HPV16 AND, SEPARATELY, FOR HPV18 ANTIBODY DETECTION.

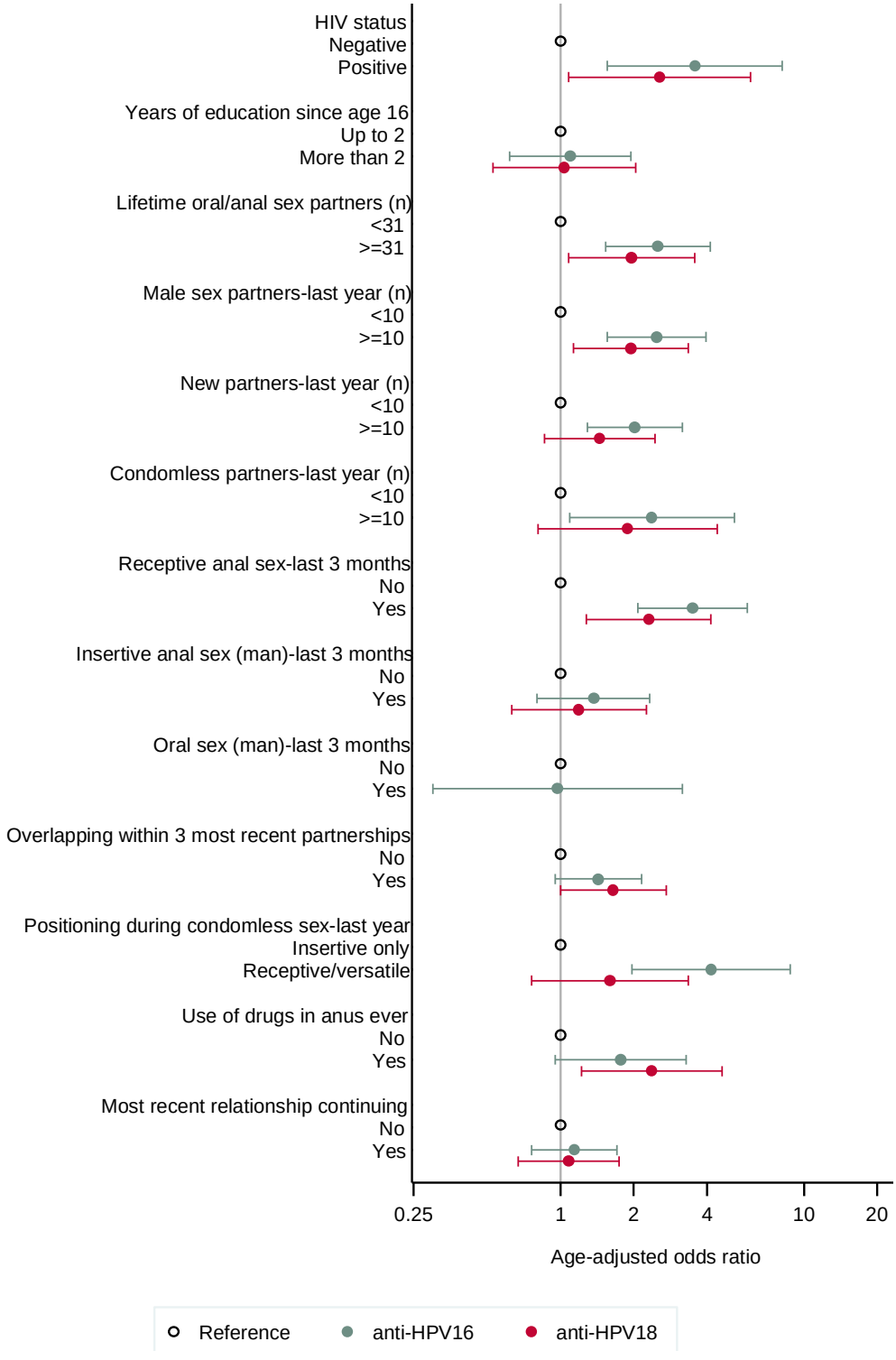
	HPV16					HPV18				
Risk factor	Seronegative n (%)	Seropositive n (%)	OR	95% CI	P	Seronegative n (%)	Seropositive n (%)	OR	95% CI	p
Number of lifetime male partners (anal and oral sex)										
Fewer than 20	87 (88.8)	11 (11.2)	1	-	<0.01	91 (92.9)	7 (7.1)	1	-	<0.01
21-30	54 (78.3)	15 (21.7)	2.20	(0.94-5.13)		59 (85.5)	10 (14.5)	2.20	(0.79-6.11)	
31-100	118 (71.5)	47 (28.5)	3.15	(1.54-6.42)		146 (88.5)	19 (11.5)	1.69	(0.68-4.18)	
101-500	93 (58.9)	65 (41.1)	5.53	(2.74-11.16)		110 (69.6)	48 (30.4)	5.67	(2.45-13.14)	
Number of male sex partners in the last year										
Male anal sex partners										
<10	213 (81.3)	49 (18.7)	1	-	<0.01	230 (87.8)	32 (12.2)	1	-	<0.01
>=10	119 (58.9)	83 (41.1)	3.03	(2.00-4.61)		152 (75.2)	50 (24.8)	2.36	(1.45-3.85)	
New anal sex partners										
<10	239 (78.1)	67 (21.9)	1	-	<0.01	261 (85.3)	45 (14.7)	1	-	0.02
>=10	91 (59.1)	63 (40.9)	2.47	(1.62-3.76)		118 (76.6)	36 (23.4)	1.77	(1.08-2.89)	
Anal sex partners without a condom										
<10	315 (72.9)	117 (27.1)	1	-	0.01	359 (83.1)	73 (16.9)	1	-	0.06
>=10	14 (48.3)	15 (51.7)	2.88	(1.35-6.16)		20 (69.0)	9 (31.0)	2.21	(0.97-5.05)	
Exclusively oral sex partners										
<10	229 (75.1)	76 (24.9)	1	-	0.06	260 (85.2)	45 (14.8)	1	-	0.07
>=10	91 (66.4)	46 (33.6)	1.52	(0.98-2.36)		107 (78.1)	30 (21.9)	1.62	(0.97-2.71)	
Each additional year of age at first sex with a man										
Oral			0.97	(0.92-1.02)				0.97	(0.91-1.04)	
Receptive anal			0.97	(0.92-1.02)	0.23			0.97	(0.92-1.03)	0.40
Oral sex with a man in last 3 months								0.19		
No	12 (75.0)	4 (25.0)	1	-	0.77*	16 (100.0)	0 (0.0)	n/a	-	0.09*
Yes	335 (71.6)	133 (28.4)	1.19	(0.38-3.76)		386 (82.5)	82 (17.5)	n/a	n/a	
Receptive anal sex with a man in last 3 months										
No	139 (85.8)	23 (14.2)	1	-	<0.01	145 (89.5)	17 (10.5)	1	-	0.01
Yes	206 (65.0)	111 (35.0)	3.26	(1.98-5.36)		252 (79.5)	65 (20.5)	2.20	(1.24-3.90)	
Insertive anal sex with a man in last 3 months										
No	82 (78.8)	22 (21.2)	1	-	0.09	90 (86.5)	14 (13.5)	1	-	0.33
Yes	258 (70.5)	108 (29.5)	1.56	(0.93-2.63)		302 (82.5)	64 (17.5)	1.36	(0.73-2.54)	
Vaginal sex in last year										
No	258 (73.5)	93 (26.5)	1	-	1.00	291 (82.9)	60 (17.1)	1	-	0.20*
Yes	23 (74.2)	8 (25.8)	0.96	(0.42-2.23)		29 (93.5)	2 (6.5)	0.33	(0.08-1.44)	

TABLE 23. UNIVARIATE ANALYSES OF SEXUAL BEHAVIOUR RISK FACTORS FOR HPV16 AND, SEPARATELY, FOR HPV18 ANTIBODY DETECTION. CONTINUED

	HPV16					HPV18				
Risk factor	Seronegative n (%)	Seropositive n (%)	OR	95% CI	P	Seronegative n (%)	Seropositive n (%)	OR	95% CI	p
Oral sex with a woman in the last year										
No	259 (72.8)	97 (27.2)	1	-	0.52	294 (82.6)	62 (17.4)	1	-	0.06*
Yes	23 (79.3)	6 (20.7)	0.70	(0.28-1.76)		28 (96.6)	1 (3.4)	0.17	(0.02-1.27)	
Anal sex with a woman in the last year										
No	276 (73.4)	100 (26.6)	1	-	0.91*	315 (83.8)	61 (16.2)	1	-	1.00*
Yes	5 (71.4)	2 (28.6)	1.10	(0.21-5.78)		6 (85.7)	1 (14.3)	0.86	(0.10-7.28)	
Position when having anal sex without a condom in the last year										
Insertive only	63 (86.3)	10 (13.7)	1	-	<0.01	62 (84.9)	11 (15.1)	1	-	0.53
Receptive only	32 (69.6)	14 (30.4)	2.76	(1.10-6.89)		36 (78.3)	10 (21.7)	1.57	(0.61-4.05)	
Versatile	98 (60.5)	64 (39.5)	4.11	(1.97-8.60)		128 (79.0)	34 (21.0)	1.50	(0.71-3.15)	
Each additional year at first attending a sexual health clinic			1.00	(0.96-1.05)				1.03	(0.98-1.08)	
Use of drugs in anus/rectum ever										
No	325 (73.5)	117 (26.5)	1	-	0.01	374 (84.6)	68 (15.4)	1	-	<0.01
Yes	27 (56.3)	21 (43.8)	2.16	(1.18-3.97)		32 (66.7)	16 (33.3)	2.75	(1.43-5.29)	
Condom use with most recent partner										
Always	166 (69.7)	72 (30.3)	1	-	0.53	196 (82.4)	42 (17.6)	1	-	0.43
Sometimes	74 (73.3)	27 (26.7)	0.84	(0.50-1.42)		88 (87.1)	13 (12.9)	0.69	(0.35-1.35)	
Never	110 (74.8)	37 (25.2)	0.78	(0.49-1.23)		119 (81.0)	28 (19.0)	1.10	(0.65-1.86)	
Most recent male partner (oral or anal)										
Each additional year of age of partner			1.04	(1.01-1.06)	0.01			1.01	(0.98-1.04)	0.42
Each additional day since last having sex with partner			1.00	(0.99-1.00)	0.11			1.00	(1.00-1.01)	0.50
Relationship type with most recent partner										
Regular	172 (72.3)	66 (27.7)	1	-	0.91	198 (83.2)	40 (16.8)	1	-	0.97
Casual	168 (71.8)	66 (28.2)	1.02	(0.68-1.53)		195 (83.3)	39 (16.7)	0.99	(0.61-1.61)	
Relationship is continuing with most recent partner										
No	171 (73.7)	61 (26.3)	1	-	0.37	194 (83.6)	38 (16.4)	1	-	0.61
Yes	178 (70.1)	76 (29.9)	1.20	(0.80-1.78)		208 (81.9)	46 (18.1)	1.13	(0.70-1.81)	
Concurrency between any of the 3 most recent partners										
No	168 (76.7)	51 (23.3)	1	-	0.03	191 (87.2)	28 (12.8)	1	-	0.02
Yes	184 (67.9)	87 (32.1)	1.56	(1.04-2.33)		215 (79.3)	56 (20.7)	1.78	(1.08-2.91)	

Seronegative : IgG antibodies were not detected in the serum; Seropositive : IgG antibodies were detected in the serum. *P value from Fisher's exact test

FIGURE 49. ASSOCIATION OF SELECTED RISK FACTORS FOR HPV SEROPOSITIVITY IN LOGISTIC REGRESSION MODELS



Odds ratios are adjusted for lifetime number of partners and age, except for lifetime partners which is adjusted for age. Only MSM who had oral sex with another man in the last 3 months had detectable anti-HPV18

Categorical socio-demographic and behavioural risk factors identified in previous chapters and those statistically significantly associated with seropositivity, having adjusted for age and lifetime number of partners, are displayed in the forest plot on page 160 (Figure 49). In addition, Table 24 shows all of the socio-demographic and HIV variables examined for their association with seropositivity and Table 25 shows all of the sexual behavioural factors, having adjusted for age and lifetime number of partners.

Table 24 shows that after adjustment for number of lifetime partners, the association between age and seropositivity, was no longer statistically significant (aOR per year HPV16=1.03; 95% CI 0.99-1.07; aOR per year HPV18=1.03; 95% CI 0.99-1.08). On the other hand, after adjustment for age, the association with number of lifetime partners remained associated with seropositivity; MSM with >100 partners were 4.7-4.8 times more likely than those with $\leq$20 lifetime partners to be seropositive (Table 25).

An HIV-positive diagnosis remained a significant predictor of HPV16 seropositivity after adjusting for age and lifetime number of partners (aOR=3.16; 95% CI 1.37-7.28) but not for HPV18 seropositivity (aOR=2.04; 95% CI 0.84-4.92) even though the point estimates for HPV18 are approximately 2-fold higher in HIV-positive MSM compared to in HIV-negative MSM.

After adjustment, reporting receptive anal sex in the last three months remained associated with HPV16 seropositivity (aOR=3.39; 95% CI 2.01-5.71) and HPV18 (aOR=2.14; 95% CI 1.18-3.90). Use of drugs anally was no longer associated with HPV16 seropositivity (aOR=1.65; 95% CI 0.88-3.09) but remained associated with HPV18 seropositivity (aOR=2.07; 95% CI 1.05-4.10) and overlapping of any of the three most recent partners was no longer associated with seropositivity. Position during condomless receptive anal sex in the last year remained associated with HPV16 seropositivity with MSM reporting versatility having 4.6 times greater odds than those who were only insertive (95% CI 2.1-9.9).

The finding that there was a significant association between number of anal partners in the last year (total and new) and HPV16 seropositivity, having adjusted for age and lifetime partners, should be interpreted in the context of probable collinearity between number of lifetime partners (oral and anal) and number of anal partners in the last year. In a model

with age, lifetime partners and total anal partners in the last year as predictors for HPV16 seropositivity, lifetime number of partners was no longer significant (p=0.10) suggesting that number of partners in the last year were more important predictors than those over a year ago. Number of lifetime partners was considered an *a priori* confounder because it was expected that cumulative risk of HPV exposure would predict serostatus rather than recent exposure.

TABLE 24. SOCIO-DEMOGRAPHIC AND HIV STATUS RISK FACTORS FOR HPV SEROPOSITIVITY, HAVING ADJUSTED FOR AGE AND LIFETIME NUMBER OF PARTNERS

	HPV16			HPV18		
Risk factor	aOR	95% CI	P value	aOR	95% CI	P value
Each additional year in age[a]	1.03	(0.99-1.07)	0.15	1.03	(0.99-1.08)	0.18
Ethnic group						
White	1	_	0.46	1	_	0.97
Black	1.41	(0.78-2.56)		0.93	(0.44-1.98)	
Asian & SE Asian	0.88	(0.43-1.80)		0.92	(0.40-2.11)	
Born in the UK						
No	1	_	0.70	1	_	0.26
Yes	0.92	(0.61-1.39)		1.32	(0.81-2.16)	
Currently smoke						
No	1	_	0.62	1	_	0.47
Yes	1.12	(0.72-1.74)		1.21	(0.72-2.06)	
Increasing or higher risk alcohol drinking (AUDIT-C)						
No	1	_	0.64	1	_	0.71
Yes	0.90	(0.59-1.39)		0.91	(0.54-1.52)	
Currently employed						
No	1	_	0.64	1	_	0.49
Yes	1.14	(0.67-1.92)		1.25	(0.66-2.37)	
Years of education post-16						
None	1	_	0.75	1	_	0.92
Up to 2 years	1.03	(0.27-3.88)		1.36	(0.25-7.27)	
3 years or more	1.18	(0.35-4.00)		1.48	(0.31-7.05)	
Still in education	0.83	(0.21-3.19)		1.18	(0.21-6.55)	
Sexual orientation						
Gay/homosexual	1	_	0.80	1	_	0.36
Bisexual	0.90	(0.38-2.09)		1.53	(0.61-3.83)	
Circumcised						
No	1	_	0.48	1	_	0.34
Yes	1.18	(0.75-1.84)		1.29	(0.77-2.17)	
HIV positive diagnosis						
No	1	-	0.01	1	-	0.11
Yes	3.16	(1.37-7.28)		2.04	(0.84-4.92)	

Abbreviations: aOR=adjusted odds ratio, SE Asian=South East Asian, AUDIT-C= Alcohol Use Disorders Identification Test Consumption, HIV=Human Immunodeficiency virus. [a]Adjusted for lifetime number of partners only

TABLE 25. SEXUAL BEHAVIOUR RISK FACTORS FOR HPV SEROPOSITIVITY, ADJUSTED FOR AGE AND LIFETIME NUMBER OF PARTNERS.

	HPV16			HPV18		
Risk factor	aOR	95% CI	P	aOR	95% CI	p
Number of lifetime male partners (anal and oral sex)[a]						
Fewer than 20	1	-	<0.01	1	-	<0.01
21-30	2.07	(0.88-4.86)		2.06	(0.74-5.74)	
31-100	2.79	(1.34-5.79)		1.47	(0.58-3.72)	
101-500	4.74	(2.29-9.85)		4.77	(1.99-11.44)	
Number of male sex partners in the last year						
Male anal sex partners						0.26
<10	1	-	<0.01	1	-	
>=10	2.19	(1.34-3.57)		1.40	(0.78-2.50)	
New anal sex partners						0.94
<10	1	-	0.02	1	-	
>=10	1.77	(1.10-2.85)		1.02	(0.58-1.80)	
Anal sex partners without a condom						0.50
<10	1	-	0.08	1	-	
>=10	2.02	(0.91-4.50)		1.35	(0.56-3.25)	
Exclusively oral sex partners						0.96
<10	1	-	0.96	1	-	
>=10	0.99	(0.61-1.60)		0.99	(0.56-1.74)	
Each additional year of age at first sex with a man						
Oral	0.98	(0.92-1.04)	0.52	1.00	(0.93-1.07)	0.95
Receptive anal	0.95	(0.89-1.01)	0.07	0.96	(0.90-1.03)	0.26
Oral sex with a man in last 3 months						
No	1	-	0.72			
Yes	0.80	(0.24-2.66)				
Receptive anal sex with a man in last 3 months						
No	1	-	<0.01	1	-	0.01
Yes	3.39	(2.01-5.71)		2.14	(1.18-3.90)	
Insertive anal sex with a man in last 3 months						
No	1	-	0.38	1	-	0.88
Yes	1.27	(0.74-2.20)		1.05	(0.55-2.03)	
Vaginal sex in last year						
No	1	-	0.33	1	-	0.32
Yes	1.58	(0.62-4.01)		0.46	(0.10-2.12)	
Oral sex with a woman in the last year						
No	1	-	0.94	1	-	0.16
Yes	1.04	(0.38-2.82)		0.23	(0.29-1.77)	
Anal sex with a woman in the last year						
No	1	-	0.71	1	-	0.96
Yes	1.40	(0.23-8.57)		0.95	(0.09-9.78)	
Position when having anal sex without a condom in the last year						
Insertive only	1	-	<0.01	1	-	0.43
Receptive only	3.52	(1.34-9.23)		1.95	(0.70-5.45)	
Versatile	4.61	(2.14-9.93)		1.45	(0.66-3.17)	

TABLE 25. SEXUAL BEHAVIOUR RISK FACTORS FOR HPV SEROPOSITIVITY, ADJUSTED FOR AGE AND LIFETIME NUMBER OF PARTNERS. CONTINUED.

	HPV16			HPV18		
Risk factor	aOR	95% CI	P	aOR	95% CI	p
Each additional year at first attending a sexual health clinic	0.98	(0.93-1.03)	0.46	1.02	(0.96-1.08)	0.57
Use of drugs in anus/rectum ever						
No	1	-	0.12	1	-	0.04
Yes	1.65	(0.88-3.09)		2.07	(1.05-4.10)	
Condom use with most recent partner						
Always	1	-	0.53	1	-	0.51
Sometimes	0.91	(0.53-1.57)		0.71	(0.36-1.43)	
Never	0.76	(0.47-1.23)		1.09	(0.63-1.90)	
Most recent male partner (oral or anal)						
Each additional year of age of partner	1.02	(0.98-1.06)	0.12	1.00	(0.98-1.08)	0.82
Each additional day since last having sex with partner	1.00	(0.98-1.06)	0.51	1.00	(1.00-1.01)	0.14
Relationship type with most recent partner						
Regular	1	-	0.88	1	-	0.86
Casual	1.03	(0.68-1.57)		0.96	(0.58-1.58)	
Relationship is continuing with most recent partner						
No	1	-	0.50	1	-	0.58
Yes	1.15	(0.76-1.75)		1.15	(0.70-1.88)	
Concurrency between any of the 3 most recent partners						
No	1	-	0.14	1	-	0.10
Yes	1.37	(0.90-2.08)		1.54	(0.92-2.56)	

Abbreviation: aOR=adjusted odds ratio. [a]Adjusted for age only

RELATIONSHIP BETWEEN HPV SEROPOSITIVITY AND HPV DNA DETECTION

Table 26 examines HPV-type specificity for the association between DNA and seropositivity. Seropositivity for anti-HPV16 was associated with anogenital HPV16 DNA detection (OR=3.81; 95% CI 2.24-6.46) and this association remained after adjusting for age and lifetime number of partners (aOR=3.58; 95% CI 2.05-6.23). There were 37/499 participants (7.4%) seropositive for HPV16 with detectable anogenital HPV16 DNA, 327 (65.5%) participants with neither DNA nor seropositivity for HPV16, 30 (6.0%) participants who had detectable DNA with undetectable anti-HPV16 and 105 (21.0%) participants with undetectable DNA but who were seropositive.

Similarly, seropositivity for anti-HPV18 was associated with anogenital HPV18 DNA detection (OR=3.21; 95% CI 1.51-6.86; aOR=2.71; 95% CI 1.17-6.27). Separately, anti-HPV18 seropositivity was associated with HPV16 DNA (OR=1.98; 95% CI 1.09-3.62) but not after adjusting for age and lifetime partners (aOR=1.71; 95% CI 0.90-3.24).

Table 27 describes the associations between HPV type groupings and seropositivity for HPV16/18 to further examine the type specificity of these associations. Quadrivalent-vaccine type infection at anogenital sites was associated with HPV16/18 seropositivity, even after adjusting for age and lifetime partner numbers (aOR=1.79; 95% CI 1.19-2.71). 101/506 (20.0%) participants were seropositive for HPV16/18 without any detectable anogenital quadrivalent-vaccine type DNA and 73/506 (14.4%) were seropositive for HPV16/18 with detectable anogenital quadrivalent-vaccine type DNA. The association between anal HPV16/18 DNA detection and HPV16/18 seropositivity (aOR=3.05; 95% CI 1.75-5.30) was stronger than for external genital (aOR=2.03; 95% CI 1.13-3.65). Anogenital LR-HPV (aOR=1.09; 95% CI 0.67-1.79) and external genital quadrivalent-vaccine type DNA detection (aOR=1.55; 95% CI 0.96-2.50) were not associated with HPV16/18 seropositivity. Furthermore there were no associations between DNA detection in oral and urine specimens (HPV16, HPV18, bivalent-vaccine types, LR-HPV, quadrivalent-vaccine types, 9-valent vaccine types and HR-HPV) and seropositivity.

TABLE 26. ASSOCIATION OF HPV DNA DETECTION WITH HPV ANTIBODY DETECTION IN MSM, FOR ANTI-HPV16 AND, SEPARATELY, FOR ANTI-HPV18

	HPV16						HPV18					
	Seronegative n (%)	Seropositive n (%)	OR	95% CI	aOR[a]	95% CI	Seronegative n (%)	Seropositive n (%)	OR	95% CI	aOR[a]	95% CI
HPV16 DNA detected												
Anal												
No	**295 (76.2)**	**92 (23.7)**	**1**	**-**	**1**	**-**	324 (83.7)	63 (16.3)	1	-	1	-
Yes	**21 (38.2)**	**34 (61.8)**	**5.19**	**(2.87-9.39)**	**4.84**	**(2.62-8.96)**	39 (70.9)	16 (29.09)	2.11	(1.11-4.01)	1.81	(0.92-3.56)
External genital												
No	**284 (72.8)**	**106 (27.2)**	**1**	**-**	**1**	**-**	325 (83.3)	65 (16.7)	1	-	1	-
Yes	**21 (47.7)**	**23 (52.3)**	**2.93**	**(1.56-5.52)**	**2.78**	**(1.43-5.44)**	34 (77.3)	10 (22.7)	1.47	(0.69-3.12)	1.24	(0.55-2.82)
Any anogenital site[b]												
No	**324 (75.5)**	**105 (24.5)**	**1**	**-**	**1**	**-**	362 (84.4)	67 (15.6)	1	-	1	-
Yes	**30 (44.8)**	**37 (55.2)**	**3.81**	**(2.24-6.46)**	**3.58**	**(2.05-6.23)**	49 (73.1)	18 (26.9)	1.98	(1.09-3.62)	1.71	(0.90-3.24)
Oral												
No	**120 (71.4)**	**48 (28.6)**	**N/A**				138 (82.1)	30 (17.9)	N/A			
Yes	**1 (100.0)**	**0 (0.0)**	**N/A**	**N/A**	**N/A**	**N/A**	1 (100.0)	0 (0.0)	N/A	N/A	N/A	N/A
HPV18 DNA detected												
Anal												
No	305 (72.3)	117 (27.7)	1	-	1	-	**351 (83.2)**	**71 (16.8)**	**1**	**-**	**1**	**-**
Yes	11 (55.0)	9 (45.0)	2.13	(0.86-5.28)	1.62	(0.59-4.44)	**12 (60.0)**	**8 (40.0)**	**3.30**	**(1.30-8.36)**	**2.59**	**(0.89-7.53)**
External genital												
No	293 (70.4)	123 (29.6)	1	-	1	-	**347 (83.4)**	**69 (16.6)**	**1**	**-**	**1**	**-**
Yes	12 (66.7)	6 (33.3)	1.19	(0.44-3.25)	1.04	(0.34-3.18)	**12 (66.7)**	**6 (33.3)**	**2.51**	**(0.91-6.93)**	**1.84**	**(0.59-5.72)**
Any anogenital site[b]												
No	334 (72.0)	130 (28.0)	1	-	1	-	**391 (84.3)**	**73 (15.7)**	**1**	**-**	**1**	**-**
Yes	20 (62.5)	12 (37.5)	1.54	(0.73-3.24)	1.29	(0.57-2.91)	**20 (62.5)**	**12 (37.5)**	**3.21**	**(1.51-6.86)**	**2.71**	**(1.17-6.27)**
Oral												
No	121 (71.6)	48 (28.4)	N/A				**139 (82.2)**	**30 (17.8)**	**N/A**			
Yes	0 (0.0)	0 (0.0)	N/A	N/A	N/A	N/A	**0 (0.0)**	**0 (0.0)**	**N/A**	**N/A**	**N/A**	**N/A**

Abbreviations: aOR=adjusted odds ratio, N/A= not applicable. [a]Adjusted for age and lifetime number of partners. [b]In MSM with at least one anogenital sample adequate for PCR and adequate serum sample. Bold formatting represents HPV type-specific associations.

TABLE 27. ASSOCIATION OF HPV DNA DETECTION WITH ANTI-HPV16/18 ANTIBODY DETECTION IN MSM

Risk factor	Seronegative n (%)	Seropositive n (%)	HPV16/18 OR	95% CI	aOR[a]	95% CI
Bivalent- vaccine type HPV DNA detected						
Anal (N=442)						
No	**303 (69.7)**	**132 (30.3)**	**1**	**-**	**1**	**-**
Yes	**29 (40.8)**	**42 (59.2)**	**3.48**	**(2.06-5.87)**	**3.05**	**(1.75-5.30)**
External genital (N=434)						
No	**303 (67.9)**	**143 (32.1)**	**1**	**-**	**1**	**-**
Yes	**29 (48.3)**	**31 (51.7)**	**2.21**	**(1.27-3.83)**	**2.03**	**(1.13-3.65)**
Any anogenital site[b] (N=496)						
No	**289 (69.8)**	**125 (30.2)**	**1**	**-**	**1**	**-**
Yes	**43 (46.7)**	**49 (53.3)**	**2.63**	**(1.66-4.18)**	**2.38**	**(1.46-3.89)**
LR-HPV (HPV6/11) DNA detected						
Anal						
No	291 (66.4)	147 (33.6)	1	-	1	-
Yes	41 (60.3)	27 (39.7)	1.33	(0.78-2.26)	1.16	(0.66-2.04)
External genital						
No	298 (65.8)	155 (34.2)	1	-	1	-
Yes	34 (64.2)	19 (35.8)	1.03	(0.57-1.88)	1.07	(0.57-2.00)
Any anogenital site[b]						
No	274 (66.3)	139 (33.7)	1	-	1	-
Yes	58 (62.4)	35 (37.6)	1.18	(0.74-1.89)	1.09	(0.67-1.79)
Quadrivalent- vaccine type HPV DNA detected						
Anal						
No	267 (70.6)	111 (29.4)	1	-	1	-
Yes	65 (50.8)	63 (49.2)	2.49	(1.63-3.81)	2.15	(1.37-3.37)
External genital						
No	273 (68.1)	128 (31.9)	1	-	1	-
Yes	59 (56.2)	46 (43.8)	1.62	(1.03-2.54)	1.55	(0.96-2.50)
Any anogenital site[b]						
No	243 (70.6)	101 (29.4)	1	-	1	-
Yes	89 (54.9)	73 (45.1)	1.98	(1.34-2.91)	1.79	(1.19-2.71)
9-valent- vaccine type HPV DNA detected						
Anal						
No	238 (72.3)	91 (27.7)	1	-	1	-
Yes	94 (53.1)	83 (46.9)	2.56	(1.71-3.83)	2.11	(1.38-3.23)
External genital						
No	245 (70.4)	103 (29.6)	1	-	1	-
Yes	87 (55.1)	71 (44.9)	1.93	(1.29-2.90)	1.66	(1.08-2.55)
Any anogenital site[b]						
No	203 (72.8)	76 (27.2)	1	-	1	-
Yes	129 (56.8)	98 (43.2)	2.04	(1.40-2.97)	1.73	(1.16-2.58)
HR-HPV DNA detected						
Anal						
No	237 (72.7)	89 (27.3)	1	-	1	-
Yes	95 (52.8)	85 (47.2)	2.66	(1.77-3.98)	2.19	(1.43-3.36)
External genital						
No	240 (71.4)	96 (28.6)	1	-	1	-
Yes	92 (54.1)	78 (45.9)	2.14	(1.43-3.20)	1.81	(1.18-2.78)
Any anogenital site[b]						
No	204 (75.8)	65 (24.2)	1	-	1	-
Yes	128 (54.0)	109 (46.0)	2.71	(1.84-3.97)	2.28	(1.53-3.42)

Analyses were restricted to MSM with respective DNA and serum samples adequate for HPV testing.There were no statistically significant associations between urine or oral HPV DNA detection and HPV16/18 seropositivity (for HPV16, HPV18, bivalent HPV types, HPV6/11, quadrivalent HPV types, 9-valent HPV types and HR-HPV types). [a]Adjusted for age and lifetime number of partners. [b]In MSM with at least one anogenital sample adequate for PCR and adequate serum sample. Bold formatting represents HPV type-specific associations.

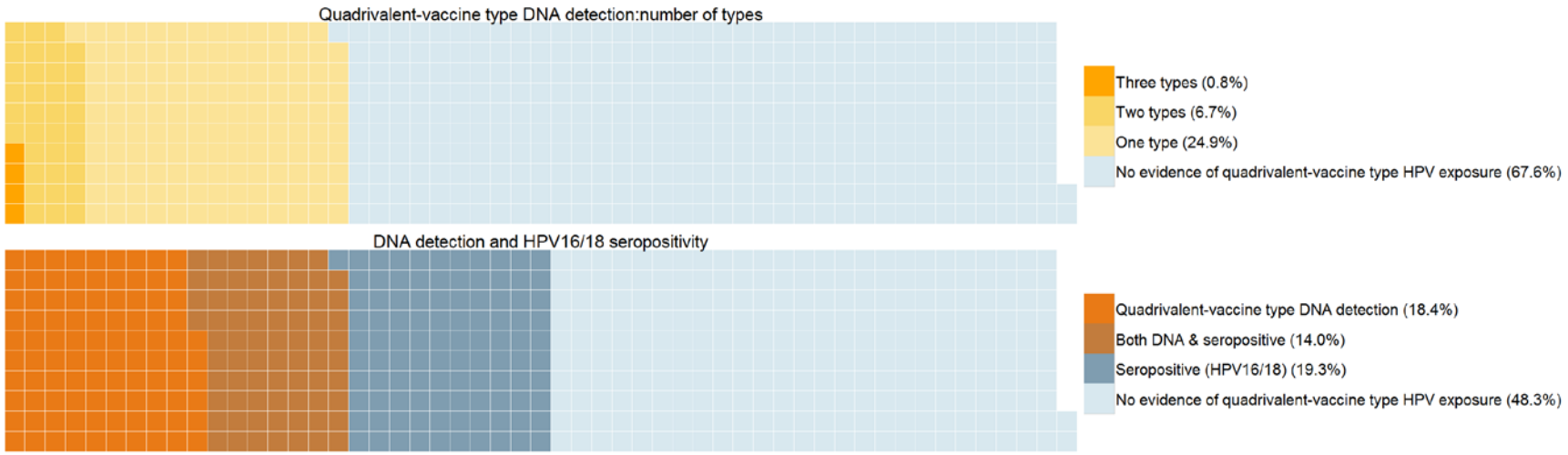
6.4 KEY FINDINGS

65.6% of HPV-MSM-MMC participants had no detectable antibodies to HPV16 and/or HPV18 (Table 21). Of the 174 HPV16/18 seropositive MSM, 49 (28.2%) also had detectable anogenital bivalent-vaccine type HPV DNA and 73 (42.0%) also had detectable quadrivalent-vaccine type HPV DNA in at least one anogenital specimen (Table 27). Using the results from Table 27, Figure 50 shows that in the overall sample of 522 MSM, 174 (33.3%) were seropositive (anti-HPV16/18) and 101/522 (19.3%) were seropositive in the absence of any detectable HPV DNA (HPV6/11/16/18) at any site. Having accounted for the 170 MSM with HPV DNA detected at one or more sites in chapter 5 (Table 15), the remaining 251/522 (48.1%) had no detectable markers for HPV6/11/16/18 in any specimen type (Figure 50).

HIV status, number of anal partners in the last year, recent receptive anal sex and position during condomless sex in the last year were associated with seropositivity after adjusting for age and lifetime number of partners. Number of lifetime partners was associated with seropositivity after adjusting for age but not after adjusting for number of anal partners in the last year, suggesting that recent partners are more important predictors of HPV16/18 seropositivity than partners over a year ago.

Anogenital HPV DNA detection was strongly associated with same HPV type seropositivity and for HPV16 this effect was stronger for DNA detected in the anal sample compared to the external genital sample.

FIGURE 50. DISTRIBUTION OF QUADRIVALENT-VACCINE TYPE HPV DNA AND HPV16/18 SEROPOSITIVITY IN 522 HPV-MSM-MMC PARTICIPANTS



1 square= 1 participant. This chart updates Figure 38, page 141 to include serology results in HPV-MSM-MMC participants. Results are adapted from Table 27 by including all participants (n= 522) in the denominator (not just MSM who have specimens adequate for HPV testing). Abbreivations: HPVa/b= HPV type a and/or HPV type b. NB. The denominator includes all participants, so those with no evidence of HPV include those men without a complete set of adequate samples. All participants had at least one adequate serum, oral or anogenital sample.

6.5 FINDINGS IN CONTEXT

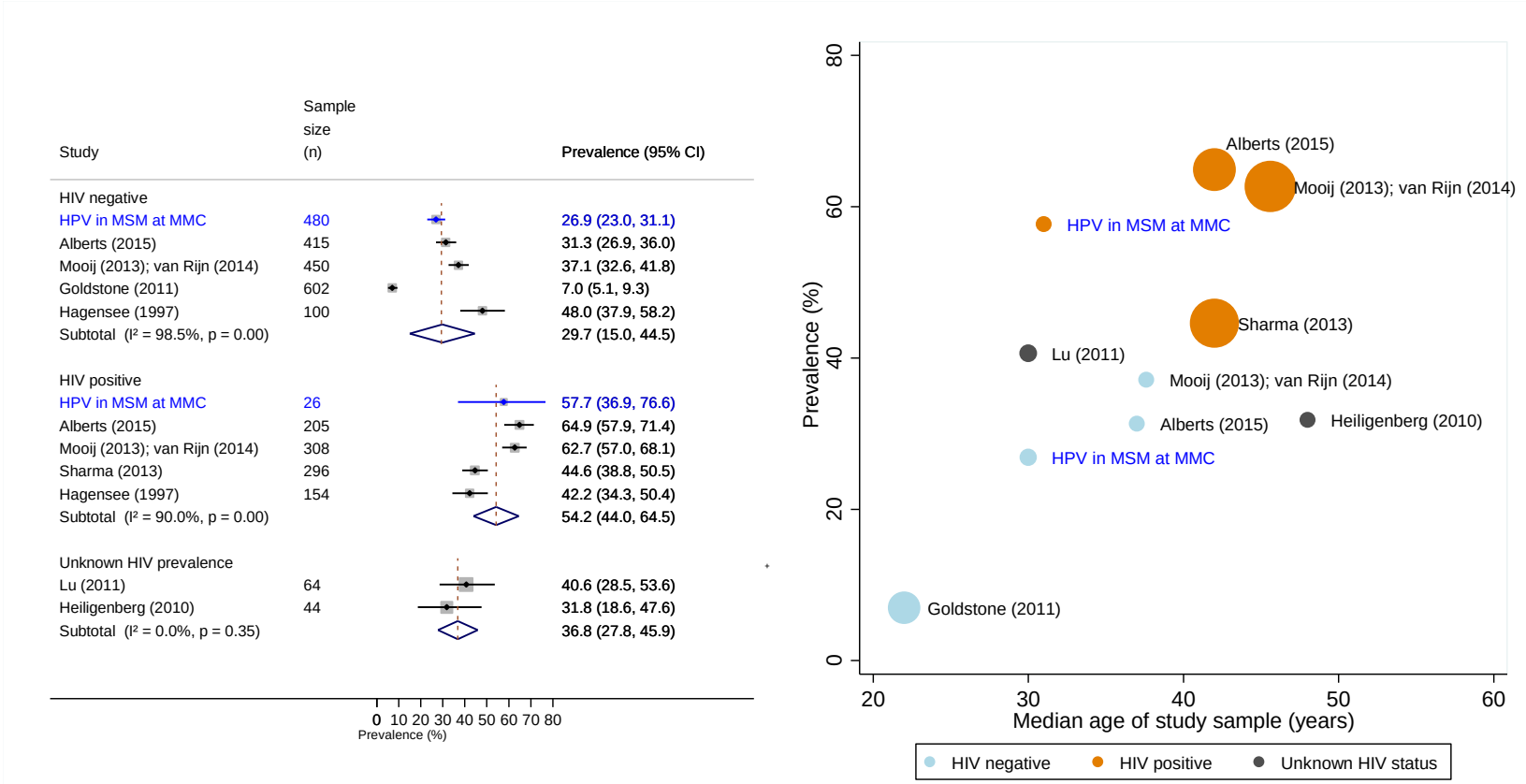
Figure 51 shows a random-effects meta-analysis of eight studies measuring HPV16 serum antibodies in MSM and includes the findings from this chapter. Three of these studies sampled from MSM populations in the Netherlands. The random-effects pooled meta-analysis revealed high heterogeneity between study estimates, even within each HIV stratum, that was partly explained by the median age of study participants in a meta-regression (adjusted R^2=40%; p=0.05).

Different assays for antibody detection are likely to introduce heterogeneity to results. Not only is the type of antibody response being measured variable, depending on target epitope(s), so that the efficacy of detected antibodies may be different, but also the variable reagents and methods have prevented the establishment of standardised cut-off values for detection resulting in variable assay sensitivity[203].

6.6 STRENGTHS AND LIMITATIONS

There are no estimates of the sensitivity and specificity of seropositivity for detecting recent or lifetime HPV infections. Only one study has estimated the rate of HPV seroconversion in men. Following penile HPV16 infection in heterosexual men, only 13% (95% CI 6.6%-24.8%) seroconverted by 24 months post-infection[85]. This is likely to be a considerable underestimate of seroconversion rate for MSM, in whom anal HPV infections predominate, compared to heterosexual men, in whom the majority of infections are penile[65,179], with anal infections having a stronger association with seropositivity than penile infections[204]. If the estimate of HPV16 seroprevalence in this chapter of 28% only represents 13% of those exposed in the last two years, with no waning immunity, this would predict the entire MSM at MMC population having been twice exposed in that time. There are no data on duration of detectable serum antibodies in men, but they are thought to last for years in women[205].

FIGURE 51. STUDIES MEASURING HPV16 SEROPREVALENCE IN MSM



[+]Studies conducted in Amsterdam, The Netherlands. References: Alberts (2015)[206], Mooij (2013)[207], van Rijn (2014)[116], Goldstone (2011) quadrivalent-vaccine trial population was selected as low-risk on age, lifetime number of partners (<5) and history of HPV-related disease variables[193]. Hagensee (1997)[88], Sharma (2013)[208], Lu (2011)[209], Heilenberg (2010)[210]. Bubble size represents sample size.

7. HPV-MSM-MMC STUDY: HPV6/11, ANOGENITAL WARTS & OTHER SEXUALLY TRANSMITTED INFECTIONS

In this chapter, I present results relating to anogenital warts (AGW) as a proxy measure for exposure to HPV6/11. I first present prevalence estimates of AGW and examine the burden of unreported AGW. I then examine factors associated with AGW, including HPV infection and other STIs and HPV seropositivity.

7.1 OBJECTIVES

1. To estimate the prevalence of AGW in MSM attending MMC
2. To estimate the sensitivity and specificity of a patient-suspected episode of AGW for the detection of diagnosed and SHAAPT-coded AGW cases
3. To estimate the age-specific prevalence of anogenital HPV6/11 DNA detection and AGW diagnoses
4. To examine demographic and behavioural associations with AGW
5. To examine the association between AGW and current HPV infection and HPV16/18 seropositivity
6. To estimate the prevalence of STIs in MSM attending MMC
7. To examine the association between STIs and markers for HPV exposure, including current anogenital HPV infection (HPV6/11 and HR-HPV), and prior exposure (history of AGWs and HPV16/18 seropositivity)
8. To discuss biases to be considered when interpreting the findings from this chapter

7.2 METHODS

Methods employed to meet the objectives are described in chapter 4. In particular, the statistical methods are described on page 97.

7.3 RESULTS

DIAGNOSED AND SUSPECTED ANOGENITAL WARTS

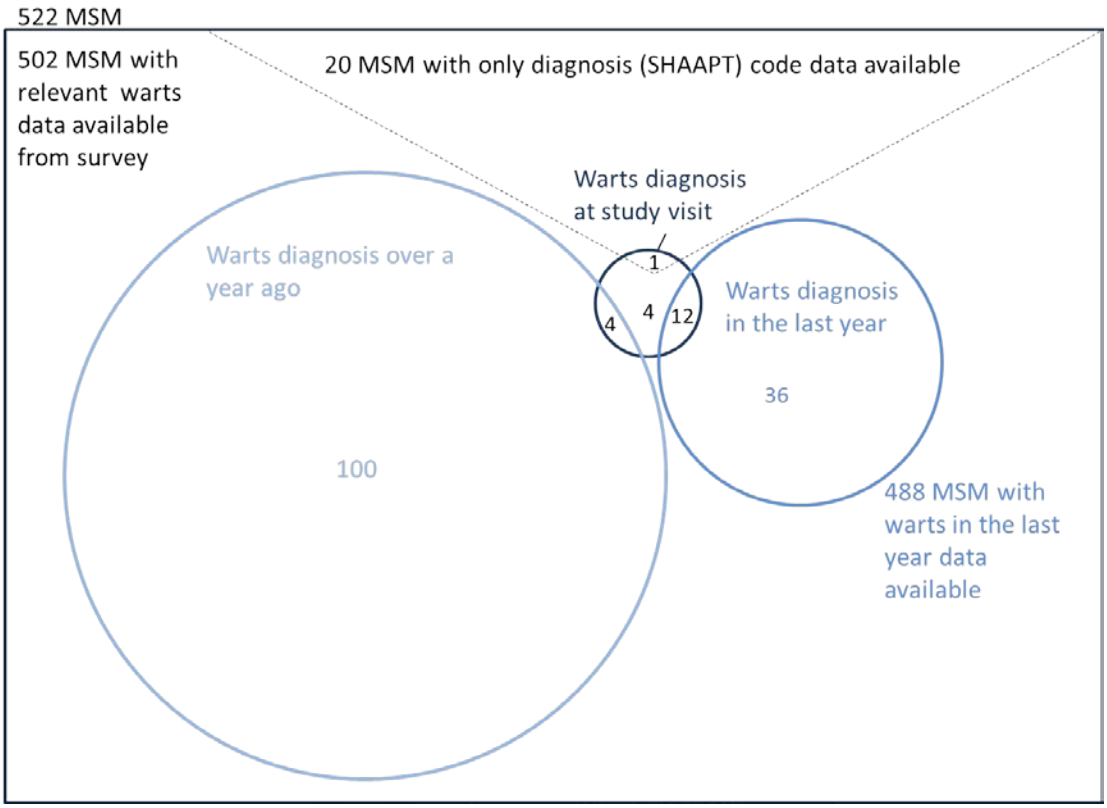
In total 157/522 (30.2%; 95% CI 26.3-34.3) MSM had received or reported having received an AGW diagnosis in their lifetime and 48 men (9.4%; 95% CI 7.0-12.3) reported having had an AGW diagnosis in the last year (Table 28 and Figure 52). Of 504 participants, 98 (19%) reported that they had had AGW episodes in their lifetime for which they did not access health services.

TABLE 28. PREVALENCE OF DIAGNOSED AND SUSPECTED AGW EPISODES IN 522 HPV-MSM-MMC PARTICIPANTS

	Total; N=522		
	n	**% (of total)**	**95% CI**
TOTAL DIAGNOSED AGW	157	30.2	26.3-34.3
Over a year ago without a diagnosis at visit	100	19.2	15.9-22.8
Over a year ago with a diagnosis at visit	4	0.8	0.2-2.0
In the last year without a diagnosis at visit	36	6.9	4.9-9.4
In the last year with a diagnosis at visit	12	2.3	1.2-4.0
New diagnosis at visit (never before)	4	0.8	0.2-2.0
New diagnosis at visit with missing questionnaire data	1	0.2	0.0-1.1
	n	**% (of 504)**	**95% CI**
TOTAL SUSPECTED undiagnosed AGW in lifetime	98	19.4	16.1-23.2

Abbreviations: AGW=anogenital warts. Suspected AGW = Participant reported having had symptoms of AGW for which they did not access health services so did not receive a diagnosis.

FIGURE 52. DISTRIBUTION OF AGW DIAGNOSES IN 522 HPV-MSM-MMC PARTICIPANTS



As a result of missing CASI survey data and item non-response, there was inconsistency in the size of the denominator for each measure of AGW. Abbreviations: AGW= anogenital warts, MSM= men who have sex with men.

In order to estimate the proportion of those episodes without health service use which represent "true" AGW episodes, the association of suspected AGW with diagnosed AGW episodes was examined. Fifty-three men (10.7%; 95% CI 8.3-13.8) attended the clinic because they suspected they had genital warts of whom 13 (25%) received a warts diagnosis at the visit. In the patient records of the 40 MSM without a corresponding AGW SHAAPT code, it was recorded that at least five had had AGW visualised on exam. Where AGWs were not seen on exam, among a variety of lesions, haemorrhoids and anal tags were recorded. A further seven men received a warts diagnosis having attended the clinic for other reasons. A suspected AGW at visit was 65% sensitive (95% CI 40.8-84.6) and 92% specific (95% CI 88.9-94.1) for the detection of a diagnosed and SHAAPT-coded AGW episode (Box 7).

BOX 7. SENSITIVITY AND SPECIFICITY OF A SUSPECTED AGW EPISODE FOR THE DETECTION OF A DIAGNOSED AND SHAAPT-CODED AGW EPISODE

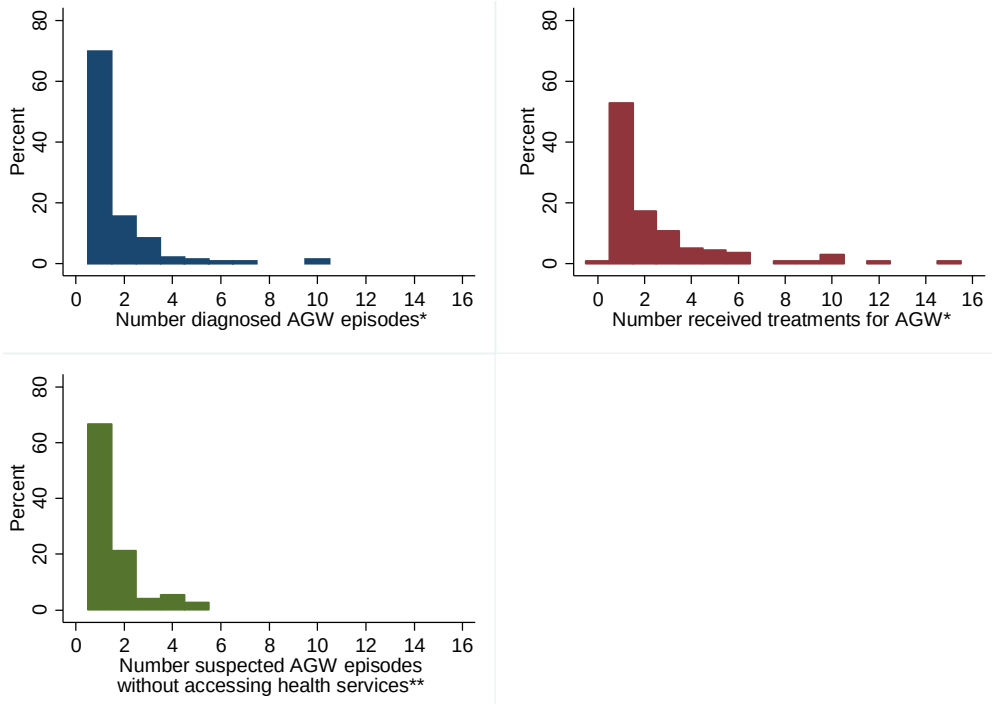
Suspected AGW	Diagnosis of AGW at visit: +ve	-ve	Total
+ve	13	38	51
-ve	7	431	438
Total	20	469	489

$$Sensitivity = \frac{13}{13+7} = 0.65$$

$$Specificity = \frac{431}{38+431} = 0.92$$

Figure 53 shows that in MSM with an AGW diagnosis before the clinic visit, the median number of diagnosed episodes was one (IQR 1-2) and the median number of AGW treatments was one, with a wider distribution (IQR 1-3) indicating that the number of treatments per episode was greater than one. In the 98 participants who reported at least one suspected AGW episode (without accessing health services), the median number of suspected episodes was one (IQR: 1-2).

FIGURE 53. HISTOGRAMS SHOWING THE DISTRIBUTION OF LIFETIME NUMBER OF AGW EPISODES

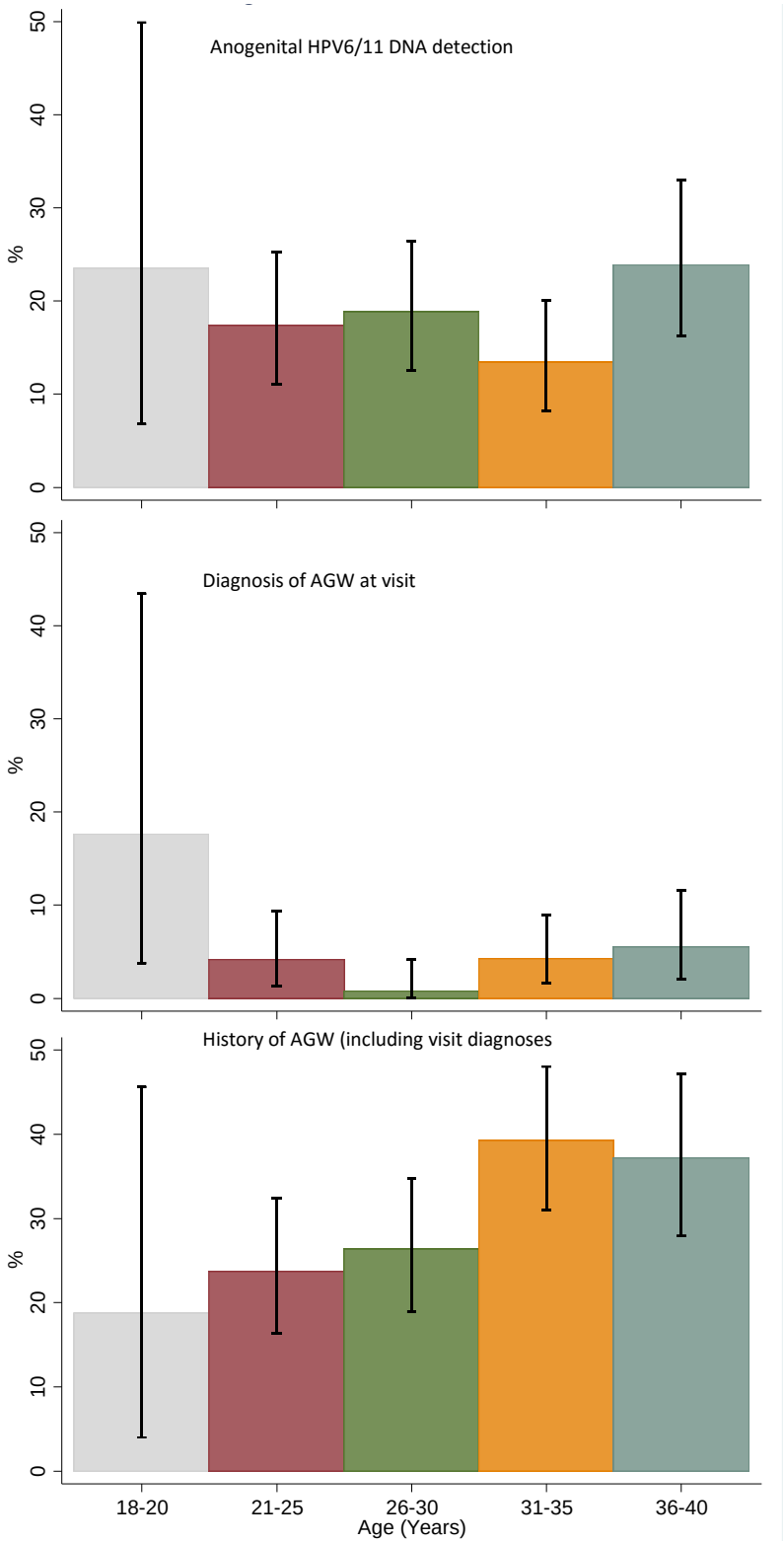


*Of MSM reporting at least one lifetime diagnosis of AGW (n=152, not including those diagnosed at study visit). **Of MSM reporting at least one suspected AGW episode in their lifetime (n=97)

AGE-SPECIFIC PREVALENCE OF AGW

In chapter 5, the prevalence of HPV6/11 was 18.6% (Table 14, page 119). Figure 54 shows the lack of an age-association with a current anogenital HPV6/11 infection or AGW diagnoses at study visit. Eighteen percent (3/17) of 18 to 20 year old MSM received an AGW diagnosis at the study visit with wide confidence intervals (95% CI 4-43) compared to 3.5% of those older than 20 (18/505; 95% CI 2.1-5.6%). As expected, increasing age group was associated with a history of AGW (p-trend 0.03).

FIGURE 54. AGE-SPECIFIC PREVALENCE OF ANOGENITAL HPV6/11 INFECTION AND DIAGNOSED AGW



Data is available in Appendix III, Appendix table 3, page 302.

FACTORS ASSOCIATED WITH AGW

Variables examined for their association with AGW history are displayed in Table 29 and Table 30. Variables found to be associated with AGW or other markers of HPV exposure are displayed in Figure 55. In this section, age was modelled as a continuous variable and was again shown to be significantly associated with a history of anogenital warts (OR=1.06; 95% CI 1.02-1.09) but the association was not statistically significant after adjusting for lifetime partner numbers (OR=1.04; 95% CI 1.00-1.07). No other demographic or lifestyle factors were associated with a history of AGW.

Table 30 shows that a number of sexual behaviour factors were associated with a history of AGW. More than 30 lifetime partners was associated with a history of AGW (OR=2.83; 95% CI 1.80-4.46) even after adjusting for age (aOR=2.49; 95% CI 1.55-3.99).

Increasing partner numbers were associated with AGW: at least ten anal partners (in total (OR=1.68; 95% CI 1.14-2.49), new partners (OR=1.80; 95% CI 1.20-2.70) and partners without a condom (OR=2.87; 95% CI 1.38-6.00) in the last year. Number of recent partners was correlated with lifetime partners and, after adjusting for age and lifetime partners, total anal partners and new anal partners in the last year were no longer statistically significantly associated with AGW (aOR=1.20; 95% CI 0.77-1.85 and aOR=0.91-2.15, respectively). However, recent condomless partner numbers remained significant predictors of AGW (aOR=2.29; 1.08-4.86).

Age of most recent partner (OR per year=1.05; 95% CI 1.03-1.08; aOR per year=1.04; 95% CI 1.02-1.07) and overlapping of any of the three most recent partnerships (OR=1.67; 95% CI 1.13-2.46; aOR=1.56; 95% CI 1.04-2.32) increased the odds of AGW.

Vaginal sex in the last year (OR=1.79; 95% CI 0.85-3.79; aOR=3.09; 95% CI 1.34-7.15) and oral sex with a woman in the last year (OR=2.05; 95% CI 0.95-4.42; aOR=3.55; 95% CI 1.52-8.30) were associated with a history of AGW, but only after adjusting for age and number of lifetime partners.

TABLE 29. DEMOGRAPHIC AND LIFESTYLE RISK FACTORS FOR AGW

Risk factor	History of diagnosed AGW[a]					
	No	Yes				
	N (%)	n (%)	OR	95% CI	aOR[b]	95% CI
Each additional year in age			1.06	(1.02-1.09)	1.04	(1.00-1.07)
Ethnic group						
White	266 (69.8)	115 (30.2)	1	-	1	-
Black	41 (61.2)	26 (38.8)	1.47	(0.86-2.51)	1.75	(1.00-3.08)
Asian & SE Asian	36 (70.6)	15 (29.4)	0.96	(0.51-1.83)	1.07	(0.55-2.07)
Born in the UK						
No	186 (70.2)	79 (29.8)	1	-	1	-
Yes	160 (67.5)	77 (32.5)	1.13	(0.78-1.65)	1.14	(0.77-1.68)
Currently smoke						
No	249 (70.3)	105 (29.7)	1	-	1	-
Yes	96 (65.3)	51 (34.7)	1.26	(0.84-1.90)	1.32	(0.86-2.01)
Increasing or higher risk alcohol drinking (AUDIT-C)						
No	118 (69.4)	52 (30.6)	1	-	1	-
Yes	225 (69.0)	101 (31.0)	1.02	(0.68-1.52)	1.04	(0.69-1.57)
Currently employed						
No	79 (75.2)	26 (24.8)	1	-	1	-
Yes	267 (67.3)	130 (32.7)	1.48	(0.91-2.42)	1.29	(0.77-2.15)
Years of education post-16						
None	10 (76.9)	3 (23.1)	1	-	1	-
Up to 2 years	43 (69.4)	19 (30.6)	1.47	(0.36-5.96)	1.79	(0.44-7.38)
3 years or more	225 (65.6)	118 (34.4)	1.75	(0.47-6.47)	2.03	(0.54-7.59)
Sexual orientation						
Gay/homosexual	317 (69.2)	141 (30.8)	1	-	1	-
Bisexual	29 (67.4)	14 (32.6)	1.09	(0.56-2.12)	1.72	(0.84-3.55)
Circumcised						
No	243 (68.6)	111 (31.4)	1	-	1	-
Yes	102 (70.3)	43 (29.7)	0.92	(0.61-1.41)	0.96	(0.62-1.48)

Abbreviations: AGW= anogenital warts, SE Asian=South East Asian, AUDIT-C=AIcohol Use Disorders Identification Test Consumption. [a]includes episodes diagnosed at study visit. [b]aOR is adjusted for age and lifetime number of partners, except for age where only adjusted for lifetime number of partners

TABLE 30. SEXUAL BEHAVIOUR RISK FACTORS FOR AGW DIAGNOSES

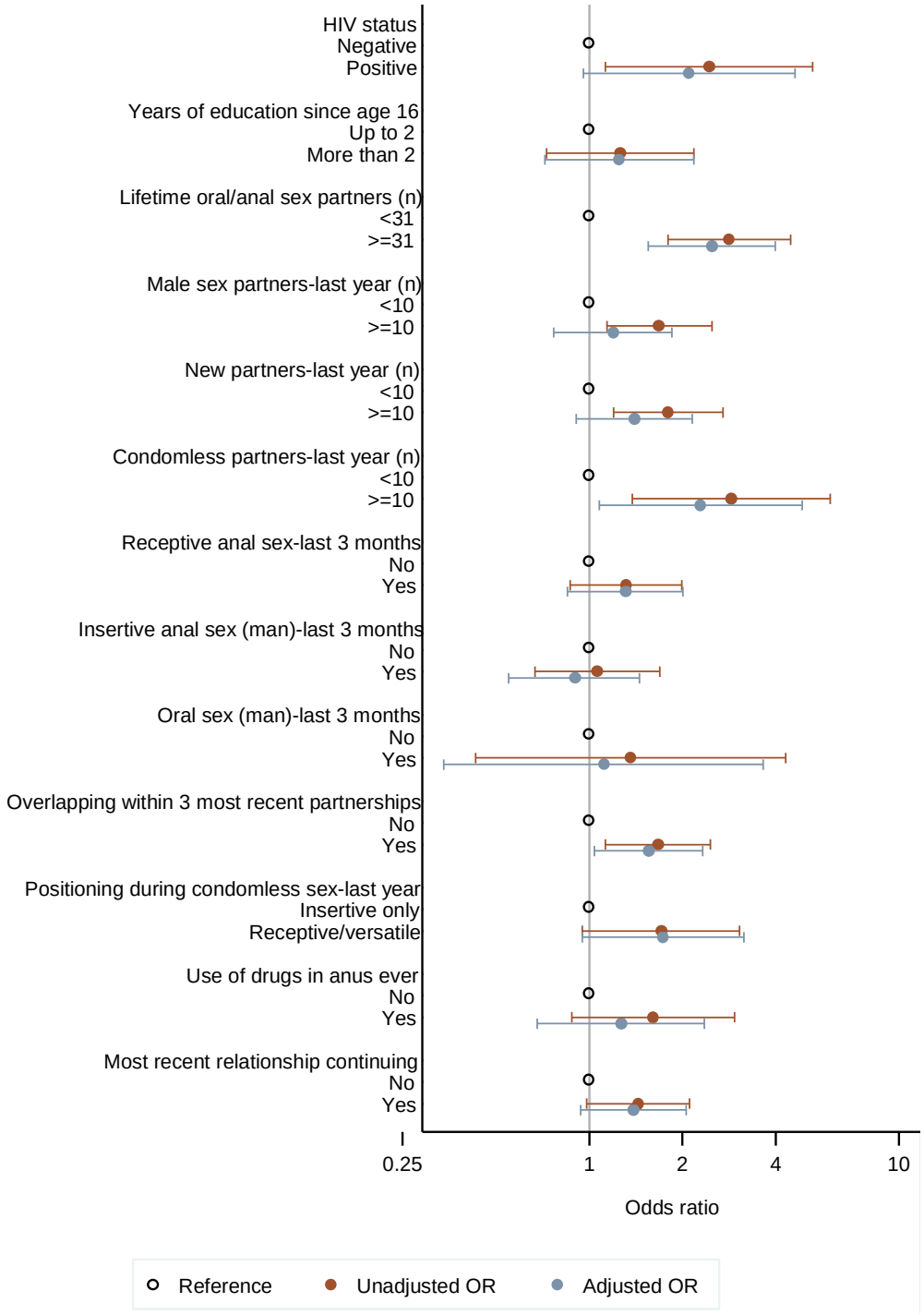
Risk factor	History of diagnosed AGW[a]					
	No n (%)	Yes n (%)	OR	95% CI	aOR[b]	95% CI
Number of lifetime male partners (anal and oral sex)						
<31	139 (82.2)	30 (17.8)	1	-	1	-
>=31	206 (62.0)	126 (38.0)	2.83	(1.80-4.46)	2.49	(1.55-3.99)
Number of male sex partners in the last year						
Male anal sex partners						
<10	196 (73.7)	70 (26.3)	1	-	1	-
>=10	130 (62.5)	78 (37.5)	1.68	(1.14-2.49)	1.20	(0.77-1.85)
New anal sex partners						
<10	228 (73.1)	84 (26.9)	1	-	1	-
>=10	95 (60.1)	63 (39.9)	1.80	(1.20-2.70)	1.40	(0.91-2.15)
Anal sex partners without a condom						
<10	310 (70.3)	131 (29.7)	1	-	1	-
>=10	14 (45.2)	17 (54.8)	2.87	(1.38-6.00)	2.29	(1.08-4.86)
Exclusively oral sex partners						
<10	226 (72.2)	87 (27.8)	1	-	1	-
>=10	88 (63.3)	51 (36.7)	1.51	(0.98-2.30)	1.11	(0.70-1.76)
Each additional year of age at first sex with a man						
Oral			0.99	(0.94-1.04)	0.99	(0.94-1.05)
Receptive anal			1.00	(0.96-1.05)	0.99	(0.94-1.05)
Oral sex with a man in last 3 months						
No	12 (75.0)	4 (25.0)	1	-	1	
Yes	330 (68.8)	150 (31.3)	1.36	(0.43-4.30)	1.12	(0.34-3.64)
Receptive anal sex with a man in last 3 months						
No	121 (72.9)	45 (27.1)	1	-	1	-
Yes	218 (67.1)	107 (32.9)	1.32	(0.87-1.99)	1.31	(0.85-2.01)
Insertive anal sex with a man in last 3 months						
No	75 (69.4)	33 (30.6)	1	-	1	-
Yes	255 (68.2)	119 (31.8)	1.06	(0.67-1.69)	0.90	(0.55-1.45)
Vaginal sex in the last year						
No	258 (71.3)	104 (28.7)	1	-	1	-
Yes	18 (58.1)	13 (41.9)	1.79	(0.85-3.79)	3.09	(1.34-7.15)
Oral sex with a woman in the last year						
No	263 (71.7)	104 (28.3)	1	-	1	-
Yes	16 (55.2)	13 (44.8)	2.05	(0.95-4.42)	3.55	(1.52-8.30)
Anal sex with a woman in the last year						
No	275 (71.1)	112 (28.9)	1	-	1	-
Yes	4 (57.1)	3 (42.9)	1.84	(0.41-8.36)	2.50	(0.51-12.34)
Position when having anal sex without a condom in the last year						
Insertive only	56 (73.7)	20 (26.3)	1	-	1	-
Receptive or versatile	133 (62.1)	81 (37.9)	1.71	(0.95-3.05)	1.73	(0.95-3.16)

TABLE 30. SEXUAL BEHAVIOUR RISK FACTORS FOR AGW DIAGNOSES CONTINUED.

Risk factor	History of diagnosed AGW[a]					
	No n (%)	Yes n (%)	OR	95% CI	aOR[b]	95% CI
Each additional year at first attending a sexual health clinic			0.97	(0.93-1.00)	0.90	(0.86-0.95)
Use of drugs in anus/rectum ever						
No	317 (70.0)	136 (30.0)	1	-	1	-
Yes	29 (59.2)	20 (40.8)	1.61	(0.88-2.94)	1.27	(0.68-2.35)
Condom use with most recent partner						
Always	163 (67.4)	79 (32.6)	1	-	1	-
Not always	182 (70.8)	75 (29.2)	0.85	(0.58-1.24)	0.89	(0.60-1.32)
Most recent male partner (oral or anal)						
Each additional year of age of partner			1.05	(1.03-1.08)	1.04	(1.02-1.07)
Each additional day since last having sex with partner			1.00	(0.99-1.00)	1.00	(0.99-1.00)
Relationship type with most recent partner						
Regular	170 (68.8)	77 (31.2)	1	-	1	-
Casual	167 (70.2)	71 (29.8)	0.94	(0.64-1.38)	0.93	(0.63-1.39)
Relationship is continuing with most recent partner						
No	172 (73.2)	63 (26.8)	1	-	1	-
Yes	173 (65.5)	91 (34.5)	1.44	(0.98-2.11)	1.39	(0.94-2.06)
Concurrency between any of the 3 most recent partners						
No	167 (74.9)	56 (25.1)	1	-	1	-
Yes	179 (64.2)	100 (35.8)	1.67	(1.13-2.46)	1.56	(1.04-2.32)

Abbreviations: AGW= anogenital warts. [a]includes episodes diagnosed at study visit. [b]aOR=adjusted odds ratio; adjusted for age and lifetime number of partners.

FIGURE 55. SELECTED FACTORS AND THEIR ASSOCIATION WITH A HISTORY OF DIAGNOSED AGW



Models adjusted for lifetime number of partners (anal and oral) and age, except for lifetime partners which was only adjusted for age.

ASSOCIATION BETWEEN AGW AND OTHER MEASURES OF HPV INFECTION

Of the 157 MSM with a lifetime diagnosis of AGW, 53 (33.8%) did not have detectable HPV6/11/16/18 DNA or antibodies in any specimen, 64 (40.8%) also had an anogenital HPV6/11/16/18 infection, one (0.64%) had an oral HPV6/11/16/18 infection and 68 (43.3%) were seropositive for HPV16/18.

In Table 31, a history of AGW is separated into episodes at visit and older episodes (over a year ago), to introduce time since diagnosis into the relationship between markers for HPV exposure and AGW. A current anogenital HPV6/11 infection was associated with a history of AGW (OR=2.11; 95% CI 1.33-3.34; aOR=2.03; 95% CI 1.25-3.29) and an AGW diagnosis at visit (OR=3.52; 95% CI 1.44-8.62; aOR=3.94; 95% CI 1.57-9.93) even after adjusting for age and lifetime number of partners. A current anogenital HPV6/11 infection was not associated with an AGW diagnosis over a year ago. There were 12 participants with an AGW diagnosis at visit who had undetectable anogenital HPV6/11.

On the other hand a current anogenital HPV16/18 infection was not associated with a history of AGW (OR=1.09 95% CI 0.67-1.78; aOR=1.04 95% CI 0.63-1.71) or a diagnosis at visit (OR=1.18; 95% CI 0.48-2.91; aOR=1.31; 95% CI 0.51-3.39). There were too few cases of oral HPV infection to assess the association with AGW.

TABLE 31. ASSOCIATION OF HPV DNA OR ANTIBODY DETECTION WITH DIAGNOSED AGW IN MSM

Risk factor	MSM with AGW history (including a diagnosis at visit)						AGW diagnosis at visit						AGW diagnosis over a year ago					
	No (n)	Yes (n)	OR	95% CI	aOR[a]	95% CI	No (n)	Yes (n)	OR	95% CI	aOR[a]	95% CI	No (n)	Yes (n)	OR	95% CI	aOR[a]	95% CI
HPV16/18 serum antibody detected[b]																		
No	246	84	1	-	1	-	319	13	1	-	1	-	240	53	1	-	1	-
Yes	106	68	1.88	1.27-2.78	1.49	0.98-2.25	166	8	1.18	0.48-2.91	1.31	0.51-3.39	101	36	1.61	1.00-2.62	1.10	0.66-1.83
Anogenital HPV16/18 DNA detected[c]																		
No	290	125	1	-	1	-	399	18	1	-	1	-	281	73	1	-	1	-
Yes	64	30	1.09	0.67-1.76	0.99	0.60-1.63	91	3	0.73	0.21-2.53	0.79	0.22-2.75	62	18	1.12	0.62-2.01	0.98	0.53-1.81
Anogenital HPV6/11 DNA detected[c]																		
No	301	113	1	-	1	-	404	12	1	-	1	-	292	79	1	-	1	-
Yes	53	42	2.11	1.33-3.34	2.03	1.25-3.29	86	9	3.52	1.44-8.62	3.94	1.57-9.93	51	12	0.87	0.44-1.71	0.70	0.35-1.42
Oral HPV16/18 DNA detected[d]																		
No	110	53					154	10					110	26				
Yes	2	0	n/a	n/a	n/a	n/a	2	0	n/a	n/a	n/a	n/a	2	0	n/a	n/a	n/a	n/a
Oral HPV6/11 DNA detected[d]																		
No	110	52	1	-	1	-	153	10					110	26				
Yes	2	1	1.06	0.09-11.93	0.87	0.07-10.41	3	0	n/a	n/a	n/a	n/a	2	0	n/a	n/a	n/a	n/a
HPV16/18 serum or anogenital HPV16/18[e]																		
No	209	71	1	-	1	-	270	12	1	-	1	-	203	44	1	-	1	-
Yes	135	79	1.72	1.17-2.54	1.31	0.87-1.99	205	9	0.99	0.41-2.39	1.08	0.43-2.76	132	43	1.50	0.94-2.41	1.01	0.61-1.67
HPV16/18 serum & anogenital HPV16/18[e]																		
No	312	133	1	-	1	-	428	19	1	-	1	-	306	78	1	-	1	-
Yes	32	17	1.25	0.67-2.32	1.22	0.63-2.34	47	2	0.96	0.22-4.24	1.03	0.23-4.62	29	9	1.22	0.55-2.68	1.09	0.48-2.47

[a] Adjusted for age and lifetime number of partners. [b] In MSM with an adequate serum sample. [c] In MSM with at least one anogenital sample adequate for PCR. [d] In MSM with an adequate oral sample. [e] In MSM with both an adequate anogenital sample and an adequate serum sample. MSM with missing observations for any AGW variable were excluded.

PREVALENCE OF SEXUALLY TRANSMITTED INFECTIONS

Table 32 displays the prevalence of individual STIs in participants. Gonorrhoea was the most common STI diagnosed at the visit, in 11.7% of MSM (95% CI 9.1-14.8) followed by HIV (5.4%; 95% CI 3.6-7.7), herpes simplex virus (HSV; 2.7%; 95% CI 1.5-4.5), chlamydia (2.7%; 95% CI 1.5-4.5), and syphilis, (1.0%; 95% CI 0.3-2.2). There were two diagnoses of primary, one of secondary and two of early latent syphilis. The prevalence of other STIs diagnosed at visit was 50/522 (9.6%; 95% 7.0-12.1).

TABLE 32. PREVALENCE OF STI DIAGNOSES IN THE LAST YEAR AND AT VISIT IN 522 HPV-MSM-MMC PARTICIPANTS

	N	n	%	95% CI
HIV diagnosis ever	522	28	5.4	3.6-7.7
Diagnosis code at visit				
Gonorrhoea	522	61	11.7	9.1-14.8
Chlamydia	522	14	2.7	1.5-4.5
HSV	522	14	2.7	1.5-4.5
Syphilis	522	5	1.0	0.3-2.2
Multiple (≥2) STIs[a]	522	6	1.2	0.4-2.5
Other STI[b]	522	50	9.6	7.2-12.4
Reported diagnosis in the last year				
Gonorrhoea	489	87	17.8	14.5-21.5
Chlamydia	489	70	14.3	11.3-17.7
HSV	489	20	4.1	2.5-6.3
Syphilis	489	18	3.7	2.2-5.8
Multiple (≥2) STIs[a]	489	40	7.7	5.5-10.3
Diagnosis code at visit and reported diagnosis in the last year				
Gonorrhoea	489	16	3.3	1.9-5.3
Chlamydia	489	6	1.2	0. 5-2.7
HSV	489	5	1.0	0.3-2.4
Syphilis	489	1	0.2	0.0-1.1
Multiple (≥2) STIs[a]	489	1	0.2	0.0-1.1
Total diagnoses in the last year (including visit)				
Gonorrhoea	522	132	25.3	21.6-29.3
Chlamydia	522	78	14.9	12.0-18.3
HSV	522	29	5. 6	3.8-7.9
Syphilis	522	22	4.2	2.7-6.3
Multiple (≥2) STIs[a]	522	54	10.3	7.9-13.3

Abbreviations: N=denominator, n=numerator, CI=Confidence Interval, HIV=Human Immunodeficiency Virus, HSV=Herpes Simplex Virus, STI=Sexually Transmitted Infection. [a] Two or more of Gonorrhoea/Chlamydia/HSV/Syphilis. [b] SHAAPT code at visit for an STI that was not Gonorrhoea/Chlamydia/HSV/Syphilis.

ASSOCIATION BETWEEN STIS AND HPV

Table 33 shows the association of STIs with AGWs and anogenital HPV6/11 infection. HIV status was associated with a history of AGW (OR=2.44; 95% CI 1.13-5.25) but not after adjusting for age and lifetime number of partners (aOR=1.83; 95% CI 0.83-4.05). Anogenital HPV6/11 was not associated with HIV status (OR=1.87; 95% CI 0.80-4.39; aOR=1.70; 95% CI 0.71-4.06). A syphilis diagnosis at visit was not associated with a history of AGW (Fisher's exact p=0.17) and was associated with anogenital HPV6/11 infection (Fisher's exact p=0.04).

Associations between STIs diagnosed in the same time period as AGW were possible from data presented in Table 34. The number of participants was too small to establish whether there was an association with STIs diagnosed at visit and an AGW diagnosis at visit, or in the last year. Table 34 also shows that there were associations between reporting a diagnosis of gonorrhoea (OR=2.61; 95% CI 1.36-5.00; aOR=2.56; 95% CI 1.31-5.01), HSV (OR=3.30; 95% CI 1.14-9.53; aOR=3.24; 95% CI 1.10-9.53), syphilis (OR=6.67; 95% CI 2.45-18.15; aOR=6.20; 95% CI 2.26-16.99) and reporting a diagnosis of AGW in the last year. Attending a SHC in the last year was not measured so it was not possible to adjust for this potential confounder.

Table 35 shows the association of STIs with HPV16/18 seropositivity and anogenital HR-HPV infection. An HIV-positive diagnosis was strongly associated with detection of HPV16/18 antibodies (OR=3.89; 95% CI 1.69-8.91; aOR=3.26; 95% CI 1.38-7.73) and anogenital HR-HPV detection (OR=3.09; 95% CI 1.33-7.15; aOR=2.54; 95% CI 1.08-5.98) even after adjusting for age and lifetime partner numbers. A HSV diagnosis at visit was associated with detectable HPV16/18 antibodies (Fisher's exact p=0.01).

TABLE 33. ASSOCIATIONS OF INDIVIDUAL STIS WITH DIAGNOSED AGW AND ANOGENITAL HPV6/11 INFECTION

	History of diagnosed AGW (including visit)						Anogenital HPV6/11 DNA detection					
	Yes (n)[a]	No (n)	OR	95% CI	aOR	95% CI	Yes (n)[b]	No (n)	OR	95% CI	aOR	95% CI
HIV diagnosis ever	14	14	2.44	(1.13-5.25)	1.83	(0.83-4.05)	8	20	1.87	(0.80-4.39)	1.70	(0.71-4.06)
Diagnosis code at visit												
Gonorrhoea	20	41	1.15	(0.65-2.03)	1.29	(0.70-2.36)	15	46	1.55	(0.83-2.92)	1.52	(0.78-2.95)
Chlamydia	6	8	1.76	(0.60-5.17)	1.97	(0.61-6.36)	3	11	1.23	(0.34-4.51)	1.38	(0.37-5.20)
HSV	4	10	0.92	(0.29-2.99)	0.92	(0.27-3.11)	1	13	0.34	(0.04-2.62)	0.36	(0.05-2.86)
Syphilis	3	2	3.52	(0.58-21.25)	2.54	(0.41-15.76)	3	2	6.93	(1.14-42.06)	6.34	(1.03-38.94)
Reported diagnosis in the last year												
Gonorrhoea	32	55	1.41	(0.87-2.30)	1.20	(0.72-2.00)	20	67	1.52	(0.86-2.67)	1.39	(0.78-2.48)
Chlamydia	29	41	1.76	(1.04-2.96)	1.45	(0.84-2.51)	15	55	1.34	(0.72-2.50)	1.19	(0.62-2.26)
HSV	9	11	1.92	(0.78-4.73)	1.83	(0.71-4.72)	1	19	0.24	(0.03-1.80)	0.24	(0.03-1.83)
Syphilis	10	8	2.98	(1.15-7.70)	2.53	(0.95-6.72)	5	13	1.85	(0.64-5.34)	1.68	(0.58-4.86)
Total reported diagnosis in the last year (including visit												
Gonorrhoea	45	84	1.33	(0.87-2.04)	1.24	(0.79-1.94)	30	102	1.47	(0.90-2.39)	1.39	(0.83-2.31)
Chlamydia	31	46	1.69	(1.03-2.80)	1.46	(0.86-2.48)	16	62	1.19	(0.65-2.17)	1.13	(0.61-2.09)
HSV	12	16	1.79	(0.83-3.88)	1.63	(0.73-3.63)	1	28	0.15	(0.02-1.13)	0.15	(0.02-1.14)
Syphilis	13	9	3.54	(1.48-8.48)	2.94	(1.20-7.22)	8	14	2.71	(1.10-6.66)	2.47	(1.00-6.12)

Abbreviations AWG=anogenital warts, HSV=Herpes simplex virus, HIV=Human immunodeficiency virus, OR=odds ratio. aOR= adjusted OR; adjusted for lifetime number of sexual partners and age (continuous). [a]In the total of 522 MSM, 157 had a history of AGW and in the 489 MSM with available survey data (diagnoses in the last year), 149 had a history of AGW. [b]In all 522 MSM, 95 had detectable anogenital HPV6/11 DNA and in those 489 MSM with available survey data, 86 had detectable anogenital HPV6/11 DNA.

TABLE 34. ASSOCIATIONS OF INDIVIDUAL STIS WITH AN AGW DIAGNOSIS AT VISIT AND A SELF-REPORTED AGW DIAGNOSIS IN THE LAST YEAR

	AGW diagnosis at visit						Reported AGW diagnosis in the last year					
	Yes (n)[a]	No (n)	OR	95% CI	aOR	95% CI	Yes (n)[b]	No (n)	OR	95% CI	aOR	95% CI
HIV diagnosis ever	1	27	0.88	(0.11-6.79)	0.98	(0.12-7.80)	5	23	2.11	(0.76-5.84)	1.95	(0.69-5.48)
Diagnosis code at visit												
Gonorrhoea	3	58	1.27	(0.36-4.45)	1.46	(0.41-5.23)	4	53	0.67	(0.23-1.93)	0.68	(0.23-1.98)
Chlamydia	1	13	1.88	(0.23-15.06)	2.34	(0.28-19.25)	1	12	0.76	(0.10-5.98)	0.76	(0.10-6.04)
HSV	2	12	4.29	(0.90-20.53)	4.59	(0.93-22.65)	1	12	0.76	(0.10-5.98)	0.73	(0.09-5.79)
Syphilis	0	5	n/a	n/a	n/a	n/a	3	2	14.63	(2.38-89.89)	13.01	(2.08-81.29)
Reported diagnosis in the last year												
Gonorrhoea	5	82	1.57	(0.56-4.45)	1.76	(0.61-5.11)	16	71	2.61	(1.36-5.00)	2.56	(1.31-5.01)
Chlamydia	5	65	2.07	(0.73-5.89)	2.40	(0.82-7.09)	10	60	1.67	(0.79-3.53)	1.59	(0.74-3.43)
HSV	1	19	1.25	(0.16-9.81)	1.17	(0.15-9.47)	5	15	3.30	(1.14-9.53)	3.24	(1.10-9.53)
Syphilis	1	17	1.40	(0.18-11.07)	1.36	(0.17-10.89)	7	11	6.67	(2.45-18.15)	6.20	(2.26-16.99)
Total reported diagnosis in the last year (including visit)												
Gonorrhoea	8	124	1.87	(0.76-4.62)	2.26	(0.88-5.80)	18	110	1.81	(0.97-3.37)	1.79	(0.94-3.39)
Chlamydia	5	73	1.83	(0.65-5.15)	2.17	(0.74-6.35)	11	66	1.69	(0.82-3.48)	1.62	(0.77-3.40)
HSV	3	26	3.04	(0.84-11.00)	3.09	(0.83-11.46)	6	22	2.72	(1.05-7.08)	2.62	(1.00-6.90)
Syphilis	1	21	1.14	(0.15-8.93)	1.12	(0.14-8.90)	10	12	9.41	(3.82-23.20)	8.74	(3.51-21.74)

Abbreviations AWG=anogenital warts, HSV=Herpes simplex virus, HIV=Human immunodeficiency virus, OR=odds ratio. aOR= adjusted OR; adjusted for lifetime number of sexual partners and age (continuous). In the total of 522 MSM, 21 had a diagnosis code for AGW at visit. In the 489 MSM with available survey data , 48 reported a diagnosis in the last year.

TABLE 35. ASSOCIATIONS OF INDIVIDUAL STIS WITH HPV16/18 SEROPOSITIVITY AND ANOGENITAL HR-HPV INFECTION

	HPV16/18 seropositivity						Anogenital HR-HPV DNA detection					
	Yes (n)[a]	No (n)	OR	95% CI	aOR	95% CI	Yes (n)[b]	No (n)	OR	95% CI	aOR	95% CI
HIV diagnosis ever	17	9	3.89	(1.69-8.91)	3.26	(1.38-7.73)	20	8	3.09	(1.33-7.15)	2.54	(1.08-5.98)
Diagnosis code at visit												
Gonorrhoea	23	35	1.29	(0.74-2.27)	1.31	(0.72-2.41)	32	29	1.33	(0.78-2.27)	1.45	(0.82-2.56)
Chlamydia	6	8	1.45	(0.49-4.24)	1.16	(0.35-3.86)	6	8	0.87	(0.30-2.55)	0.94	(0.30-2.94)
HSV	9	4	4.47	(1.36-14.74)	5.72	(1.48-22.15)	9	5	2.14	(0.71-6.48)	2.72	(0.81-9.18)
Syphilis	1	3	0.63	(0.07-6.14)	0.53	(0.05-5.18)	4	1	4.73	(0.52-42.57)	3.96	(0.43-36.31)
Reported diagnosis in the last year												
Gonorrhoea	35	47	1.56	(0.96-2.54)	1.35	(0.81-2.26)	45	42	1.27	(0.80-2.02)	1.1	(0.68-1.78)
Chlamydia	28	39	1.47	(0.87-2.49)	1.16	(0.67-2.02)	35	35	1.16	(0.70-1.92)	0.97	(0.57-1.65)
HSV	10	9	2.22	(0.88-5.58)	2.01	(0.77-5.24)	12	8	1.74	(0.70-4.34)	1.71	(0.67-4.39)
Syphilis	10	8	2.51	(0.97-6.48)	2.13	(0.80-5.70)	13	5	3.07	(1.08-8.75)	2.69	(0.93-7.77)

Abbreviations AWG=anogenital warts, HSV=Herpes simplex virus, HIV=Human immunodeficiency virus, OR=odds ratio. aOR= adjusted OR; adjusted for lifetime number of sexual partners and age (continuous). [a]In the 506 MSM with adequate serum samples, 174 were seropositive for HPV16 and/or HPV18 and in the 475 MSM with available survey data (diagnoses in the last year), 162 were seropositive for HPV16 and/or HPV18. [b]In all 522 MSM, 241 had detectable anogenital HR-HPV DNA and in those 489 MSM with available survey data, 229 had detectable anogenital HR-HPV DNA.

7.4 KEY FINDINGS

Figure 56 updates Figure 38, page 141, and Figure 50, page 170, to show that 6.9% of participants in the HPV-MSM-MMC study had a history of AGW and detectable quadrivalent-vaccine type DNA, a further 5.6% were also seropositive to HPV16/18. A separate 8.4% were seropositive and had a history of AGW and a further 10.2% had a history of AGW in the absence of any other markers for HPV exposure. Therefore in HPV-MSM-MMC participants, 38% had no evidence of quadrivalent-vaccine type HPV exposure using the combined markers of HPV DNA testing, anti-HPV16/18 serum testing and a history of AGW.

AGW episodes were a significant burden with a third of participants having had an AGW diagnosis in their lifetime. There was an indication of additional burden in MSM not accessing health services: only 25% of MSM attending the SHC because they suspected having an AGW episode had it confirmed with a diagnosis at visit. If 25% of suspected cases are indeed AGW, then 5% (25% of 19%) of this population had had additional AGW episodes for which they did not access health services.

There was no indication that MSM in a particular age range were more or less at risk of having an anogenital HPV6/11 infection or an AGW diagnosis. The cumulative number of lifetime partners, which increases with age, explained the increase in prior AGW episodes with age.

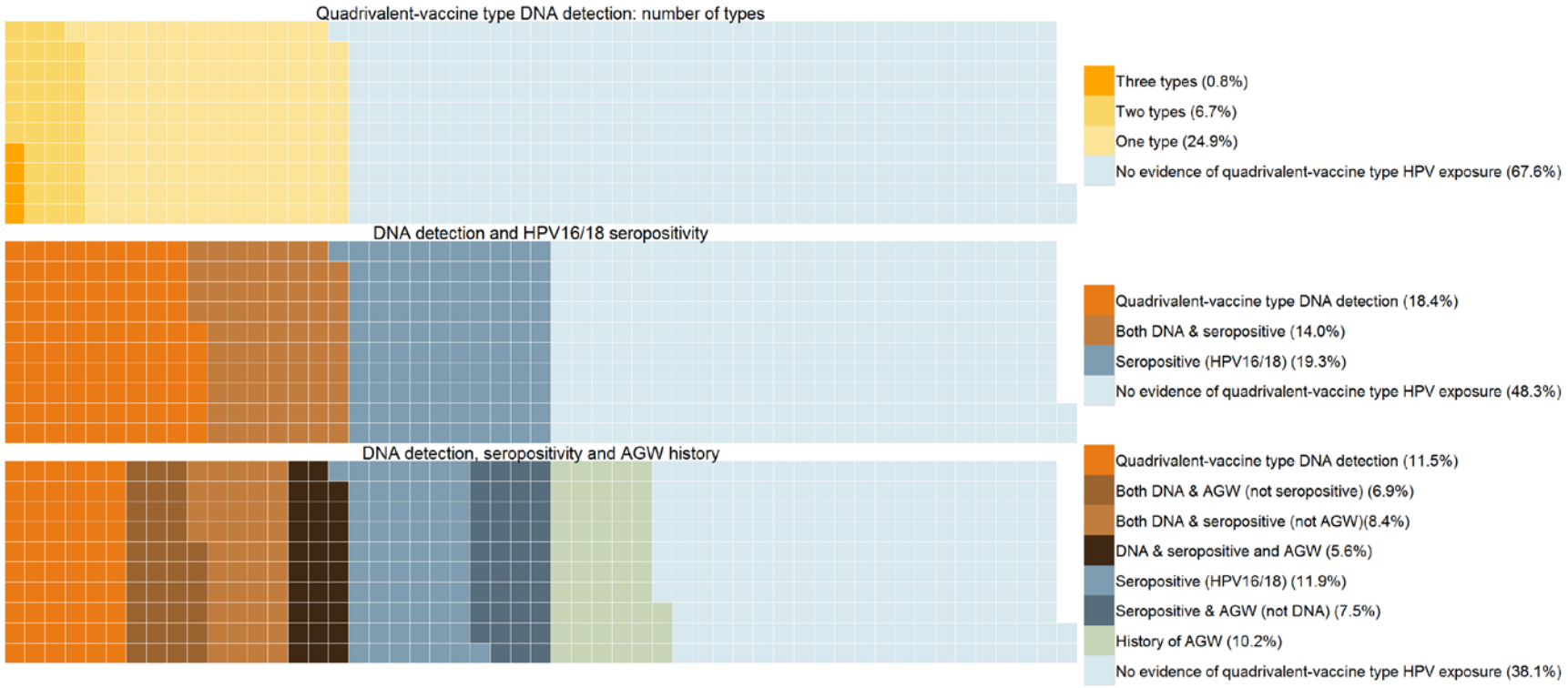
Number of lifetime anal, oral and condomless anal sex partners in the last year, age of most recent partner and concurrency within the three most recent partnerships were associated with a history of AGW.

A history of AGW and a diagnosis at visit were associated with a current anogenital HPV6/11 infection but not with an HPV16/18 infection. However there were 12 AGW diagnoses at visit with undetectable anogenital HPV6/11. One possible explanation for this non-concordance could be that swabbing the surface of an AGW does not capture the HPV types within and responsible for lesion development[211]. That current anogenital HPV6/11 detection was not associated with AGW episodes over a year ago is supported by estimates

of HPV6/11 duration of infection in longitudinal studies in men, in which the median time to clearance is six months[212].

HIV status was not associated with an anogenital HPV6/11 infection and, after adjusting for age and lifetime number of partners, was not associated with a history of AGW. There were few statistically significant associations between STI diagnoses and markers for HPV exposure and the numbers for these analyses were small. However some associations were identified: syphilis was associated with HPV6/11 infection and a reported AGW diagnosis in the last year, HSV was associated with a reported AGW diagnosis in the last year and HPV16/18 seropositivity and a gonorrhoea diagnosis in the last year was associated with an AGW diagnosis in the last year.

FIGURE 56. DISTRIBUTION OF HPV DNA DETECTION, SEROPOSITIVITY AND HISTORY OF AGW IN 522 HPV-MSM-MMC PARTICIPANTS



1 square= 1 participant. This chart updates Figure 50, page 170, to include AGW results in HPV-MSM-MMC participants. Relevant AGW results are described on page 184 and all participants (n= 522) are included in the denominator.

7.5 FINDINGS IN CONTEXT

The estimate of AGW prevalence of 4.1% in HPV-MSM-MMC participants was similar to that in MSM attending a SHC in Melbourne, Australia, between 2002 and 2013 (4.0%), despite Australia's routine use of the quadrivalent vaccine in girls since 2008 and boys since 2013[213]. In 40 SHCs in the US, between 2010 and 2011, the prevalence of AGW was 7.5% in an MSM population with 18.2% HIV prevalence[214]. In HIV-positive MSM in the CARH-MEN cohort in Spain, the prevalence of AGW was considerably higher at 27.9%[215].

The estimate of a history of AGW of 30.2% in HPV-MSM-MMC participants is more than that in an internet sample of MSM in Denmark (25.2%)[216] and considerably more than that reported by men in Britain in the Natsal-2 survey (3.6%) [217].

It is estimated that 1/12 MSM living in London are in infected with HIV and that in England in 2014, among male SHC attendees, 86% (3,477/ 4,054) of syphilis diagnoses, 68% (18,029/ 26,575) of gonorrhoea diagnoses, 21% (11,468/ 55,807) of chlamydia diagnoses, 12% (1,474/ 11,889) of genital herpes diagnoses and 9% (3,456/ 39,349) of genital warts diagnoses were among MSM[218].

7.6 STRENGTHS AND LIMITATIONS

The denominator was not consistent across the three AGW measurements (Figure 52) so combining these measurements into a single measure (a history of AGW), with missing observations for some measures in some participants, has potential to underestimate the AGW burden.

There was some potential misclassification for SHAAPT coding because all MSM who attended with suspected AGW are likely to have been examined but it is not routine to examine men for AGWs if they do not report symptoms. There was also evidence for incomplete reporting of AGW episodes through SHAAPT codes. Incomplete SHAAPT coding is more likely for AGW, which is diagnosed from clinical symptoms, than for bacterial STIs, such as chlamydia, which are diagnosed from laboratory tests. The data were too sparse to adjust for potential confounders when examining the associations of STIs and AGWs and, as in chapters 5 and 6, associations with behaviours that were of high prevalence would be difficult to detect.

8. HPV-MSM-MMC STUDY: POTENTIAL VACCINE UPTAKE AND COVERAGE

In this chapter, I present results relating to potential vaccine uptake and health service use in MSM in order to inform estimates of potential vaccine coverage. I begin by estimating the age at first attendance at a SHC, which represents the earliest opportunity to vaccinate, and relate this to the age at first sexual experience. I then examine the population of first time attenders in terms of HPV exposure. Participants' preferred health service for AGW diagnosis and treatment and Hepatitis B virus vaccination is then explored. Finally I explore potential uptake and barriers to uptake via HPV knowledge, STI risk perception, HBV vaccine uptake and reported likelihood of, and reasons for, accepting the vaccine.

8.1 OBJECTIVES

1. To estimate age of first attending a SHC in the UK and examine its association with HPV infection, HPV seropositivity and AGW
2. To estimate the prevalence of HPV infection, HPV seropositivity and AGW in MSM attending a SHC in the UK for the first time and compare these in repeat attenders
3. To describe types of health services used for HBV vaccination and AGW diagnosis and treatment in MSM attending a SHC
4. To describe HPV knowledge, in particular, risk and expectation of HPV vaccine outcomes, and explore the association with HPV infection
5. To describe reported HBV virus vaccine uptake, STI risk perception and likelihood of accepting an HPV vaccine and explore associations with HPV infection
6. To examine reasons for and against reported likelihood of accepting an HPV vaccine

8.2 METHODS

Methods employed to meet the objectives are described in chapter 4. In particular, the basis for asking questions relating to use of health services, risk perception, vaccine outcome expectancy and perceived self-efficacy is described on page 82 and the

development of knowledge items on page 82. Furthermore, the statistical methods are described on page 98.

8.3 RESULTS

AGE AT FIRST ATTENDANCE AT SHC

The median age at first attending a SHC in the UK was 24 (IQR 20-27) (Figure 57). Table 36 shows that there was no difference in the mean age of first attending a SHC in the UK between MSM with and without detectable anogenital HPV6/11 (t=0.48, p=0.63), HPV16/18 (t=-0.21, p=0.83), serum anti-HPV16/18 (t=-1.28, p=0.20) or suspected AGW (t=-0.55, p=0.58) or a history of diagnosed AGW (t=1.73, p=0.08). MSM diagnosed with AGW at study visit reported attending a SHC for the first time an average of two years earlier (mean=22 years) than MSM without a diagnosis at visit (mean=24 years, t=2.18, p=0.03).

FIGURE 57. HISTOGRAM OF AGE AT FIRST ATTENDING A SHC IN THE UK

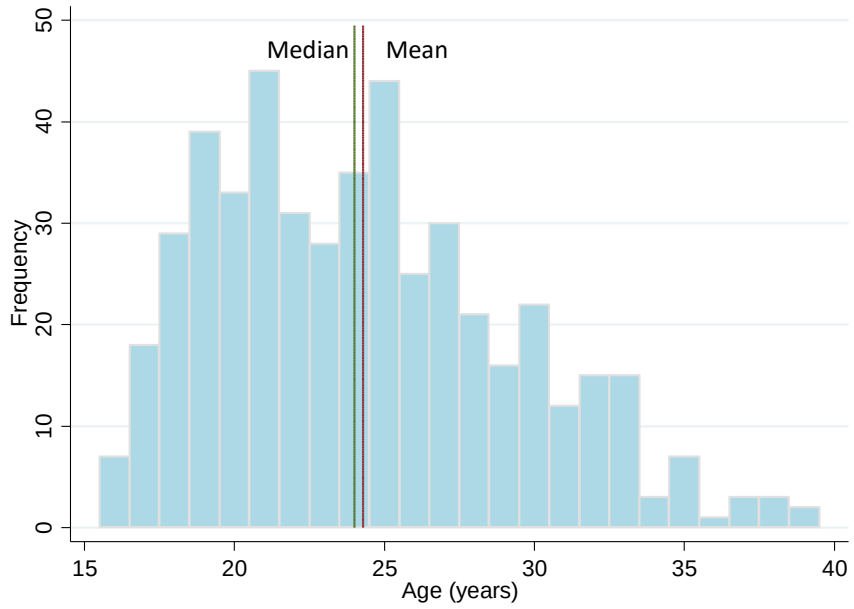


TABLE 36. MEAN AGE AT FIRST ATTENDING AN SHC IN THE UK, BY MARKERS FOR HPV EXPOSURE

Marker of HPV exposure	Mean age at first attending a SHC in the UK (95% CI)	t-statistic	p-value
Anogenital LR-HPV DNA detection			
No (n=393)	24.3 (23.9-24.8)	0.48	0.63
Yes (n=91)	24.1 (23.0-25.1)		
Anogenital bivalent-vaccine type DNA detection			
No (n=395)	24.3 (23.8-24.8)	-0.21	0.83
Yes (n=89)	24.4 (23.3-25.5)		
Anogenital quadrivalent-vaccine type DNA detection			
No (n=326)	24.3 (23.7-24.8)	-0.19	0.85
Yes (n=158)	24.4 (23.6-25.2)		
Anogenital 9-valent-vaccine type DNA detection			
No (n=264)	24.3 (23.7-24.9)	0.04	0.97
Yes (n=220)	24.3 (23.6-25.0)		
Anogenital HPV16/18 seropositivity			
No (n=317)	24.1 (23.5-24.6)	-1.28	0.20
Yes (n=163)	24.7 (23.9-25.5)		
Suspected AGW at visit			
No (n=442)	24.2 (23.8-24.7)	-0.55	0.58
Yes (n=51)	24.6 (23.2-26.1)		
Diagnosed AGW at visit			
No (n=473)	24.4 (23.9-24.8)	2.18	0.03
Yes (n=20)	21.9 (19.8-24.0)		
Diagnosed AGW in the last year			
No (n=431)	24.2 (23.8-24.7)	-0.47	0.64
Yes (n=48)	24.6 (23.1-26.1)		
History of AGW			
No (n=338)	24.5 (24.0-25.1)	1.73	0.08
Yes (n=154)	23.7 (22.9-24.4)		

Abbreviations: SHC=sexual health clinic, LR-HPV=HPV6/11, bivalent HPV=HPV16/18, quadrivalent HPV=HPV6/11/16/18, 9-valent HPV=HPV6/11/16/18/31/33/45/52/58, AGW= anogenital wart.

HPV MEASUREMENT IN FIRST TIME ATTENDERS

Of the 40 (8%) MSM who were attending a SHC in the UK for the first time when they participated in the study, five (13%) had detectable anogenital HPV6/11, seven (18%) had anogenital HPV16/18 (two with both HPV6/11 and HPV16/18), four (10%) were HPV16/18 seropositive, one attended because he suspected he had an episode of AGW, none had an AGW diagnosis, and two had an AGW diagnosis over a year ago, elsewhere. Over half

(27/40) of first-time attenders had no evidence of exposure to quadrivalent–vaccine type HPV, considering history of diagnosed AGW, anogenital HPV6/11/16/18 and seropositivity to HPV16/18.

Table 37 shows the distribution of markers for HPV exposure in first-time SHC attenders compared to repeat SHC attenders. There was no statistically significant difference in the detection of HR-HPV (OR=1.10; 95% CI 0.57-2.11) or quadrivalent-vaccine type (OR=1.48; 95% CI 0.70-3.11) DNA at anogenital sites. There was a significant difference in the proportion seropositive for HPV16/18 who were first-time attenders compared to repeat attenders (Fisher's exact p<0.05) and in the proportion reporting a history of AGW (Fisher's exact p<0.05).

TABLE 37. DISTRIBUTION OF MARKERS FOR HPV EXPOSURE, IN FIRST-TIME SHC ATTENDERS COMPARED TO REPEAT SHC ATTENDERS.

	First time attenders (N=40) n (%)	Repeat attenders n/N (%)
Anogenital HR-HPV DNA detection[a]		
No	22 (55.0)	239/454 (52.6)
Yes	18 (45.0)	215/454 (47.4)
Anogenital quadrivalent vaccine type DNA detection[a]		
No	30 (75.0)	304/454 (67.0)
Yes	10 (25.0)	150/454 (33.0)
Seropositive for HPV16/18[b]		
No	36 (90.0)	285/449 (63.5)
Yes	4 (10.0)	164/449 (36.5)
History of AGW		
No	38 (95.0)	308/462 (66.7)
Yes	2 (5.0)	154/462 (33.3)

[a]Among MSM with at least one anogenital sample adequate for PCR. [b]Among MSM with a serum specimen adequate for HPV ELISA testing.

TYPES OF HEALTH SERVICES USED BY MSM AT MMC

Table 38 shows that in MSM with survey data and an anogenital sample adequate for HPV testing, 77.1% (381/494) had visited their GP in the last year but only 43.8% (167/381) of these had disclosed their sexuality. Of the 130 MSM who had ever been treated for AGW, the large majority 116 (89.2%) were treated at a SHC, five (3.9%) were last treated at a GP, and nine (6.9%) at another service reported as "… hospital" or a doctor/clinic outside the UK. 438/502 (87.3%) of participants had received at least one dose of HBV vaccine and the median number of doses received was 3 (IQR: 2-3), including booster doses. Most HBV vaccinations (335/429; 78.1%) were administered in a SHC with 16.3% (70/429) being delivered by a GP and 7.5% (32/429) at another service, for example, in other countries.

HPV KNOWLEDGE

For each knowledge question, the proportion of respondents who selected the correct answer is displayed in Figure 59. Only 1.2% of the sample answered all nine knowledge items correctly. The median number of correct answers was 5 (IQR: 3-6; mean=4.4) (Figure 58). Difficult questions, based on lower number correctly responding, related to the efficacy and safety of the HPV vaccine.

FIGURE 58. DISTRIBUTION OF THE NUMBER OF CORRECT ANSWERS AMONG THE 487 MSM WHO ANSWERED ALL NINE KNOWLEDGE QUESTIONS

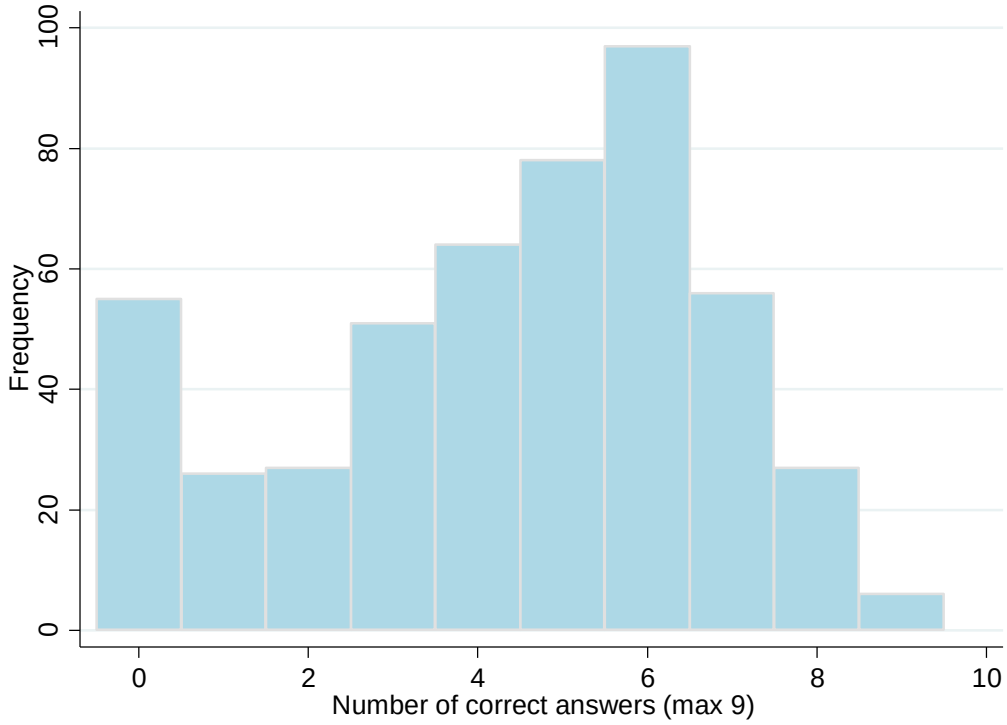
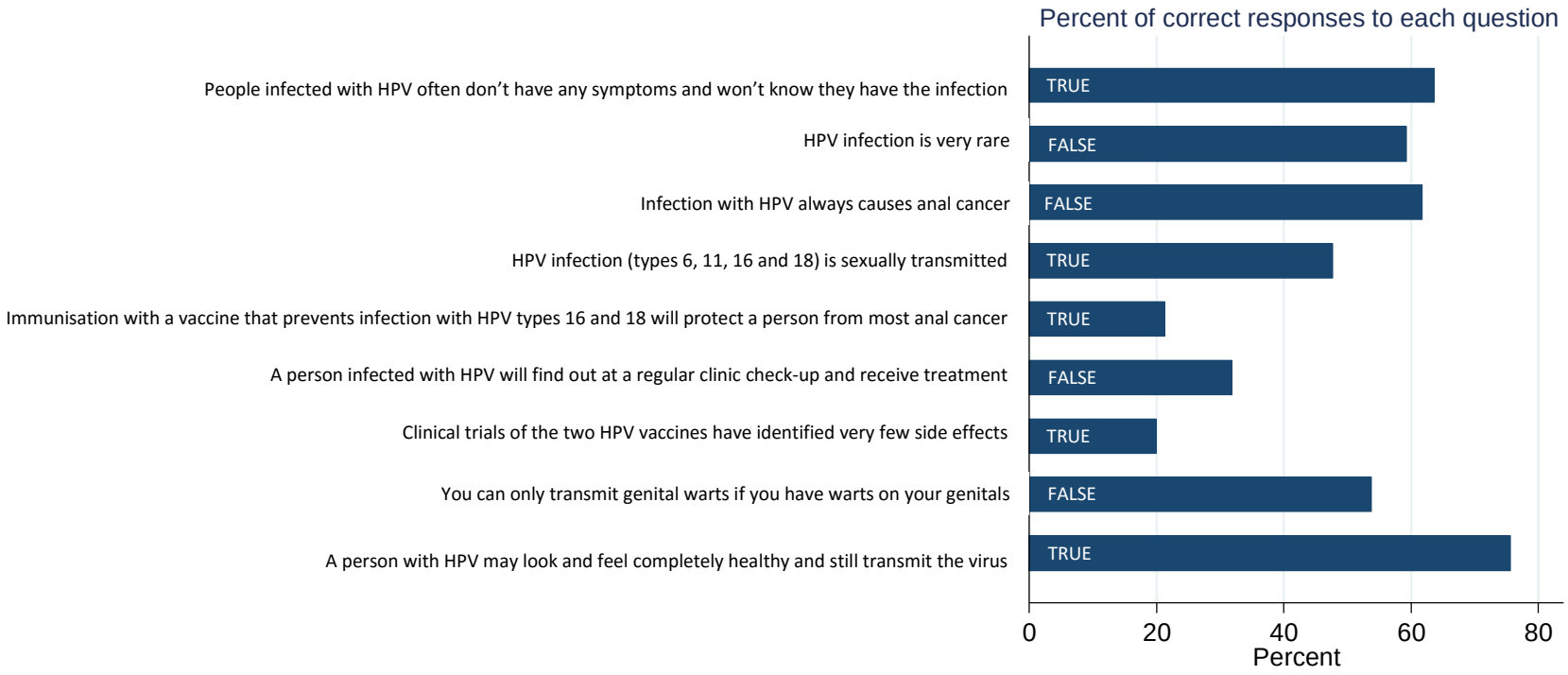


FIGURE 59. DISTRIBUTION OF ANSWERS TO THE KNOWLEDGE QUESTIONS ABOUT HPV



Association of determinants of vaccine uptake with anogenital quadrivalent-vaccine HPV type infection

There were no significant differences in health-seeking behaviour, HPV knowledge, STI risk perception, or expected vaccine acceptance between those with anogenital quadrivalent-vaccine type DNA detected and those without quadrivalent-vaccine type DNA detected (Table 38 and Table 39).

Reported likelihood of accepting the HPV vaccine

The distribution of likelihood of accepting the 3-dose, 6-month, HPV vaccine if it was offered is displayed in Figure 60. Only 21/503 (4.2%) of MSM reported that they would probably or definitely refuse the HPV vaccine if it was offered and 292/503 (58.1%) reported that they would definitely accept it. Overall, 438/502 (87.3%) had received the HBV vaccine. In MSM who would definitely or probably accept the HPV vaccine, 371/418 (88.8%) had been vaccinated for HBV, in those who would possibly accept, 49/63 (78%) had received HBV vaccine, and for those would probably not or definitely not, 14/15 (93%) and 4/6 (67%) had received the HBV vaccine, respectively. History of HBV vaccination was associated with intention for HPV vaccine uptake (nonparametric test for trend p=0.02).

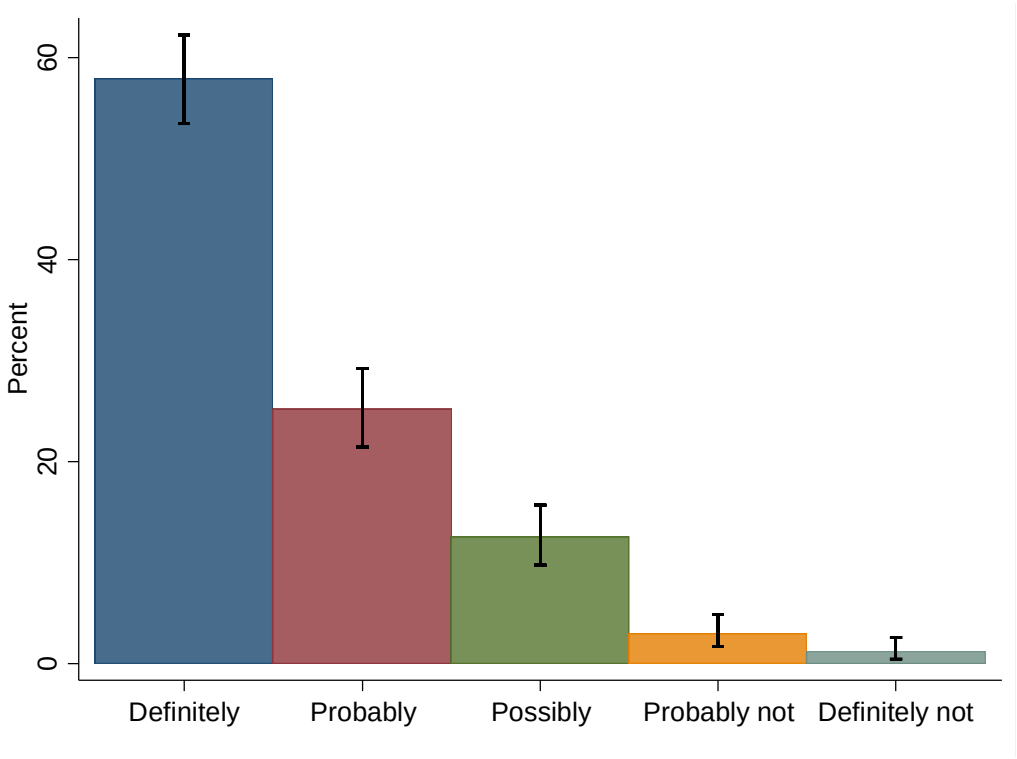
All participants were asked to give a reason for this intention. If the response was "definitely"/ "probably"/ "possibly" then 168/482 (34.9%) of MSM gave a reason but if response was "probably not" or "definitely not" then 8/15 (57%) and 4/6 (67%) gave a reason, respectively. Figure 61 displays the frequency of the groups that arose from the open-ended free text field in which participants gave their reasons for their intentions. Some participants described more than one theme.

Reasons for vaccine uptake likelihood

The most common reason, reported 98 times by the 145 MSM in the definitely/probably group, was for the expected outcomes (protection and health benefit). Reasons reported less frequently included trust in the clinic and its staff, feeling at higher risk of STIs, the benefit to others (reducing onward transmission) and general positivity, for example "no reason not to". However this group also reasoned that more information would be needed before decision-making and would need evidence on vaccine safety.

Of the 23 MSM who gave a reason for possibly accepting the vaccine, 16 required more information and 10 mentioned vaccine safety. Three MSM reasoned that they were at lower risk so did not consider themselves in need of protection. Of the 12 MSM who wouldn't accept the vaccine, and gave a reason, barriers included practical inconvenience, for example "I am leaving the UK in a few weeks", general views on vaccination, for example "I do not take vaccines", understanding the vaccine to be a trial drug, low risk perception and needing more information on vaccine safety. One man reported already having received the vaccine privately however he was not seropositive to HPV16/18.

FIGURE 60. DISTRIBUTION OF REPORTED LIKELIHOOD OF ACCEPTING THE HPV VACCINE COURSE IF A, 3-DOSE, 6-MONTH COURSE WAS OFFERED AT A SHC.



Prevalence of response category is displayed with 95% CI. Denominator= 503 respondents.

TABLE 38. HEALTH SERVICE USE, BY ANOGENITAL QUADRIVALENT-VACCINE TYPE DETECTION, IN 495 HPV-MSM-MMC PARTICIPANTS[a]

	Total		HPV Not detected[b]		HPV Detected[b]				
	N[c]	%	N[c]	%	N[c]	%	aOR	95% CI	p
Age at first attendance at UK SHC (years)									
15 to 18	54	11.2	34	10.4	20	12.7	1.27	(0.62-2.59)	0.50
19 to 24	211	43.6	147	45.1	64	40.5	0.92	(0.56-1.53)	
25 to 29	136	28.1	91	27.9	45	28.5	1	-	
30 to 35	74	15.3	46	14.1	28	17.7	1.20	(0.66-2.19)	
36 to 39	9	1.9	8	2.5	1	0.6	0.24	(0.03-2.00)	
Visited GP in last year									
No	85	17.2	60	18.0	25	15.6	1	-	0.82
Yes	381	77.1	255	76.4	126	78.8	1.18	(0.71-1.98)	
Not registered with GP	28	5.7	19	5.7	9	5.6	1.13	(0.45-2.84)	
Told GP sexuality									
No	285	61.2	191	60.6	94	62.3	1	-	0.74
Yes	181	38.8	124	39.4	57	37.8	0.93	(0.63-1.39)	
Ever had an HIV test									
No	28	5.7	20	6.0	8	5.0	1	-	0.70
Yes	466	94.3	314	94.0	152	95.0	1.18	(0.51-2.76)	
Most recent test									
In the last year	360	78.6	241	78.3	119	79.3	1	-	0.77
More than a year ago	98	21.4	67	21.8	31	20.7	0.93	(0.58-1.51)	
Ever had HBV vaccine									
No	63	12.8	47	14.1	16	10.1	1	-	0.23
Yes	430	87.2	287	85.9	143	89.9	1.46	(0.80-2.67)	
Where received the HBV vaccine									
GP	62	14.5	46	16.0	16	11.3	1	-	0.46
Sexual health clinic (SHC)	325	75.8	215	74.9	110	77.5	1.48	(0.79-2.75)	
SHC & GP	8	1.9	4	1.4	4	2.8	2.87	(0.64-12.86)	
Other	32	7.5	22	7.7	10	7.0	1.31	(0.51-3.36)	
Other & SHC	2	0.5	0	0.0	2	1.4			
Number of HBV vaccine doses received									
1	37	8.8	25	8.8	12	8.6	1	-	0.62
2	62	14.7	42	14.8	20	14.3	0.99	(0.42-2.38)	
3	138	32.6	90	31.8	48	34.3	1.11	(0.51-2.40)	
4	60	14.2	36	12.7	24	17.1	1.39	(0.59-3.31)	
Not sure	126	29.8	90	31.8	36	25.7	0.84	(0.38-1.84)	

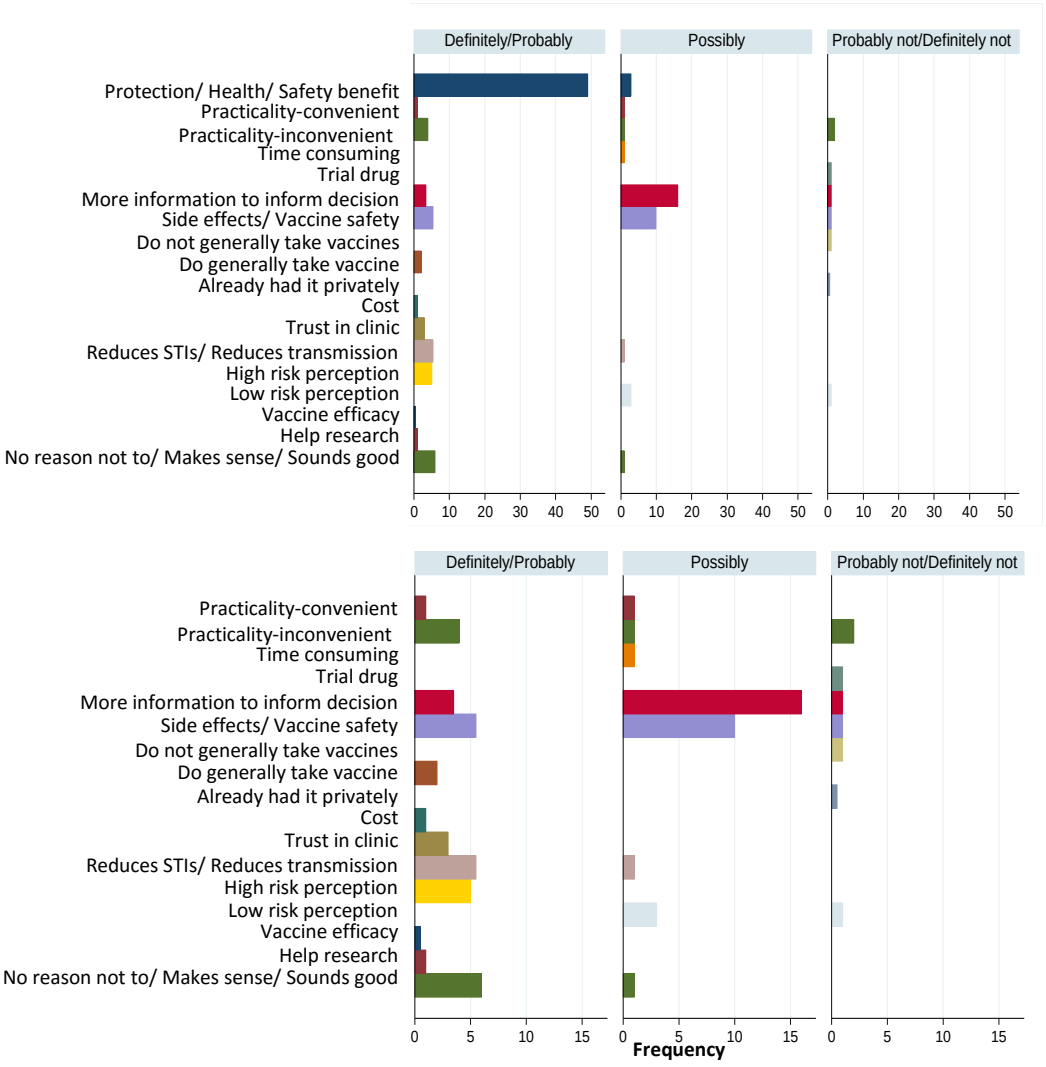
Abbreviations: aOR=age-adjusted odds ratio, SHC=sexual health clinic, GP= general practitioner, HIV= human immunodeficiency virus, HBV=hepatitis B virus. [a]A total of 495 MSM had complete survey data and at least one anogenital sample that was adequate for HPV testing. [b]Detection of HPV DNA of quadrivalent-vaccine types in any anogenital specimen. [c]Total numbers vary for each question due to missing items: survey questions that were not asked (due to routing) or not answered.

TABLE 39. HPV KNOWLEDGE, RISK PERCEPTION AND VACCINE ACCEPTANCE, BY ANOGENITAL QUADRIVALENT-VACCINE TYPE DETECTION, IN 495 HPV-MSM-MMC PARTICIPANTS[a]

	Total		HPV Not detected[b]		HPV Detected[b]				
	N[c]	%	N[c]	%	N[c]	%	aOR	95% CI	p
Knowledge about HPV									
0 to 4 correct answers	218	45.5	148	45.7	70	45.2	1	-	0.89
5 to 9 correct answers	261	54.5	176	54.3	85	54.8	1.03	(0.70-1.51)	
Risk perception-compared to other people same age									
Much below average	19	3.9	14	4.2	5	3.1	1	-	0.16
Below average	66	13.4	53	15.9	13	8.2	0.68	(0.21-2.23)	
Average	193	39.2	128	38.3	65	40.9	1.42	(0.49-4.12)	
Above average	173	35.1	114	34.1	59	37.1	1.44	(0.49-4.18)	
Much above average	42	8.5	25	7.5	17	10.7	1.89	(0.57-6.23)	
Risk perception- compared to other MSM same age									
Much below average	34	7.0	26	7.9	8	5.2	1	-	0.57
Below average	119	24.5	83	25.2	36	23.2	1.40	(0.58-3.39)	
Average	232	47.8	159	48.2	73	47.1	1.48	(0.64-3.43)	
Above average	75	15.5	46	13.9	29	18.7	2.02	(0.81-5.08)	
Much above average	25	5.2	16	4.9	9	5.8	1.84	(0.59-5.75)	
Self-perceived likelihood of accepting the 3-dose HPV vaccine schedule									
Definitely	288	58.3	186	55.7	102	63.8	1	-	0.40
Probably	124	25.1	87	26.1	37	23.1	0.78	(0.49-1.23)	
Possibly	62	12.6	47	14.1	15	9.4	0.58	(0.31-1.10)	
Probably not	14	2.8	9	2.7	5	3.1	1.01	(0.33-3.10)	
Definitely not	6	1.2	5	1.5	1	0.6	0.37	(0.04-3.17)	

Abbreviations: aOR=age-adjusted odds ratio [a]A total of 495 MSM had complete survey data and at least one anogenital sample that was adequate for HPV testing. [b]Detection of HPV DNA of quadrivalent-vaccine types in any anogenital specimen. [c]In participants with survey responses and adequate anogenital samples for HPV testing.Total numbers vary for each question due to missing items: survey questions that were not asked (due to routing) or not answered.

FIGURE 61. FREQUENCY OF REASONS CITED FOR INTENTION TO ACCEPT/NOT TO ACCEPT THE HPV VACCINE, STRATIFIED BY SELF-REPORTED LIKELIHOOD OF ACCEPTING THE VACCINE.



NB.Different X-axis scales between upper and lower panels after excluding the most common reason (protection/safety/health benefit).

8.4 KEY FINDINGS

The average age at first attendance at a SHC was 24 years, representing the earliest age, on average, at which HPV vaccination would occur, assuming that SHC service use patterns would not change due to vaccine availability. Average age of first attendance was an average of five years after the initiation of anal sex. One in three MSM aged 18 to 24 had detectable quadrivalent-vaccine type DNA. In MSM attending MMC, SHCs were the predominant service type used for AGW diagnosis and treatment and for HBV vaccine uptake.

HPV knowledge, relating to HPV vaccine outcomes and safety and to HPV risk, was low. However, MSM had strong intentions to accept the vaccine if it was offered, with reported barriers being a lack of information, particularly about vaccine safety, reflecting the findings from the knowledge questions. There remain a small minority of MSM who would not accept the vaccine, due to negative attitudes to vaccines in general.

8.5 FINDINGS IN CONTEXT

Studies examining the attitudes of MSM towards the HPV vaccine were systematically reviewed in 2014[219]. There were 18 studies identified, with only two in Europe (Italy and Sweden) and eight in the US where vaccines are not always free at the point of care as they would be in the UK's NHS. In twelve studies, only half would accept the vaccine (mean=56%, median=65%, range 0–86%), a substantially lower estimate than that reported in the HPV-MSM-MMC participants. This difference might be because the vaccine would be free in the NHS but also because HPV-MSM-MMC participants were engaged with and more likely to trust the NHS as demonstrated by their access to the clinic and their participation in the research study. This proactivity towards health and trust in the clinic (a reason cited for intending to accept the vaccine) is likely to influence the positive intentions to accept the vaccine compared to MSM who do not attend SHCs. The only study in the review that recruited from a SHC (New York) and quantified likelihood of acceptance estimated 86% would accept[220].

8.6 STRENGTHS AND LIMITATIONS

This study recruited from the potential target population for HPV vaccination and represents the only estimate, to date, of HPV vaccine uptake in MSM attending SHCs in the UK. However there is likely to be a correlation between participation in the study and attitude to health systems such as trust in the clinic and its staff, which were cited as reasons for intending to accept the vaccine. MSM who did not consent to participate have different engagement with healthcare and health research which is likely to be reflected in their attitudes to vaccination. This potential bias would result in overestimation of vaccine acceptance in the population of MSM attending SHCs. Considering the worst-case scenario, where all of the MSM who declined to take part in the study would opt out of HPV vaccination, 20% of MSM at MMC would not receive the vaccine; which would still represent high expected uptake.

In this study, reported likelihood of accepting the HPV vaccine was used as a marker for intention to accept it. In most social cognition models, intention is the strongest determinant of behaviour yet it does not directly translate into behaviour because it interacts with other determinants that were not measured in this study. For example, in the theory of planned behaviour, "perceived behavioural control" works in combination with intention to predict behaviour[221]. In this study we measured HBV vaccine uptake as a marker for predicted HPV vaccine uptake behaviour and found the gap between intention and behaviour to be only 7% (96% intention-89% HBV vaccine uptake).

9. MATHEMATICAL MODEL OF HPV16 AND ANAL CANCER IN MSM ATTENDING SEXUAL HEALTH CLINICS IN THE UK: IMPACT OF HPV VACCINATION

In this chapter, I present a preliminary estimation of vaccine effectiveness against HPV16 and related anal cancer using a static, deterministic, compartmental cohort model. I first describe the model, its parameters and underlying assumptions, before presenting results of the model output compared to the observed data followed by the expected reduction in HPV16 prevalence and anal cancer, by age, resulting from different vaccine scenarios.

9.1 OBJECTIVES

1. To develop a deterministic compartmental model of HPV16 infection and anal cancer in MSM attending SHCs in the UK that can inform other dynamic probabilistic transmission models of HPV in MSM
2. To perform a preliminary analysis to estimate the vaccine-associated reduction in HPV16 prevalence and related anal cancer incidence in MSM attending SHCs.

9.2 METHODS

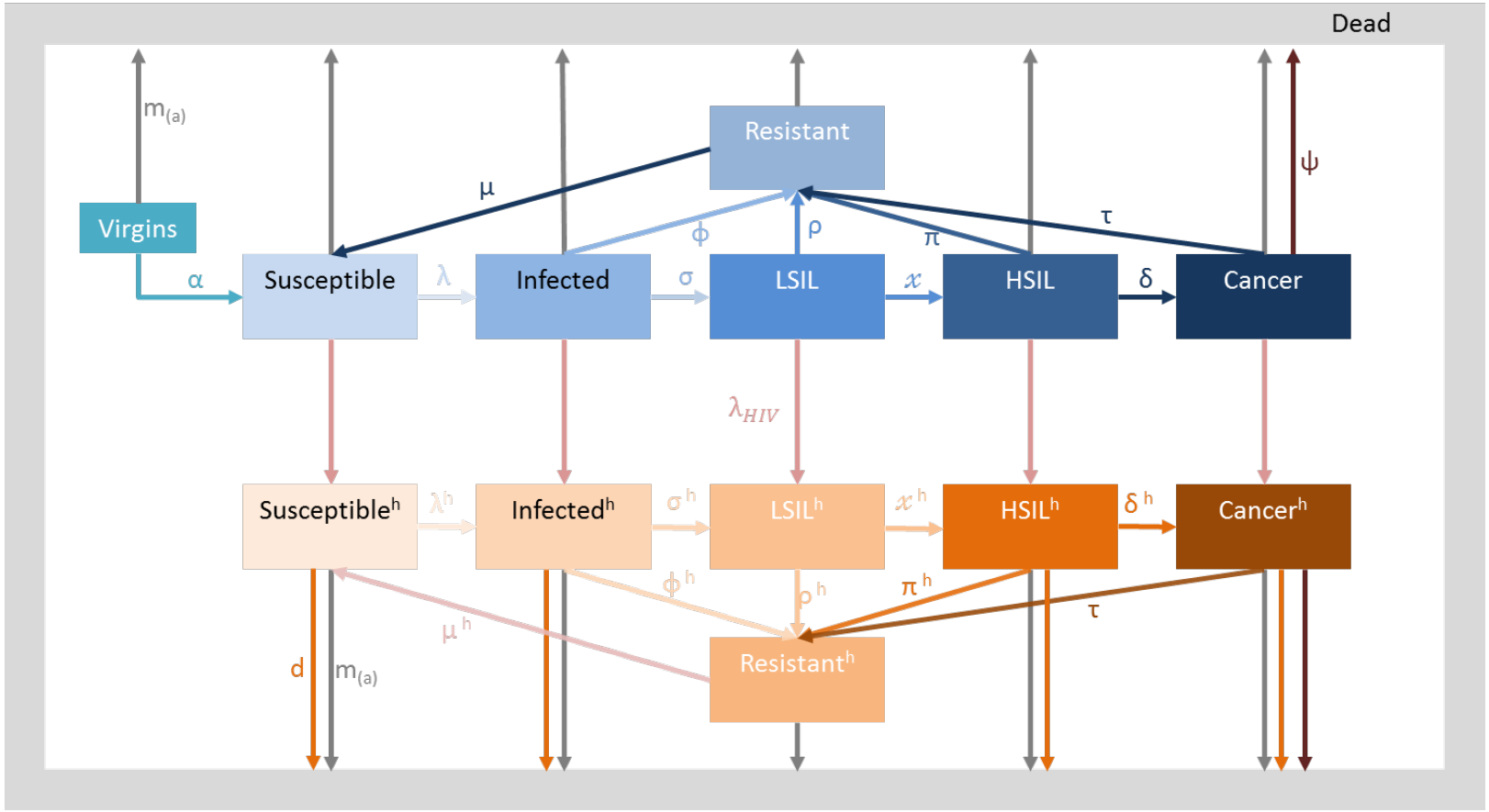
OVERVIEW

A compartmental model for anal HPV16, with progression to anal cancer, was developed. A total of 100,000 hypothetical HIV-negative boys aged ten, who would report having sex with men at least once during their lifetime, and would attend a SHC between the ages of 16 and 40, were followed in the model until age 77. Available data constrained the age ranges in the model. Model compartments represent HPV16 infection/immune status, stratified by HIV status, and, when HPV16-infected, endpoints specific to anal cancer and its precursors. The sequence of transition through model compartments, the model structure (Figure 62), was developed to represent the natural history of anal HR-HPV infection while maintaining the balance of model-complexity with utility. There was a monthly deterministic probability,

corresponding to the current compartment (i.e. no model memory), of transitioning from one compartment to the next.

Model parameter values were assigned following in-depth literature searches in 2011 and updated as and when more data became available until January 2014. Some parameter values were inferred following fitting of the model to available data. The model was calibrated to both HPV prevalence and anal cancer incidence. Data sources included the HPV-MSM-MMC study (previous chapters), age-specific prevalence estimates in MSM identified via a published systematic literature review and cancer registry data from the Office of National Statistics (ONS). Model equations and state variables can be found in Appendix V, page 312.

FIGURE 62. SCHEMATIC OF THE HPV16 AND ANAL CANCER MODEL STRUCTURE



Compartments are represented by rectangles: Infected=HPV16 infection with normal or ASCUS histology, LSIL= low-grade squamous intraepithelial lesion, HSIL= high-grade squamous intraepithelial lesion, Cancer=anal squamous cell carcinoma and superscript h (^{h}) represents HIV infection. Transition parameters, represented by arrows, are defined in the following sections.

DEMOGRAPHIC FACTORS

The size of the closed model population was only influenced by mortality. From the age of 10, boys/men had an age-specific risk of mortality, parameterised from ONS data, which determined the transition into the "dead" compartment (Table 40). See below for the additional risk of mortality associated with HIV and anal cancer.

TABLE 40. DEMOGRAPHIC AND ANAL SEX DEBUT PARAMETER NAMES, DEFINITIONS, VALUES AND DATA SOURCES

Parameter name	Definition	Default value	Source
$m_{(a)}$	Natural mortality	Age-specific	2005-2007 data from UK life tables, Office for National Statistics, UK[222]
α	Probability of having anal sex with another man for the first time in lifetime between the a and a+1	8.9×10^{-3}	See section entitled "Initiation of anal sex", below, for details.

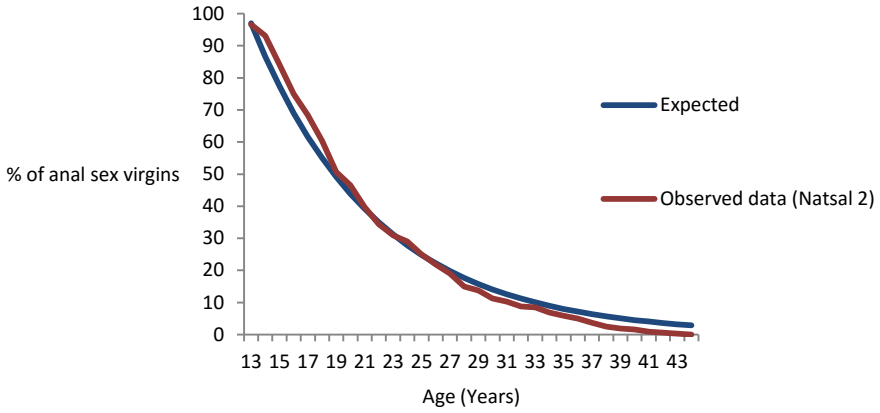
INITIATION OF ANAL SEX

At age 10, all boys were assumed to be HPV-naïve, HIV-negative with no sexual history and were in the "virgins" compartment with potential to initiate anal sex. All men in the model were assumed to have sex exclusively with men. Age of anal sex debut, collected in respondents older than 12 in the Natsal-2 survey, was used to derive the probability of transitioning from the "virgin" into the "susceptible" compartment (α; Table 40). The expected proportion of "virgins" (V) was assumed to decline annually at a constant rate, α, as shown in Equation 3, where a equals age in years. The value of annual α was estimated by fitting age-specific expected proportion of "virgins" in men who will have sex with men to that observed in Natsal-2 by minimising the sum of squares of the differences (Figure 63). Annual transition probabilities were converted to monthly using: $1\text{-}e^{\frac{-\alpha}{12}}$

EQUATION 3. AGE RELATIONSHIP OF EXPECTED PROPORTION OF "VIRGINS"

$$V_a = V_{a-1} - \alpha V_{a-1}$$

FIGURE 63. COMPARING OBSERVED AND EXPECTED PERCENTAGE OF ANAL SEX VIRGINS, BY AGE, AT THE MINIMUM SUM OF SQUARED DIFFERENCES

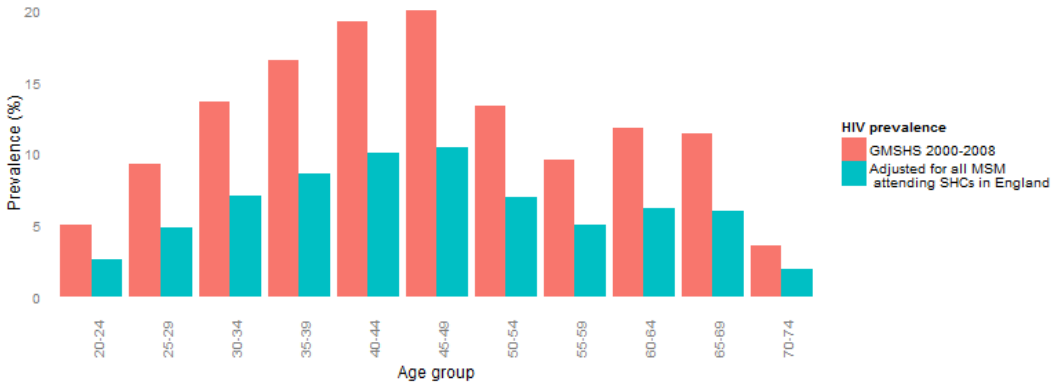


Expected proportion of virgins in boys who will have sex with men fitted to observed behavioural data on initiation of anal sex from Natsal-2. The minimum value of sum of squares of the differences was achieved when α =8.9x10^{-3}/ month.

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

HIV-related parameter names, definitions, values and sources are displayed in Table 41. Observed age-specific HIV prevalence was derived by applying the age distribution of HIV prevalence in the GMSHS between 2000 and 2008[223] to the estimated aggregate prevalence of HIV infection in MSM (including undiagnosed), aged 20-44 years, attending SHCs in England and Wales (6.7%)[224]. Prevalence was assumed to remain at this level after 44 years (Figure 64).

FIGURE 64. HIV PREVALENCE IN MSM ATTENDING SHCS IN ENGLAND, ADJUSTED TO THE AGE PROFILE OF HIV PREVALENCE IN MSM IN PUBS AND CLUBS IN LONDON 2000-2008.



In the model, HIV infection did not occur until age 18 and expected age-specific HIV prevalence was fitted to observed prevalence by changing the parameters of a gamma distribution of the force of infection (FOI) for HIV. HIV incidence per month was calculated by multiplying the FOI and the number of HIV-negative MSM that month.

HIV-positive MSM were at additional risk of dying (d; HIV-specific mortality rate) representing HIV-related deaths. HPV infection and disease progression parameters were modified by HIV status but HIV FOIs were unaffected by HPV status.

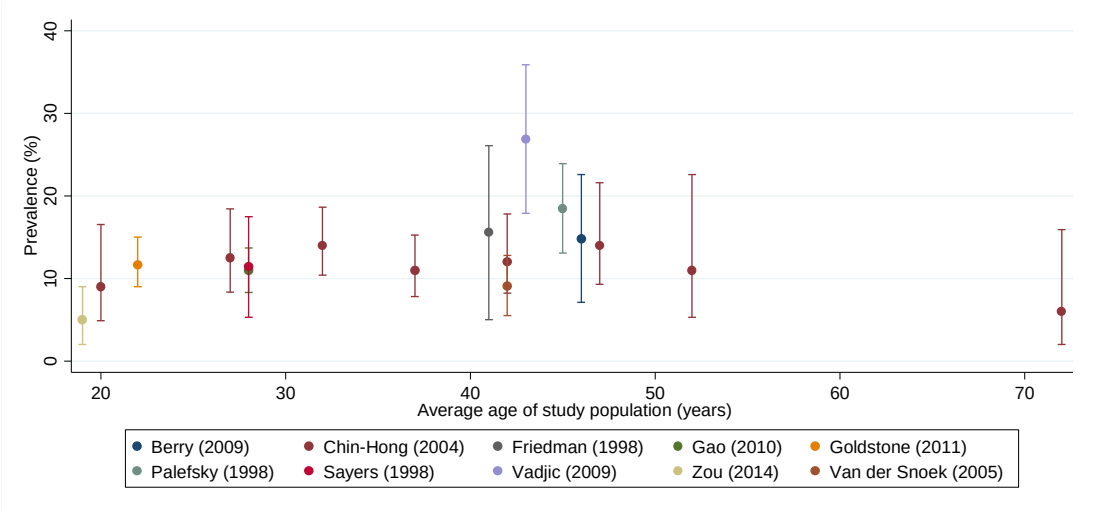
TABLE 41. HIV PARAMETER NAMES, DEFINITIONS, VALUES AND DATA SOURCES

Name	Definition	Default value	Source
λ_{HIV}	Probability of acquiring HIV infection between a and a+1	Gamma-distributed by age: values of alpha and beta parameters of the gamma distribution were estimated during calibration by fitting to observed age-specific HIV prevalence, see section entitled "Human immunodeficiency virus infection", above, for details.	
d	Probability of HIV-related death between a and a+1	$5.1x10^{-4}$	Bhaskaran *et al* estimated HIV-associated fatality among HIV-positive individuals, at risk between 2004-2006, in a large multinational collaboration of HIV seroconverter cohorts (CASCADE). Mortality following HIV seroconversion was compared with expected mortality, calculated by applying general population death rates matched on demographic factors[225]. Monthly parameter value derived from 6.1/1000 excess deaths being attributed to HIV per year by dividing by 12.

HUMAN PAPILLOMAVIRUS INFECTION

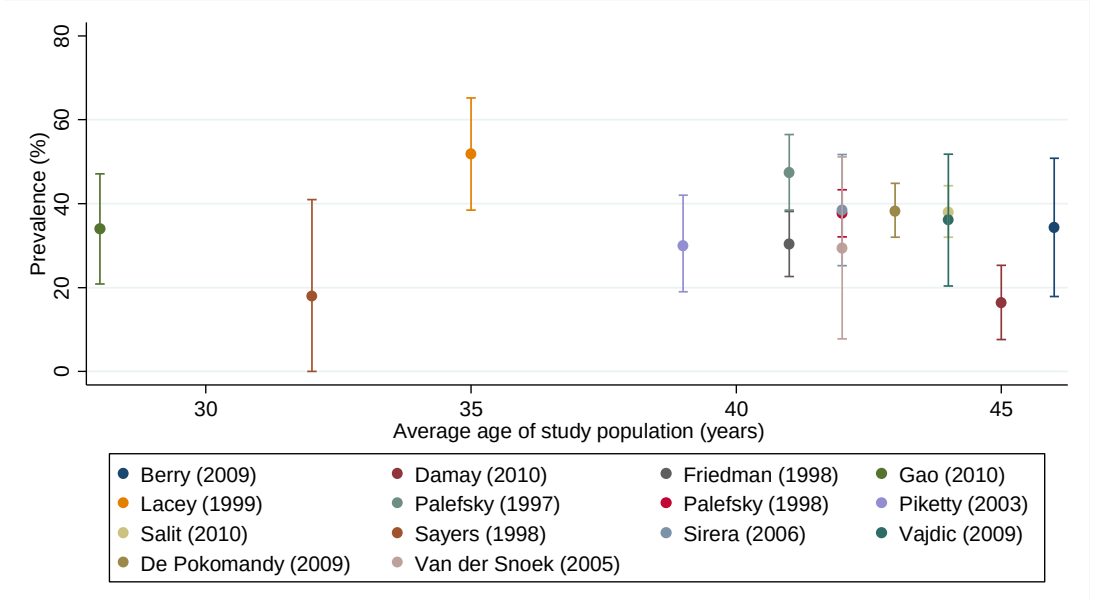
HPV infection related parameter names, definitions, values and sources are displayed in Table 42. After initiating anal sex activity, represented by transition into the "susceptible" to HPV16 compartment, the risk of becoming infected with HPV (FOI) was age specific and HIV status specific. The FOI for HPV16 was gamma distributed by age and the parameter values (α and β) were determined by fitting the proportion of MSM in infected compartments (including those with disease progression) in the number of alive MSM to the observed anal HPV16 prevalence (Figure 31-page 124, Figure 65 and Figure 66) using maximum likelihood estimation (MLE) (Model calibration, page 222).

FIGURE 65. OBSERVED AGE-SPECIFIC ESTIMATES OF ANAL HPV16 PREVALENCE IN INTERNATIONAL POPULATIONS OF HIV-NEGATIVE MSM



HPV16 estimates are plotted at the average age of the study population, or age group if age-specific estimates were available. During calibration, observed prevalence was assumed across the age range of each study. Berry (2009)[171], Chin-Hong (2004)[54], Friedman (1998)[56], Gao (2010)[174], Goldstone (2011)[193], Palefsky (1998)[57], Sayers (1998)[60], Vajdic (2009)[84], Zou (2014)[122] and Van der Snoek (2005)[226].

FIGURE 66. OBSERVED AGE-SPECIFIC ESTIMATES OF ANAL HPV16 PREVALENCE IN INTERNATIONAL POPULATIONS OF HIV-POSITIVE MSM



NB. Axis scales differ from Figure 65. Berry (2009)[171], Damay (2010)[182], Friedman (1998)[56], Gao (2010)[174], Lacey (1999)[59],Palefsky (1997)[64], Palefsky (1998)[57], Piketty (2003)[227], Salit (2010)[228], Sayers (1998)[60], Sirera (2006)[63], Vajdic (2009)[84], de Pokomandy (2009)[93] and Van der Snoek (2005)[226].

TABLE 42. HPV INFECTION PARAMETER NAMES, DEFINITIONS, VALUES AND DATA SOURCES

Parameter name	Definition	Default value	Source
$\lambda_{HPV,}$ λ_{HPVh}	HIV-dependent risk of becoming infected (I) with HPV16 at time a+1 if susceptible at time a.	Gamma-distributed by age: values of alpha and beta parameters of the gamma distribution were estimated during calibration as described in section entitled "Model calibration", below	
μ	HIV-independent probability of effective natural immunity to HPV16 waning in 1 month.	0.5	Duration of effective natural immunity is unknown. See section entitled "Scenario analyses", below, for details on varying this parameter from the default value of 0.5 to 0, 0.25 and 1 (representing duration of natural immunity ranging from 1 month-lifelong).
ϕ, ϕ_h	HIV-dependent probability of resolving an HPV16 infection, with normal or ASCUS cytology/histology between a and a+1	0.065, 0.008	See Box 8, below, for details
ρ, ρ_h	HIV-dependent probability of clearing HPV16 infection, with detectable LSIL/LGAIN, between a and a+1.	0.003, 0.001	
π, π_h	HIV-dependent probability of clearing an HPV16 infection, with detectable HSIL/HGAIN, between a and a+1.	0.013, 0.001	

Resolution of infections occurred with a probability that was independent of age but dependent on HIV status (Box 8) and resulted in a period of natural immunity represented by the "resistant" compartment. There was an age-independent probability of waning natural immunity (see section entitled "Scenario analyses", below, page 222) when MSM returned to the "susceptible" compartment. No partial immunity was modelled.

BOX 8. ESTIMATION OF THE CLEARANCE RATE OF HPV16 INFECTION

Total anal HPV16 infection clearance rate:

HIV-negative MSM

MSM in the HIM study (N=156), that recruited from low HIV prevalence communities in Mexico, Florida and Brazil (2005), were assessed for type-specific clearance, which was defined as a anal type-specific HPV infection with prevalent HPV16 at enrolment (N=11) that was then undetectable at the 6-month visit (N=3) [229]. Therefore, in HIV-negative MSM, the total clearance rate from HPV 16 infections (including those associated with cancer pre-cursors) was estimated at 0.045/month.

HIV-positive MSM

Clearance rate was assessed in HIV-positive MSM, participating in the HIPVIRG cohort study, which recruited from 4 HIV clinics in Montreal, Canada (2002-2005). Clearance of a prevalent anal type-specific HPV infection at baseline was considered to have occurred at the first follow-up visit at which that infection was no longer detected Clearance and incidence rates by type were determined using appropriate incidence density calculation based on person-time denominators (person-months). At enrolment, 92 MSM had HPV16 detected and 28 of these cleared during the 2286 person-months of follow-up[93]. Therefore, in HIV-positive MSM, the total clearance rate from both clinically undetectable and detectable HPV 16 infections was estimated at 0.012 /month.

Relative contribution of HPV16 infection stages (I, LSIL and HSIL) to clearance rate:

Overall prevalence

A meta-analysis estimated the pooled prevalence on HPV16, LSIL and HSIL by HIV status in MSM. The pooled prevalence of HPV16 infection was 12.5% in HIV-negative and 35.4% in HIV-positive MSM. This estimate was assumed to include infections associated with cancer pre-cursors. The pooled prevalence estimate of LSIL was 6.6% in HIV-negative and 27.5% in HIV-positive MSM and of HSIL was 2.7% (HIV-negative) and 6.7% (HIV-positive)[230].

Proportion of LSIL/HSIL associated with HPV16

There have been two systematic reviews of the literature of the HPV-association with anal cancer and its pre-cursors. The first, up until July 2007, was not stratified by HIV status but did have an estimate for the proportion of LSIL associated with HPV16 of 7.3% in men[32]. The other, searching records until 2008[33], estimated that 76.6% of HSIL was HPV16-associated in HIV-negative (or unreported) male populations and 55.3% in HIV-positive male populations.

Prevalence of HPV16-associated HSIL/LSIL

Therefore, it was assumed that the prevalence of HSIL adjusted for HPV16-association was 0.76*2.7=2.05% for HIV-negative MSM and 0.55*6.7=5.1% for HIV-positive MSM.

It was assumed that the prevalence for HPV16-associated LSIL was 0.07*6.6=0.46% in HIV-negative MSM and 0.07*27.5=1.9% in HIV-positive MSM.

Prevalence of HPV16-associated with normal/ASCUS cytology/histology

It follows that the ratio of HPV16 infection prevalence of normal/ASCUS: LSIL: HSIL was 9.99:0.46:2.05 in HIV-negative MSM and 29.8:1.9:3.7 in HIV-positive MSM.

Clearance rate calculations. clearance probability per month for HPV16 infection can be calculated as follows:

with normal/ASCUS cytology or histology= (Prevalence of I/Total HPV16 prevalence)*total clearance rate

ϕ =(9.99/12.5)*0.045=0.065, ϕ_h =(29.8/35.4)*0.01=0.008

With associated LSIL= (Prevalence of LSIL/Total HPV16 prevalence)*total clearance rate

ρ =(0.46/12.5)*0.045=0.003, ρ_h=(1.9/35.4)*0.012=0.001

With associated HSIL= (Prevalence of HSIL/Total HPV16 prevalence)*total clearance rate

π =(2.05/12.5)*0.045=0.013, π_h==(3.7/35.4)*0.012=0.001

ANAL CANCER DEVELOPMENT

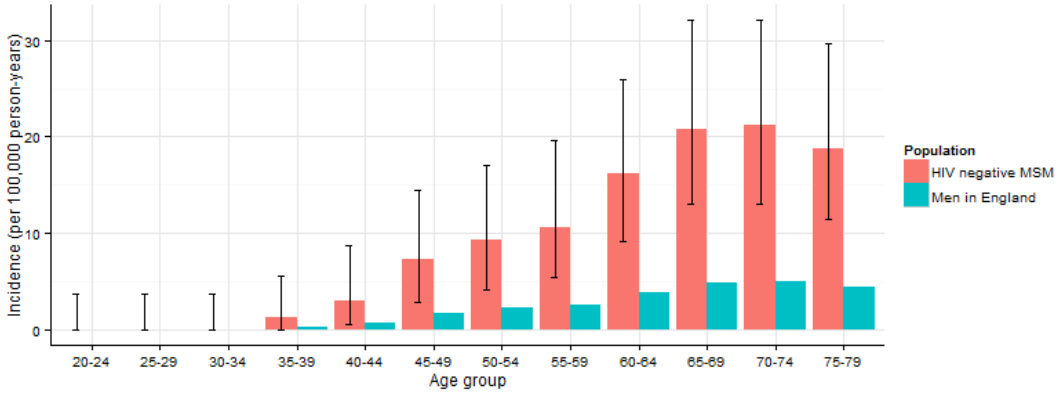
Anal cancer related parameters are displayed in Table 43. Following infection, MSM could progress sequentially to compartments representing low-grade or high-grade lesions, or revert to the immune state ("resistant"), depending on a set of age-independent parameters. However, the progression from a high-grade lesion to anal cancer was assumed to be age-associated: *p(HSIL* to anal cancer)=$\mu_1 e^{(\mu_2 a)}$. Expected anal cancer incidence was calculated by multiplying the number of new cases per 100,000 months by the inverse probability of anal cancer being attributed to HPV16 (SCC_{16}). Values for μ were estimated by fitting the expected to the observed anal cancer incidence using MLE (Model calibration, page 222).

TABLE 43. ANAL CANCER PARAMETER DEFINITIONS AND DATA SOURCES

Name	Definition	Default value	Source
σ, σ_h	The probability a man develops LSIL/LGAIN at time a+1 if he HPV16 infection (I, I^h) at time a.	0.006, 0.028	Derived from annual transition probabilities in Czoski-Murray *et al*[231] which are based on data from Palefsky *et al*, 1998[73]. Annual transition from normal/ ASCUS to LGAIN if HIV-negative= 0.079 and if HIV-positive=0.338.
x, x_h	The probability a man develops HSIL/HGAIN at time a+1 if he had LSIL/LGAIN (L, L^h) at time a.	0.013, 0.018	Derived from annual transition probabilities in Czoski-Murray *et al*[231] (Box 9).
$\delta_{(a)}, \delta_{h(a)}$	HIV-dependent probability of developing cancer at time a+1 if had HSIL/HGAIN (H) at time a.	Age-dependent: mu1*exp^(mu2*age) Values of mu estimated via calibration	
SCC_{16}	Proportion of cancer cases caused by HPV16	0.761	De Vuyst *et al.*[33] and Abramowitz *et al* have similar estimates. No significant difference between HIV-negative and HIV-positive[232].
ψ	Case fatality rate for anal cancer	0.004	Risk of dying from anal cancer was 36.2% at 12-years in the treated arm of an RCT of anal cancer treatment conducted in the UK[233]. Monthly risk was calculated (assuming a constant probability of dying over the 12 years), as follows: Annual=0.362/12 Monthly=0.362/(12x12)
τ=1- ψ	HIV-independent probability of surviving anal cancer between a and a+1	0.996	It was assumed that survival coincides with clearance of HPV. It was assumed that all anal cancers are diagnosed and treated

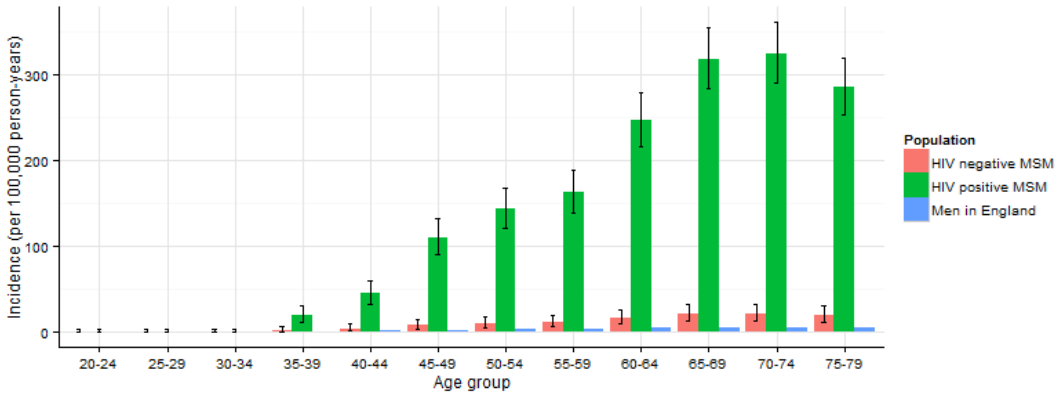
The cancer registry for England 2010[234], did not collect behavioural or sexual orientation data to determine the observed incidence of anal cancer specific to MSM. The age-distribution of anal cancer incidence in all men in England in 2010 was applied to pooled estimates for anal cancer incidence in HIV-negative (Figure 67) and HIV-positive MSM (Figure 68) from a global meta-analysis of anal cancer incidence in MSM (Box 10)[230]. Poisson distributed 95% confidence intervals were determined around the observed counts of anal cancer in 100,000 person years using STATA v13.1.

FIGURE 67. OBSERVED AGE-SPECIFIC ANAL CANCER INCIDENCE ESTIMATES IN HIV-NEGATIVE MSM IN THE UK, COMPARED TO MEN IN ENGLAND



Age-specific weights, derived from cancer registry estimates for anal cancer incidence in men, were attached to the aggregate estimate of anal cancer incidence in HIV-negative MSM (Box 10), to provide age-specific observed anal cancer incidence. Poisson-distributed 95% CI.

FIGURE 68. OBSERVED AGE-SPECIFIC ANAL CANCER INCIDENCE ESTIMATES IN MSM IN THE UK, COMPARED TO MEN IN ENGLAND, BY HIV STATUS



Due to inconsistent referral patterns from primary care services in the UK, anal cancer onset was assumed to coincide with diagnosis and treatment, which informed the parameters for

additional risk of anal cancer-related mortality and probability of recovering from anal cancer. Recovery was represented by transition to the "resistant" compartment, which assumed that recovery coincided with clearing of the HPV16 infection. Relapse was not modelled. Men with anal cancer were not offered the vaccine.

BOX 9. SOURCE OF PARAMETER VALUES FOR DEVELOPING HGAIN/HSIL

The monthly probability of developing HSIL/HGAIN from LSIL/LGAIN was calculated by Czoski-Murray *et al* (2010) [231].

Calculations were based on data from the San Francisco cohort of MSM, presented by Palefsky et al (2008) [73].

Person-years at risk were estimated assuming:

- Men who develop HGAIN had half of the follow-up of those who do not develop HGAIN
- Half of the observed cases of HGAIN (in individuals with no AIN at baseline) experienced prior LG-AIN.

Annual incidence rates for HG-AIN by HIV status

	n	No HGAIN	HGAIN	Person-years	Person-years at risk: Per non-HGAIN case	Person-years at risk: Per HGAIN case
Summary data						
HIV negative	221	188	33	671	3.3	1.65
HIV positive	277	170	107	593	2.7	1.35

LGAIN to HGAIN annual transition probabilities

LSIL at baseline	n	No HGAIN	HGAIN	Total person-years at risk: Mean
HIV negative	17	10	7	0.158
HIV positive	90	43	47	0.215

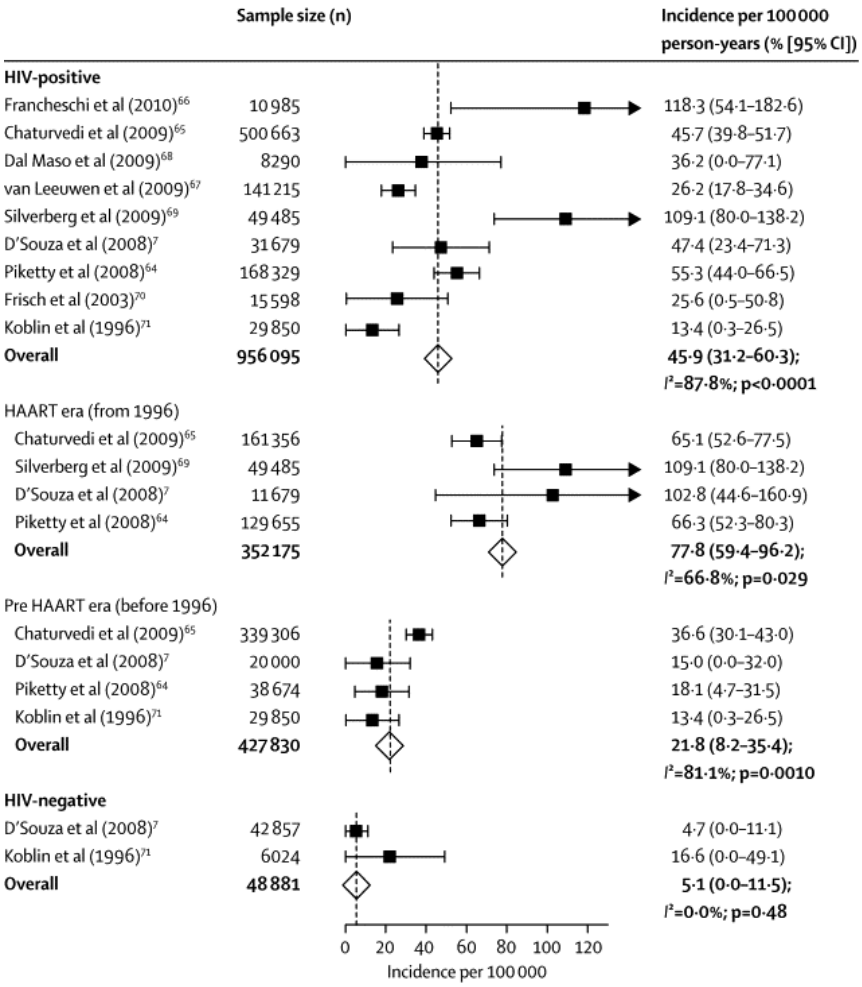
Source: Czoski-Murray *et al* (2010) [231]. Abbreviations: HGAIN=High grade anal intraepithelial neoplasia, LGAIN=Low grade AIN, LSIL= Low grade squamous intraepithelial lesion

$$x = \frac{0.158}{12} = 0.013$$

$$x_h = \frac{0.215}{12} = 0.018$$

BOX 10. ANAL CANCER INCIDENCE ESTIMATES FROM A RANDOM-EFFECTS META-ANALYSIS OF STUDIES IN HIV-NEGATIVE AND HIV-POSITIVE MSM POPULATIONS

A systematic review and meta-analysis in 2012 identified two studies of anal cancer incidence in HIV-negative MSM giving a pooled estimate of 5.1/100,000 person years compared to that from nine studies in HIV-positive MSM of 45.9/100,000 person years. Incidence in HIV-positive MSM has risen from 21.8/100,000 person years since the introduction of highly active anti-retroviral therapy (HAART) in 1996 to 77.8/100,000 person years which is attributed to the reduction in HIV-related mortality resulting in a longer period at risk of anal cancer[230].



Source: Machalek *et al.* (2012)[230]

SHC ATTENDANCE AND VACCINATION

In all scenarios both HIV-negative and HIV-positive MSM populations were eligible for vaccination. Vaccine coverage depended on SHC attendance rate which was modelled in two scenarios in HIV-negative MSM: first-time attendance and at first time or any subsequent attendance (any attendance). For first-time attendance only, the age-specific probability of attending a SHC for the first time was parameterised using data from the HPV in MSM study (chapter 7). A six-month lag was introduced to represent the delay in completing the vaccine dosing schedule. For the scenario in which HIV-negative MSM were offered the vaccine at any attendance (including first time), an average period of one year between attendances was assumed. HIV-positive MSM were offered the vaccine at any visit. It was assumed that in 76% of HIV-positive MSM the diagnosis had been made and they attended a SHC/HIV clinic 7.3 times per year[23,235]. Dosing schedule period was not modelled in scenarios where vaccine was offered at any attendance.

Likelihood of accepting the vaccine, if offered during a SHC/HIV clinic attendance, was estimated from the HPV in MSM study as 96% (chapter 7). All MSM were assumed to complete the 3-dose vaccine course. If MSM received the vaccine, they either transitioned into vaccine success (effectively immunised) or vaccine failure (vaccinated but not immune) compartments with probabilities of vaccine efficacy (VE) and 1-VE, respectively. The course and probability of HPV infection was unaltered in MSM in whom the vaccine was not effective.

Effective vaccination resulted in MSM in the uninfected (“susceptible”, “virgin” and “resistant”) compartments transitioning to corresponding “vaccine success” compartments where there was no risk of HPV infection. The course of infection was unaltered for MSM in the infected compartments who responded successfully to vaccination, but following recovery, they remained in “vaccine success” compartments representing immunity to re-infection.

Vaccine immunity was assumed to wane independently of natural immunity, when men transit from a “vaccine success” compartment to the corresponding “vaccine failure”

compartment with a probability of one divided by average duration of effective vaccine immunity.

MODEL CALIBRATION

It was assumed that anal HPV16 DNA would be detected for all infected states in observed prevalence estimates. Expected HPV16 prevalence was therefore equal to the sum of all infected compartments in the total alive population. Expected age-specific HPV16 prevalence, HIV prevalence and anal cancer incidence were simultaneously deterministically fitted to all observed estimates by minimising the negative log likelihood (Box 11) using the generalized reduced gradient (GRG) nonlinear solving method in Microsoft Office Excel's add-in program, Solver.

BOX 11. LIKELIHOOD CALCULATIONS

	likelihood calculation	Negative log likelihood	
Binomial (prevalence)	$p_i^{x_i}(1-p_i)^{n_i-x_i}$	$-\sum_{i=1}^{N} x_i \ln p_i + (n_i - x_i)\ln(1-p_i)$	p=Observed prevalence x=Number with HPV16 infection n=Sample size i=age-specific observed estimate N=Number of age-specific observed estimates
Poisson (anal cancer incidence)	$\frac{\lambda^{\kappa}}{\kappa!}e^{-\lambda}$	$-\sum \kappa \ln \lambda - \lambda - \ln \kappa!$	λ= number of cancers in model in age range (cohort of 100,000) κ =count= number of cancers in cancer registry data in age range/100,000

SCENARIO ANALYSES

Due to scarcity of data, uncertainty was introduced to the model from natural history parameters, particularly, the duration of effective natural immunity. The monthly probability of losing natural resistance (μ) was varied in scenarios (0, 0.25, 0.5, 0.75 and 1),

with re-calibration for each scenario, to examine the effect on expected anal cancer incidence and HPV16 prevalence.

VACCINE SCENARIOS

Vaccine efficacy against HPV16 infection was modelled at 50% (MSM in the intention-to-treat analysis with history of HPV infection), 75% and 100%. Average duration of vaccine-induced effective immunity was modelled at 20, 40, 60 and 1000 years (lifelong).

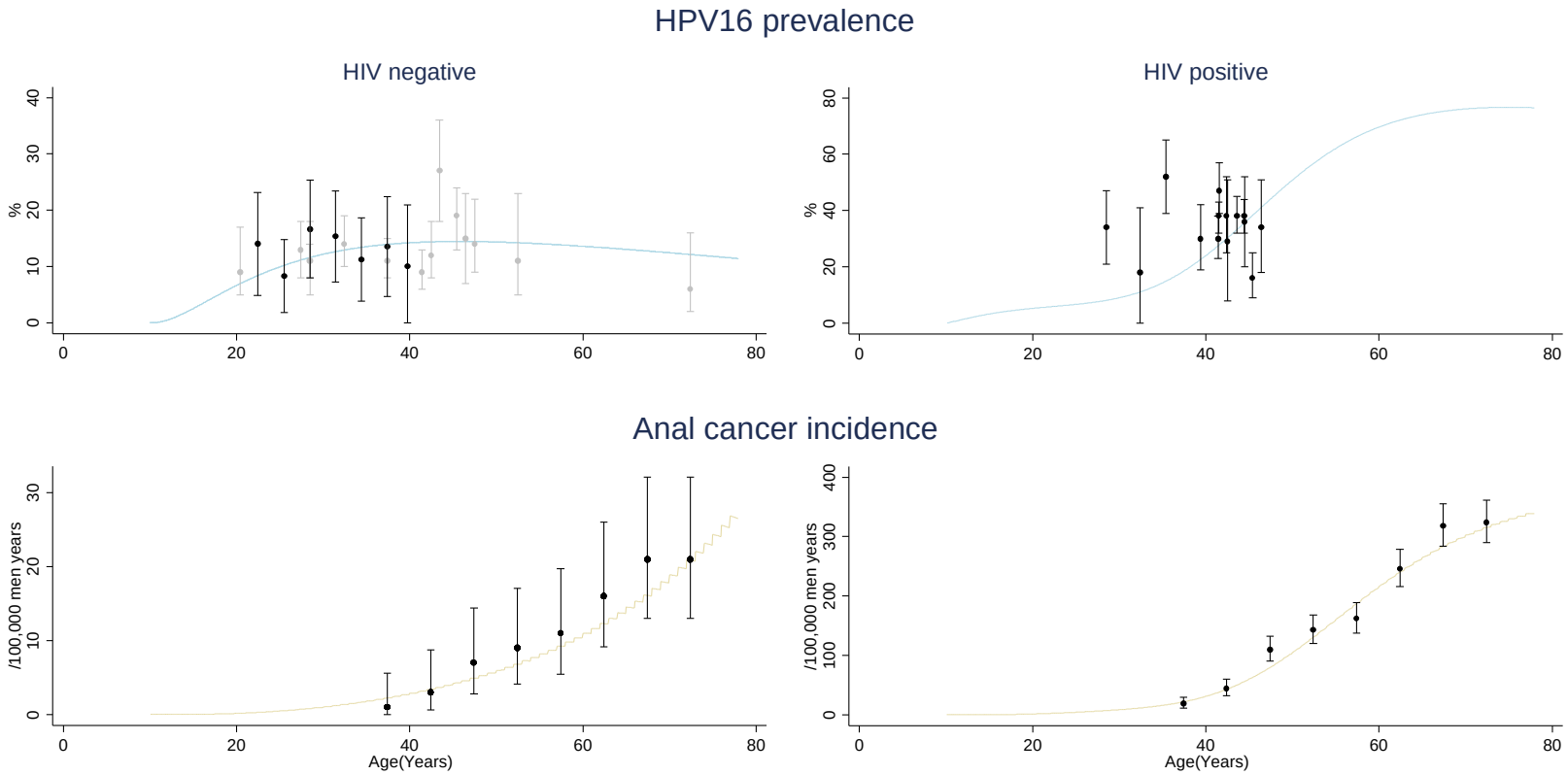
9.3 RESULTS

CALIBRATION

The comparison between observed and modelled anal cancer incidence and HPV16 prevalence are displayed in Figure 69 and between observed and modelled HIV prevalence in Figure 70. The modelled mean HPV16 prevalence in HIV-negative MSM was 11.3%. Prevalence increased with age, peaked at 14.4% at 46 years, and thereafter declined with age to 11.4% at 77 years. The mean prevalence in HIV-positive MSM was 38.0%. Prevalence was underestimated by the model in HIV-positive MSM aged 18-40 years (mean 8.3%), compared to the estimate of 29.6% in the same age-group in HIV-positive MSM in the HPV-MSM-MMC study. Above 45 years, where no observed estimates were available to restrain the model, the estimated HPV16 prevalence in HIV-positive MSM was very high years (mean 66.2%).

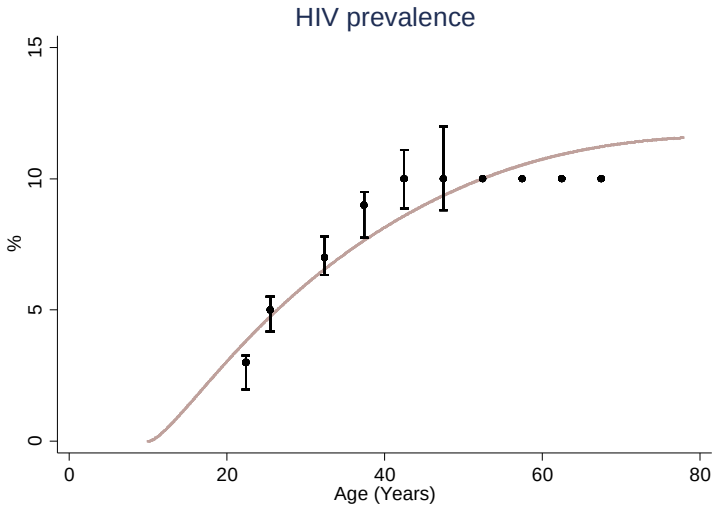
Mean anal cancer incidence was 7 and 112 per 100,000 person years for HIV-negative and HIV-positive MSM, respectively. In MSM aged 60 years and older, incidence was 18/100,000 years for HIV-negative and 288/100,000 person years for HIV-positive MSM. Modelled mean HIV prevalence was 7.7%.

FIGURE 69. COMPARISON OF MODEL OUTPUT AND OBSERVED ESTIMATES FOR ANAL CANCER INCIDENCE AND ANAL HPV16 PREVALENCE



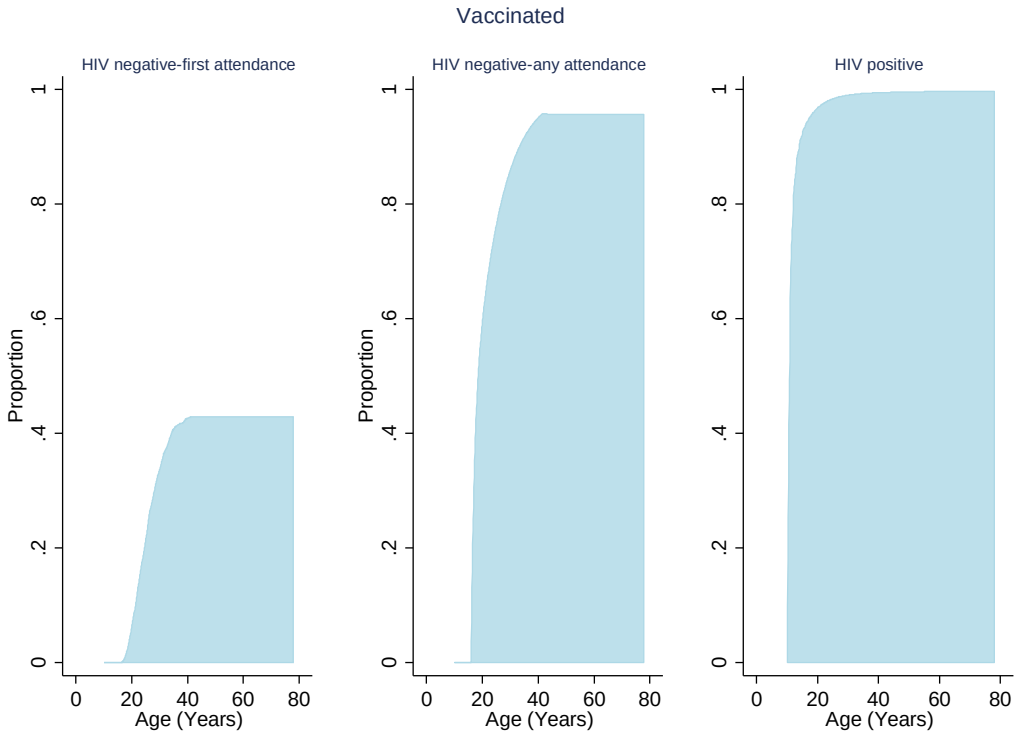
Model outputs (expected) are displayed as lines and observed estimates are displayed as points with 95% CIs. For observed HIV-negative HPV16 prevalence, black points represent estimates from the HPV-MSM-MMC study and grey points represent estimates from other published studies. Anal cancer observed estimates as in Figure 68, page 218.

FIGURE 70. COMPARISON OF MODEL OUTPUT AND OBSERVED ESTIMATES FOR HIV PREVALENCE



Observed estimates displayed with 95% confidence intervals calculated using the binomial exact method.

FIGURE 71. PROPORTION OF MSM ATTENDING A SEXUAL HEALTH CLINIC WHO WOULD RECEIVE THE HPV VACCINE, BY AGE

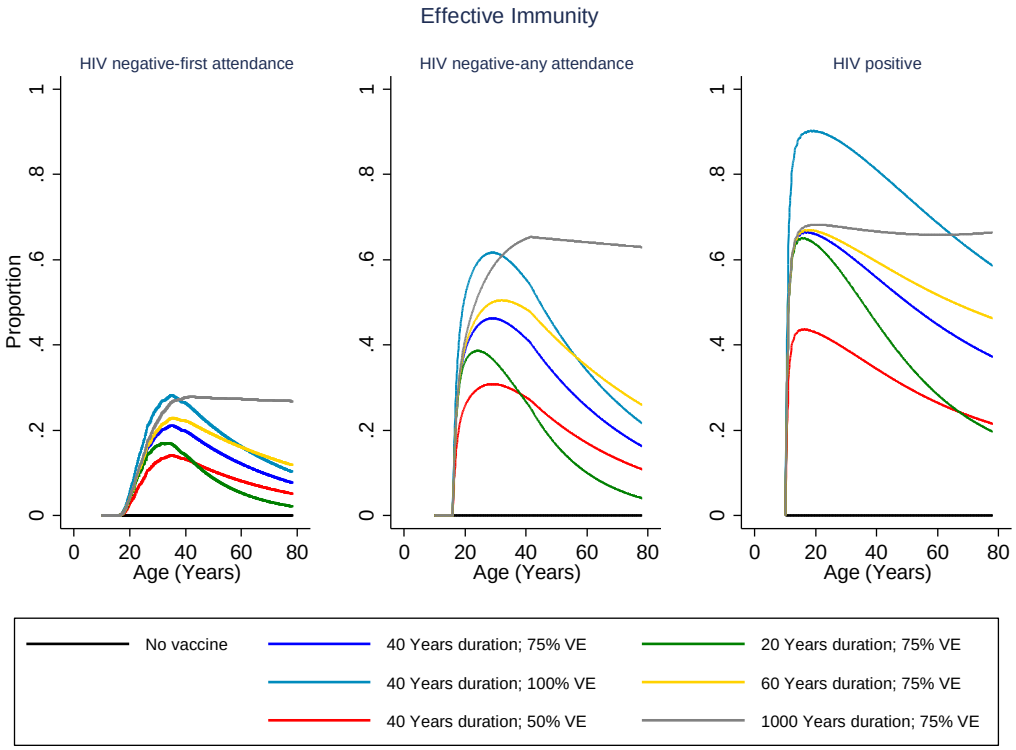


Any attendance=first and any subsequent visit to SHC, assumed to occur annually. In all scenarios both HIV-negative and HIV-positive MSM were eligible for vaccination.

Proportion of MSM vaccinated

Figure 71 shows that if offered the vaccine at first SHC attendance, with 96% uptake, a maximum of 43% of HIV-negative MSM would receive the vaccine by the age of 39 years. If offered at any attendance, assuming 96% uptake, the vaccine would be administered to 95% of HIV-negative MSM attending SHCs by the age of 40 years and 99% of HIV-positive MSM by the age of 29 years.

Figure 72. Proportion of MSM with effective protection against HPV16, by age, as a result of different vaccination scenarios



Abbreviations: VE= vaccine efficacy, Years duration= average duration of vaccine protection (years). Any attendance=first and any subsequent visit to SHC, assumed to occur annually. In all scenarios both HIV-negative and HIV-positive MSM were eligible for vaccination.

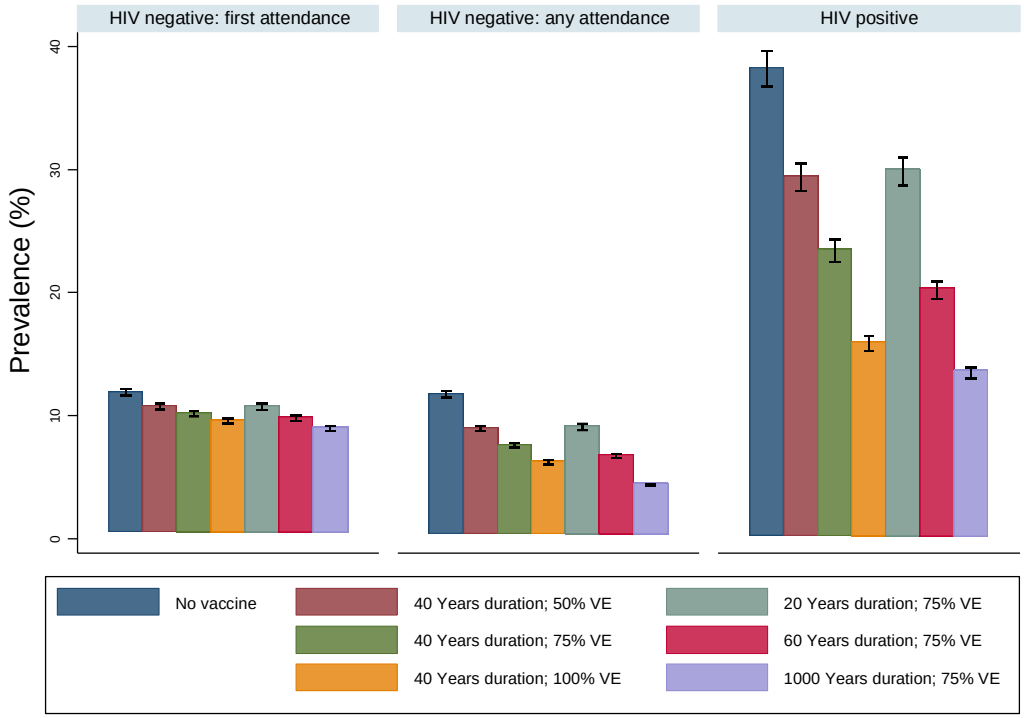
Proportion of MSM effectively immunised

Figure 72 shows that for HIV-negative MSM increasing vaccine efficacy increased the proportion of immune MSM, and increasing the duration of protection increased both the maximum proportion of immune MSM and the time to reach that maximum. Modelling lifelong immunity at 75% efficacy resulted in the highest proportion of HPV16 immune MSM for the longest period. In HIV-negative MSM, from age 60 years, whether vaccine was given

at first or at any visit, increasing vaccine duration of protection from 40 to 60 years compensated for the reduction in efficacy from 100 to 75%. From approximately age 40, increasing the duration of protection from 20 to 40 years compensated for a reduction in efficacy from 75 to 50%.

For HIV-positive MSM, the proportion immune was influenced more by vaccine efficacy than by duration of protection. The highest proportion of immune MSM, sustained for the longest period, resulted from a vaccine efficacy of 100% lasting for 40 years. Above the age of 60, increasing duration of protection from 40 years to lifelong compensated for a reduction in efficacy from 100 to 75%, and increasing duration of protection from 20 to 40 years compensated for an efficacy reduction from 75 to 50%.

FIGURE 73. MODELLED MEAN HPV16 PREVALENCE IN HIV SUBPOPULATIONS OF MSM ATTENDING SHCS, BY VACCINE SCENARIO, WHEN VACCINATING ALL MSM.



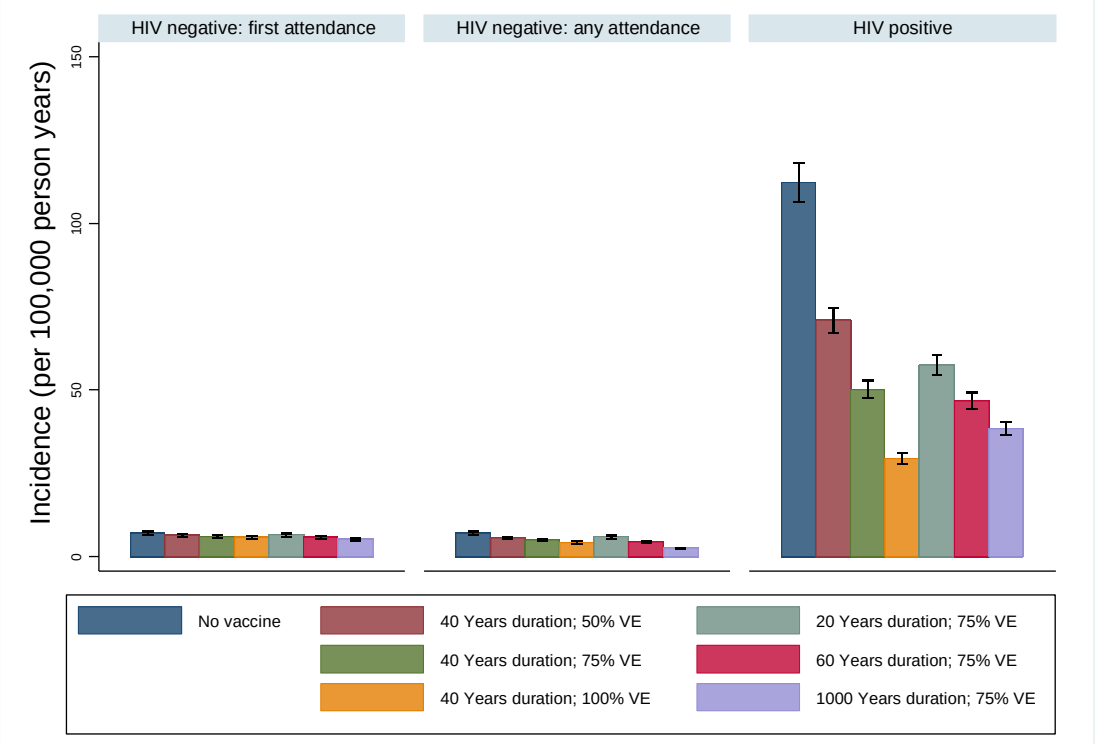
Abbreviations: VE= vaccine efficacy, Years duration= average duration of vaccine protection (years). Any attendance=first and any subsequent visit to SHC, assumed to occur annually. In all scenarios both HIV-negative and HIV-positive MSM were eligible for vaccination.

IMPACT OF VACCINATION ON ANAL CANCER INCIDENCE

Figure 73 shows that the mean HPV16 prevalence was reduced from 11.3% to 8.5% for HIV-negative MSM, with vaccine efficacy of 75% and lifelong protection, and if the vaccine was offered only at the first clinic attendance in their lifetime. Prevalence was reduced to 4.0% if HIV-negative MSM were offered the vaccine at any annual visit. For HIV-positive MSM, prevalence was reduced from 38.0% to 13.4% with vaccine efficacy of 75% and lifelong protection.

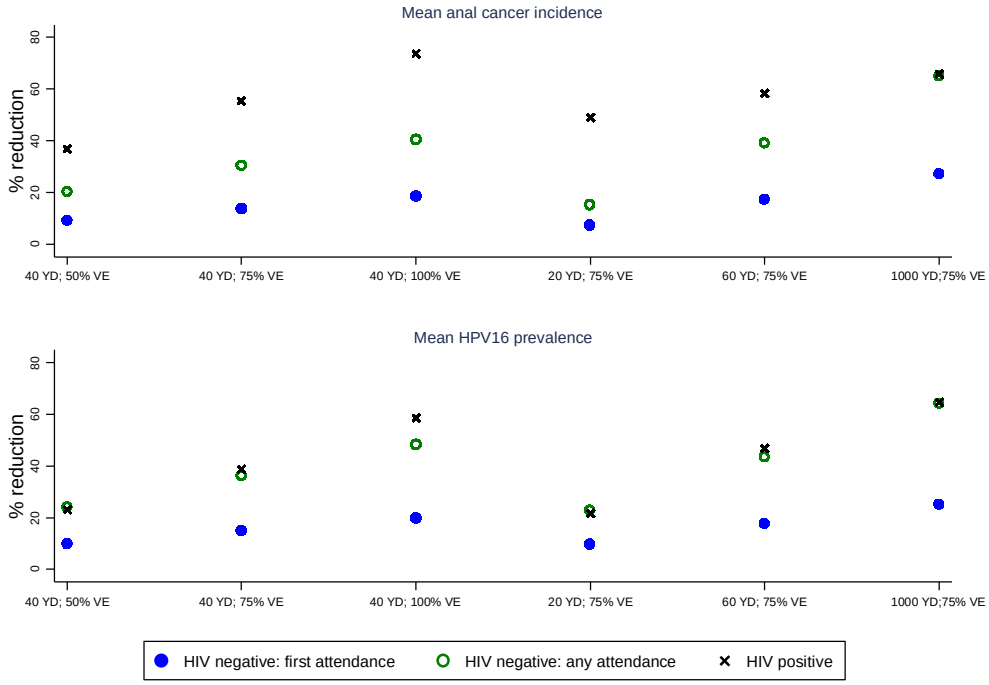
Figure 74 shows that the mean anal cancer incidence was reduced from 6.9 to 5.0/100,000 person years for HIV-negative MSM, with vaccine efficacy of 75% and lifelong protection, and if the vaccine was offered only at the first clinic attendance in their lifetime. Incidence was reduced to 2.4/100,000 person years if HIV-negative MSM were offered the vaccine at any annual visit. For HIV-positive MSM, incidence was reduced from 112.3 to 38.3/100,000 person years with vaccine efficacy of 75% and lifelong protection.

FIGURE 74. MODELLED MEAN ANAL CANCER INCIDENCE, BY HIV STATUS, RESULTING FROM DIFFERENT VACCINE SCENARIOS, WHEN VACCINATING ALL MSM



Abbreviations: VE= vaccine efficacy, Years duration= average duration of vaccine protection (years). Any attendance=first and any subsequent visit to SHC, assumed to occur annually. In all scenarios both HIV-negative and HIV-positive MSM were eligible for vaccination.

FIGURE 75. PERCENT REDUCTION IN MEAN ANAL CANCER INCIDENCE AND HPV16 PREVALENCE, BY HIV STATUS, RESULTING FROM DIFFERENT HPV VACCINE SCENARIOS.

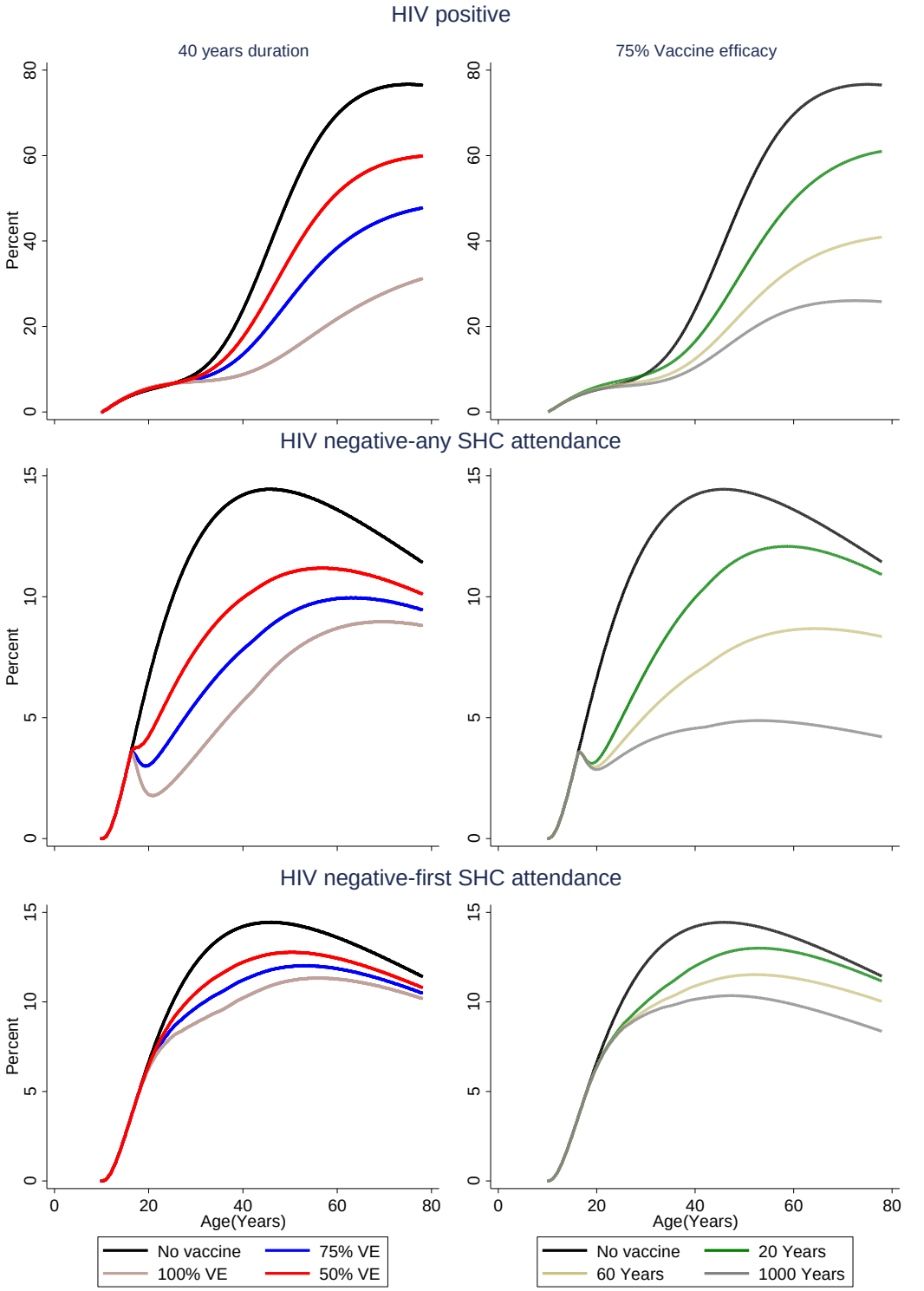


Abbreviations: VE=Vaccine efficacy, YD= average years duration of protection. HIV-negative and HIV-positive MSM populations were both eligible for vaccination in all scenarios.

Figure 75 shows the relative reduction in mean anal cancer incidence and HPV16 prevalence. For HIV-negative MSM, lifelong immunity has the greatest impact on anal cancer incidence (27% reduction for first-time attendance; 65% for any attendance) and is the only scenario in which as much relative reduction occurs for HIV-negative as for HIV-positive MSM (66% reduction for HIV-positive MSM). HPV16 prevalence relative reduction is similar for HIV-positive and HIV-negative MSM if they are offered the vaccine at any visit.

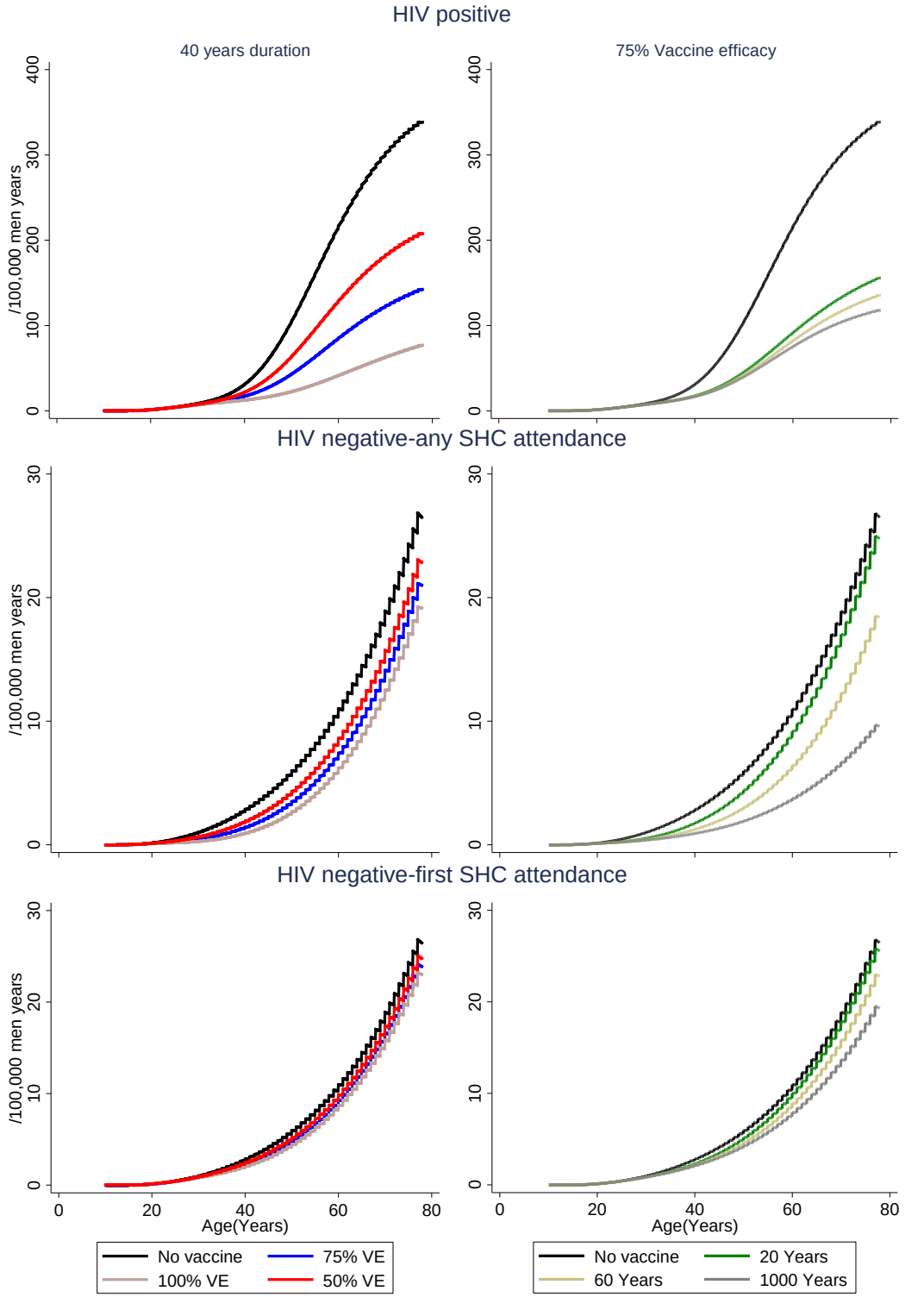
Figure 76 displays age-specific HPV16 prevalence under different vaccination scenarios and reflects the proportion of immune MSM in Figure 72. The impact of vaccination on HPV16 prevalence was greater and earlier in the scenarios where the vaccine was offered at any attendance compared to when HIV-negative MSM were only offered the vaccine at their first SHC attendance. Figure 77 shows that, for HIV-negative MSM, a longer duration of protection has more impact as age increases and as anal cancer incidence increases, so having more relative impact in older age.

FIGURE 76. THE EFFECT OF THE HPV VACCINE ON AGE-SPECIFIC HPV16 PREVALENCE, OVER A 67-YEAR PERIOD, IN A COHORT OF 100,000 MSM



Abbreviations: VE= vaccine efficacy, Years duration= average duration of vaccine protection (years). Any attendance=first and any subsequent visit to SHC, assumed to occur annually. In all scenarios both HIV-negative and HIV-positive MSM were eligible for vaccination.

FIGURE 77. EFFECT OF THE HPV16 VACCINE ON ABSOLUTE AGE-SPECIFIC ANAL CANCER INCIDENCE, OVER A 67-YEAR PERIOD, IN A COHORT OF 100,000 MSM

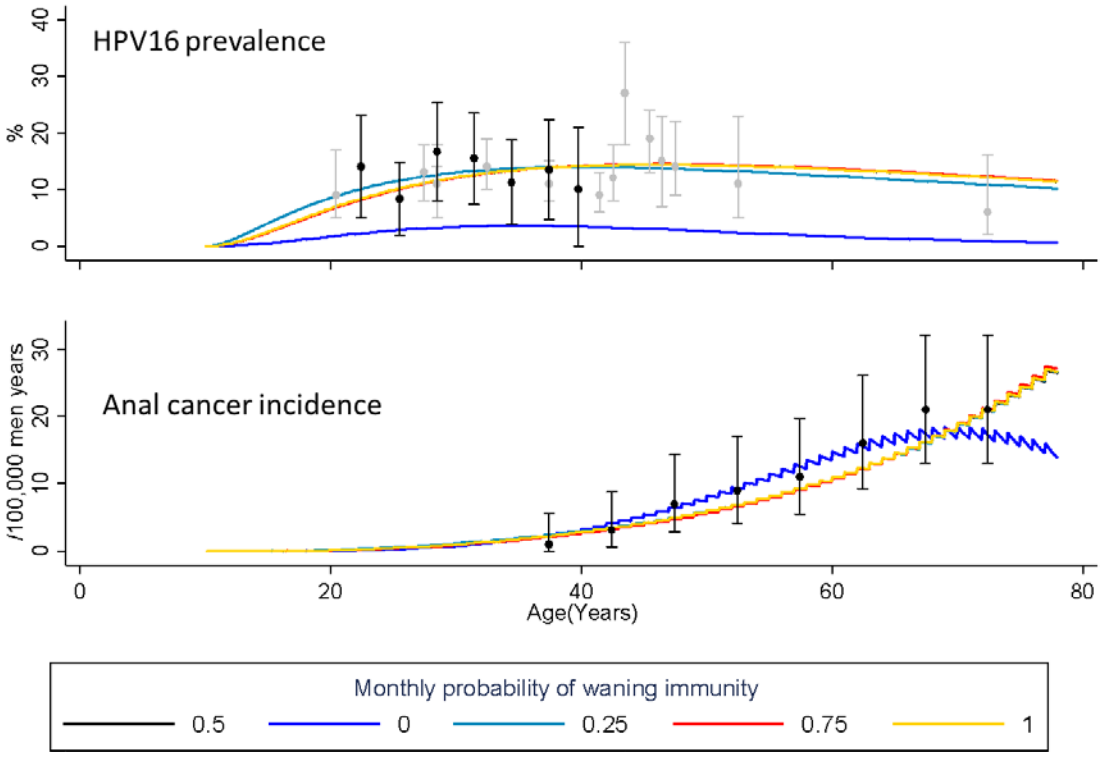


Abbreviations: VE= vaccine efficacy, Years duration= average duration of vaccine protection (years). Any attendance=first and any subsequent visit to SHC, assumed to occur annually. In all scenarios both HIV-negative and HIV-positive MSM were eligible for vaccination.

SENSITIVITY ANALYSIS: RISK OF WANING NATURAL IMMUNITY

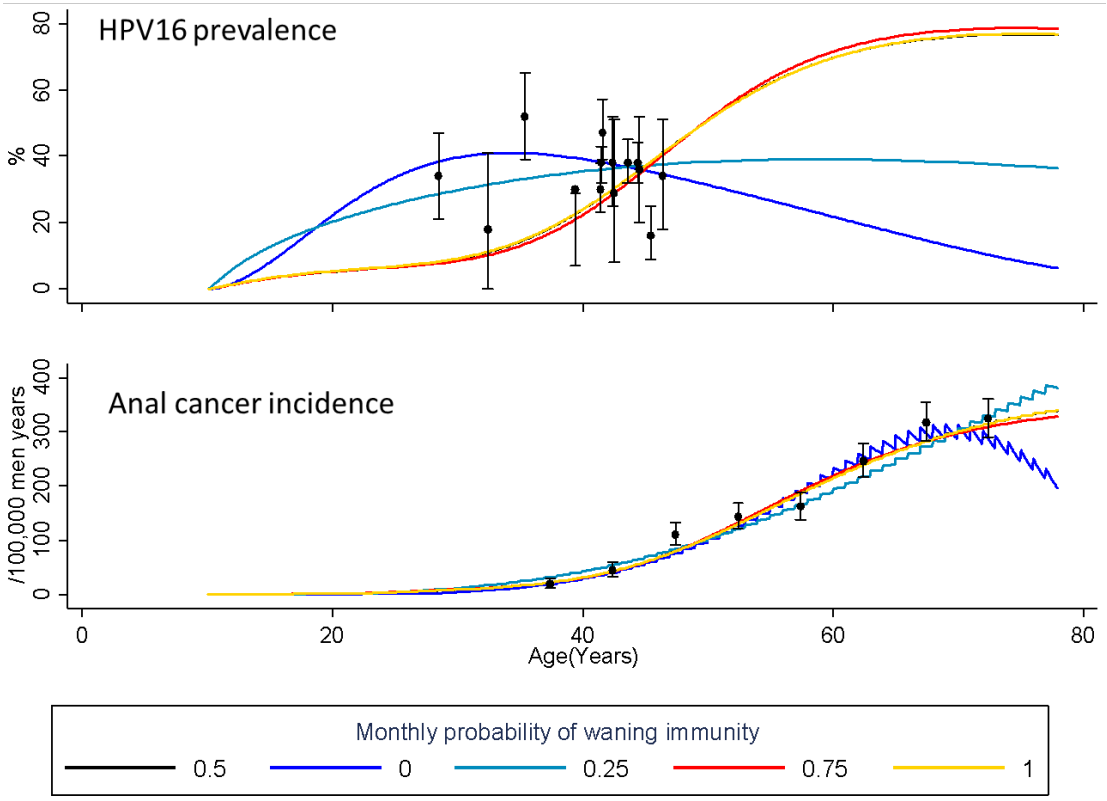
The results of model re-calibration to different values of monthly probability of losing natural immunity are displayed in Figure 78 and Figure 79. The fit of model output to observed data was improved, especially for HIV-positive MSM, when the probability was reduced from the default (0.5 per month to 0.25 per month). When lifelong natural immunity was modelled (monthly probability of losing natural immunity=0) the model output did not fit well to observed data. Increasing the probability of losing natural immunity above 0.5 per month had little impact on the model fit to observed data. Figure 80 shows that the relative reduction in mean anal cancer incidence and HPV16 prevalence was not sensitive to the waning natural immunity rate, even below 0.5 per month.

FIGURE 78. EFFECT OF VARYING THE RATE OF WANING NATURAL IMMUNITY ON MODELLED HPV16 PREVALENCE AND ANAL CANCER INCIDENCE IN HIV-NEGATIVE MSM



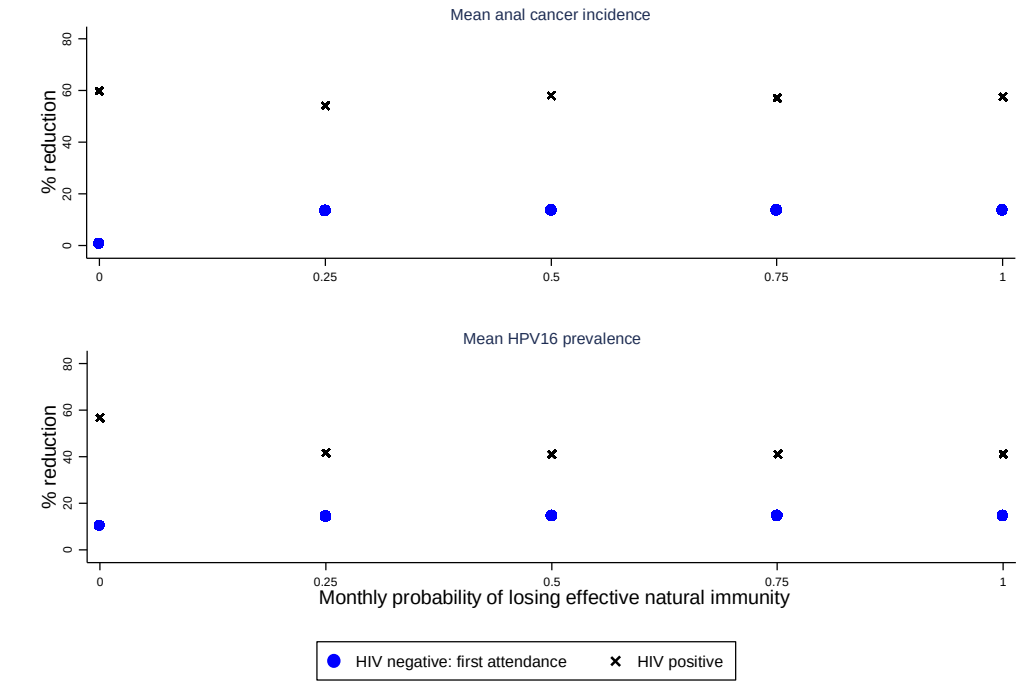
For observed HIV-negative HPV16 prevalence (upper panel): Black points represent age-specific estimates from the HPV-MSM-MMC study and grey points represent estimates from other published studies.

FIGURE 79. EFFECT OF VARYING THE RATE OF WANING NATURAL IMMUNITY ON MODELLED HPV16 PREVALENCE AND ANAL CANCER INCIDENCE IN HIV-POSITIVE MSM.



NB. Axis scales differ from Figure 78.

FIGURE 80. EFFECT OF WANING NATURAL IMMUNITY RATE ON THE PERCENT REDUCTION OF MEAN ANAL CANCER INCIDENCE AND HPV16 PREVALENCE, BY HIV STATUS



Vaccine efficacy=75%, 40 years average duration of protection

KEY FINDINGS

This preliminary modelling study has shown that HIV-positive MSM would benefit more than HIV-negative MSM from a vaccine against HPV16 to prevent anal cancer, assuming that vaccine efficacy is not reduced in HIV infection or due to antiretroviral treatment. A strategy in which the vaccine was offered to HIV-negative MSM at any SHC attendance would be more effective than targeting first-time attenders. Values of waning natural immunity between 0 and 0.5 per month are likely to result in better fitting models than values above 0.5 per month.

9.4 STRENGTHS AND LIMITATIONS

The model population was restricted to MSM attending SHCs in the UK and no HPV transmission was modelled. Therefore the impact of vaccination will have been underestimated because the indirect effects of vaccination on unvaccinated MSM in the model, and on the wider MSM population not modelled, could not be estimated.

Current HPV vaccines also protect against HPV18 infection and future vaccines will expand to cover more HPV types associated with anal cancer. The model was not designed to assess the additional reduction in anal cancer that would result from broader spectrum vaccines, or from cross-protection against other HPV types, and has therefore underestimated potential vaccine impact.

There was substantial uncertainty surrounding the parameters values for many of the natural history parameters for HPV16 infection and anal cancer development in MSM. For example, the clearance rate estimation from different stages of HPV infection for HIV-negative MSM was only based on 11 prevalent cases. Further refinement of this model would involve updating these parameter values, with their distributions, from the recent literature. A probabilistic uncertainty analysis, in which the inputted uncertainty is translated into output credibility, should also be incorporated into future models of HPV in MSM.

Furthermore, there is now data suggesting that detection of HPV DNA on the surface does not directly correspond to detection within the lesion[211]. Given that, in addition to the 'I' compartment, HSIL, LSIL and cancer compartments contributed to modelled HPV16 prevalence, which was fitted to observed data, HPV16 prevalence may have been underestimated by the model.

This model was calibrated to age-specific estimates of anal cancer incidence, HPV prevalence and HIV prevalence. These point estimates are affected by cohort effects and may have introduced bias. For example, older HIV-positive MSM in the UK have had continued improvement in the efficacy of HIV therapy during their lifetimes, when HIV-related mortality would have been higher than if they had lived in the current generation. Therefore the observed HIV prevalence in the older ages is likely to have been underestimated. Furthermore, these men, who were prematurely removed from the MSM population, did not contribute to the anal cancer incidence data in older age. The current generation's diagnosed HIV-positive MSM population will live longer, contributing to the person-time at risk in the older age groups, where effective ART does not reduce anal

cancer risk. This would result in higher anal cancer incidence than observed in 2010 at older ages.

This model assumes that HIV-positive MSM attend SHC/HIV clinics more frequently than HIV-negative MSM, regardless of whether they are diagnosed. Given the high uptake (95% in 2014) for HIV testing in SHCs[25], the proportion undiagnosed may be lower than in MSM in the general population, however this bias in attendance rate should be considered when interpreting these findings.

10. DISCUSSION

In this chapter, I summarise the main findings presented in this thesis and describe how they underpin estimates of HPV vaccine effectiveness in MSM who attend SHCs in the UK. To do so, I add context, particularly an update of the literature on vaccine efficacy in men and specifically MSM, which has accrued since 2009, when the PhD was conceptualised. At the end of each results chapter, I have identified specific strengths and limitations. Here I discuss the strengths and limitations of this thesis as a whole. The structure of this discussion updates the literature and then addresses the following questions:

1. *Is a prophylactic HPV vaccine programme targeted at MSM attending SHCs likely to intervene too late in their lifetime to be effective?*
2. *To what extent can an MSM-targeted SHC-delivered HPV vaccine programme interrupt HPV transmission in the wider MSM population (including those who do not attend SHCs) in the UK?*
3. *What are the estimates for effectiveness and cost-effectiveness of an MSM-targeted SHC-delivered HPV vaccine programme?*

10.1 SUMMARY OF THESIS

This thesis addresses the question of whether a targeted HPV vaccine programme for MSM in the UK, delivered in SHCs, would be effective (page 21). Data collected from 522 MSM attending a central London SHC (MMC) were analysed to define the SHC-attending MSM population in the UK in terms of HPV exposure (including estimates of current, prior and future HPV risk) and to estimate vaccine uptake. A mathematical model of HPV16 infection and anal cancer was developed and used to estimate vaccine effectiveness.

10.2 THE EVOLVING CONTEXT SURROUNDING ESTIMATES OF HPV VACCINE EFFECTIVENESS

Since 2009 there have been significant changes in the context and data to inform the research question. These include:

- Quadrivalent vaccine trials in men
- Adoption of gender-neutral vaccination programmes by some countries
- Population-level estimates of vaccine effectiveness
- An increase in studies measuring current HPV infection (reviewed in chapter 5, page 142) and seropositivity in MSM (reviewed in chapter 6, page 171)

Here, the current estimates of vaccine efficacy and safety and population-level estimates of vaccine effectiveness, with respect to men and MSM are reviewed.

VACCINE EFFICACY, EFFECTIVENESS AND SAFETY

Vaccine trials in men and MSM

The quadrivalent vaccine has now been tested in male populations (Table 44 displays estimates of efficacy and Table 45 displays estimates of effectiveness). Between 2004 and 2008 a randomised, placebo-controlled, double-blind, multicentre (71 sites), international (18 countries) trial in 4065 healthy boys and men, including 602 HIV-negative MSM, was conducted. Results were reported by Giuliano *et* al in 2011[236] and are displayed in Table 44. It showed substantial efficacy against persistent HPV infection, external genital lesions (EGL; predominantly AGW) and AIN. There were no reported vaccine-related serious adverse events and there was a lower reported rate of adverse events than reported in the trials in young women. Almost all vaccinees seroconverted for vaccine type HPV antibodies by seven months after starting the course of vaccination. Heterosexual men had higher peak mean antibody concentration than MSM; men of black ethnicity had higher mean antibody concentration than those of white or Asian ethnicity; and the vaccine was less immunogenic in older men than younger men. The clinical significance of these differences in antibody concentration was thought to be negligible based on the efficacy results[237].

In MSM, aged 16-26 years, irrespective of baseline HPV status or vaccine course completion (ITT population), the quadrivalent vaccine was 70% efficacious against EGL and 55% against HPV16/18-related AIN[238]. Confidence intervals of vaccine efficacy

estimates in this trial in men overlap with the estimates from the trial in women, so the authors suggest that vaccine efficacy was similar in the two sexes[236].

The MSM population was restricted to those younger than 27 reporting fewer than six lifetime male or female partners to represent men at low risk of having already been exposed to HPV. These efficacy estimates are therefore limited in their generalisability to other MSM populations.

Vaccine-related reductions in AIN and AGWs have been demonstrated in older, previously HPV-exposed MSM attending an anorectal surgery practice in New York[239,240] and vaccine-induced HPV seroconversion and safety have been demonstrated in HIV-positive MSM (Table 45)[241]. In HIV-positive MSM the vaccine increased the antibody levels in those with pre-existing antibodies, and ART use at vaccination was associated with higher concentration. After adjustment, CD4 cell count, nadir CD4 count and age were not associated with antibody concentrations[241].

Cross-protection

Currently available vaccines are designed to protect against types 6, 11, 16 and 18 but in clinical trials also conferred partial cross-protection (production of cross-neutralising antibodies that offer protection against non-vaccine HPV types) against persistent infection with types 31, 33, 45 and 52[242–245]. In Australia, repeat cross-sectional HPV surveillance demonstrated partial vaccine effectiveness against types 31, 33 and 45 (58%; 95% CI 27-76) following the introduction of the quadrivalent vaccine[246].

9-valent vaccine

Given the limited effectiveness of cross-protection, extending the valency of VLPs offers an alternative strategy for preventing infection and disease caused by a wider range of HR-HPV types. In December 2014, a 9-valent vaccine was licensed for use following evidence that the induced antibody responses to HPV6, 11, 16 and -18 were non-inferior to the quadrivalent vaccine and that it additionally prevented disease related to HPV types 31, 33, 45, 52, and 58. There was no evidence of cross-protection against non-vaccine types[15,247].

Two-dose schedule

Reduction in the original three-dose vaccine schedule to two doses has recently been assessed. Immunogenicity trials demonstrated non-inferior antibody titres in young

participants receiving two doses of the quadrivalent vaccine compared to the full three-dose course[248,249].

Long-term safety and efficacy

After nearly ten years of follow-up, the HPV vaccine trials in women demonstrate sustained efficacy and a continued excellent safety record. Short-lived reactions at injections sites are common but serious vaccine-attributable adverse events, such as anaphylaxis, are rare[96,250].

TABLE 44. STUDIES ASSESSING THE EFFICACY OF THE QUADRIVALENT VACCINE IN MEN

Study design	Publication	Recruitment period	Follow-up	Endpoint	ATP-VE (95% CI)	ITT-VE (95% CI)
1. 3463 heterosexual healthy boys and men aged 16-23. Excluded if history/baseline anogenital lesions, including those caused by other STI. ATP=seronegative and DNA negative for vaccine types at baseline until 7 months with no protocol violations. ITT population=irrespective of baseline HPV /did not complete the full vaccine course (minimum 1 dose) & returned for follow-up.						
Randomised, placebo-controlled, double-blind, multicenter (71 sites), international (18 countries)	Giuliano (2011)[236]	2004-2008	Median=2.9 years.	Incident external genital lesions (EGL=AGW & penile, perianal or perineal neoplasia or cancer)	92.4% (69.6-99.1)	63.7% (39.3-79.1)
2. Subsample of above trial: 602 HIV-negative MSM (oral or anal sex with boy/man in last year) aged 16-26.Thirty-three MSM were diagnosed with HIV during the trial and were included in the analyses.						
	Giuliano (2011)			Incident EGL (AGW & penile, perianal or perineal neoplasia or cancer)	79.0% (97.9-99.6)	70.2% (23.0-90.2)
				Persistent HPV6/11/16/18 infection	94.9% (80.4-99.4)	59.4% (43.0-71.4)
				HPV6/11/16/18 detection at any time	84.0% (68.6-92.7)	48.5% (32.3-61.1)
	Palefsky (2011)[238]		Mean=2.2 years	AIN	54.9% (8.4-79.1)	25.7% (-1.1-45.6)
				HPV6/11/16/18-related AIN	77.5% (39.6-93.3)	50.3% (25.7-67.2)
				HPV16/18-related AIN	78.6% (-0.4-97.7)	55.2 % (8.5-79.3)
3. 112 HIV-positive men > 18 years old, cytology=normal/ASCUS/LSIL & stable HIV-infection (no low CD4 counts or high viral loads, on or off ART). Excluded if both HPV16 &HPV18 detected/current or history of HSIL (or cell dysplasia suggestive of)/HGAIN/anal or perianal carcinoma. ATP= seronegative and DNA negative for endpoint HPV type at baseline; ITT=irrespective of baseline HPV status						
Multicentre (8 sites in US), single-arm, open-label, pilot trial	Wilkin *et al* (2010)[241]	2008	18 months	HPV6 seroconversion at week 28	98% (1-sided, 92%)	97% (NR)
				HPV11	99% (1-sided, 93%)	98% (NR)
				HPV16	100% (1-sided, 95%)	99% (NR)
				HPV18	95% (1-sided, 89%)	96% (NR)

Abbreviations: ATP =According to protocol; VE= Vaccine efficacy; CI=Confidence Interval; ITT=Intention-to-treat; EGL=External genital lesions; HPV=Human papillomavirus; AGW=anogenital warts; AIN=anal intra-epithelial neoplasia; HGAIN=High-grade AIN; ASCUS= Atypical Squamous Cells of Undetermined Significance; LSIL=Low-grade squamous intraepithelial lesion; ART=antiretroviral therapy; HSIL=high-grade squamous intraepithelial lesion; NR=Not reported

TABLE 45. STUDIES ASSESSING THE EFFECTIVENESS OF THE QUADRIVALENT VACCINE IN MSM

Study design	Publication	Recruitment period	Follow-up	Endpoint	ATP-HR (95% CI)	ITT-HR (95% CI)
1. 202 HIV-negative MSM, > 18 years old, history of biopsy-proven treated HGAIN. Mean age 40.4 years. ATP= all participants ITT=anal oncogenic HPV detected at baseline or 8 months before vaccination. Cox proportional hazards analysis						
Single-site (anorectal surgery practice in NY, US), non-concurrent cohort study	Swedish (2012)[239]	2007-2010	median unvaccinated =722 days; vaccinated= 489 days	Recurrent HGAIN 1 year	0.42 (0.22-0.82)	0.40 (0.19-0.86)
				Recurrent HGAIN 2 years	0.50 (0.26-0.98)	0.47 (0.22-1.00)
				Recurrent HGAIN 3 years	0.52 (0.27-1.02)	0.48 (0.22-1.04)
2. 313 HIV-negative MSM, > 26 years old, No prior anal condyloma (AGW) or previously-treated and recurrence-free for 12 months prior to study entry. Mean age 42.1years. ATP= all participants. Cox proportional hazards analysis						
Single-site (anorectal surgery practice in NY, US), non-concurrent cohort study	Swedish & Goldstone (2014)[240]	2007-2010	median unvaccinated =1039 days; vaccinated=880 days	Anal condyloma (AGW)	0.49 (0.24-0.98)	NR
					aHR=0.45 (0.22-0.92)	NR

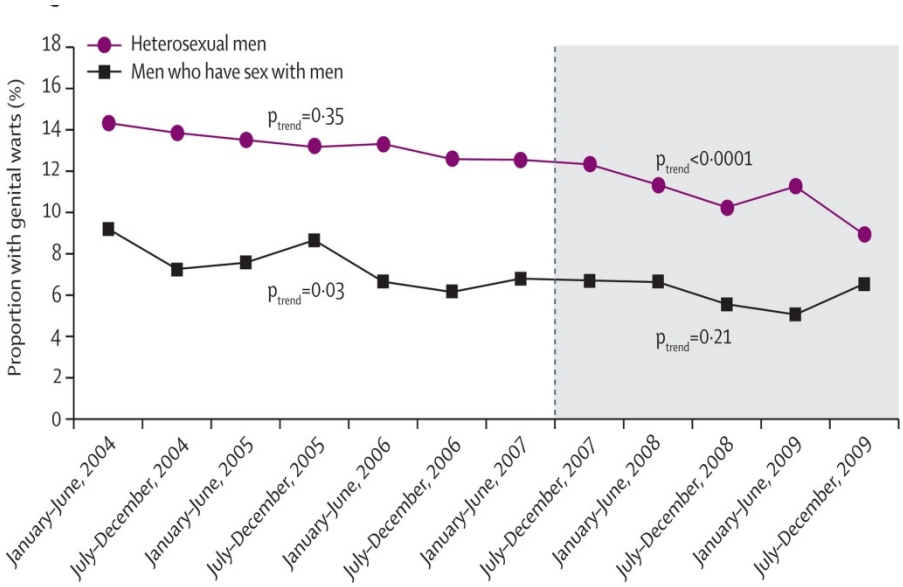
Abbreviations: ATP =According to protocol; HR=hazard ratio; CI=Confidence Interval; ITT=Intention-to-treat; HPV=Human papillomavirus; AGW=anogenital warts; AIN=anal intra-epithelial neoplasia; HGAIN=High-grade AIN; aHR=adjusted hazard ratio; ASCUS= Atypical Squamous Cells of Undetermined Significance; LSIL=Low-grade squamous intraepithelial lesion; HSIL=high-grade squamous intraepithelial lesion; NR=Not reported

10.3 POPULATION-LEVEL ESTIMATES OF VACCINE EFFECTIVENESS

Population-level estimates of vaccine effectiveness have recently been systematically reviewed by Drolet *et al*[251]. Of the 52 countries that have implemented HPV vaccine programmes (41% of high-income countries; 15% of low/middle-income countries), time-series studies had been conducted in nine high-income countries that were eligible for inclusion in the review. In general, high-income countries started programmes in 2007/8 using the quadrivalent vaccine. The UK was an exception, starting with the bivalent vaccine in 2008 and switching to the quadrivalent in 2012. The UK, Australia, Canada and New Zealand opted for school-based programmes and Denmark, Germany and the US for primary care/community-based programmes. Catch-up programmes for older girls were also implemented in most cases. Coverage estimates were variable. Overall, school-based programmes had higher coverage and the UK reached 84-90% of school girls[252]. The US began vaccinating boys, and MSM aged 22-26 years, in 2011 and Australia included all boys in their school-based programme from 2013.

These ecological studies, with inherent difficulties in determining causal association, were able to capture the indirect effects of female vaccination including the reduction in non-vaccine HPV types. Consistent with transmission model predictions[19], countries with high vaccine coverage (>50%) showed both direct and indirect effects one to four years after implementation: at least a 60% reduction in HPV16/18 and AGW in girls younger than 20 years, cross-protection against HPV 31/33/45 and a reduction in AGW in men and older women. Countries with low coverage only showed direct effects, with the magnitude correlating with coverage (dose-response relationship), with no evidence of cross-protection or herd immunity[251]. In SHCs in Australia, where school-based coverage was high (70%), the proportion of AGW-related consultations reduced in heterosexual men but not in MSM two years after implementation (Figure 81) with greater reduction in men after five years[253,254].

FIGURE 81. PREVALENCE OF AGW IN MEN ATTENDING SHCS IN AUSTRALIA BEFORE AND AFTER THE INTRODUCTION OF THE QUADRIVALENT VACCINE TO WOMEN AGED 12-27 IN 2007.



Adapted from Donovan *et al,* 2011[254]. P test for trend within the pre-vaccine period or the vaccine period (grey region).

10.4 WOULD A TARGETED HPV VACCINE PROGRAMME FOR MSM IN THE UK, DELIVERED IN SHCS, BE LIKELY TO BE COST-EFFECTIVE?

10.4.1 IS A PROPHYLACTIC HPV VACCINE PROGRAMME TARGETED AT MSM ATTENDING SEXUAL HEALTH CLINICS LIKELY TO INTERVENE TOO LATE IN THEIR LIFETIME TO BE EFFECTIVE?

SHCs are arguably the most feasible setting to deliver MSM-targeted vaccines in the National Health Service (NHS) yet they serve an MSM population that differs in terms of HPV-exposure, sexual experience, age and setting from the MSM vaccine trial population (page 238[238]). Because of the age-relationship of HPV infection in women, there is a high-level assertion in this field that age is the most important variable to consider for targeting the HPV vaccine in other populations (including MSM) because of four underlying assumptions:

A. The vaccine is not therapeutic and current HPV infection in women is related to age; this has been taken to imply that the vaccine is wasted on those already infected and that those infected are older (current HPV infection)

B. Age is related to cumulative risk of exposure and intervention is most effective prior to exposure, so vaccine programmes have not been considered worthwhile in populations with prior exposure (prior HPV exposure)

C. HPV incidence declines with age reducing the need for preventive interventions (future risk of HPV infection)

D. Following infection, HPV-related cancer takes years to develop; vaccines would be wasted in older populations who would be more likely to die of other causes before developing HPV-related cancer. (future risk of HPV-related disease)

Considering the findings from this thesis, and those of others, the strength of these assumptions, in relation to MSM populations, is discussed below and summarised at the end of this section (Box 12, page 253).

A. CURRENT HPV INFECTION: HPV INFECTION ONLY PARTIALLY REDUCES VACCINE EFFICACY AND HR-HPV INFECTION IS NOT RELATED TO AGE IN MSM

HPV vaccines do not alter the course of a pre-existing infection[97–101]. In HIV-positive MSM, detection of anal HPV11 DNA at baseline was associated with lower post-vaccine anti-HPV11 concentrations and likewise for HPV16[241]. Therefore MSM infected with any vaccine-preventable type at the time of intervention would continue to be at risk of developing HPV-related diseases unless the infection clears. However, if vaccinated while infected, following clearance there is evidence that the vaccine confers protection against re-infection from the cleared types[239,243,255]. Furthermore, MSM infected with some, but not all, of the vaccine types may still be protected against the other vaccine types and even those HPV types not targeted by the vaccine because of cross-protection[256,257].

As shown in chapter 5, of 522 MSM attending MMC, 68% had no detectable vaccine-type (6/11/16/18) HPV DNA at any tested anatomical site with the potential to be protected against all four vaccine types; 75% had one or fewer vaccine types detected with potential to be protected against the remaining three types; and 100% of the population had fewer than four vaccine types detected, therefore having potential to be protected against at least one other HPV type. In addition, each additional sexual partner increased the odds of a current anogenital infection (quadrivalent HPV type), after adjusting for age. However, there was no association between age and HR-HPV detection so, based on current infection,

there was no age group (between 18 and 40 years) in which the vaccine should be targeted or avoided.

B. Prior HPV infection: The impact of prior exposure on reducing vaccine efficacy is likely to be small

Cumulative exposure to HPV infection cannot be determined from DNA detection because the majority of infections are transient. In chapters 6 and 7, in addition to those with a current HPV6/11/16/18 infection (32%), a further 30% of the MMC MSM had evidence of prior exposure to HPV, either detected because of seroconversion (HPV types 16/18) (Table 27, page 168) or a diagnosis of AGWs (LR-HPV; Table 31, page 185). Having already been exposed to HPV, or having a pre-existing infection at the time of vaccination (current, as above) would reduce vaccine effectiveness if:

- That exposure had resulted in effective lifelong immunity against all vaccine types, in which case there would be no need for vaccine-induced immunity; the vaccine would be redundant.
- Prior exposure to HPV resulted in an infection that did not resolve, but instead a state of viral latency, and the vaccine was not efficacious at preventing re-activation.
- Exposure to and clearance of HPV interferes with the mechanism that leads to vaccine-induced immunogenicity.

Here, the complexity in measuring prior exposure is discussed and the assumption that prior exposure substantially reduces vaccine effectiveness is challenged by describing the duration and effectiveness of the immune response to HPV and the effectiveness estimates in previously-exposed populations.

Seropositivity as a marker for prior exposure

Antibody detection lacks sensitivity for measuring previous HPV exposure because of low seroconversion rates[85,236,258,259] and unknown duration of detection. For example, only 8% of HIV-negative MSM with detectable anogenital HPV16 DNA in Amsterdam seroconverted to HPV16 within a year[259]. It is likely that HPV infection-induced antibodies in MSM are short-lived. In chapter 6, the strong association that was found between type-specific

seropositivity and anogenital DNA positivity would be present if both duration of infection and duration of detectable antibodies following infection were short-lived. On the other hand, if antibodies remained at detectable concentrations for life and there was a high turnover of infections, there would be no association with current infection.

If seropositivity (detectable IgG) reverts to seronegativity (undetectable IgG) within a couple of years of exposure, due to waning serum antibodies, then estimates of seroprevalence are poor markers for cumulative risk. Prior exposure to the bivalent vaccine types in the HPV-MSM-MMC population would have been substantially underestimated.

History of AGW as a marker for prior exposure

History of AGW is also likely to be an insensitive marker for prior exposure to LR-HPV infection because not all LR-HPV infections will develop into AGW, not all AGW episodes will be detected by the individual and not all detected episodes will be diagnosed. In addition, in the HPV-MSM-MMC study, recall bias would have been likely as men were reporting on lifetime diagnoses, perhaps in the context of a complex STI history, which could have introduced confusion. The specificity of an AGW diagnosis for LR-HPV infection should be considered as some cases may be misdiagnosed and there is some evidence that HR-HPV is also associated with AGW[260,261]. It is probable that all diagnosed AGW are caused by LR-HPV but that in 20-50% of cases there are multiple type infections which include HR-HPV[262].

Effectiveness of natural immunity against re-infection

It is not clear that antibodies resulting from infection are efficacious against re-infection as they are found at much lower concentrations than vaccine-induced antibodies and seroconversion is not necessary for clearance of an HPV infection. In MSM in the Netherlands, seropositivity, resulting from natural infection, regardless of antibody concentration at baseline, was not associated with a reduction in incident HR-HPV infections after a year[263].

Cell-mediated immune responses (CMI) were not measured in the HPV-MSM-MMC study. Considering that HIV infection, which depletes T cell function, increases HPV susceptibility[264], CMI is likely to be important in the successful resolution of HPV infections. The extent to which CMI is important in preventing re-infection, including by other HPV

types, is not known. It is therefore difficult both to measure prior exposure to HPV and to establish the protective value of having successfully resolved an HPV infection.

Relevance of prior exposure to expected vaccine effectiveness

In the HPV-MSM-MMC study, the median age of first attending a SHC in the UK was 24 years, an average of five years after anal sex debut. During that five-year period, MSM are likely to have been exposed to the common HPV types, which may not be detectable from measuring seropositivity and/or AGW history.

Not only is prior exposure to HPV infection difficult to measure but it is also of questionable relevance to expected vaccine effectiveness. HPV exposure does not result in effective lifelong immunity against all vaccine types, and there are expected fluctuations in CMI competency during a lifetime, especially if infected with HIV. So there is benefit in immunising previously exposed MSM to prevent infections with HPV types to which they have not yet been exposed and to prevent re-infections, especially during periods when natural immunity has waned or is impaired. The probability that prior HPV exposure does not strongly influence vaccine effectiveness is supported by evidence that the quadrivalent HPV vaccine is efficacious in preventing recurrent high-grade AIN in older MSM with a history of HPV-related AIN[239].

C. Future risk of HPV infection: Vaccines are still needed in older MSM who remain at high risk of HPV infection

The remaining risk of infection after a specific age is determined by the subsequent lifetime cumulative incidence. Cumulative incidence, the number of new infections in a population in a given time period, can be estimated from age-specific HPV prevalence, age-specific STI transmission behaviours, and age-specific HPV seroprevalence (cumulative HPV infection). It can also be directly measured in longitudinal studies of incidence and duration of HPV infection.

HIV infection increases susceptibility to HPV infection which increases the frequency of HPV detection in HIV-positive populations, either as incident infections or reactivations from latency[264]. HPV incidence in MSM will therefore also depend on the prevalence of HIV infection in the MSM population.

Estimating age-specific incidence

Age-specific cumulative risk of infection, measured as seroprevalence or history of AGW, cannot accurately predict age-specific incidence because sensitivity and specificity for HPV infection are too low and duration of infections and frequency of re-infections, which would be counted once as seropositive, are unknown.

In both chapters 6 and 7, the age relationship with seropositivity and AGW was confounded by lifetime number of partners, which also predicted current HPV infection. The study found that recent (last year) high rates of partner change were more influential than lifetime partner numbers in predicting current and prior HPV infection, so number of partners in the last year may represent a useful proxy measure for HPV transmission and associated incidence. In chapter 4, number of partners in the last year in the HPV-MSM--MMC study was not associated with age; a high rate of partner change was maintained between 16 and 40 years old. Behavioural measures in the HPV-MSM-MMC study therefore do not suggest that there would be a decline in HPV incidence with age.

Incidence can be estimated from current HPV prevalence, provided the duration of infection is known. The distribution of duration of infection is likely to change with age and due to other co-factors such as HIV infection. The finding in chapter 5 that HR-HPV prevalence was not associated with age could suggest that duration of infection and incidence of HR-HPV are constant with age, or that duration of infections increase with age, whilst incidence declines.

In men the median time to clearance of genital HPV16 or any HR-HPV was estimated to be 12.2 and 7.2 months, respectively[265]. In HIV-positive MSM in Montreal, the mean duration of anal HPV16 infection was 35.8 months[93].

Longitudinal studies measuring incidence

Cross-sectional assessments of HPV prevalence cannot provide estimates for the dynamic processes underlying the spread of HPV infection. Longitudinal studies of anogenital HPV infection have estimated HPV type-specific incidence and suggests a high turnover of infections. For example, HIV-negative MSM in Thailand had a 12-month cumulative

incidence of 7.2% (95% CI 3.0-17.5%) and 33.9% (21.1-54.5%) for HPV16 and HR-HPV, respectively[172].

Recently, in young MSM (median 19 years), in Melbourne, Australia, the incidence of anal HPV16 and HPV16/18 DNA detection was 10.2 and 22.1 per 100 person-years, respectively. It was 40.8 per 100 person-years for any quadrivalent vaccine types and 55.2 for any 9-valent type. For definite infections, those detected at two or more consecutive visits, the incidence estimates were 13.6, 31.3 and 34.9 per 100 person-years for bivalent, quadrivalent and 9-valent vaccine types, respectively. The authors identified that the incidence rates in young MSM were three to four times higher than those in women of the same age[195].

In older HIV-negative MSM (median 38 years) in Amsterdam, the incidence of anal HPV16 DNA detection was 9.7 per 100 person-years[263], similar to that in the young Australian MSM population. In an HIV-positive MSM population (mean age 45 years), in San Francisco, the incidence of anal HPV16 DNA detection was 14.8 per 100 person-years and in HIV-positive MSM in Montreal, Canada (median age 43 years), it was 13.0 per 100 person-years[93].

In the young Australian MSM population, penile incidence was lower than anal incidence and simulation, using the vaccine trial population as sexual partners, resulted in estimates of the per-partner transmission probabilities by HPV type and according to whether sex was insertive or receptive. Approximately 46% of receptive anal sex partnerships resulted in transmission of HPV16 and HPV11 infections (63% for HPV18 and HPV6). The transmission risk was much lower for insertive anal sex partnerships (range=0.8-9.3%). This is consistent with findings from chapter 5, where positioning during condomless sex and receptive anal sex, but not insertive anal sex, were risk factors for HPV detection.

The incidence of oral HPV infections was higher in HIV-positive than HIV-negative MSM in Amsterdam. For example, the incidence of detectable HPV16 DNA in the oral cavity was 4.2 per 100 person-years in HIV-positive MSM and 1.1 in HIV-negative MSM[266].

Given these high rates of new infections in MSM populations of all ages, the expected cumulative lifetime risk would remain high in older MSM compared to in older women, where incidence declines after a peak in the youngest age group (18-24 years)[71].

Factors other than age and rate of partner change that affect HPV infection risk

Cumulative incidence is also influenced by factors, other than age and lifetime partner number, that increase susceptibility to HPV. For example HIV and smoking are thought to alter the risk and progression of HPV infection[262]. In the HPV-MSM-MMC population, current smoking was measured and prevalence was similar (29.4%) to that in men aged 25-34 in the general population (30.4%[159]) and there was no association with HPV status. In fact, few demographic and behavioural factors were associated with HPV infection (chapter 5) or history of infection (chapters 7 and 8). The factors found to associated with HPV exposure were HIV status, number of partners, use of drugs in the anus, recent receptive anal intercourse and positioning during condomless receptive anal sex. There were high levels of correlated STI transmission behaviours reported among participants in the HPV-MSM-MMC study, and because these risk factors were not broadly distributed, it was difficult to establish which specific behaviours were associated with markers for HPV.

In chapter 7 it was shown that 5% of HPV-MSM-MMC participants had been diagnosed as HIV-positive, which is similar to that estimated for MSM in London (6.6% diagnosed) but higher than the estimate outside London (2.5% diagnosed)[267]. The median age of HIV diagnosis for MSM in the UK was 34 in 2013[268], so HPV-MSM-MMC participants were still at risk of HIV infection which would result in a lower HIV prevalence estimate in this younger population. It is estimated, using the GMSHS, that 20% of MSM in the UK have undiagnosed HIV[224,267]. In a SHC, where annual testing is promoted, with 83% offered and 95% uptake in 2014[269], this proportion is likely to be lower, however there is still potential for HIV-positive MSM to have been misclassified as HIV-negative in this study.

As a cohort of MSM ages, those with higher STI transmission behaviours are more likely to become HIV-positive, which increases their future risk of HPV. The residual HIV-negative population is also affected, becoming smaller with lowered average risk behaviour. These changes in the denominator for HIV-negative and HIV-positive MSM over time should be considered when exploring the associations of HPV with age in MSM.

Furthermore, recent changes in HIV treatment guidelines will impact on HPV epidemiology in HIV-positive populations. In the UK, and elsewhere, ART is now initiated earlier in HIV infection, at higher CD4+ T cell counts, than in the cohorts studied for HPV-related cancer incidence in this thesis[270]. HPV-related diseases are expected to be less likely in HIV-positive cohorts who started ART at higher CD4+ T cell counts. This is partly because the population-average nadir CD4+ count will be higher, so there will be less loss of immune system functionality following ART-related immune reconstitution, which may result in increased HPV clearance and reduced HPV-related disease progression[271].

Relevance of future risk of HPV infection to expected vaccine effectiveness

The future risk of HPV infection was estimated in the HPV-MSM-MMC study to be constant across the age-range of participants (18-40 years), having measured both age-specific STI transmission behaviours, for example number of anal sex partners in the last year, and markers for HPV exposure, including current infection. This leads to the conclusion that there is significant remaining risk of HPV infection in MSM attending SHCs in the UK, which could be prevented by HPV vaccines. This is in contrast to women who reduce partner change rates after a peak age (approximately 24 years) with an associated decline in HPV prevalence.

D. Future risk of developing HPV-related disease: the expected period of remaining life following first SHC attendance is sufficient for anal cancer development

The earlier vaccination occurs the more the potential it has to benefit the MSM population, not only because of the greater the size of the HPV-naïve portion and the greater the future risk of infection but also because of the slow rate of disease progression for HPV-related cancers. Following HPV infection, the probability of dying from other causes, before the onset of carcinoma, increases with age and reduces the benefit of vaccination.

If anal cancer, like cervical cancer, takes approximately 30 years to develop[272], in an average 80 year lifetime[273], the opportunity to prevent considerable disease burden remains after age 24, the median age of first attending a SHC (Chapter 8).

BOX 12. SUMMARY: SUBSTANTIAL BURDEN OF VACCINE-PREVENTABLE HPV IN MSM, AFTER SEXUAL DEBUT, HPV EXPOSURE AND SHC-ATTENDANCE

A: Current infection

- Whilst the vaccine is not therapeutic, the reduction in re-infections and the prevention of other type infections does not preclude its use in MSM with pre-existing infections
- Current HR-HPV infections are not associated with age in MSM so only considering current infection, there are no age groups, between 16-40 years, that should be targeted

B: Prior exposure

- Cumulative risk of HPV exposure is associated with lifetime number of partners, which is associated with age
- Seropositivity and history of AGWs provide underestimates of prior HPV exposure
- Whilst vaccine effectiveness is optimal in HPV-naïve populations, MSM attending SHCs are unlikely to be naïve to all vaccine types
- The reduction in vaccine effectiveness related to prior exposure is likely to be small

C: Future risk of HPV infection:

- MSM remain at high risk of HPV infection after attending SHCs, at least until the age of 40

D: Future risk of HPV-related cancer development

- After first SHC attendance, MSM have sufficient remaining life years to develop HPV-related AGW and cancer

10.4.2 INTERRUPTION OF HPV TRANSMISSION IN MSM IN THE UK

Having established that there is an opportunity to prevent a significant amount of HPV infection and disease in MSM younger than 40 years, attending SHCs (Box 12, page 253), the question remains: what coverage of the MSM population could be expected in terms of proportion expected to receive the HPV vaccine at SHCs and HPV transmission characteristics of those vaccinated? This question is addressed in terms of:

- Expected direct effects of an SHC HPV vaccine programme, including;
    - expected vaccine uptake at SHCs,
    - expected attendance at SHCs , and
- Expected indirect effects of the proposed vaccine programme.

VACCINE UPTAKE

Nearly all (96%) of HPV-MSM-MMC participants reported that they would probably or definitely accept the HPV vaccine at a SHC, as shown in chapter 8. Misconceptions relating to vaccine safety and requirement of additional information were the most frequently reported potential barriers to uptake. Furthermore, knowledge relating to risk of HPV exposure and lack of treatment for infection was poor and likely to result in falsely low perception of HPV risk, a determinant of vaccine uptake. Given these findings, it is likely that an educational component to a vaccine programme would improve HPV vaccine uptake in MSM at SHCs.

MSM USE OF HEALTH SERVICES

There is a suggestion that use of SHCs is increasing in MSM with 30% (95% CI 20.1–41.2%) reporting attending a SHC in the last 5 years in Natsal-1 in 1990, 36% (95% CI 27.2–44.9%) in Natsal-2 in 2000 and 45% (95% CI 35.0–55.5) in Natsal-3 in 2010-2012[8,274]. Also, attendance appears to be higher in MSM populations in cities: of MSM participating in the GMSHS in 2011 in London 457/834 (55%) attended an STI clinic in the previous year[156]. In 2010, between 40 and 44% of respondents to the European MSM internet survey living in Birmingham (135/338; 40%), Manchester (241/586; 41%) and London (2100/4816; 44%) reported an STI screen in the last year[275]. Considering these data, it is reasonable to estimate that at least half of the UK's young MSM population today will access an SHC in their lifetime.

Furthermore, the findings in chapter 8 suggest that other services would not be successful at reaching at-risk MSM. For HPV-MSM-MMC participants, the SHC was the preferred service for AGW diagnosis and treatment and for HBV vaccination. For example, less than half of participants that visited their GP in the last year had disclosed their sexuality.

In addition, it is possible that younger MSM would attend specifically to access the HPV vaccine if it was known to be available and this would result in a lower median age at first attendance, increased capture of HPV-naïve MSM and increased vaccine effectiveness. Unlike the HBV vaccine, the cervical cancer HPV vaccine promotion activities are likely to have resulted in widespread awareness of HPV vaccines, especially in school-age children, and could provide additional motivation to get protected. Younger men, including MSEW, may be more likely to attend for HPV vaccination, especially as health promotion has targeted younger ages.

MSM AND THE INDIRECT OF EFFECTS OF HPV VACCINATION

'High' HPV vaccine coverage was defined as coverage of at least half of the population in a recent meta-analysis of population-level impacts of HPV vaccination[251]. Quantifying vaccine coverage does not take into account the heterogeneity of populations with respect to STI transmission risk behaviours. Vaccinating sub-populations with more network connections and higher R_n more efficiently interrupts transmission compared to vaccinating sub-populations, such as those who do not attend SHCs with lower rates of partner change. Assuming that they are not already immune, vaccination of SHC-attending MSM probably represents the most efficient way to interrupt HPV transmission in MSM because it targets those at highest risk of acquiring and transmitting HPV and therefore will maximise direct and indirect protective effects.

SHC-attending MSM, especially those in London, probably have a higher HPV R_n than the wider MSM population. High STI transmission behaviour (chapter 4) and high prevalence of syphilis (chapter 7), a marker for increased STI transmission[276], were found in the HPV-MSM-MMC population compared to other MSM populations in the UK. The higher HPV R_n in SHC-attending MSM is probable, not only because SHC-attending individuals are health-seeking,

in part, because of perceived risk, which is likely to reflect "risky" behaviour[156], but also because living in London is associated with a variety of complex individual and socio-cultural influences that increase STI transmission risk behaviour[277]. This London bias should be considered when generalising the results in this thesis beyond London MSM populations.

Heterogeneity in the value of HPV R_n across MSM sub-populations has implications for HPV control, and these depend on the amount of sexual mixing between men residing in different geographical regions, including outside the UK. By lowering the disproportionately large R_n of the SHC-attending MSM sub-population, through vaccination, the overall R_n should be efficiently lowered. The SHC-attending MSM population is probably dynamically important in the UK's MSM sexual network. Interrupting transmission in this part of the network would therefore confer substantial indirect benefits to MSM with fewer STI transmission risk behaviours in the wider MSM population.

The SHC-attending MSM population might also receive small indirect benefits from the current routine vaccination programme in girls since 8% of HPV-MSM-MMC participants reported having had vaginal sex in the last year. Findings from the meta-analysis in chapter 3, where there was no evidence that MSM were at increased risk of oral HPV compared to heterosexual men were supported in chapter 5, where anal sex with women was associated with oral HPV infection in the MSM at MMC. The latter should be interpreted with caution given the low oral HPV prevalence and reduced sample size for this analysis. There is a possibility that the indirect consequences of female vaccination in MSM would be greater at the oral site than the anogenital.

At MMC, 85% of MSM had lived in the UK for more than three years (38%) or were born there (47%). Migration in and out of the UK would impact on vaccine effectiveness and cost-effectiveness. If MSM entered from regions with gender-neutral HPV vaccine programmes herd immunity would increase but would decrease if MSM entered from unvaccinated regions with high HPV prevalence. Vaccinated MSM leaving the UK would reduce cost-effectiveness of a targeted HPV vaccine programme at SHCs.

Over half of HPV-MSM-MMC participants (256/504) were born outside the UK, of whom three-quarters (193/256) had lived in the UK for more than three years (chapter 4, page

104). This indicator of migration is unlikely to be generalizable to the rest of the UK, because London represents a unique multicultural setting, but highlights an important consideration.

Migration should be considered when comparing vaccine coverage of the MSM population through a gender-neutral school-based programme to a targeted SHC-delivered programme. HPV vaccine programme effectiveness would be over-estimated if the emigration of vaccinated MSM and the immigration of unvaccinated MSM were not included in assessments, which effectively reduce vaccine coverage. Vaccinating MSM at SHCs would be cheaper than a gender-neutral programme and, given migration patterns, might also result in higher coverage of the MSM population. This is especially significant given that a gender-neutral programme would only be considered for the prevention of disease in MSM.

Given the enthusiasm for the HPV vaccine and the exceptionally high STI transmission risk behaviours demonstrated in the HPV-MSM-MMC study as well as the frequent use of SHCs by MSM in the UK, approximately half of the UK's MSM population, representing the 'inner core' of the MSM core risk group, could be expected to receive the HPV vaccine at SHCs and this should have significant effects on MSM who do not attend SHCs.

ESTIMATES FOR MSM-TARGETED SHC-DELIVERED HPV VACCINE PROGRAMME EFFECTIVENESS AND COST-EFFECTIVENESS.

Vaccine effectiveness

In chapter 9, percentage reduction in anal HPV16 prevalence and anal cancer incidence were estimated as measures of vaccine effectiveness in a cohort of MSM from age 10 to 77. Given that the expected vaccine impact on other HPV types, on other HPV-related diseases at other anatomical sites, in MSM older than 77 and those not attending SHCs, and women in the UK, were not modelled, these estimates represent the minimum potential reduction. Substantial reductions in anal cancer incidence were projected, with HIV-positive MSM benefiting to a greater extent than HIV-negative MSM, probably due to higher vaccine coverage estimates. Targeting HIV-negative MSM at their first SHC attendance was not as effective as targeting MSM at any attendance and duration of vaccine-induced immunity significantly influenced estimates.

The preliminary work presented in chapter 9 has been expanded and refined by colleagues at PHE to include transmission, parameter uncertainty, all quadrivalent vaccine types and additional outcomes, including AGWs and penile, oropharyngeal and oral cancers yet the results remain confidential (Appendix VII, page 335).

Vaccine cost-effectiveness

For a vaccine programme to be implemented, it has not only to be feasible with substantial expected effectiveness, but also affordable. In the UK, decisions are influenced by the incremental cost-effectiveness ratio, a measure of the cost-effectiveness of an intervention strategy; relative costs and effects of vaccine programme implementation compared to no vaccine programme[278].

The direct healthcare costs associated with no vaccine programme (the status quo) are a function of incidence of, and costs associated with, vaccine-preventable outcomes. Anal cancer is rare in HIV-negative MSM but more common in HIV-positive MSM and, when diagnosed, is associated with expensive treatment (approximately £15, 000 per cancer case in the NHS in 2009) which may include surgery[279,280]. In contrast, as shown in chapter 7, AGWs are very common in MSM and each episode is estimated to cost the NHS £113[281].

The costs associated with implementing a vaccine programme include both programme costs: vaccine price, delivery, administration and health promotion, and costs associated with breakthrough disease. Here, breakthrough disease refers to cases in MSM who were not vaccinated, in MSM in whom the vaccine was not effective and cases resulting from non-vaccine types. The proportion of anal cancer attributed to vaccine-type HPV infections is lower than that for AGW and therefore proportionally more breakthrough cases of anal cancer might be expected.

The effects of no vaccine programme are usually measured using the reduction in quality-adjusted life years (QALY), which measure both the quality and quantity of life lived. Similar to the pattern with cost, anal cancer is less frequent and associated with greater reduction in quality and length of life compared to AGWs, which are more frequent with less, but significant, reduction of quality of life[282]. The effects of the vaccine programme depend on vaccine coverage, the number of cases averted and the QALYs gained.

The rate of disease progression is higher for AGW than for cancer and this is relevant for estimating costs and benefits because the reduction in AGW will occur sooner after vaccine introduction than the reduction in cancer. In economic models, future costs and benefits are standardised to present values by attaching declining weights to future events (discounting). Therefore, the QALYs gained by averting cancer cases (that take approximately 30 years to develop) will, in discounted models, be reduced more than the QALYs gained by averting AGW cases raising the influence of AGW prevention in the contribution to overall vaccine effectiveness.

This is important when comparing a school-based gender-neutral vaccine programme, which would intervene, on average, a decade earlier than an SHC-based vaccine programme. The accrual of cancer-related benefits, using a SHC-based programme, would occur, approximately a decade earlier than a school-based programme. The cancer-related benefits would therefore be significantly more discounted in a school-based model (discount factor=0.36; discounting to 3.5%) compared to a SHC-based model (discount factor=0.50; discounting to 3.5%).

HPV vaccine policy in the UK

As displayed in Box 13, in the UK, in 2008, the Joint Committee on Vaccination and Immunisation (JCVI), acknowledged a lack of evidence to assess the value of an HPV vaccine programme targeted at MSM. In 2012, the routine programme in girls switched to the quadrivalent vaccine and the JCVI issued a call for evidence for potential benefits of HPV vaccine for those not currently offered immunisation, particularly men who have sex with men (MSM)[283]. In 2014, the JCVI recommended a switch from the three-dose to a two-dose schedule for the quadrivalent vaccine in girls aged younger than 15 years[284].

The JCVI has now assessed the MSM-targeted HPV vaccine programme (October 2014). The Committee discussed prevalence estimates from chapter 5 alongside the transmission model of HPV infection in MSM, developed by PHE. The JCVI's interim position, subject to consultation, was that the evidence indicates that a targeted programme undertaken in SHC and HIV clinics, using the quadrivalent vaccine, could be cost-effective, subject to availability of the vaccine and delivery at an appropriate price. The committee advised that it would be very important to closely monitor vaccine coverage and completion and the impact of the

programme if implemented, as the outcome would also influence the consideration of a programme for adolescent boys. The JCVI is currently developing its final advice to the Secretary of State for Health.

BOX 13. HISTORY OF JCVI RECOMMENDATIONS AND CALLS FOR EVIDENCE

2008	• Lack of evidence to assess the value of an HPV vaccine programme targeted at MSM • School-based programme in girls using bivalent vaccine (& catch-up in older girls)
2012	• Call for evidence for potential benefits of HPV vaccine for those not currently offered immunisation, particularly men who have sex with men (MSM) • Girls school-based programme switch to the quadrivalent vaccine
2014	• Meeting to assess the MSM-targeted HPV vaccine programme • Girls school-based programme switched to 2-dose schedule

Further policy recommendations

Whilst the findings of this thesis support the introduction of a targeted HPV vaccine programme for MSM at SHCs, further consideration of a school-based gender-neutral programme is warranted given that the vaccine is efficacious in girls (and probably boys) using a two-dose schedule, which will alter the cost: benefit ratio. Furthermore, there is improved data availability for other HPV disease outcomes and vaccine coverage that could inform an updated assessment of including boys in the current routine school-based programme[19]. If a gender-neutral programme is recommended then a catch-up programme in MSM would still be likely to be beneficial.

The UK's central government would need to procure the HPV vaccine in order to negotiate the lowest price. This has implications for a targeted programme that would be delivered as part of integrated sexual health services, which are commissioned by local governments, and possibly as part of HIV treatment and care services, which are commissioned by NHS England[285]. The commissioning system would therefore need to be adapted in order to deliver a targeted vaccine programme, having procured the vaccine at the minimum cost.

If a targeted HPV vaccine programme is implemented, both programme evaluation and monitoring would be required for continued strategic decision-making. Programme evaluation aims to assess the overall relevance, efficiency, effectiveness, sustainability or impact of the programme design, implementation and outcomes. Plans for targeted HPV vaccine programme evaluation will need to be developed alongside plans for implementation.

Monitoring is an ongoing system of gathering information and tracking programme performance. Indicators, such as the cross-sectional measures of HPV prevalence presented in this thesis, are used to measure progress. The findings from this thesis provide not only detailed baseline data prior to HPV vaccine programme implementation, but also data on the relative detection of HPV DNA at different anatomical sites, which suggest that in MSM, the optimal sample for monitoring HPV infection is the anal swab.

Conclusion

This thesis aimed to inform the policy decision of whether to vaccinate MSM attending SHCs in the UK (page 21). It provides strong evidence for HPV vaccine effectiveness in MSM attending SHCs in the UK and has provided evidence of effectiveness to the JCVI for their decision-making. A substantial burden of HPV infection could be prevented after sexual debut, after HPV exposure and after first SHC attendance in MSM. A third of HPV-MSM-MMC participants had no evidence of HPV infection, an additional third showed evidence of prior infection, which may have little reduction on vaccine efficacy, and a further third had current infection with one or more of the quadrivalent vaccine types so could still benefit from protection from re-infection from those type(s) and infection from other vaccine HPV types.

At least half of the UK's MSM population could be expected to receive the HPV vaccine at SHCs and these men represent those at high risk of acquiring and transmitting HPV infection, so would efficiently interrupt HPV transmission.

Building on these data and on the anal cancer model in chapter 9, a refined transmission model was developed by PHE that estimated that the targeted programme is also expected to be cost-effective. If the JCVI now recommends this programme, the UK's complex health

commissioning system would need to be adapted in order to procure the vaccine at the lowest price. A programme that includes public engagement, including education, should be developed to enhance uptake. Monitoring and evaluation of such a programme would be needed, and would include measuring HPV prevalence and medium- to long-term cancer incidence in MSM.

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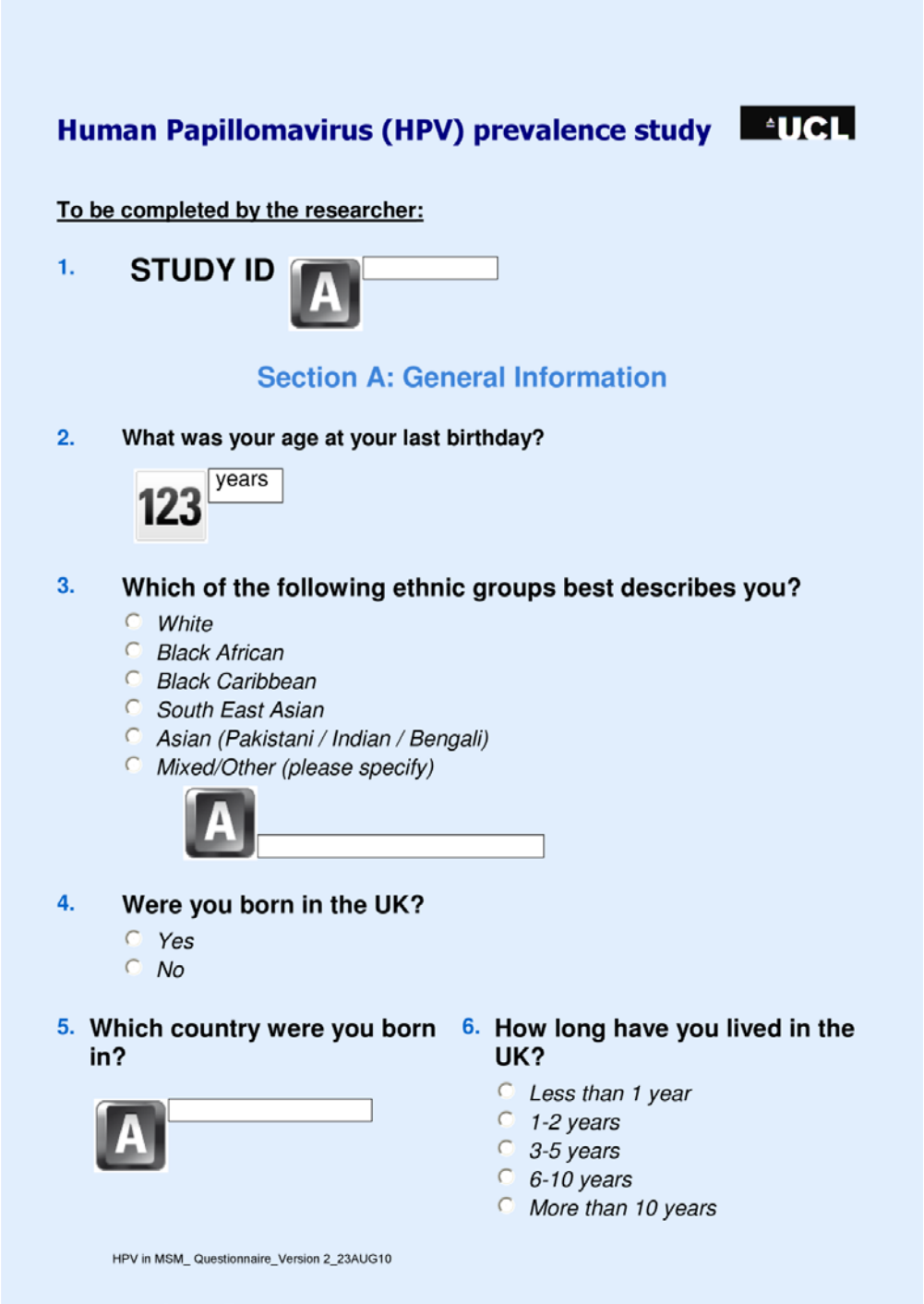
APPENDICES

APPENDIX I. HPV-MSM-MMC STUDY CASI QUESTIONNAIRE



Human Papillomavirus (HPV) prevalence study UCL

To be completed by the researcher:

1. **STUDY ID** A

Section A: General Information

2. **What was your age at your last birthday?**

123 years

3. **Which of the following ethnic groups best describes you?**
   - *White*
   - *Black African*
   - *Black Caribbean*
   - *South East Asian*
   - *Asian (Pakistani / Indian / Bengali)*
   - *Mixed/Other (please specify)*

   A

4. **Were you born in the UK?**
   - *Yes*
   - *No*

5. **Which country were you born in?**

   A

6. **How long have you lived in the UK?**
   - *Less than 1 year*
   - *1-2 years*
   - *3-5 years*
   - *6-10 years*
   - *More than 10 years*

HPV in MSM_ Questionnaire_Version 2_23AUG10

7. **Do you currently smoke cigarettes?**

- *Yes*
- *No*

8. **On average how many cigarettes do you smoke a day?**

123 cigarette(s)

9. **How often do you have a drink containing alcohol?**

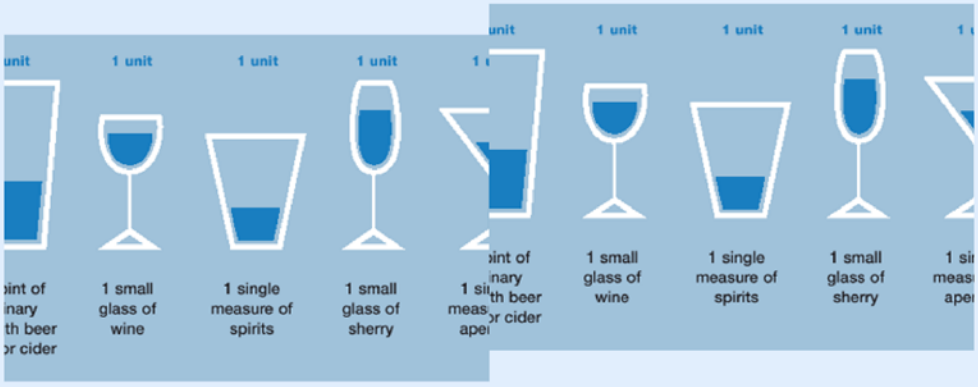
- *4 or more times per week*
- *2 - 3 times per week*
- *2 - 4 times per month*
- *Monthly or less*
- *Never*

10. **How many units of alcohol do you drink on a typical day when you are drinking?** (please don't count special occasions)

- *1-2*
- *3-4*
- *5-6*
- *7-9*
- *10 or more*

11. **How often have you had 8 or more units on a single occasion in the last year?**

- *Daily or almost daily*
- *Weekly*
- *Monthly*
- *Less than Monthly*
- *Never*



12. Are you currently employed?

- Yes
- No

13. How much do you earn before tax each year?

- Less than £10,000
- £10,000-£19,999
- £20,000-£24,999
- £25,000-£29,999
- £30,000-£34,999
- £35,000-£39,999
- £40,000-£99,999
- £100,000 or more
- It varies
- Don't know
- Prefer not to answer

14. How many years of full time education have you had since age 16?

- None
- Up to 2 years
- 3 years or more
- Still in education

15. How would you describe your sexual orientation?

- Gay / Homosexual
- Straight / Heterosexual
- Bisexual
- Other (please specify)

Section B: Sexual Behaviour

16. Altogether in your life so far, with how many men have you had sex (that is anal or oral sex)?

--Click Here--

- less than 20 men
- 21-30 men
- 31-100 men
- 101-500 men
- more than 500 men

17. **Please can you estimate how many men that is?**

123 ☐ ıen

18. **When was the last time you had each of the following types of sex?**

	In the last 3 months	*In the last year*	*Between 1 and 5 years ago*	*Over 5 years ago*	*Never*
Oral sex with a man	○	○	○	○	○
Receptive (bottom / passive) anal sex with a man	○	○	○	○	○
Insertive (top / active) anal sex with a man	○	○	○	○	○
Vaginal sex	○	○	○	○	○
Oral sex with a woman	○	○	○	○	○
Anal sex with a woman	○	○	○	○	○

19. **How old were you the FIRST time you had sex with a man?**

Oral sex 123 ☐ *years old*

Receptive (bottom / passive) anal sex 123 ☐ *years old*

Insertive (top / active) anal sex 123 ☐ *years old*

20. **NOW THINKING ABOUT THE LAST YEAR, with how many men have you had anal sex...**

...altogether? 123 _____ *men*

... that were new partners that you had anal sex with for the **first time** during the last year? 123 _____ *men*

...without a condom? 123 _____ *men*

21. **IN THE LAST YEAR, with how many men have you only had oral sex...**

123 _____ men

22. **When you had anal sex WITHOUT a condom in the last year, were you...?**

- ○ *Always insertive (top / active)*
- ○ *Always receptive (bottom / passive)*
- ○ *Versatile - equally active and passive*
- ○ *Mostly insertive*
- ○ *Mostly receptive*

23. **Have you EVER used drugs by inserting them into your anus / rectum?**

- ○ *Yes*
- ○ *No*

24. Age
(if you don't know, please estimate)

Age of Partner 1 *(most recent)* 123 ____ *years*

Age of Partner 2 123 ____ *years*

Age of Partner 3 123 ____ *years*

25. How certain are you of their age?

	Certain	*Estimate*
	○	○
	○	○
	○	○

Please provide the following information about your 3 most recent male partners, if you had anal or oral sex with them in the last year

26. Ethnic group (if you don't know, please estimate)

	White	*Black African*	*Black Car ibbean*	*South East Asian*	*Asian*	*Mixed/ Other*
Ethnic group of partner 1	○	○	○	○	○	○
Ethnic group of partner 2	○	○	○	○	○	○
Ethnic group of partner 3	○	○	○	○	○	○

Please provide the following information about your 3 most recent male partners, if you had anal or oral sex with them in the last year

27. Did you use a condom with this partner?
(even if you only had oral sex with this partner)

	Always	*Sometimes*	*Never*
Partner 1 *(most recent)*	○	○	○
Partner 2	○	○	○
Partner 3	○	○	○

28. Is this this regular (main) or a casual partner?

Regular	*Casual*
○	○
○	○
○	○

Please provide the following information about your 3 most recent male partners, if you had anal or oral sex with them in the last year

29. How many partners do you think this partner has had in the last year?
(If you don't know, please estimate)

	1	2-4	5-10	11-50	51-100	more than 100	Really can't guess
Partner 1 *(most recent)*	○	○	○	○	○	○	○
Partner 2	○	○	○	○	○	○	○
Partner 3	○	○	○	○	○	○	○

30. How certain are you about the number of partners they have had?

Certain	Estimate
○	○
○	○
○	○

Please provide the following information about your 3 most recent male partners, if you had anal or oral sex with them in the last year

Please enter the **number** of days/weeks/months on the **left hand side** and then select the **unit of time** on the **right hand side**.

For example, if the last time was **4 days ago**, complete the question as follows:

Ago

vas the LAST time you had sex with this partner?

		Days	Weeks
(most recent)	123 4	☑	☐

When was the LAST time you had sex with this partner?

31.

Ago

		Days	Weeks	Months
Partner 1 *(most recent)*	123	○	○	○
Partner 2	123	○	○	○
Partner 3	123	○	○	○

Please provide the following information about your 3 most recent male partners, if you had anal or oral sex with them in the last year

Please enter the number of days/weeks/months/years on the left hand side and then select the unit of time on the right hand side

33. When was the FIRST time you had sex with this partner?

		Ago			
		Days	*Weeks*	*Months*	*Years*
Partner 1 *(most recent)*	123	○	○	○	○
Partner 2	123	○	○	○	○
Partner 3	123	○	○	○	○

Please provide the following information about your 3 most recent male partners, if you had anal or oral sex with them in the last year

35. Are you still having sex with this partner?

	Yes	*No*
Partner 1 *(most recent)*	○	○
Partner 2	○	○
Partner 3	○	○

Section C: Your health

36. How is your health in general?

Very good	*Good*	*Fair*	*Bad*	*Very bad*
○	○	○	○	○

37. Are you circumcised (cut)?

- ○ *Yes*
- ○ *No*
- ○ *Don't know*

38. **In the last year, have you been diagnosed with any of the following sexually transmitted infections?** (tick all that apply)

- ☐ *Chlamydia*
- ☐ *Gonorrhoea*
- ☐ *Genital warts (Venereal warts)*
- ☐ *Syphilis*
- ☐ *Herpes (Genital herpes)*
- ☐ *Yes, but I can't remember which*
- ☐ *No*
- ☐ *Other (please specify)*

39. **In the last year, have you had any of the following symptoms?** (tick all that apply)

- ☐ *Pain, burning or stinging when passing urine*
- ☐ *Passing small amounts of urine more often than normal (increased urinary frequency)*
- ☐ *Genital ulcer / sore*
- ☐ *Painful testicles*
- ☐ *Discharge from the anus*
- ☐ *Bleeding from the anus*
- ☐ *Discharge from the end of your penis*
- ☐ *None of these*

40. **Have you ever had an HIV test where you could find out the result?**

- ○ *Yes*
- ○ *No*

41. **When was your most recent test?**

- ○ *In the last 12 months*
- ○ *Between 1 and 3 years ago*
- ○ *Over 3 years ago*

42. **What was the result of this test?**

- ○ *HIV negative (I did not have HIV)*
- ○ *HIV positive (I do have HIV)*
- ○ *Don't know*

43. **Have you come to the clinic today because you think that you have genital or anal warts?**

- ○ *Yes*
- ○ *No*

44. **Apart from today, have you ever had a diagnosis of genital or anal warts?**

- *Yes*
- *No*
- *Don't know*

45. **Have you ever had a diagnosis of genital or anal warts?**

- *Yes*
- *No*
- *Don't know*

46. **How many times have you had genital or anal warts DIAGNOSED?**

123 time(s)

47. **How many times have you received TREATMENT for genital or anal warts?**

123 time(s)

48. **Where did you last receive a DIAGNOSIS of genital or anal warts?**

- *GP (General Practitioner)*
- *Sexual Health Clinic (GUM clinic)*
- *Other (please specify)*

A

49. **Where did you last receive TREATMENT for genital or anal warts?**

- *GP (General Practitioner)*
- *Sexual Health Clinic (GUM clinic)*
- *Never received treatment*
- *Other (please specify)*

A

50. **How many times in your lifetime do you think you have had genital or anal warts and not had them diagnosed or treated?**

Please include times where you did not seek medical advice.

123 _____ time(s)

Section D: Your use of health services

51. **Have you visited a GP (General Practitioner) in the last year?**

- ○ *Yes*
- ○ *No*
- ○ *I am not registered with a GP*

52. **Have you told your GP your sexual orientation?**

- ○ *Yes*
- ○ *No*

53. **When did you FIRST attend a sexual health (GUM) clinic in the UK?**

- ○ *This is my first time to a sexual health (GUM) clinic*
- ○ *In the last 12 months*
- ○ *1-2 years ago*
- ○ *More than 2 years ago*
- ○ *I have been to a sexual health clinic before but I can't remember when*

54. **How old were you the first time you attended a sexual health (GUM) clinic in the UK?**

123 _____ years old

Section E: HPV vaccines

55. **The HPV vaccine course is 3 injections in a 6 month period. If you were offered the HPV vaccine in this clinic, how likely would you be to accept it?**

Definately	*Probably*	*Possibly*	*Probably not*	*Definitely not*
○	○	○	○	○

Please give reason below

56. **We are interested in how much people already know about HPV** (the virus that causes genital and anal warts)**. For each statement, please tick 'true', 'false' or 'not sure'**

	True	*False*	*Not sure*
People infected with HPV often don't have any symptoms and won't know they have the infection	○	○	○
HPV infection is very rare	○	○	○
Infection with HPV always causes cancer	○	○	○
HPV infection (types 6, 11, 16, and 18) is sexually transmitted	○	○	○

57. **We are interested in how much people already know about HPV** (the virus that causes genital and anal warts)**. For each statement, please tick 'true', 'false' or 'not sure'**

	True	*False*	*Not sure*
Immunisation with a vaccine that prevents infection with HPV types 16 and 18 will protect a person from most anal cancer	○	○	○
A person infected with HPV will find out at a regular clinic check-up and receive treatment	○	○	○
Clinical trials of the two HPV vaccines have identified very few side effects	○	○	○
You can only transmit genital warts if you have warts on your genitals	○	○	○
A person with HPV may look and feel completely healthy and still transmit the virus	○	○	○

58. **Compared with other people your age, do you think that your risk of getting a sexually transmitted infection is...**

- *Much below average?*
- *Below average?*
- *Average for a person of my age?*
- *Above average?*
- *Much above average?*

59. **Compared with other men who have sex with men your age, do you think that your risk of getting a sexually transmitted infection is...**

- *Much below average?*
- *Below average?*
- *Average?*
- *Above average?*
- *Much above average?*

60. **Have you ever been vaccinated against Hepatitis B virus?**

- *Yes*
- *No*

61. **Where were you vaccinated?**

- *GP (General Practitioner)*
- *Sexual Health Clinic (GUM clinic)*
- *Other (please specify)*

62. **How many injections did you have when you were vaccinated?**

- *1*
- *2*
- *3*
- *4 (3 in the first 6 months, then a booster 5 years later)*
- *Not sure*

APPENDIX II. RESULTS FROM THE QUESTIONNAIRE PILOT

Pilot 1	Could not answer open-ended "Altogether in your life so far, with how many men have you had sex (that is anal or oral sex)?" Could not even guess "Number of partner's partners". Need a don't know option
Pilot 2	Wanted to know the answers to the knowledge questions at the end
Pilot 3	Could not answer open-ended "Altogether in your life so far, with how many men have you had sex (that is anal or oral sex)?" Wanted more information for the vaccine likelihood question. Asked if this could be an option
Pilot 4	Could not answer open-ended "Altogether in your life so far, with how many men have you had sex (that is anal or oral sex)?" Suggested simplifying the "new partners in the last year" section Age of partner needs to be a category Certain of age? Needs to be in line Change order: partner's partners to after age of partner HIV test question. Make clearer
Pilot 5	Could not answer open-ended "Altogether in your life so far, with how many men have you had sex (that is anal or oral sex)?" Wanted more information for the vaccine likelihood question. Asked if this could be an option
Pilot 6	Could not answer open-ended "Altogether in your life so far, with how many men have you had sex (that is anal or oral sex)?" Ranges would work. Number of condomless partners: need to remind that this still applies to exclusively oral sex partners Partner's partners estimation: Allow free text e.g. "a lot", could guess if ranges were given Risk perception: need another question. Compared to other MSM your age… Where HBV vaccinated. Need to convert to tick all that apply.
Pilot 7	Could not answer open-ended "Altogether in your life so far, with how many men have you had sex (that is anal or oral sex)?" Ranges would work. Partners altogether and last year oral: Needs to be approximately. Number of condomless partners: need to remind that this still applies to exclusively oral sex partners Partner's partners estimation: Allow free text e.g. "a lot", could guess if ranges were given Last time you had sex with…: Layout needs to be clearer Knowledge questions: split over 2 pages Compared with (not to)
Pilot 8	Order partners in the last year. New partners above condomless so it is clear is includes all.
Pilot 9	No issues identified
Pilot 10	Could not answer open-ended "Altogether in your life so far, with how many men have you had sex (that is anal or oral sex)?" Ranges would work.

APPENDIX III. AGE-SPECIFIC PREVALENCE DATA

APPENDIX TABLE 1. AGE-SPECIFIC ANOGENITAL HPV DATA IN 511 MSM (DATA FOR FIGURE 31)

HPV type	Age	Prevalence (%)	95% CI
any HPV	18-20	58.8	32.9-81.6
	21-25	68.1	58.9-76.3
	26-30	67.7	58.8-75.7
	31-35	74.3	66.2-81.3
	36-40	81.5	72.9-88.3
HR-HPV	18-20	41.2	18.4-67.1
	21-25	40.3	31.4-49.7
	26-30	48.0	39.1-57.1
	31-35	50.0	41.4-58.6
	36-40	50.9	41.1-60.7
Quadrivalent vaccine type HPV	18-20	29.4	10.3-56.0
	21-25	29.4	21.4-38.5
	26-30	36.2	27.9-45.2
	31-35	27.9	20.6-36.1
	36-40	38.0	28.8-47.8
9-valent vaccine type HPV	18-20	41.2	18.4-67.1
	21-25	40.3	31.4-49.7
	26-30	49.6	40.6-58.6
	31-35	41.4	33.2-50.1
	36-40	51.9	42.0-61.6
HPV6	18-20	17.6	3.8-43.4
	21-25	6.7	2.9-12.8
	26-30	9.4	5.0-15.9
	31-35	10.0	5.6-16.2
	36-40	10.2	5.2-17.5
HPV11	18-20	17.6	3.8-43.4
	21-25	13.4	7.9-20.9
	26-30	11.0	6.2-17.8
	31-35	6.4	3.0-11.9
	36-40	15.7	9.4-24.0
HPV16	18-20	0.0	0.0-19.5
	21-25	13.4	7.9-20.9
	26-30	17.3	11.2-25.0
	31-35	13.6	8.4-20.4
	36-40	11.1	5.9-18.6
HPV18	18-20	11.8	1.5-36.4
	21-25	5.9	2.4-11.7
	26-30	5.5	2.2-11.0
	31-35	5.0	2.0-10.0
	36-40	8.3	3.9-15.2
HPV31/33/45/52/58	18-20	17.6	3.8-43.4
	21-25	16.8	10.6-24.8
	26-30	27.6	20.0-36.2
	31-35	20.0	13.7-27.6
	36-40	22.2	14.8-31.2
HPV16/18	18-20	11.8	1.5-36.4
	21-25	16.8	10.6-24.8
	26-30	21.3	14.5-29.4
	31-35	17.9	11.9-25.2
	36-40	18.5	11.7-27.1
HPV6/11	18-20	23.5	6.8-49.9
	21-25	17.6	11.3-25.7
	26-30	19.7	13.2-27.7
	31-35	13.6	8.4-20.4
	36-40	24.1	16.4-33.3

Frequency of detecting HPV DNA in any anogenital specimen in participants of the HPV-MSM-MMC study with at least one anogenital sample that was adequate for HPV testing (n=511).

Data are displayed graphically in chapter 5, Figure 31, page 124.

APPENDIX TABLE 2. AGE-SPECIFIC HPV SEROPREVALENCE IN 506 MSM (DATA FOR FIGURE 46)

		TOTAL (N=506)		HIV negative (N=480)		HIV positive (N=26)	
HPV type	Age	Prevalence (%)	95% CI	Prevalence (%)	95% CI	Prevalence (%)	95% CI
HPV16 seropositive	18-20	6.3	0.2-30.2	6.3	0.2-30.2		
	21-25	19.8	13.0-28.3	18.9	12.1-27.5	40.0	5.3-85.3
	26-30	30.8	23.0-39.5	28.5	20.7-37.3	71.4	29.0-96.3
	31-35	29.5	22.1-37.8	26.9	19.5-35.4	66.7	29.9-92.5
	36-40	37.1	27.9-47.1	37.0	27.6-47.2	40.0	5.3-85.3
HPV18 seropositive	18-20	6.3	0.2-30.2	6.3	0.2-30.2		
	21-25	9.5	4.8-16.3	8.1	3.8-14.8	40.0	5.3-85.3
	26-30	14.6	9.0-21.9	13.0	7.6-20.3	42.9	9.9-81.6
	31-35	24.5	17.6-32.5	23.8	16.8-32.1	33.3	7.5-70.1
	36-40	21.0	13.6-30.0	21.0	13.5-30.3	20.0	0.5-71.6
HPV16 and/or 18 seropositive	18-20	12.5	1.6-38.3	12.5	1.6-38.3		
	21-25	21.6	14.5-30.1	20.7	13.6-29.5	40.0	5.3-85.3
	26-30	34.6	26.5-43.5	32.5	24.4-41.6	71.4	29.0-96.3
	31-35	41.7	33.4-50.4	38.5	30.1-47.4	88.9	51.8-99.7
	36-40	41.9	32.3-51.9	42.0	32.2-52.3	40.0	5.3-85.3
HPV16 and 18 seropositive	18-20	0.0	0.0-20.6	0.0	0.0-20.6		
	21-25	7.8	3.6-14.2	6.3	2.6-12.6	40.0	5.3-85.3
	26-30	10.8	6.0-17.4	8.9	4.5-15.4	42.9	9.9-81.6
	31-35	12.2	7.3-18.9	12.3	7.2-19.2	11.1	0.3-48.2
	36-40	16.2	9.7-24.7	16.0	9.4-24.7	20.0	0.5-71.6

Data (total, N=506) are displayed graphically in chapter 6, Figure 46, page 154

APPENDIX TABLE 3. AGE-SPECIFIC ESTIMATES FOR LR-HPV AND AGW PREVALENCE (DATA FOR FIGURE 54)

HPV type	Age	Prevalence (%)	95% CI
Anogenital HPV6/11	18-20	23.5	6.8-49.9
	21-25	17.4	11.1-25.3
	26-30	18.8	12.5-26.5
	31-35	13.4	8.3-20.1
	36-40	23.9	16.2-33.0
AGW warts diagnosis at study visit	18-20	17.6	3.8-43.4
	21-25	4.1	1.4-9.4
	26-30	0.8	0.0-4.1
	31-35	4.2	1.6-9.0
	36-40	5.5	2.0-11.6
History of AGW	18-20	17.6	3.8-43.4
	21-25	23.1	16.0-31.7
	26-30	25.8	18.5-34.1
	31-35	37.6	29.6-46.1
	36-40	35.8	26.8-45.5

Data are displayed graphically in chapter 7, Figure 54, page 178

APPENDIX IV. RISK FACTOR ANALYSES TABLES

ANAL AND EXTERNAL GENITAL SWABS

APPENDIX TABLE 4. RISK FACTORS FOR THE DETECTION OF HR-HPV DNA IN THE ANAL AND EXTERNAL GENITAL SWABS

	ANAL						EXTERNAL					
	Number of MSM						Number of MSM					
Risk factor	HR-HPV neg. (n)	HR-HPV pos. (n)	OR	95% CI	aOR	95% CI	HR-HPV neg. (n)	HR-HPV pos.(n)	OR	95% CI	aOR	95% CI
HIV positive diagnosis												
no	253	167	1		1		255	154	1		1	
yes	9	13	2.33	(1.48-3.66)	2.29	(1.46-3.60)	9	16	2.21	(1.43-3.40)	2.20	(1.43-3.39)
Each additional year in age			1.02	(0.99-1.04)	N/A	N/A			1.01	(0.98-1.03)	N/A	N/A
Ethnic group												
White	188	147	1		1		198	130	1		1	
Black	40	18	0.63	(0.39-1.04)	0.64	(0.39-1.04)	36	17	0.78	(0.49-1.27)	0.79	(0.49-1.27)
Asian & SE Asian	30	13	0.63	(0.36-1.11)	0.64	(0.36-1.12)	30	17	0.81	(0.49-1.33)	0.81	(0.49-1.34)
Born in the UK												
no	143	92	1		1		150	84	1		1	
yes	118	86	1.03	(0.77-1.37)	1.04	(0.78-1.38)	116	81	1.12	(0.84-1.49)	1.12	(0.83-1.49)
Currently smoke												
no	189	118	1		1		190	114	1		1	
yes	72	59	1.10	(0.80-1.50)	1.12	(0.82-1.53)	75	51	1.05	(0.76-1.44)	1.06	(0.77-1.45)
Increasing or higher risk alcohol drinking (AUDIT-C)												
No	86	67	1		1		89	56	1		1	
Yes	172	108	0.91	(0.68-1.24)	0.91	(0.68-1.24)	174	107	0.88	(0.65-1.19)	0.88	(0.65-1.20)
Currently employed												
no	54	38	1		1		54	35	1		1	
yes	207	140	0.99	(0.69-1.41)	0.93	(0.65-1.34)	212	130	0.83	(0.59-1.17)	0.80	(0.57-1.14)
Years of education post-16												
0-2 years	35	26	1.40	(0.94-2.07)	1.42	(0.96-2.11)	28	33	1.73	(1.21-2.48)	1.74	(1.21-2.50)
3 years or more	182	117	1		1		192	106	1		1	
Sexual orientation												
Gay/homosexual	235	168	1		1		238	154	1		1	
Bisexual	25	10	0.48	(0.23-0.97)	0.49	(0.24-1.00)	27	11	0.71	(0.40-1.27)	0.72	(0.40-1.30)
Circumcised												
No	175	130	1		1		186	118	1		1	
Yes	83	47	0.92	(0.66-1.26)	0.91	(0.66-1.26)	78	45	0.93	(0.67-1.29)	0.93	(0.67-1.29)

APPENDIX TABLE 4. RISK FACTORS FOR THE DETECTION OF HR-HPV DNA IN THE ANAL AND EXTERNAL GENITAL SWABS CONTINUED

	ANAL						EXTERNAL					
	Number of MSM						Number of MSM					
Risk factor	**HR-HPV neg. (n)**	**HR-HPV pos. (n)**	**OR**	**95% CI**	**aOR**	**95% CI**	**HR-HPV neg. (n)**	**HR-HPV pos.(n)**	**OR**	**95% CI**	**aOR**	**95% CI**
Number of lifetime male partners (anal and oral sex)												
<31	107	44	1		1		99	40	1		1	
>=31	153	134	1.97	(1.40-2.77)	1.97	(1.38-2.82)	167	125	1.48	(1.05-2.06)	1.48	(1.04-2.10)
Number of male sex partners in the last year												
male anal sex partners												
<10	156	79	1		1		156	67	1		1	
>=10	88	92	1.54	(1.14-2.06)	1.51	(1.13-2.04)	95	89	1.87	(1.38-2.53)	1.86	(1.38-2.52)
New anal sex partners												
<10	173	102	1		1		175	87	1		1	
>=10	69	68	1.35	(1.00-1.82)	1.33	(0.99-1.81)	74	68	1.51	(1.11-2.04)	1.50	(1.11-2.03)
Anal sex partners without a condom												
<10	230	154	1		1		236	139	1		1	
>=10	11	17	1.43	(0.86-2.39)	1.42	(0.85-2.36)	13	16	1.62	(1.00-2.62)	1.61	(0.99-2.61)
Exclusively oral sex partners												
<10	175	98	1		1		176	89	1		1	
>=10	65	60	1.25	(0.90-1.72)	1.23	(0.89-1.71)	64	58	1.42	(1.03-1.95)	1.41	(1.03-1.95)
Each additional year of age at first sex with a man												
Oral			0.97	(0.93-1.01)	0.96	(0.92-1.00)			0.97	(0.93-1.00)	0.96	(0.92-1.00)
Receptive anal			0.98	(0.95-1.02)	0.97	(0.93-1.01)			0.97	(0.93-1.00)	0.96	(0.92-1.00)
Oral sex with a man in last 3 months												
No	9	2	1		1		10	2	1		1	
Yes	248	175	3.23	(0.68-15.45)	3.22	(0.67-15.37)	253	161	2.07	(0.61-7.06)	2.10	(0.62-7.16)
Receptive anal sex with a man in last 3 months												
No	106	38	1		1		92	40	1		1	
Yes	149	137	2.35	(1.64-3.37)	2.43	(1.70-3.49)	168	124	1.57	(1.12-2.20)	1.61	(1.14-2.27)
Insertive anal sex with a man in last 3 months												
No	62	31	1		1		63	29	1		1	
Yes	185	141	1.41	(0.96-2.06)	1.39	(0.95-2.03)	196	128	1.52	(1.02-2.27)	1.52	(1.01-2.26)

APPENDIX TABLE 4. RISK FACTORS FOR THE DETECTION OF HR-HPV DNA IN THE ANAL AND EXTERNAL GENITAL SWABS CONTINUED

	ANAL						EXTERNAL					
	Number of MSM						Number of MSM					
Risk factor	HR-HPV neg. (n)	HR-HPV pos. (n)	OR	95% CI	aOR	95% CI	HR-HPV neg. (n)	HR-HPV pos.(n)	OR	95% CI	aOR	95% CI
Vaginal sex in the last year												
No	194	122	1		1		198	114	1		1	
Yes	16	8	0.91	(0.46-1.78)	0.92	(0.47-1.79)	20	8	0.75	(0.37-1.49)	0.75	(0.37-1.49)
Oral sex with a woman in the last year												
No	195	126	1		1		199	118	1		1	
Yes	16	6	0.71	(0.33-1.53)	0.72	(0.33-1.55)	20	6	0.63	(0.29-1.35)	0.63	(0.29-1.36)
Anal sex with a woman in the last year												
No	208	130	1		1		214	121	1		1	
Yes	2	1	0.66	(0.08-5.53)	0.62	(0.07-5.21)	2	3	2.24	(0.84-5.98)	2.26	(0.85-6.05)
Position when having anal sex without a condom in the last year												
Insertive only	44	23	1		1		50	15	1		1	
Receptive or versatile	94	96	1.95	(1.24-3.08)	2.00	(1.27-3.16)	103	89	1.99	(1.21-3.28)	2.00	(1.21-3.29)
Each additional year at first attending a sexual health clinic			0.99	(0.96-1.02)	0.97	(0.93-1.00)			1.01	(0.98-1.03)	1.00	(0.96-1.04)
Use of drugs in anus/rectum ever												
No	242	153	1		1		244	139	1		1	
Yes	19	25	1.63	(1.08-2.45)	1.60	(1.06-2.41)	22	26	1.64	(1.11-2.43)	1.63	(1.10-2.41)
Condom use with most recent partner												
Always	121	86	1		1		124	82	1		1	
Not always	138	91	0.94	(0.70-1.25)	0.95	(0.71-1.26)	139	82	0.88	(0.66-1.17)	0.88	(0.66-1.17)
Most recent male partner (oral or anal)												
Each additional year of age of partner			1.01	(0.99-1.03)	1.00	(0.98-1.02)			1.00	(0.98-1.02)	1.00	(0.98-1.02)
Each additional day since last having sex with partner			1.00	(0.99-1.00)	1.00	(0.99-1.00)			1.00	(1.00-1.00)	1.00	(1.00-1.00)
Relationship type with most recent partner												
Regular	121	97	1		1		135	80	1		1	
Casual	131	74	0.85	(0.63-1.14)	0.85	(0.63-1.14)	123	78	1.19	(0.88-1.60)	1.19	(0.89-1.60)
Relationship is continuing with most recent partner												
No	131	76	1		1		119	75	1		1	
Yes	128	102	1.20	(0.90-1.60)	1.19	(0.89-1.59)	144	90	0.88	(0.66-1.18)	0.88	(0.66-1.17)
Concurrency between any of the 3 most recent partners												
No	121	70	1		1		124	66	1		1	
Yes	140	108	1.24	(0.92-1.66)	1.22	(0.91-1.64)	142	99	1.21	(0.90-1.63)	1.21	(0.90-1.63)

Abbreviations: HR-HPV neg.=DNA of HR-HPV types not detected. HR-HPV pos.=DNA of at least one HR-HPV type detected. aOR=age-adjusted odds ratio. N/A=Not applicable. Logistic regression models fitted using the generalised equation estimation (GEE) method.

ORAL AND URINE SPECIMENS

APPENDIX TABLE 5. RISK FACTORS FOR THE DETECTION OF HR-HPV DNA IN THE ORAL AND URINE SPECIMENS

	ORAL						URINE					
	Number of MSM						Number of MSM					
Risk factor	**HR-HPV neg. (n)**	**HR-HPV pos. (n)**	**OR**	**95% CI**	**aOR**	**95% CI**	**HR-HPV neg. (n)**	**HR-HPV pos. (n)**	**OR**	**95% CI**	**aOR**	**95% CI**
HIV positive diagnosis												
no	140	7	1				441	20	1		1	
yes	12	0	N/A	N/A	N/A	N/A	20	5	5.35	(2.09-13.69)	5.42	(2.11-13.90)
Each additional year in age			0.96	(0.86-1.08)	N/A	N/A			0.99	(0.93-1.06)	N/A	N/A
Ethnic group												
White	117	6	1		1		341	19	1		1	
Black	21	2	1.79	(0.37-8.54)	1.69	(0.35-8.15)	53	5	1.48	(0.53-4.15)	1.48	(0.53-4.15)
Asian & SE Asian	17	1	1.14	(0.14-9.00)	1.13	(0.14-8.96)	49	0	N/A	N/A	N/A	N/A
Born in the UK												
No	77	6	1		1		240	12	1		1	
Yes	79	3	0.50	(0.13-1.95)	0.50	(0.13-1.93)	206	12	1.16	(0.51-2.60)	1.16	(0.51-2.60)
Currently smoke												
No	114	7	1		1		316	17	1		1	
Yes	42	2	0.78	(0.17-3.64)	0.75	(0.16-3.50)	129	7	1.09	(0.45-2.61)	1.09	(0.45-2.63)
Increasing or higher risk alcohol drinking (AUDIT-C)												
No	51	2	1		1		151	12	1		1	
Yes	103	7	1.69	(0.36-7.83)	1.67	(0.36-7.76)	289	12	0.63	(0.28-1.44)	0.63	(0.28-1.44)
Currently employed												
No	30	3	1		1		92	8	1		1	
Yes	126	6	0.50	(0.13-1.93)	0.55	(0.13-2.40)	354	16	0.51	(0.22-1.19)	0.49	(0.20-1.17)
Years of education post-16												
0-2 years	20	4	4.97	(1.28-19.25)	4.96	(1.28-19.25)	65	4	1.10	(0.36-3.35)	1.08	(0.35-3.33)
3 years or more	114	4	1		1		305	16	1		1	
Sexual orientation												
Gay/homosexual	142	7	1		1		411	20	1		1	
Bisexual	14	2	2.68	(0.58-12.46)	2.60	(0.56-12.11)	34	4	2.07	(0.67-6.41)	2.09	(0.67-6.55)
Circumcised												
No	104	4	1		1		311	18	1		1	
Yes	51	5	2.42	(0.67-8.74)	2.37	(0.65-8.56)	131	6	0.88	(0.35-2.21)	0.88	(0.35-2.21)

APPENDIX TABLE 5. RISK FACTORS FOR THE DETECTION OF HR-HPV DNA IN THE ORAL AND URINE SPECIMENS CONTINUED

	ORAL						URINE					
	Number of MSM						Number of MSM					
Risk factor	**HR-HPV neg. (n)**	**HR-HPV pos. (n)**	**OR**	**95% CI**	**aOR**	**95% CI**	**HR-HPV neg. (n)**	**HR-HPV pos. (n)**	**OR**	**95% CI**	**aOR**	**95% CI**
Number of lifetime male partners (anal and oral sex)												
<31	56	4	1		1		147	7	1		1	
>=31	100	5	0.71	(0.20-2.58)	0.80	(0.21-3.09)	298	17	1.33	(0.54-3.29)	1.37	(0.52-3.57)
Number of male sex partners in the last year												
Male anal sex partners												
<10	75	5	1		1		231	14	1		1	
>=10	71	3	0.65	(0.16-2.62)	0.66	(0.16-2.68)	189	8	0.89	(0.37-2.11)	0.88	(0.37-2.11)
New anal sex partners												
<10	89	7	1		1		274	16	1		1	
>=10	56	1	0.24	(0.03-1.85)	0.25	(0.03-1.92)	142	6	0.98	(0.40-2.41)	0.98	(0.40-2.41)
Anal sex partners without a condom												
<10	135	7	1		1		390	20	1		1	
>=10	11	1	1.69	(0.22-13.17)	1.78	(0.23-13.88)	27	2	2.03	(0.57-7.18)	2.03	(0.57-7.17)
Exclusively oral sex partners												
<10	92	7	1		1		276	15	1		1	
>=10	40	1	0.34	(0.04-2.65)	0.36	(0.05-2.76)	125	7	1.10	(0.45-2.70)	1.12	(0.46-2.74)
Each additional year of age at first sex with a man												
Oral			1.01	(0.86-1.19)	1.03	(0.86-1.23)			0.96	(0.85-1.07)		
Receptive anal			0.97	(0.82-1.14)	0.99	(0.82-1.19)			1.00	(0.90-1.10)		
Oral sex with a man in last 3 months												
No	4	1	1		1		15	0				
Yes	152	8	0.25	(0.03-1.90)	0.23	(0.03-1.78)	427	23				
Receptive anal sex with a man in last 3 months												
No	49	4	1		1		148	8	1		1	
Yes	102	5	0.62	(0.17-2.23)	0.57	(0.16-2.09)	290	15	1.09	(0.45-2.64)	1.08	(0.44-2.64)
Insertive anal sex with a man in last 3 months												
No	27	3	1		1		97	3	1		1	
Yes	123	5	0.39	(0.10-1.58)	0.39	(0.09-1.56)	331	20	2.09	(0.59-7.40)	2.10	(0.59-7.41)

APPENDIX TABLE 5. RISK FACTORS FOR THE DETECTION OF HR-HPV DNA IN THE ORAL AND URINE SPECIMENS CONTINUED

	ORAL						URINE					
	Number of MSM						Number of MSM					
Risk factor	HR-HPV neg. (n)	HR-HPV pos. (n)	OR	95% CI	aOR	95% CI	HR-HPV neg. (n)	HR-HPV pos. (n)	OR	95% CI	aOR	95% CI
Vaginal sex in the last year												
No	118	5	1		1		328	14				
Yes	10	1	2.25	(0.27-18.49)	2.25	(0.27-18.89)	25	1	0.82	(0.09-7.47)	0.80	(0.09-7.27)
Oral sex with a woman in the last year												
No	118	5	1		1		333	15				
Yes	10	1	2.25	(0.27-18.49)	2.24	(0.27-18.84)	24	1	0.82	(0.09-7.31)	0.80	(0.09-7.11)
Anal sex with a woman in the last year												
No	126	5	1		1		349	16	N/A			
Yes	1	1	13.58	(1.60-115.07)	14.14	(1.57-127.21)	6	0	N/A	N/A	N/A	N/A
Position when having anal sex without a condom in the last year												
Insertive only	21	3	1		1		68	5	1		1	
Receptive or versatile	72	2	0.21	(0.04-1.24)	0.22	(0.04-1.27)	191	9	0.80	(0.25-2.58)	0.81	(0.25-2.64)
Each additional year at first attending a sexual health clinic			1.05	(0.92-1.20)	1.18	(0.95-1.46)	161		1.02	(0.94-1.11)		
Use of drugs in anus/rectum ever												
No	138	7	1		1		404	21	1		1	
Yes	18	2	2.08	(0.45-9.67)	2.38	(0.49-11.47)	42	3	1.72	(0.57-5.23)	1.73	(0.57-5.26)
Condom use with most recent partner												
Always	71	4	1		1		213	12	1		1	
Not always	83	5	1.07	(0.30-3.85)	1.09	(0.30-3.92)	230	11	1.01	(0.44-2.32)	1.01	(0.44-2.31)
Most recent male partner (oral or anal)												
Each additional year of age of partner			1.02	(0.94-1.11)	1.04	(0.95-1.13)			1.02	(0.97-1.07)	1.02	(0.97-1.08)
Each additional day since last having sex with partner			0.90	(0.77-1.05)	0.90	(0.77-1.05)			1.00	(0.99-1.01)	1.00	(0.99-1.01)
Relationship type with most recent partner												
Regular	82	4	1		1		221	13	1		1	
Casual	68	5	1.48	(0.41-5.32)	1.50	(0.41-5.40)	211	10	0.83	(0.36-1.91)	0.83	(0.36-1.91)
Relationship is continuing with most recent partner												
No	70	4	1		1		205	11	1		1	
Yes	84	5	1.04	(0.29-3.75)	1.05	(0.29-3.78)	237	13	1.01	(0.45-2.27)	1.01	(0.45-2.27)
Concurrency between any of the 3 most recent partners												
No	76	5	1		1		198	10	1		1	
Yes	80	4	0.77	(0.21-2.78)	0.82	(0.22-3.03)	248	14	1.27	(0.56-2.90)	1.27	(0.56-2.91)

Abbreviations: HR-HPV neg.=DNA of HR-HPV types not detected. HR-HPV pos.=DNA of at least one HR-HPV type detected. aOR=age-adjusted odds ratio. N/A=Not applicable. Logistic regression models fitted using the generalised equation estimation (GEE) method.

APPENDIX TABLE 6. RISK FACTORS FOR HR-HPV TYPE-SPECIFIC ANOGENITAL CONCORDANT INFECTIONS IN MSM

Risk factor	**ANOGENITAL CONCORDANCE** HR-HPV detected at <2 sites (n)	HR-HPV detected at ≥2 sites (n)	OR	95% CI	aOR	95% CI	**ANOGENITAL CONCORDANCE compared to SINGLE INFECTION** MSM with HR-HPV detected at one site (n)	HR-HPV detected at ≥2 sites (n)	OR	95% CI	aOR	95% CI
Each additional year in age			0.99	(0.96-1.02)	N/A	N/A			0.97	(0.93-1.02)	N/A	N/A
Ethnic group												
White	194	88	1		1		74	88	1		1	
Black	33	10	0.69	(0.36-1.31)	0.69	(0.36-1.31)	10	10	0.96	(0.42-2.19)	0.96	(0.42-2.20)
Asian & SE Asian	31	8	0.69	(0.35-1.35)	0.69	(0.35-1.35)	11	8	0.95	(0.40-2.24)	0.95	(0.40-2.24)
Born in the UK												
No	154	53	1		1		54	53	1		1	
Yes	107	53	1.16	(0.80-1.68)	1.16	(0.80-1.68)	42	53	1.04	(0.65-1.66)	1.04	(0.65-1.67)
Currently smoke												
No	186	70	1		1		70	70	1		1	
Yes	74	36	1.14	(0.77-1.69)	1.13	(0.76-1.68)	25	36	1.24	(0.75-2.06)	1.19	(0.71-2.00)
Increasing or higher risk drinking (AUDIT-C)												
No	86	42	1		1		35	42	1		1	
Yes	172	62	0.77	(0.53-1.12)	0.76	(0.52-1.11)	60	62	0.78	(0.48-1.27)	0.76	(0.47-1.25)
Currently employed												
No	50	25	1		1		18	25	1		1	
Yes	211	81	0.77	(0.51-1.18)	0.78	(0.50-1.21)	78	81	0.87	(0.50-1.51)	0.93	(0.52-1.64)
Years of education post-16												
0 to 2 years	48	22	1.72	(1.07-2.77)	1.70	(1.06-2.74)	15	23	1.34	(0.75-2.42)	1.33	(0.74-2.42)
3 years or more	275	64	1		1		89	67	1		1	
Sexual orientation												
Gay/homosexual	238	100	1		1		87	100	1		1	
Bisexual	22	6	0.60	(0.26-1.41)	0.59	(0.25-1.39)	9	6	0.72	(0.26-2.01)	0.70	(0.25-1.96)
Circumcised												
No	174	79	1		1		65	79	1		1	
Yes	84	26	0.73	(0.47-1.12)	0.73	(0.47-1.12)	30	26	0.67	(0.39-1.13)	0.66	(0.39-1.13)

APPENDIX TABLE 6. RISK FACTORS FOR HR-HPV TYPE-SPECIFIC ANOGENITAL CONCORDANT INFECTIONS IN MSM CONTINUED.

Risk factor	ANOGENITAL CONCORDANCE: HR-HPV detected at <2 sites (n)	HR-HPV detected at ≥2 sites (n)	OR	95% CI	aOR	95% CI	ANOGENITAL CONCORDANCE compared to SINGLE INFECTION: MSM with HR-HPV detected at one site (n)	HR-HPV detected at ≥2 sites (n)	OR	95% CI	aOR	95% CI
Number of lifetime male partners (anal and oral sex)												
<31	89	26	1		1		22	26	1		1	
>=31	172	80	1.40	(0.91-2.14)	1.52	(0.96-2.40)	74	80	0.66	(0.38-1.17)	0.74	(0.40-1.35)
Number of male sex partners in the last year												
Male anal sex partners												
<10	146	44	1		1		48	44	1		1	
>=10	101	56	1.67	(1.14-2.45)	1.69	(1.15-2.49)	46	56	1.16	(0.71-1.88)	1.17	(0.71-1.91)
New anal sex partners												
<10	170	55	1		1		63	55	1		1	
>=10	75	45	1.55	(1.05-2.27)	1.56	(1.06-2.30)	30	45	1.43	(0.87-2.34)	1.47	(0.89-2.41)
Anal sex partners without a condom												
<10	228	90	1		1		82	90	1		1	
>=10	16	10	1.4	(0.74-2.63)	1.41	(0.75-2.65)	11	10	0.77	(0.36-1.66)	0.79	(0.36-1.71)
Exclusively oral sex partners												
<10	170	59	1		1		56	59	1		1	
>=10	70	36	1.19	(0.79-1.80)	1.19	(0.79-1.81)	30	36	0.88	(0.52-1.48)	0.89	(0.53-1.51)
Each additional year of age at first sex with a man												
Oral			0.97	(0.92-1.02)	0.96	(0.85-1.08)			1.01	(0.94-1.09)	0.97	(0.92-1.02)
Receptive anal			0.98	(0.94-1.03)	1.00	(0.89-1.11)			1.01	(0.95-1.07)	0.99	(0.94-1.04)
Oral sex with a man in last 3 months												
No	6	1	1		1		1	1	1		1	
Yes	252	105	2.47	(0.32-19.03)	2.47	(0.32-19.05)	93	105	0.69	(0.04-11.07)	0.77	(0.05-12.46)
Receptive anal sex with a man in last 3 months												
No	89	21	1		1		22	21	1		1	
Yes	166	84	2.17	(1.35-3.49)	2.17	(1.35-3.50)	73	84	1.06	(0.57-1.97)	1.01	(0.54-1.88)
Insertive anal sex with a man in last 3 months												
No	59	16	1		1		19	16	1		1	
Yes	193	84	1.64	(0.96-2.81)	1.65	(0.96-2.82)	75	84	1.18	(0.61-2.29)	1.19	(0.61-2.32)

APPENDIX TABLE 6. RISK FACTORS FOR HR-HPV TYPE-SPECIFIC ANOGENITAL CONCORDANT INFECTIONS IN MSM CONTINUED.

Risk factor	ANOGENITAL CONCORDANCE: HR-HPV detected at <2 sites (n)	HR-HPV detected at ≥2 sites (n)	OR	95% CI	aOR	95% CI	ANOGENITAL CONCORDANCE compared to SINGLE INFECTION: MSM with HR-HPV detected at one site (n)	HR-HPV detected at ≥2 sites (n)	OR	95% CI	aOR	95% CI
Vaginal sex in the last year												
No	276	70	1		1		90	70	1		1	
Yes	25	4	0.7	(0.25-1.94)	0.69	(0.25-1.93)	7	4	0.73	(0.25-2.12)	0.79	(0.27-2.33)
Oral sex with a woman in the last year												
No	280	72	1		1		93	72	1		1	
Yes	24	3	0.54	(0.17-1.76)	0.54	(0.17-1.75)	6	3	0.48	(0.13-1.78)	0.52	(0.14-1.96)
Anal sex with a woman in the last year												
No	297	74	N/A		N/A		96	74	N/A		N/A	
Yes	6	0	N/A	N/A	N/A	N/A	4	0	N/A	N/A	N/A	N/A
Position when having anal sex without a condom in the last year												
Insertive only	49	9	1		1		18	9	1		1	
Receptive or versatile	106	61	2.88	(1.47-5.64)	2.84	(1.45-5.57)	47	61	2.29	(1.00-5.25)	2.22	(0.96-5.14)
Each additional year at first attending a sexual health clinic			0.99	(0.96-1.03)	1.04	(0.93-1.16)			1.00	(0.95-1.05)	1.00	(0.95-1.05)
Use of drugs in anus/rectum ever												
No	238	90	1		1		84	90	1		1	
Yes	23	16	1.63	(0.98-2.69)	1.64	(0.99-2.72)	12	16	1.06	(0.56-2.03)	1.07	(0.56-2.06)
Condom use with most recent partner												
Always	121	52	1		1		45	52	1		1	
Not always	138	53	0.89	(0.61-1.28)	0.89	(0.61-1.29)	51	53	0.92	(0.57-1.47)	0.90	(0.56-1.45)
Most recent male partner (oral or anal)												
Each additional year of age of partner			1.01	(0.98-1.03)	1.02	(0.97-1.08)			0.99	(0.96-1.03)	1.01	(0.98-1.04)
Each additional day since last having sex with partner			1.00	(1.00-1.01)	1.00	(0.99-1.01)			1.02	(1.01-1.03)	1.00	(1.00-1.01)
Relationship type with most recent partner												
Regular	136	54	1		1		59	54	1		1	
Casual	117	47	1.12	(0.77-1.64)	1.12	(0.77-1.63)	34	47	1.56	(0.96-2.53)	1.57	(0.96-2.55)
Relationship is continuing with most recent partner												
No	113	52	1		1		30	52	1		1	
Yes	146	54	0.78	(0.54-1.12)	0.78	(0.54-1.13)	66	54	0.54	(0.34-0.86)	0.55	(0.34-0.88)
Concurrency between any of the 3 most recent partners												
No	115	43	1		1		33	43	1		1	
Yes	146	63	1.18	(0.81-1.71)	1.18	(0.81-1.73)	63	63	0.88	(0.54-1.43)	0.88	(0.54-1.43)

Abbreviations: aOR=age-adjusted odds ratio. N/A=Not applicable. Logistic regression models fitted using the generalised equation estimation (GEE) method.

APPENDIX V. MATHEMATICAL MODEL STATE VARIABLE DEFINITIONS AND EQUATIONS

APPENDIX TABLE 7. MATHEMATICAL MODEL STATE VARIABLE DEFINITIONS

	State Variable	Definition
UNVACCINATED (no subscript)	N	The number of HIV negative men who have not been vaccinated and have not had anal sex with a man in their lifetime.
	S, S^h	The number of HIV negative/positive MSM who have not been vaccinated and are susceptible to HPV16 infection
	R, R^h	The number of HIV negative/positive MSM who have not been vaccinated and have effective natural immunity to HPV16 infection
	I, I^h	The number of HIV negative/positive MSM who have not been vaccinated and are infectious with HPV16 and have normal or ASCUS cytology/histology
	L^t, L^{th}	The number of HIV negative/positive MSM who have not been vaccinated and are infectious with HPV16, with detectable LSIL/LGAIN
	H^t, H^{th}	The number of HIV negative/positive MSM who have not been vaccinated and are infectious with HPV16, with detectable HSIL/HGAIN
	C^t, C^h	The number of HIV negative/positive MSM who have not been vaccinated and are infectious with HPV16, with HPV-related anal cancer that is diagnosed and treated
SUCCESSFULLY VACCINATED (V/subscript v)	V, V^h	The number of HIV negative /positive MSM who have been successfully vaccinated and are immune to HPV16 infection.
	S_v, S_v^h	The number of HIV negative /positive MSM who have been successfully vaccinated and are immune to HPV16 infection, have no natural immunity and are not infectious.
	R_v, R_v^h	The number of HIV negative /positive MSM who have been successfully vaccinated and are immune to HPV16 infection and have natural immunity to HPV16 infection.
	I_v, I_v^h	The number of HIV negative/positive MSM that is successfully vaccinated is infectious with HPV16 and has normal or ASCUS cytology/histology
	L_v, L_v^{th}	The number of HIV negative/positive MSM that is successfully vaccinated, is infectious with HPV16, with detectable LSIL/LGAIN
	H_v, H_v^{th}	The number of HIV negative/positive MSM that is successfully vaccinated, is infectious with HPV16, with detectable HSIL/HGAIN
	C_v, C_v^h	The number of HIV negative/positive MSM that is successfully vaccinated, is infectious with HPV16, with HPV-related anal cancer that is diagnosed and treated

	State Variable	Definition
VACCINE FAILURES (F/subscript f)	F, F^h	The number of HIV negative /positive MSM who have been vaccinated but do not have vaccine-induced immunity to HPV16 infection.
	$\mathrm{S}_f, \mathrm{S}_f^h$	The number of HIV negative /positive MSM who have been vaccinated but are susceptible to HPV16 infection.
	R_f, R_f^h	The number of HIV negative /positive MSM who have natural immunity to HPV16 infection. No vaccine-induced immunity despite having received vaccine.
	I_f, I_f^h	The number of HIV negative/positive MSM who have been vaccinated and are infectious with HPV16 and have normal or ASCUS cytology/histology
	L_f, L_f^{th}	The number of HIV negative/positive MSM who have been vaccinated and are infectious with HPV16, with detectable LSIL/LGAIN
	H_f, H_f^{th}	The number of HIV negative/positive MSM who have been vaccinated and are infectious with HPV16, with detectable HSIL/HGAIN
	C_f, C_f^h	The number of HIV negative/positive MSM who have been vaccinated and are infectious with HPV16, with HPV-related anal cancer that is diagnosed and treated

HPV16 AND ANAL CANCER MODEL EQUATIONS

UNVACCINATED-HIV NEGATIVE

$$\mathrm{N}_{(a=0)} = 100{,}000$$

$$\mathrm{S}_{(a=0)} = \mathrm{R}_{(a=0)} = \mathrm{I}_{(a=0)} = L^{a}_{(a=0)} = L^{b}_{(a=0)} = L^{c}_{(a=0)} = H^{a}_{(a=0)} = H^{b}_{(a=0)} = H^{c}_{(a=0)} = C_{(a=0)} = 0$$

$$\mathrm{N}_{(a+1)} = \left(1 - \alpha_{(a)} - \mathrm{m}_{(a)}\right)\mathrm{N}_{(a)} - \gamma_1 \mathrm{ny}\mathrm{N}_{(a)} - (1-\gamma_1)\mathrm{ny}\mathrm{N}_{(a)}$$

$$\mathrm{S}_{(a+1)} = \left(1 - \lambda_{HPVi(a)} - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)\mathrm{S}_{(a)} + \alpha_{(a)}\mathrm{N}_{(a)} + \mu\mathrm{R}_{(a)} - \gamma_1 \mathrm{ng}_{(a)} S_{(a)} - (1-\gamma_1)\mathrm{ng}_{(a)} S_{(a)}$$

$$\mathrm{R}_{(a+1)} = \left(1 - \mu - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)\mathrm{R}_{(a)} + \rho L^{t}_{(a)} + \pi H^{t}_{(a)} + \tau\mathrm{C}_{(a)} + \phi\mathrm{I}_{(a)} - \gamma_1 n\mathrm{g}_{(a)} R_{(a)} - (1-\gamma_1) n\mathrm{g}_{(a)} R_{(a)}$$

$$\mathrm{I}_{(a+1)} = \left(1 - \sigma - \phi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)\mathrm{I}_{(a)} + \lambda_{HPVi(a)}\mathrm{S}_{(a)} - \gamma_2 n\mathrm{g}_{(a)} I_{(a)} - (1-\gamma_2) n\mathrm{g}_{(a)} I_{(a)}$$

$$L^{t}_{(a)} = L^{a}_{(a)} + L^{b}_{(a)} + L^{c}_{(a)}$$

$$L^{a}_{(a+1)} = \left(1 - 2x - \rho - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)L^{a}_{(a)} + \sigma\mathrm{I}_{(a)} - \gamma_2 n\mathrm{g}_{(a)} L^{a}_{(a)} - (1-\gamma_2) n\mathrm{g}_{(a)} L^{a}_{(a)}$$

$$L^{b}_{(a+1)} = \left(1 - 2x - \rho - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)L^{b}_{(a)} + xL^{a}_{(a)} - \gamma_2 n\mathrm{g}_{(a)} L^{b}_{(a)} - (1-\gamma_2) n\mathrm{g}_{(a)} L^{b}_{(a)}$$

$$L^{c}_{(a+1)} = \left(1 - x - \rho - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)L^{c}_{(a)} + xL^{b}_{(a)} - \gamma_2 n\mathrm{g}_{(a)} L^{c}_{(a)} - (1-\gamma_2) n\mathrm{g}_{(a)} L^{c}_{(a)}$$

$$H^{t}_{(a)} = H^{a}_{(a)} + H^{b}_{(a)} + H^{c}_{(a)}$$

$$H^{a}_{(a+1)} = \left(1 - 2\delta_{(a)} - \pi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)H^{a}_{(a)} + xL^{t}_{(a)} - \gamma_2 n\mathrm{g}_{(a)} H^{a}_{(a)} - (1-\gamma_2) n\mathrm{g}_{(a)} H^{a}_{(a)}$$

$$H^{b}_{(a+1)} = \left(1 - 2\delta_{(a)} - \pi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)H^{b}_{(a)} + \delta_{(a)} H^{a}_{(a)} - \gamma_2 n\mathrm{g}_{(a)} H^{b}_{(a)} - (1-\gamma_2) n\mathrm{g}_{(a)} H^{b}_{(a)}$$

$$H^{c}_{(a+1)} = \left(1 - \delta_{(a)} - \pi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)H^{c}_{(a)} + \delta_{(a)} H^{b}_{(a)} - \gamma_2 n\mathrm{g}_{(a)} H^{c}_{(a)} - (1-\gamma_2) n\mathrm{g}_{(a)} H^{c}_{(a)}$$

$$\mathrm{C}_{(a+1)} = \left(1 - \tau - \psi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)\mathrm{C}_{(a)} + + \delta_{(a)} H^{t}_{(a)}$$

UNVACCINATED-HIV POSITIVE (superscript h)

$$S^{h}_{(a=0)} = R^{h}_{(a=0)} = I^{h}_{(a=0)} = L^{ha}_{(a=0)} = L^{hb}_{(a=0)} = L^{hc}_{(a=0)} = H^{ha}_{(a=0)} = H^{hb}_{(a=0)} = H^{hc}_{(a=0)} = C^{h}_{(a=0)} = 0$$

$$S^{h}_{(a+1)} = \left(1 - \lambda_{HPVih(a)} - m_{(a)} - d\right)S^{h}_{(a)} + \lambda_{HIV(a)}S_{(a)} + \mu_h R_{(a)} - \gamma_3 nz S^{h}_{(a)} - (1-\gamma_3)nz S^{h}_{(a)}$$

$$R^{h}_{(a+1)} = \left(1 - \mu_h - m_{(a)} - d\right)R^{h}_{(a)} + \rho_h L^{ht}_{(a)} + \pi_h H^{ht}_{(a)} + \tau_h C^{h}_{(a)} + \phi_h I^{h}_{(a)} + \lambda_{HIV(a)}R_{(a)} - \gamma_3 nz R^{h}_{(a)} - (1-\gamma_3)nz R^{h}_{(a)}$$

$$I^{h}_{(a+1)} = \left(1 - \sigma_h - \phi_h - m_{(a)} - d\right)I^{h}_{(a)} + \lambda_{HPVih(a)}S^{h}_{(a)} + \lambda_{HIV(a)}I_{(a)} - \gamma_4 nz I^{h}_{(a)} - (1-\gamma_4)nz I^{h}_{(a)}$$

$$L^{ht}_{(a)} = L^{ha}_{(a)} + L^{hb}_{(a)} + L^{hc}_{(a)}$$

$$L^{ha}_{(a+1)} = \left(1 - 2x_h - \rho_h - m_{(a)} - d\right)L^{ha}_{(a)} + \sigma_h I^{h}_{(a)} + \lambda_{HIV(a)}L^{a}_{(a)} - \gamma_4 nz\, L^{ha}_{(a)} - (1-\gamma_4)nz L^{ha}_{(a)}$$

$$L^{hb}_{(a+1)} = \left(1 - 2x_h - \rho_h - m_{(a)} - d\right)L^{hb}_{(a)} + x_h L^{ha}_{(a)} + \lambda_{HIV(a)}L^{b}_{(a)} - \gamma_4 nz\, L^{hb}_{(a)} - (1-\gamma_4)nz L^{hb}_{(a)}$$

$$L^{hc}_{(a+1)} = \left(1 - x_h - \rho_h - m_{(a)} - d\right)L^{hc}_{(a)} + x_h L^{hb}_{(a)} + \lambda_{HIV(a)}L^{c}_{(a)} - \gamma_4 nz\, L^{hc}_{(a)} - (1-\gamma_4)nz L^{hc}_{(a)}$$

$$H^{ht}_{(a)} = H^{ha}_{(a)} + H^{hb}_{(a)} + H^{hc}_{(a)}$$

$$H^{ha}_{(a+1)} = \left(1 - 2\delta_{h(a)} - \pi_h - m_{(a)} - d\right)H^{ha}_{(a)} + x_h L^{ht}_{(a)} + \lambda_{HIV(a)}H^{a}_{(a)} - \gamma_4 nz\, H^{ha}_{(a)} - (1-\gamma_4)nz H^{ha}_{(a)}$$

$$H^{hb}_{(a+1)} = \left(1 - 2\delta_{h(a)} - \pi_h - m_{(a)} - d\right)H^{hb}_{(a)} + \delta_{hj} H^{ha}_{(a)} + \lambda_{HIV(a)}H^{b}_{(a)} - \gamma_4 nz\, H^{hb}_{(a)} - (1-\gamma_4)nz H^{hb}_{(a)}$$

$$H^{hc}_{(a+1)} = \left(1 - \delta_{h(a)} - \pi_h - m_{(a)} - d\right)H^{hc}_{(a)} + \delta_{hj} H^{hb}_{(a)} + \lambda_{HIV(a)}H^{c}_{(a)} - \gamma_4 nz\, H^{hc}_{(a)} - (1-\gamma_4)nz H^{hc}_{(a)}$$

$$C^{h}_{(a+1)} = \left(1 - \tau_h - \psi - m_{(a)} - d\right)C^{h}_{(a)} + \delta_{h(a)}H^{ht}_{(a)} + \lambda_{HIV(a)}C_{(a)}$$

SUCCESSFULLY VACCINATED-HIV NEGATIVE

$$\mathrm{N}_{v(a=0)} = \mathrm{S}_{v(a=0)} = \mathrm{R}_{v(a=0)} = \mathrm{I}_{v(a=0)} = L^{a}_{v(a=0)} = L^{b}_{v(a=0)} = L^{c}_{v(a=0)} = H^{a}_{v(a=0)} = H^{b}_{v(a=0)} = H^{c}_{v(a=0)} = C_{v(a=0)} = 0$$

$$\mathrm{V}_{(a)} = \mathrm{N}_{v(a)} + \mathrm{R}_{v(a)} + \mathrm{I}_{v(a)} + \mathrm{L}^{t}_{v(a)} + H^{t}_{v(a)} + \mathrm{S}_{v(a)}$$

$$\mathrm{N}_{v(a+1)} = \left(1 - \alpha_{(a)} - \mathrm{m}_{(a)}\right)\mathrm{N}_{v(a)} + \gamma_1 \mathrm{ny}\mathrm{N}_{(a)} - \omega \mathrm{N}_{v(a)}$$

$$\mathrm{S}_{v(a+1)} = \left(1 - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)\mathrm{S}_{v(a)} + \alpha_{(a)}\mathrm{N}_{v(a)} + \mu \mathrm{R}_{v(a)} + \gamma_1 \mathrm{ng}_{(a)} S_{(a)} - \omega S_{v(a)}$$

$$\mathrm{R}_{v(a+1)} = \left(1 - \mu - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)\mathrm{R}_{v(a)} + \rho L^{t}_{v(a)} + \pi H^{t}_{v(a)} + \tau \mathrm{C}_{v(a)} + \phi \mathrm{I}_{v(a)} + \gamma_1 n \mathrm{g}_{(a)} R_{(a)} - \omega R_{v(a)}$$

$$\mathrm{I}_{v(a+1)} = \left(1 - \sigma - \phi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)\mathrm{I}_{v(a)} + \gamma_2 n \mathrm{g}_{(a)} I_{(a)} - \omega I_{v(a)}$$

$$L^{t}_{v(a)} = L^{a}_{v(a)} + L^{b}_{v(a)} + L^{c}_{v(a)}$$

$$L^{a}_{v(a+1)} = \left(1 - 2x - \rho - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)L^{a}_{v(a)} + \sigma \mathrm{I}_{v(a)} + \gamma_2 n \mathrm{g}_{(a)} L^{a}_{(a)} - \omega L^{a}_{v(a)}$$

$$L^{b}_{v(a+1)} = \left(1 - 2x - \rho - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)L^{b}_{v(a)} + x L^{a}_{v(a)} + \gamma_2 n \mathrm{g}_{(a)} L^{b}_{v(a)} - \omega L^{b}_{v(a)}$$

$$L^{c}_{v(a+1)} = \left(1 - x - \rho - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)L^{c}_{v(a)} + x L^{b}_{v(a)} + \gamma_2 n \mathrm{g}_{(a)} L^{c}_{(a)} - \omega L^{c}_{v(a)}$$

$$H^{t}_{v(a)} = H^{a}_{v(a)} + H^{b}_{v(a)} + H^{c}_{v(a)}$$

$$H^{a}_{v(a+1)} = \left(1 - 2\delta_{(a)} - \pi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)H^{a}_{v(a)} + x L^{t}_{v(a)} + \gamma_2 n \mathrm{g}_{(a)} H^{a}_{(a)} - \omega H^{a}_{v(a)}$$

$$H^{b}_{v(a+1)} = \left(1 - 2\delta_{(a)} - \pi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)H^{b}_{v(a)} + \delta_{(a)} H^{a}_{v(a)} + \gamma_2 n \mathrm{g}_{(a)} H^{b}_{(a)} - \omega H^{b}_{v(a)}$$

$$H^{c}_{v(a+1)} = \left(1 - \delta_{(a)} - \pi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)H^{c}_{v(a)} + \delta_{(a)} H^{b}_{v(a)} + \gamma_2 n \mathrm{g}_{(a)} H^{c}_{(a)} - \omega H^{c}_{v(a)}$$

$$\mathrm{C}_{v(a+1)} = \left(1 - \tau - \psi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)\mathrm{C}_{v(a)} + \delta_{(a)} H^{t}_{v(a)}$$

SUCCESSFULLY VACCINATED -HIV POSITIVE (superscript h)

$$S^{h}_{v(a=0)} + R^{h}_{v(a=0)} + I^{h}_{v(a=0)} + L^{ha}_{v(a=0)} + L^{hb}_{v(a=0)} + L^{hc}_{v(a=0)} + H^{ha}_{v(a=0)} + H^{hb}_{v(a=0)} + H^{hc}_{v(a=0)} + C^{h}_{v(a=0)} = V^{h}_{(a=0)} = 0$$

$$S^{h}_{v(a+1)} = \left(1 - m_{(a)} - d\right)S^{h}_{v(a)} + \lambda_{HIV(a)}S_{v(a)} + \mu_h R^{h}_{v(a)} + \gamma_3 nz S^{h}_{(a)} - \omega S^{h}_{v(a)}$$

$$R^{h}_{v(a+1)} = \left(1 - \mu_h - m_{(a)} - d\right)R^{h}_{v(a)} + \rho_h L^{ht}_{v(a)} + \pi_h H^{ht}_{v(a)} + \tau_h C^{h}_{v(a)} + \phi_h I^{h}_{v(a)} + \lambda_{HIV(a)}R_{v(a)} + \gamma_3 nz R^{h}_{(a)} - \omega R^{h}_{v(a)}$$

$$I^{h}_{v(a+1)} = \left(1 - \sigma_h - \phi_h - m_{(a)} - d\right)I^{h}_{v(a)} + \lambda_{HIV(a)}I_{v(a)} + \gamma_4 nz I^{h}_{(a)} - \omega I^{h}_{v(a)}$$

$$L^{ht}_{v(a)} = L^{ha}_{v(a)} + L^{hb}_{v(a)} + L^{hc}_{v(a)}$$

$$L^{ha}_{v(a+1)} = \left(1 - 2x_h - \rho_h - m_{(a)} - d\right)L^{ha}_{v(a)} + \sigma_h I^{h}_{v(a)} + \lambda_{HIV(a)}L^{a}_{v(a)} + \gamma_4 nz\, L^{ha}_{(a)} - \omega L^{ha}_{v(a)}$$

$$L^{hb}_{v(a+1)} = \left(1 - 2x_h - \rho_h - m_{(a)} - d\right)L^{hb}_{v(a)} + x_h L^{ha}_{v(a)} + \lambda_{HIV(a)}L^{b}_{v(a)} + \gamma_4 nz\, L^{hb}_{(a)} - \omega L^{hb}_{v(a)}$$

$$L^{hc}_{v(a+1)} = \left(1 - x_h - \rho_h - m_{(a)} - d\right)L^{hc}_{v(a)} + x_h L^{hb}_{v(a)} + \lambda_{HIV(a)}L^{c}_{v(a)} + \gamma_4 nz\, L^{hc}_{(a)} - \omega L^{hc}_{v(a)}$$

$$H^{ht}_{v(a)} = H^{ha}_{v(a)} + H^{hb}_{v(a)} + H^{hc}_{v(a)}$$

$$H^{ha}_{v(a+1)} = \left(1 - 2\delta_{h(a)} - \pi_h - m_{(a)} - d\right)H^{ha}_{v(a)} + x_h L^{ht}_{v(a)} + \lambda_{HIV(a)}H^{a}_{v(a)} + \gamma_4 nz\, H^{ha}_{(a)} - \omega H^{ha}_{v(a)}$$

$$H^{hb}_{v(a+1)} = \left(1 - 2\delta_{h(a)} - \pi_h - m_{(a)} - d\right)H^{hb}_{v(a)} + \delta_{hj}H^{ha}_{v(a)} + \lambda_{HIV(a)}H^{b}_{v(a)} + \gamma_4 nz\, H^{hb}_{(a)} - \omega H^{hb}_{v(a)}$$

$$H^{hc}_{v(a+1)} = \left(1 - \delta_{h(a)} - \pi_h - m_{(a)} - d\right)H^{hc}_{v(a)} + \delta_{hj}H^{hb}_{v(a)} + \lambda_{HIV(a)}H^{c}_{v(a)} + \gamma_4 nz\, H^{hc}_{(a)} - \omega H^{hc}_{v(a)}$$

$$C^{h}_{v(a+1)} = \left(1 - \tau_h - \psi - m_{(a)} - d\right)C^{h}_{v(a)} + \delta_{h(a)}H^{ht}_{v(a)} + \lambda_{HIV(a)}C_{v(a)}$$

VACCINE FAILURES-HIV NEGATIVE

$$\mathrm{N}_{f(a=0)} + \mathrm{S}_{f(a=0)} + \mathrm{R}_{f(a=0)} + \mathrm{I}_{f(a=0)} + \mathrm{L}^{a}_{f(a=0)} + \mathrm{L}^{b}_{f(a=0)} + \mathrm{L}^{c}_{f(a=0)} + H^{a}_{f(a=0)} + H^{b}_{f(a=0)} + H^{c}_{f(a=0)} + \mathrm{C}_{f(a=0)} = F_{(a=0)} = 0$$

$$\mathrm{N}_{f(a+1)} = \left(1 - \alpha_{(a)} - \mathrm{m}_{(a)}\right)\mathrm{N}_{f(a)} + (1-\gamma_1)\mathrm{ny}\mathrm{N}_{(a)} + \omega \mathrm{N}_{v(a)}$$

$$\mathrm{S}_{f(a+1)} = \left(1 - \mathrm{m}_{(a)} - \lambda_{HIV(a)} - \lambda_{HPV,i(a)}\right)\mathrm{S}_{f(a)} + \alpha_{(a)}\mathrm{N}_{f(a)} + \mu \mathrm{R}_{f(a)} + (1-\gamma_1)\mathrm{ng}_{(a)} S_{(a)} + \omega S_{v(a)}$$

$$\mathrm{R}_{f(a+1)} = \left(1 - \mu - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)\mathrm{R}_{f(a)} + \rho L^{t}_{f(a)} + \pi H^{t}_{f(a)} + \tau \mathrm{C}_{f(a)} + \phi \mathrm{I}_{f(a)} + [(1-\gamma_1)]\mathrm{ng}_{(a)} R_{(a)} + \omega R_{v(a)}$$

$$\mathrm{I}_{f(a+1)} = \left(1 - \sigma - \phi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)\mathrm{I}_{f(a)} + \lambda_{HPV,i(a)}\mathrm{S}_{f(a)} + (1-\gamma_2)n\mathrm{g}_{(a)} I_{(a)} + \omega I_{v(a)}$$

$$L^{t}_{f(a)} = L^{a}_{f(a)} + L^{b}_{f(a)} + L^{c}_{f(a)}$$

$$L^{a}_{f(a+1)} = \left(1 - 2x - \rho - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)L^{a}_{f(a)} + \sigma \mathrm{I}_{f(a)} + (1-\gamma_2)n\mathrm{g}_{(a)}\, L^{a}_{(a)} + \omega L^{a}_{v(a)}$$

$$L^{b}_{f(a+1)} = \left(1 - 2x - \rho - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)L^{b}_{f(a)} + x L^{a}_{f(a)} + (1-\gamma_2)n\mathrm{g}_{(a)}\, L^{b}_{v(a)} + \omega L^{b}_{v(a)}$$

$$L^{c}_{f(a+1)} = \left(1 - x - \rho - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)L^{c}_{f(a)} + x L^{b}_{f(a)} + (1-\gamma_2)n\mathrm{g}_{(a)}\, L^{c}_{(a)} + \omega L^{c}_{v(a)}$$

$$H^{t}_{f(a)} = H^{a}_{f(a)} + H^{b}_{f(a)} + H^{c}_{f(a)}$$

$$H^{a}_{f(a+1)} = \left(1 - 2\delta_{(a)} - \pi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)H^{a}_{f(a)} + x L^{t}_{f(a)} + (1-\gamma_2)n\mathrm{g}_{(a)}\, H^{a}_{(a)} + \omega H^{a}_{v(a)}$$

$$H^{b}_{f(a+1)} = \left(1 - 2\delta_{(a)} - \pi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)H^{b}_{f(a)} + \delta_{(a)} H^{a}_{f(a)} + (1-\gamma_2)n\mathrm{g}_{(a)}\, H^{b}_{(a)} + \omega H^{b}_{v(a)}$$

$$H^{c}_{f(a+1)} = \left(1 - \delta_{(a)} - \pi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)H^{c}_{f(a)} + \delta_{(a)} H^{b}_{f(a)} + (1-\gamma_2)n\mathrm{g}_{(a)}\, H^{c}_{(a)} + \omega H^{c}_{v(a)}$$

$$\mathrm{C}_{f(a+1)} = \left(1 - \tau - \psi - \mathrm{m}_{(a)} - \lambda_{HIV(a)}\right)\mathrm{C}_{f(a)} + \delta_{(a)} H^{t}_{f(a)}$$

VACCINE FAILURES -HIV POSITIVE (superscript h)

$$S^{h}_{f(a=0)} + R^{h}_{f(a=0)} + I^{h}_{f(a=0)} + L^{ha}_{f(a=0)} + L^{hb}_{f(a=0)} + L^{hc}_{f(a=0)} + H^{ha}_{f(a=0)} + H^{hb}_{f(a=0)} + H^{hc}_{f(a=0)} + C^{h}_{f(a=0)} = F^{h}_{(a=0)} = 0$$

$$S^{h}_{f(a+1)} = \left(1 - m_{(a)} - d - \lambda^{h}_{HPV,i(a)}\right)S^{h}_{f(a)} + \lambda_{HIV(a)}S_{f(a)} + \mu_h R^{h}_{f(a)} + (1-\gamma_3)nzS^{h}_{(a)} + \omega S^{h}_{v(a)}$$

$$R^{h}_{f(a+1)} = \left(1 - \mu_h - m_{(a)} - d\right)R^{h}_{f(a)} + \rho_h L^{ht}_{f(a)} + \pi_h H^{ht}_{f(a)} + \tau_h C^{h}_{f(a)} + \phi_h I^{h}_{f(a)} + \lambda_{HIV(a)}R_{f(a)} + (1-\gamma_3)nzR^{h}_{(a)} + \omega R^{h}_{v(a)}$$

$$I^{h}_{f(a+1)} = \left(1 - \sigma_h - \phi_h - m_{(a)} - d\right)I^{h}_{f(a)} + \lambda^{h}_{HPV,i(a)}S^{h}_{f(a)} + \lambda_{HIV(a)}I_{f(a)} + (1-\gamma_4)nzI^{h}_{(a)} + \omega I^{h}_{v(a)}$$

$$L^{ht}_{f(a)} = L^{ha}_{f(a)} + L^{hb}_{f(a)} + L^{hc}_{f(a)}$$

$$L^{ha}_{f(a+1)} = \left(1 - 2x_h - \rho_h - m_{(a)} - d\right)L^{ha}_{f(a)} + \sigma_h I^{h}_{f(a)} + \lambda_{HIV(a)}L^{a}_{f(a)} + (1-\gamma_4)nz\,L^{ha}_{(a)} + \omega L^{ha}_{v(a)}$$

$$L^{hb}_{f(a+1)} = \left(1 - 2x_h - \rho_h - m_{(a)} - d\right)L^{hb}_{f(a)} + x_h L^{ha}_{f(a)} + \lambda_{HIV(a)}L^{b}_{f(a)} + (1-\gamma_4)nz\,L^{hb}_{(a)} + \omega L^{hb}_{v(a)}$$

$$L^{hc}_{f(a+1)} = \left(1 - x_h - \rho_h - m_{(a)} - d\right)L^{hc}_{f(a)} + x_h L^{hb}_{f(a)} + \lambda_{HIV(a)}L^{c}_{f(a)} + (1-\gamma_4)nz\,L^{hc}_{(a)} + \omega L^{hc}_{v(a)}$$

$$H^{ht}_{f(a)} = H^{ha}_{f(a)} + H^{hb}_{f(a)} + H^{hc}_{f(a)}$$

$$H^{ha}_{f(a+1)} = \left(1 - 2\delta_{h(a)} - \pi_h - m_{(a)} - d\right)H^{ha}_{f(a)} + x_h L^{ht}_{f(a)} + \lambda_{HIV(a)}H^{a}_{f(a)} + (1-\gamma_4)nz\,H^{ha}_{(a)} + \omega H^{ha}_{v(a)}$$

$$H^{hb}_{f(a+1)} = \left(1 - 2\delta_{h(a)} - \pi_h - m_{(a)} - d\right)H^{hb}_{f(a)} + \delta_{h(a)}H^{ha}_{f(a)} + \lambda_{HIV(a)}H^{b}_{f(a)} + (1-\gamma_4)nz\,H^{hb}_{(a)} + \omega H^{hb}_{v(a)}$$

$$H^{hc}_{f(a+1)} = \left(1 - \delta_{h(a)} - \pi_h - m_{(a)} - d\right)H^{hc}_{f(a)} + \delta_{h(a)}H^{hb}_{f(a)} + \lambda_{HIV(a)}H^{c}_{f(a)} + (1-\gamma_4)nz\,H^{hc}_{(a)} + \omega H^{hc}_{v(a)}$$

$$C^{h}_{f(a+1)} = \left(1 - \tau_h - \psi - m_{(a)} - d\right)C^{h}_{f(a)} + \delta_{h(a)}H^{ht}_{f(a)} + \lambda_{HIV(a)}C_{f(a)}$$

Where:
λ =Force of Infection
ω =Waning natural immunity
ϕ = I_R, The probability of clearing a disease-free HPV16 infection between t and t+1.
ρ =The probability of clearing an infection with symptoms of LSIL between t and t+1.
π =HSIL_R, The probability of clearing an infection with symptoms of HSIL between t and t+1.
τ =C_R , The probability of surviving anal cancer between t and t+1
m =Probability of dying naturally
γ=Vaccine efficacy
κ=Vaccine uptake
ν=Duration of vaccine-induced immunity (months)

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SHORT REPORT

Oral human papillomavirus (HPV) infection in men who have sex with men: prevalence and lack of anogenital concordance

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ABSTRACT

Objectives To estimate the prevalence of oral detectable human papillomavirus (HPV) DNA in HIV-negative men who have sex with men (MSM) attending a sexual health clinic in London and concordance with anogenital HPV infection. Such data are important to improve our understanding of the epidemiology of oral HPV and the potential use of vaccines to prevent oropharyngeal cancers.

Methods Paired oral rinse samples and anogenital samples were available from 151 HIV-negative MSM within a larger cross-sectional survey. All samples were tested in parallel for 21 types of HPV DNA using an in-house assay.

Results The median age of participants was 30 (IQR 25–35). The prevalence of any oral HPV and of high-risk HPV (HR-HPV) was 13.7% (n=21; 95% CI 8.7 to 20.2) and 5.9% (n=9; 95% CI 2.7 to 10.9) compared with 64.9% (n=98; 95% CI 56.7 to 72.5) and 34.4% (n=52; 95% CI 26.9 to 42.6) in any anogenital sample, respectively. The prevalence of types prevented by the bivalent (HPV16/18), quadrivalent (HPV6/11/16/18) and nonavalent (HPV6/11/16/18/31/33/45/52/58) vaccines was 1.3% (95% CI 0.2 to 4.7), 2.6% (95% CI 0.7 to 6.6) and 4.6% (95% CI 1.9 to 9.3), respectively. There was no concordance between HPV genotypes detected in oral and anogenital sites.

Conclusions HR-HPV DNA, including HPV 16/18, was detected in oral specimens from HIV-negative MSM attending sexual health clinics, suggesting a potential role for vaccination, but is far less common than anogenital infection. How this relates to the risk and natural history of HPV-related head and neck cancers warrants further study. Lack of concordance with anogenital infection also suggests that oral HPV infection should be considered separately when estimating potential vaccine impact.

INTRODUCTION

Human papillomavirus (HPV) infection is associated with cancers at a number of sites in the head and neck, most importantly oropharyngeal cancer, which has been rising in incidence in recent decades.[1] The global estimate of oral HPV prevalence in men was 5%[2] and estimates in men who have sex with men (MSM) outside the UK range from 3% to 57%,[3 4] yet few studies have compared oral HPV prevalence in heterosexual and MSM populations.[3] Furthermore, the natural history of oral HPV infection and its role in the development of head and neck cancers is not well understood.[5] HPV infection and related disease in MSM is of particular interest, given the potential for prevention by vaccination.[6]

Estimating the potential benefit of vaccinating MSM requires knowledge of the epidemiology of oral HPV infection. To date, only three studies involving a total of 877 HIV-negative MSM have been conducted to estimate oral high-risk HPV (HR-HPV) prevalence, and results are not consistent (2%,[7] 9%,[4] 17%[8]). Likewise, the relationship between oral and anogenital HPV infection in MSM is not well understood.

Most transmission models of HPV infection used to inform vaccine programme design assume that infection occurs through anogenital contact, ignoring the role of oral–anogenital contact. Indeed, estimates of concordance between oral and anogenital HPV infection not only have implications for vaccine assessment but also for understanding the key epidemic characteristics such as route of acquisition, whether anogenital infections are acquired simultaneously or via separate risk acts/partnerships, or whether men transfer infections from one anatomical site to another (auto-inoculation).

We describe age-specific oral HPV prevalence and the concordance between detection of type-specific HPV DNA in oral and anogenital specimens from HIV-negative MSM attending a sexual health clinic in central London.

METHODS

Study methods, including sample size calculations, have been reported elsewhere.[9] In brief, from October 2010 to July 2012, a cross-sectional study was conducted to examine the risk factors and prevalence of HPV DNA in MSM attending the sexual health clinic at the Mortimer Market Centre (MMC), London. Consecutive men aged 16–40 years, who reported anal or oral sex with another man in the last 5 years, were invited to participate. Participants provided written informed consent, completed a computer-assisted self-interview questionnaire and anogenital specimens (first-void urine, intra-anal swab and external genital swab (glans penis/coronal sulcus/penile shaft/scrotum/perianal area)) were collected by the study nurse using a standardised protocol.

Participants who enrolled in the final five months of the study were also invited to provide an oral specimen involving a 30 s gargle/rinse with 15 mL

of Scope mouthwash according to a published protocol.[3] Oral samples were refrigerated immediately and processed the same day. To process, the rinse was centrifuged at 3200 rpm for 15 min at 4°C and, after the supernatant was discarded, the pellet was resuspended in 20 mL of cold phosphate buffered saline (PBS) (4°C). The centrifugation/resuspension was repeated twice and the final pellet was resuspended in 1.2 mL of PBS with repeat pipetting and vortexing to ensure a homogeneous sample. Samples were stored at −20°C until shipment to the laboratory on dry ice at the end of the study. Specimens were removed for batch processing wherein all available specimens from each individual were processed for DNA extraction and HPV testing in the same run. Nucleic acid extraction and PCR amplification, HPV genotyping and determination of specimen integrity methods have been previously described.[10] HPV genotypes 16/18/31/33/35/39/45/51/52/56/58/59/68 were considered HR-HPV types.

Here we report HPV prevalence and demographic and behavioural characteristics among participating MSM with both oral and anogenital specimens that were adequate for PCR-based HPV detection, for bivalent (HPV16/18), quadrivalent (HPV6/11/16/18) and nonavalent (HPV6/11/16/18/31/33/45/52/58) vaccine-preventable types together and individually, and for selected other HPV types: 35/39/51/56/59/68/26/53/66/70/73/82. CIs (95%) around prevalence estimates were determined by the Clopper–Pearson (exact) method.

RESULTS

There were 522 participants in the full study (n=522) and 177 gave an oral specimen. Participant and specimen numbers are shown in online supplementary figure S1. The study population was slightly younger than MSM attending MMC during the recruitment period (data not shown) and were more likely to be a new patient at the clinic than those who declined to participate; 163/173 (94%) HIV-negative MSM provided oral specimens, 153/173 (88%) were adequate for HPV testing and 151/173 (87%) had at least one matching anogenital specimen (ie, urine, anal swab or external genital swab). Also, 127/151 (84%) had an anal swab, 135/151 (89%) had an external genital swab and 143 (95%) had a urine specimen.

Online supplementary table S1 displays characteristics of substudy participants. The median age of respondents with adequate paired specimens was 30 (IQR 25–35), 75% were of white ethnicity and 64% had >30 lifetime sexual partners.

Nine MSM had HR-HPV DNA detected in their oral specimens, and three had LR-HPV. Table 1 shows the oral prevalence of any HPV was 14% (95% CI 9% to 21%), HR-HPV was 6% (95% CI 3% to 11%) and of HPV16 was 0.7% (95% CI 0% to 4%). Prevalence estimates of bivalent, quadrivalent and nonavalent vaccine-preventable types were 1%, 3% and 5%, respectively. By comparison, the anogenital prevalence of any HPV was 65% (n=98; 95% CI 57 to 73) and HR-HPV was 34% (n=52; 95% CI 27 to 43). None of the 151 pairs had the same HPV type detected in both oral and anogenital samples; 14 (9%) pairs had any HPV detected in both oral and anogenital sites (see online supplementary table S2).

Table 1 Human papillomavirus (HPV) DNA prevalence in oral cavity of men who have sex with men

	n	Per cent	N=151 95% CI
Any HPV type*	21	13.9	8.8 to 20.5
Multiple types (two or more)	1	0.7	0.0 to 3.6
Multiple HR types† (two or more)	0	0.0	0.0 to 2.4
Any bivalent vaccine types‡	2	1.3	0.2 to 4.7
Any quadrivalent vaccine types‡	4	2.6	0.7 to 6.6
Any nonavalent vaccine types‡	7	4.6	1.9 to 9.3
Possible high-risk types§	0	0.0	0.0 to 2.4
High-risk HPV types (HR-HPV)†	9	6.0	2.8 to 11.0
HPV16	1	0.7	0.0 to 3.6
HPV18	1	0.7	0.0 to 3.6
HPV31	0	0.0	0.0 to 2.4
HPV33	1	0.7	0.0 to 3.6
HPV35	0	0.0	0.0 to 2.4
HPV39	0	0.0	0.0 to 2.4
HPV45	1	0.7	0.0 to 3.6
HPV51	1	0.7	0.0 to 3.6
HPV52	1	0.7	0.0 to 3.6
HPV56	3	2.0	0.4 to 5.7
HPV58	0	0.0	0.0 to 2.4
HPV59	0	0.0	0.0 to 2.4
HPV68	0	0.0	0.0 to 2.4
Low-risk HPV types			
6 and/or 11¶	3	2.0	0.4 to 5.7
6¶	3	2.0	0.4 to 5.7
11	0	0.0	0.0 to 2.4

*Sample reacted to the universal probe for HPV DNA.
†HR types 16/18/31/33/35/39/45/51/52/56/58/59/68 classified according to the International Agency for Research on Cancer monograph carcinogenic or probably carcinogenic.
‡Vaccine types: HPV16/18 are bivalent, HPV6/11/16/18 are quadrivalent and HPV6/11/16/18/31/33/45/52/58 are nonavalent.
§Possible high-risk types: 26/53/66/70/73/82.
¶One with co-infection with HPV18.

DISCUSSION

Our observed prevalence of oral HR-HPV of 6% was higher than that of the global estimate in healthy men and women (3.5%; 95% CI 3.0% to 4.1%) yet the CIs overlap.[2] Our results lie within the range of estimates for HIV-negative MSM.[4 7 8] Although MSM are at high risk of anogenital HPV-related disease, none of the men with an oral HPV infection had the same genotype of HPV infection at any anogenital site. The prevalence of any HPV type was also higher in anogenital than oral samples.

Differences in estimates of oral prevalence between studies could be due to both technical and population differences. Methods of oral specimen collection, processing, storage, DNA extraction and test sensitivity and specificity differ across studies. We followed the oral rinse collection protocol from the Human Papillomavirus Infection in Men (HIM) study that is thought to yield more HPV DNA from the entire oral cavity than oral swabs and used a similar processing method.[w1]

In the longitudinal Multicenter AIDS Cohort (MAC) study, HPV, particularly HR-HPV, in MSM was more likely to persist at the anus than the oral cavity, while heterosexual men were as likely to have persistent oral HPV as MSM, but less likely to have persistent anal HPV.[8] In the HIM study in which only 3.5% were MSM, HPV persistence was similar at oral and anogenital sites but the incidence was lower in the oral cavity compared with anogenital sites.[w2] In a cross-sectional assessment, persistent infections cannot be differentiated from those that are transient, and we did not measure oral cavity symptoms, but our lower oral prevalence as compared to anogenital prevalence may be due to both a lower incidence at oral sites and a lower proportion of persistent infections. While we have grouped HR-HPV types, defined by their oncogenic potential at the

cervix, there is only evidence for HPV16 being associated with head-and-neck cancers.[w3]

Our finding of a lack of concordance between oral and anogenital specimens is similar to those in HIV-positive men reported by Videla *et al* (predominantly MSM)[w4] and Parisi *et al*.[w5] However, Edelstein *et al* found that 15/17 men (predominantly heterosexual) had the same type detected at oral and anogenital sites.[w6] Lower prevalence in the oral cavity and the lack of concordance with anogenital infection suggest that oral HPV infections are acquired independently of anogenital infections, or that they are less likely to reactivate from latency than anogenital infections, and would also suggest that auto-inoculation does not commonly occur. Differences in sensitivity of the detection methods may also have contributed to some disparity in HPV detection between anatomical sites but is unlikely to account for the magnitude of the difference observed.

We have previously demonstrated that our study population is at greater risk of STI acquisition than MSM attending other SHCs in England and MSM who attend SHCs in the general population of Britain.[9] If oral HPV infection is a function of partner change, the estimates of oral HPV prevalence in our MSM population may be inflated compared with MSM attending SHCs more generally in Britain.

The sample size of this substudy was too small to accurately estimate oral–anogenital concordance (if true population prevalence is below 6%) but could estimate oral prevalence within 5% if the true population prevalence was 13%.

HPV vaccines can prevent oral HPV infections,[w7] but whether they are effective against HPV-related head and neck cancers has yet to be shown. The lack of concordance between oral and anogenital specimens suggests that the additional potential benefit of HPV vaccination for preventing oral HPV-related disease should be considered in epidemiological and natural history models, in addition to anogenital HPV infection. Further studies, including meta-analyses, are needed to elucidate the epidemiology and natural history of oral HPV infection.

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Contributors The study was conceived by EMK, RG, and PS. The study was designed by EMK, RG, SB, KS, MJ, WJE and PS. CY was responsible for participant recruitment and oral sample processing. The laboratory protocol development and testing was conducted by SB and KP. EMK designed the questionnaire and was responsible for study management, data management and analysis, under the supervision of RG (principal investigator) and PS. EMK wrote the first draft of the paper with contributions, and additional interpretation of findings, from RG, SB, KS, MJ, WJE and PS. All authors have approved the final draft.

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Competing interests WJE's partner works for GSK.

Ethics approval Reviewed by Camden and Islington Research ethics committee (REC reference number: 09/H0722/71) and received NHS approval (R&D ref: CSP 30296).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Contact the corresponding author for data requests.

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HPV in MSM attending a sexual health clinic in London, UK. Evidence to inform HPV vaccination policy

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Background

- MSM have relatively high rates of HPV-related disease, particularly genital warts and anal cancer
- Human papillomavirus (HPV) vaccination of adolescent girls will have relatively little effect on HPV-related disease in men who have sex with men (MSM).
- We determined HPV prevalence and risk factors in MSM attending a sexual health clinic (SHC) to inform the likely effectiveness of vaccination of this population.

Methods

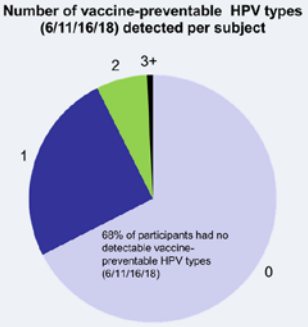
- Cross-sectional survey of MSM attending the Mortimer Market Centre in central London between 10/2010-7/2012
- Age 18-40
- Computer-assisted self-interview for demographic and behavioural data
- Urine, anal canal and penis/scrotum/perianal swabs were tested for HPV DNA (in-house Luminex-based HPV genotyping assay)

Results – Demographics & health seeking

- N=522 enrolled
- Median age = 30 (IQR 25-35)
- Median age at first anal sex = 19 (IQR 17-23)
- Median age at first SHC attendance = 23 (IQR 20-27)
- Proportion disclosed sexuality to their GP = 39%

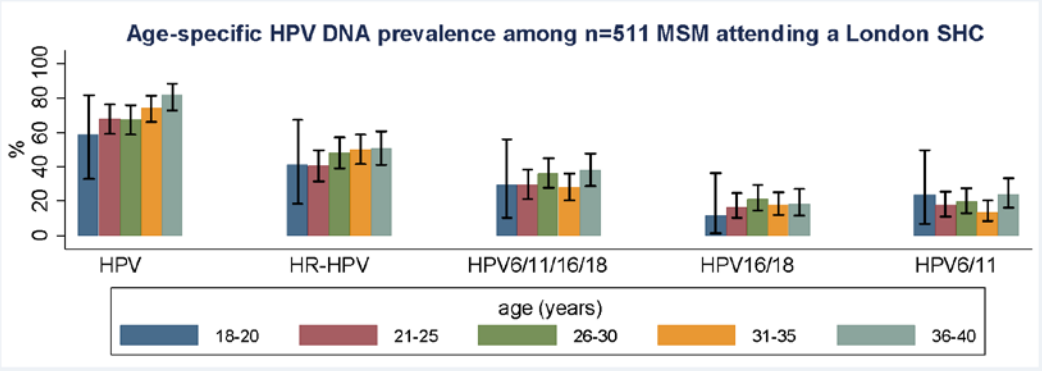
Results – HPV

- Prevalence of HPV6/11/16/18 was 166/511 (32.5%; 95% confidence interval 28.6-36.7)
- HPV prevalence increase with age = 4.7% (95%CI 1.2-8.4) increase in odds per year (bar chart)
- 25.1% had 1 and 7.4% had 2+ of the 4 HPV types (6/11/16/18) (pie chart)



Conclusions

- A high proportion of MSM were not currently infected with HPV6/11/16/18; suggesting that targeted vaccination may be effective.
- Prevalence data are consistent with ongoing risk – increasing prevalence with age.
- Most MSM had not disclosed their sexuality to their GP, making sexual health clinics a promising venue to offer vaccination.
- A targeted vaccination strategy for MSM in the UK could have substantial benefits.



HPV 2014
Poster
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HPV in MSM attending a sexual health clinic in London, UK: evidence to inform HPV vaccination policy

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Background

- Current UK policy on HPV vaccination of adolescent girls will have relatively little effect on HPV-related disease in men who have sex with men (MSM).
- We determined HPV prevalence and risk factors in MSM attending a sexual health clinic (SHC) to inform the likely effectiveness of quadrivalent vaccination targeted at this group.

Methods

- Cross-sectional survey of MSM attending a central London SHC (Mortimer Market Centre) 10/2010-7/2012
- Computer-assisted self-interview for behaviour data
- Age 18-40
- Specimens tested for HPV DNA (in-house Luminex-based HPV genotyping assay): urine, anal canal and penis/scrotum/perianal swab

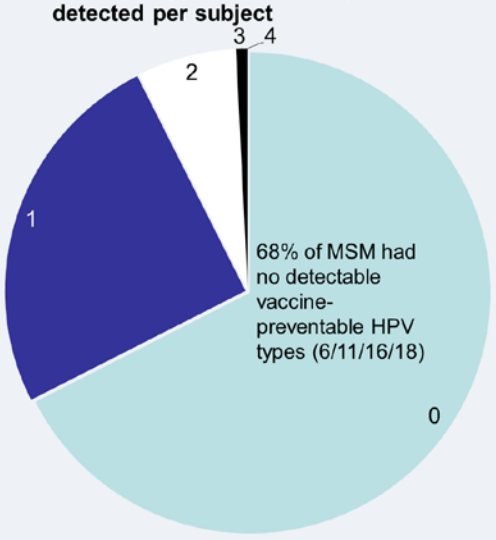
Results - 1

- N=522 enrolled; n=511 with adequate samples to test
- Median age = 30 (IQR 25-35)
- Median age at first anal sex = 19 (IQR 17-23)
- Median age at first SHC attendance = 23 (IQR 20-27)

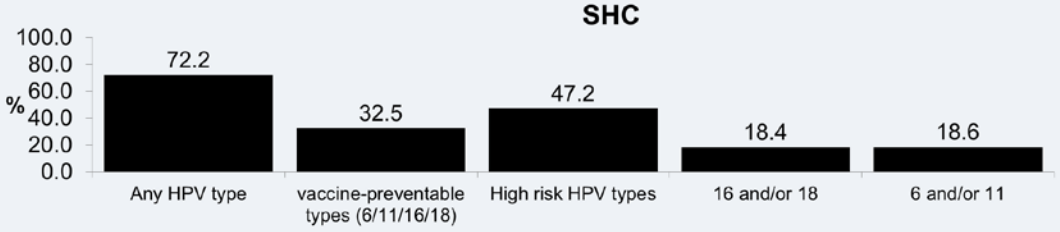
Results - 2

- Proportion disclosed sexuality to their GP = 39%
- HPV prevalence increase with age = 4.7% (95%CI 1.2-8.4) increase in odds per year

Number of quadrivalent vaccine-preventable HPV types (6/11/16/18) detected per subject



HPV DNA prevalence among n=511 MSM attending a London SHC



Conclusions

A high proportion of MSM were not currently infected with HPV6/11/16/18; suggesting that targeted vaccination may be effective. Prevalence data are consistent with ongoing risk – increasing prevalence with age. A small proportion had disclosed their sexuality to their primary care physician (GP), making sexual health clinics the most promising venue to offer vaccination. The impact of different vaccination strategies in the UK are now being modelled, including an economic analysis.

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

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

Introduction

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.

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.

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.

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.

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

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.

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].

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

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%.

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 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.

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

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.

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]

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 20143, 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

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 Medicine6.

[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

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.

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.

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

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.

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

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

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.

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.

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

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.

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.

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.

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

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.

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.

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.

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

Conclusion and advice

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.

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.

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

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

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.

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

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 H PV 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

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"*.

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."*