



HPV Vaccination of Adults

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BACKGROUND DOCUMENT

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Content

This pre-meeting document contains a list of selected abstracts/references from a Pubmed MEDLINE search on different search terms.

This document guides in the preparation of the meeting, it should not be considered as a complete literature review. However, it gives an an overview of what has been published on the topic of the meeting.

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Introduction

Meeting Objectives:

- Provide an overview of the current situation of HPV vaccine for adults .
- Discuss the immunogenicity, safety and efficacy data of existing HPV vaccine studies in adults.
- Gain insight into efficacy of HPV vaccine at mucosal level and systemic level.
- Discuss ways and methods to conduct research on potential benefits of vaccinating exposed adults.
- Discuss challenges and benefits of vaccination of adults including high risk groups.
- Discuss cervical cancer elimination strategies.
- Discuss potential implication of vaccination of adults on vaccine supplies in Low and Middle-Income Countries (LMIC).

Target audience:

The HPV Prevention & Control Board brings together the immunization, screening, clinical, health economics and academic key experts, as well as patient/advocacy groups and government officials in countries/regions so that they could present their data and discuss programs, strategies, successes and problems. Board members will use their experience to give advice on how challenges might be addressed. Lessons learnt will be collected and disseminated via the web site www.hpvboard.org, a meeting report and possibly via a publication in a peer reviewed journal.

Purpose of the background document

This background document provides an overview of articles related to the meeting and a concise bibliography of speakers. The main purpose of the document is to frame the topic of the meeting on **'HPV Vaccination of Adults'**.

The document should not be considered as an an exhaustive report of scientific articles related to the themes of the meeting.

Inclusion of references in this document does not indicate that the Executive Secretariat agrees with the content or correctness of the content. The first objective of this list is to give an overview of what has been published on this topic.

A brief overview of meeting topic and objectives are summarized in the publication below.



Perspective

HPV vaccination: Are we overlooking additional opportunities to control HPV infection and transmission?

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ABSTRACT

Human papillomavirus virus-like particles (HPV VLPs) have distinctive immunogenic properties that generate a durable antibody response, producing high-quality neutralizing antibodies. By vaccination, i.e., intramuscular injection of these HPV VLPs, the viral survival strategy of avoiding exposure to the systemic immune system is completely overruled, and large amounts of vaccine-induced systemic antibodies are generated. These systemic circulating antibodies are easily transuded to the genital mucosa and are detectable in female genital secretions. It is well accepted that these antibodies interact with the virions presented by an infected partner and inhibit infection. However, much less attention has been paid to the role of anti-HPV vaccine-induced antibodies in an HPV-infected individual where infectious virions are encountered by neutralizing antibodies in mucosal secretions. There is a clear need to further investigate and document this role. Indeed, if HPV vaccination of HPV-infected women has an effect on HPV transmission, auto-inoculation, and relapse after treatment, this may influence how we model, assess, and implement HPV vaccination programmes.

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Introduction

The impact of human papillomavirus (HPV) vaccination, provided sufficient vaccination coverage is reached, has been overwhelming. Important decreases in the prevalence of detectable HPV DNA and genital warts have been reported in vaccinees, as well as in unvaccinated individuals, regardless of sex, through herd protection (Cameron et al., 2016; Drolet et al., 2015). A rapid and significant decline in genital warts over time has also occurred in boys and men younger than 30 years of age in population programmes of female-only vaccination (quadrivalent vaccine) reaching vaccination coverage over 50% (Drolet et al., 2015).

To better understand the potential impact of HPV vaccination, it is important to recognize that HPV and its mode of infection have particular characteristics that shape the host immune response and permit vaccine-induced antibodies to counter the infection.

A unique combination of potent antigens and a susceptible immune ignored virus

First, HPV viral-like particles (VLPs) have distinctive antigenic properties. In fact, B-cell receptors interact with the dense, optimally spaced, and repetitive protein arrays on the surface of the VLPs, which promote the induction of an exceptionally potent antibody response. Indeed, the oligomerization of B-cell receptor/VLP signalling complexes leads to robust activation and proliferation signals, high levels of antibodies with high avidity, and long-lived plasma cells that continuously produce antibodies for many years after vaccination (Gomes et al., 2017). Interestingly, this potent antibody response underpins the ongoing randomized trials of single-dose schedules (Kreimer et al., 2018).

Second, HPVs have evolved to maintain immune ignorance rather than develop mechanisms to actively counter the mucosal and systemic immune system (Schwarz and Leo, 2008; Roden and Stern, 2018). Fortunately, injection of the parental VLPs, as is done when vaccinating, overcomes this immune system evasion strategy. In fact, HPV vaccination generates 10- to 100-fold higher levels of L1-specific serum neutralizing antibodies than a natural infection (Stanley, 2010).

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Finally, anti-HPV antibodies play a unique and decisive role in the protection against HPV infection. This has been elegantly shown in animal models. Passive immunization, injecting sera from 4vHPV immunized mice interperitoneally, conferred neutralizing protection in mice genitally challenged with pseudovirions (PsVs) (Longet et al., 2011). It is important to mention that anti-HPV IgG antibodies were also detected at the mucosal level, demonstrating the transudation of IgG.

Neutralizing antibodies play a crucial role

The current understanding of antibody-mediated protection is built on the major role of neutralizing antibodies, and different potentially complementary mechanisms have been postulated (Stanley, 2010). For virions to access the basal mucosal cells, epithelial microlesions are required. It has been proposed that virions are neutralized by systemic neutralizing antibodies that exude from these microlesions and scavenge the mucosal membrane. As internalization is a relatively slow process that requires a series of conformational changes, there is sufficient time for vaccine-induced antibodies to interact with the virions and disrupt this process. However, vaccine-induced antibodies present at the mucosal level, which are also transudated, most likely via interaction with the neonatal Fc receptor, may play a major role (Schwarz, 2009; Einstein et al., 2011; Stanley et al., 2006; Li et al., 2011). Previous studies have shown that the genital mucosa of vaccinated girls also harbours detectable vaccine-induced transudated IgG, and moderate to high correlation coefficients between serum and cervical IgG titres have been reported (Schwarz et al., 2009). Scherpenisse et al. reported transudated anti-HPV IgG antibody concentrations in cervicovaginal samples of up to 2% of the concentration detected in serum (Scherpenisse et al., 2013). This finding indicates that we may have, solely by transudation, anti-HPV antibodies at 'neutralizing' concentrations. Indeed, Longet et al. reported in their animal model that serum antibody levels >100-fold lower than those detectable by *in vitro* PsV neutralization assays are sufficient to confer protection against an HPV PsV genital infection (Longet et al., 2011). The neutralizing capacity of cervicovaginal lavage samples from immunized non-human primates has also been demonstrated in an HPV-11 athymic mouse xenograft neutralization assay (Lowe et al., 1997). It is important to add that levels of detectable vaccine-induced cervicovaginal antibodies vary across the menstrual cycle (Nardelli-Haeffliger et al., 2003). The potential impact of this variation on protection and prevention of transmission should be taken into account in future research.

HPV vaccination of HPV-infected women is equally immunogenic and completely safe

It has been shown that HPV vaccination of previously HPV-infected women is safe and generates a high-level immune response (Arbyn et al., 2018; Group FIS, 2007; Haupt et al., 2011; Meites et al., 2019). Therefore, even in women with a productive infection, vaccination will lead to a potentially neutralizing amount of transudated anti-HPV antibodies in their cervicovaginal secretions. Furthermore, protection against non-prevalent HPV types included in the vaccine is activated as in HPV-naïve women.

First, this concept suggests that vaccination may prevent infectious virions from a productive infection spreading from sites with low potential for malignant progression to the cervical transformation zone with higher potential for progression (Schiller and Davies, 2004). Second, vaccination may also decrease the likelihood that women with a productive infection transmit the infection to their sexual partner, as already postulated by Schiller et al. in 2004 (Schiller and Davies, 2004). Indeed, in

HPV-vaccinated women, newly produced viral particles are shed in a milieu with highly potent anti-HPV antibodies that are able to interact with and neutralize the viral particles. This finding may imply that HPV-infected HPV-vaccinated women will no longer (or to a lesser extent) be able to re-infect themselves or transmit their infection(s). A special discussion of transmission interruption could be initiated in relation to the high-risk groups for transmission, e.g. commercial sex workers, currently outside of any special vaccination programmes (Schim van der Loeff et al., 2019).

Paradoxically, during follow-up of women with an existing infection in randomized controlled vaccine trials (RCTs), no impact of vaccination on the rate of progression was shown. However, it should be noted that these trials were not designed to demonstrate the potential impact of vaccination on auto-inoculation. In most RCTs, cervical sampling occurred prior to vaccination, which as we discuss below, may impact the risk of acquisition and perhaps the natural course of the infection. In addition, HPV DNA assays with a defined clinical cut-off will predominantly identify women who already have a clinical lesion that is not affected by vaccination.

Although it remains difficult to investigate experimentally or epidemiologically whether vaccination does block transmission, further efforts are needed. For instance, including self-collected none invasive cervicovaginal secretion sampling and using sensitive analytical assays in the design of future vaccine trials may help to further investigate what is happening at the level of the genital mucosa.

The potential impact of vaccination on HPV transmission will likely be more prominent in women than in men; viral particles are less likely to come into contact with mucosal transduced antibodies in men.

Potential benefit of HPV vaccination when screening HPV-positive women

Cervical screening is a major tool contributing to the early detection and subsequent removal of precancerous lesions. However, the collection of cervical cells from women with a productive genital HPV infection could also create new infection sites for circulating infectious virions in the genital tract. Indeed, the principle of a cytobrush is to remove epithelial cells and consequently create microlesions, which in turn provide passage for HPV to infect mucosal basal cells. Of note, in the animal model mentioned above, cytobrushes were also used to create effective entry sites for pseudovirions (Roberts et al., 2007). The more direct and compelling study of Roberts et al. in macaques confirms the hypothesis that cytology screening in women might lead to a transient enhancement of susceptibility to HPV infection (Roberts et al., 2011). Currently, the impact of screening on auto-inoculation is unknown, so further research on this topic is merited. In this context, vaccination of young women prior to cervical cancer screening may be beneficial in addition to the well-established advantage of vaccinating prior to sexual debut.

It is recognized that these biologically plausible hypotheses warrant further proof. However, if confirmed, these may have a substantial impact on how we model, assess, and implement HPV vaccination programmes more effectively.

Most vaccine impact models disregard vaccinating adult women because type-specific HPV exposure is likely to have occurred and the benefits to the individual are seen as marginal. However, if the hypothesis above is true, vaccination of HPV-infected women will not only reduce auto-inoculation but also offer additional protection to the group (herd protection) by neutralizing the infectious virions being shed. Asymptomatic individuals with productive lesions shedding infectious viral particles are the main source for spreading the infection in the

population. Therefore, strategies that potentially reduce this transmission must be explored to accelerate the reduction in infection. The change to primary HPV DNA screening will identify HPV DNA-positive women who have no or only low-grade lesions (approximately 5–10%), for whom current treatment is not recommended.

Clearly, from this perspective, the indication for vaccination would benefit from expanding the target population, including HPV-positive women identified at screening (in addition to the conventional high-risk groups) and eventually include a broader age range in primary vaccination campaigns (Bosch et al., 2016). A temporal drawback in this proposal reflects that in the current global context of ongoing vaccine shortage, and the big disparity between high income and low and middle income countries, other strategies instead of extending the target group for vaccination may provide a much bigger global public health benefit. However, the better we understand the potential of HPV vaccination, the better we can make informed decisions.

Vaccination reduces the risk of clinical disease relapse after treatment

The first evidence that HPV vaccination also reduces post-treatment relapse is becoming available. As well as the previous clinical observations of Kang et al., Ghelardi et al. showed that post-treatment vaccination of women resulted in an 81.2% (95% confidence interval 34.3–95.7%) risk reduction of clinical disease relapse (Ghelardi et al., 2018; Kang et al., 2013). These observations are an additional argument for vaccination of HPV-positive women, as they show an additional individual benefit in the case of disease progression.

Conclusions

Based on the discussion above, we would like to call for further investigation and documentation of the potential public health benefits of vaccination of HPV-positive women. For modellers, these data would provide an additional effect that should be considered when designing HPV vaccination impact models exploring and quantifying the herd protection observed in population programmes. Finally, these additional modes of protection may also reduce the existing reluctance to vaccinate (young) women post-sexual debut or known high-risk groups such as sex workers.

Funding source

No funding was provided for this manuscript.

Ethical approval

Ethical approval was not required.

Conflict of interest

AV University of Antwerp obtained unrestricted educational grants from GSK, Merck, and Sanofi Pasteur; speakers fees from Merck were paid directly to an educational fund held by the University of Antwerp. AV is co-founder of Novosanis, a spin-off company of the University of Antwerp. FXB received research funding via his institution from GSK, Merck, Qiagen, Roche, and SPMSD, and reimbursement of travel expenses for attending symposia, meetings and/or speaking at conferences from GSK, Merck, Qiagen, Roche, and SPMSD. PVD acts as principal investigator for HPV vaccine trials conducted on behalf of the University of Antwerp, for which the University obtained research grants from vaccine manufacturers; speaker's fees for

presentations were paid directly to an educational fund held by the University of Antwerp. PVD is co-founder of Novosanis, a spin-off company of the University of Antwerp.

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Part 1: Presentation related references by session

List obtained via speaker forms or (if speaker form was not available) via a Pubmed search on Name of the speaker. Maximum ten articles are shown.

Session 1

SITUATIONAL ANALYSIS OF HPV VACCINATION OF ADULTS: IMMUNOGENECITY AND SAFETY DATA

Presentation: *Efficacy and safety of prophylactic HPV vaccination in adults*

Speaker: Marc Arbyn

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- (1) Arbyn M, Xu L, Simoens C, Martin-Hirsch PP. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. *Cochrane Database Syst Rev* 2018; 5: CD009069.
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Presentation: *Immunogenicity and tolerability of HPV Vaccine in women aged 15-55 years; findings and way forward*

Speaker: Tino F. Schwarz

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Session 2

HPV IMMUNOLOGICAL DYNAMICS AT MUCOSAL AND SYSTEMIC LEVEL

Presentation: *Potential Benefits of HPV Vaccine in sexually active women: delivering the promise*

Speaker: John Schiller

References provided by the speaker

1. Effect of Pap smear collection and carrageenan on cervicovaginal HPV16 infection in a rhesus macaque model. Roberts JN, Kines RC, Katki HA, Lowy DR, Schiller JT. *N Natl Cancer Inst* 2011; 103(9): 737-43.

Presentation: *Immune cross talk of HPV Specific Antibody Response; Cross Reactivity, Neutralizing Activity, Mucosal Secretion and Infection Prevention.*

Speaker: Fiona van der Klis

References provided by the speaker

1. Pasmans H, Schurink-Van't Klooster TM, Bogaard MJM, van Rooijen DM, de Melker HE, Welters MJP, van der Burg SH, van der Klis FRM, Buisman AM. Long-term HPV-specific immune response after one versus two and three doses of bivalent HPV vaccination in Dutch girls. *Vaccine*. 2019 Sep 28. pii: S0264-410X(19)31294-0. doi: 10.1016/j.vaccine.2019.09.066.
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Presentation: *Vaccine-induced HPV-specific antibodies in cervicovaginal secretions.*

Speaker: *Jade Pattyn*

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Session 3

COMPREHENSIVE ANALYSIS OF CHALLENGES AND POTENTIAL BENEFITS OF HPV VACCINATION OF ADULTS

Presentation: *Pap smear collection: an increased risk of HPV infection? An objective study in rhesus macaques' model.*

Speaker: John Schiller

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Effect of Pap smear collection and carrageenan on cervicovaginal HPV16 infection in a rhesus macaque model. Roberts JN, Kines RC, Katki HA, Lowy DR, Schiller JT. *N Natl Cancer Inst* 2011; 103(9): 737-43.

Presentation: *HPV vaccine post treatment: a pathway to prevent disease relapse.*

Speaker: Alessandro Ghelardi

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Speaker: Marta del Pino

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Presentation: *HPV vaccination in relation to conization: A Danish nationwide study.*

Speaker: *Susanne Krüger Kjær*

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Presentation: *Transmission Reduction and Prevention with HPV Vaccination (TRAP-HPV) study.*

Speakers: *Aaron MacCosham and Eduardo Franco*

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Presentation: *Predicting cohort-specific cervical cancer incidence from population-based HPV prevalence surveys.*

Speaker: *Iacopo Bausanno*

References provided by the speakers

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Presentation: *Overview of Health Economics Models for HPV Vaccination of Mid-Adults.*

Speakers: *Harrell Chesson*

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Session 4

HPV Vaccination of High Risk Groups

Presentation: *Directionality of HPV Infection transmission in heterosexual couples; a systematic review and meta-analysis*

Speakers: Aaron MacCosham and Eduardo Franco

References provided by the speaker

Not yet

Presentation: *HPV Vaccination for sex workers: finding a balance between pros and cons.*

Speaker: Schim van der Loeff MF

References provided by the speaker

1. Schim van der Loeff MF, Vorsters A, Marra E, Van Damme P, Hogewoning A. Should female sex workers be offered HPV vaccination? *Hum Vaccin Immunother.* 2019;15(7-8):1544-1548. doi: 10.1080/21645515.2019.1602432. Epub 2019 May 7. PubMed PMID: 31063078; PubMed Central PMCID: PMC6746505.
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Presentation: *Baseline HPV Prevalence in rectal swabs from men attending a sexual health clinic in Scotland: assessing the potential impact of a selective HPV Vaccination programme for men who have sex with men*

Speaker: Ross Cameron

References provided by the speaker

1. Cameron RL, Cuschieri K, Pollock KGJ. Baseline HPV prevalence in rectal swabs from men attending a sexual health clinic in Scotland: assessing the potential impact of a selective HPV vaccination programme for men who have sex with men. *Sex Transm Infect*, epub ahead of print: doi:10.1136/sextrans-2018-053668

Session 5

LIMITATIONS AND ELIMINATION GOALS

Presentation: *Towards cervical cancer elimination: the context of HPV Vaccination.*

Speaker: Paul Bloem

References provided by the speakers

1. For WHO data on vaccine introductions and coverage, proposed reference: “WHO IVB Database, October 2019” Data can be found at https://www.who.int/immunization/monitoring_surveillance/data/en/
2. WHO Global strategy towards the elimination of cervical cancer: <https://www.who.int/cancer/cervical-cancer/cervical-cancer-elimination-strategy>

Part 2: References based on a Pubmed search, by session

Session 1 *Situational Analysis of HPV Vaccine in Adults; Immunogenicity and Safety data*

A Pubmed search was performed with the following selection criteria: **HPV Vaccine AND IMMUNOGENICITY AND Adults in the last 10 years**: 214 items were retrieved. References were imported in EndNote. Herein, a relevant manual selection of **18** publications between 2009-2019 based on title and abstract was made.

Schwarz, T. F., A. Galaj, M. Spaczynski, J. Wysocki, A. M. Kaufmann, S. Poncelet, P. V. Suryakiran, N. Folschweiller, F. Thomas, L. Lin and F. Struyf (2017). "**Ten-year immune persistence and safety of the HPV-16/18 AS04-adjuvanted vaccine in females vaccinated at 15-55 years of age.**" *Cancer Med* 6(11): 2723-2731.

Women remain at risk of human papillomavirus (HPV) infection for most of their lives. The duration of protection against HPV-16/18 from prophylactic vaccination remains unknown. We investigated the 10-year immune response and long-term safety profile of the HPV-16/18 AS04-adjuvanted vaccine (AS04-HPV-16/18 vaccine) in females aged between 15 and 55 years at first vaccination. Females who received primary vaccination with three doses of AS04-HPV-16/18 vaccine in the primary phase-III study (NCT00196937) were invited to attend annual evaluations for long-term immunogenicity and safety. Anti-HPV-16/18 antibodies in serum and cervico-vaginal secretions (CVS) were measured using enzyme-linked immunosorbent assay (ELISA). Serious adverse events (SAEs) were recorded throughout the follow-up period. Seropositivity rates for anti-HPV-16 remained high ($\geq 96.3\%$) in all age groups 10 years after first vaccination. It was found that 99.2% of 15-25-year olds remained seropositive for anti-HPV-18 compared to 93.7% and 83.8% of 26-45-year olds and 45-55-year olds, respectively. Geometric mean titers (GMT) remained above natural infection levels in all age groups. Anti-HPV-16 and anti-HPV-18 titers were at least 5.3-fold and 3.1-fold higher than titers observed after natural infection, respectively, and were predicted to persist above natural infection levels for ≥ 30 years in all age groups. At Year 10, anti-HPV-16/18 antibody titers in subjects aged 15-25 years remained above plateau levels observed in previous studies. Correlation coefficients for antibody titers in serum and CVS were 0.64 (anti-HPV-16) and 0.38 (anti-HPV-18). This study concluded that vaccinated females aged 15-55 years elicited sustained immunogenicity with an acceptable safety profile up to 10 years after primary vaccination, suggesting long-term protection against HPV.

Wheeler, C. M., S. R. Skinner, M. R. Del Rosario-Raymundo, S. M. Garland, A. Chatterjee, E. Lazcano-Ponce, J. Salmeron, S. McNeil, J. T. Stapleton, C. Boucharad, M. G. Martens, D. M. Money, S. C. Quek, B. Romanowski, C. S. Vallejos, B. Ter Harmsel, V. Prilepskaya, K. L. Fong, H. Kitchener, G. Minkina, Y. K. T. Lim, T. Stoney, N. Chakhtoura, M. E. Cruickshank, A. Savicheva, D. P. da Silva, M. Ferguson, A. C. Molijn, W. G. V. Quint, K. Hardt, D. Descamps, P. V. Suryakiran, N. Karkada, B. Geeraerts, G. Dubin and F. Struyf (2016). "**Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study.**" *Lancet Infect Dis* 16(10): 1154-1168.

BACKGROUND: Although the risk of human papillomavirus (HPV) infection is greatest in young women, women older than 25 years remain at risk. We present data from the VIVIANE study of the HPV 16/18 AS04-adjuvanted vaccine in adult women after 7 years of follow-up. **METHODS:** In this phase 3, double-blind, randomised controlled trial, healthy women older than 25 years were enrolled (age stratified: 26-35 years, 36-45 years, and ≥ 46 years). Up to 15% in each age stratum had a history of HPV infection or disease. Women were randomly

assigned (1:1) to receive HPV 16/18 vaccine or aluminium hydroxide control, with an internet-based system. The primary endpoint was vaccine efficacy against 6-month persistent infection or cervical intraepithelial neoplasia grade 1 or greater (CIN1+) associated with HPV 16/18. We did analyses in the according-to-protocol cohort for efficacy and total vaccinated cohort. Data for the combined primary endpoint in the according-to-protocol cohort for efficacy were considered significant when the lower limit of the 96.2% CI around the point estimate was greater than 30%. For all other endpoints and cohorts, data were considered significant when the lower limit of the 96.2% CI was greater than 0%. This study is registered with ClinicalTrials.gov, number NCT00294047. FINDINGS: The first participant was enrolled on Feb 16, 2006, and the last study visit took place on Jan 29, 2014. 4407 women were in the according-to-protocol cohort for efficacy (n=2209 vaccine, n=2198 control) and 5747 women in the total vaccinated cohort (n=2877 vaccine, n=2870 control). At month 84, in women seronegative for the corresponding HPV type in the according-to-protocol cohort for efficacy, vaccine efficacy against 6-month persistent infection or CIN1+ associated with HPV 16/18 was significant in all age groups combined (90.5%, 96.2% CI 78.6-96.5). Vaccine efficacy against HPV 16/18-related cytological abnormalities (atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesion) and CIN1+ was also significant. We also noted significant cross-protective efficacy against 6-month persistent infection with HPV 31 (65.8%, 96.2% CI 24.9-85.8) and HPV 45 (70.7%, 96.2% CI 34.2-88.4). In the total vaccinated cohort, vaccine efficacy against CIN1+ irrespective of HPV was significant (22.9%, 96.2% CI 4.8-37.7). Serious adverse events related to vaccination occurred in five (0.2%) of 2877 women in the vaccine group and eight (0.3%) of 2870 women in the control group. INTERPRETATION: In women older than 25 years, the HPV 16/18 vaccine continues to protect against infections, cytological abnormalities, and lesions associated with HPV 16/18 and CIN1+ irrespective of HPV type, and infection with non-vaccine types HPV 31 and HPV 45 over 7 years of follow-up. FUNDING: GlaxoSmithKline Biologicals SA.

Giuliano, A. R., K. Isaacs-Soriano, B. N. Torres, M. Abrahamsen, D. J. Ingles, B. A. Sirak, M. Quiterio and E. Lazcano-Ponce (2015). "**Immunogenicity and safety of Gardasil among mid-adult aged men (27-45 years)--The MAM Study.**" *Vaccine* **33**(42): 5640-5646.

BACKGROUND: The quadrivalent (types 6/11/16/18) human papillomavirus (HPV) vaccine, Gardasil, has demonstrated efficacy against persistent HPV infection and associated anogenital disease in males. The goal of this Phase II trial was to establish the immunogenicity and safety of Gardasil among mid-adult men ages 27-45 years. METHODS: One hundred and fifty men from Tampa, FL, US, and Cuernavaca, Mexico who met eligibility criteria (male, 27-45 years old, completed four years of follow-up in the HPV Infection in Men (HIM) natural history study) were enrolled. Subjects completed four visits over seven months, with Gardasil administered at Day 1 and Months 2 and 6. Sera were collected at Day 1 (pre-vaccination) and Month 7 (one month post-dose three). Anti-HPV6, 11, 16, and 18 IgG levels were determined by competitive Luminex immunoassay. FINDINGS: 100% of men seroconverted to each of the four HPV vaccine components, and the vaccine was generally well-tolerated. Antibody responses to vaccine did not differ by age group or sexual orientation, regardless of HPV type, and were significantly higher at Month 7 among men who entered the trial seropositive for HPV 6 or 11. INTERPRETATION: The immune response to HPV vaccination in men ages 27-45 was comparable to that observed in younger men, in whom clinical efficacy was demonstrated. Further trials to assess the efficacy of HPV vaccines to prevent persistent HPV infections in mid-adult men are needed. FUNDING: Merck & Co. Inc. was the main sponsor of this trial (IISP39256) and provided the study product.

Schwarz, T., M. Spaczynski, A. Kaufmann, J. Wysocki, A. Galaj, K. Schulze, P. Suryakiran, F. Thomas and D. Descamps (2015). "**Persistence of immune responses to the HPV-16/18 AS04-adjuvanted vaccine in women aged 15-55 years and first-time modelling of antibody responses in mature women: results from an open-label 6-year follow-up study.**" *Biog* 122(1): 107-118.

OBJECTIVE: Evaluation of the long-term HPV-16/18 AS04-adjuvanted vaccine immunogenicity persistence in women. DESIGN: Multicentre, open-label, long-term follow-up (NCT00947115) of a primary phase-III study (NCT00196937). SETTING: Six centres in Germany and Poland. POPULATION: 488 healthy women (aged 15-55 years, age-stratified into groups: 15-25, 26-45, and 46-55 years) who received three vaccine doses in the primary study. METHODS: Immune responses were evaluated in serum and cervicovaginal secretion (CVS) samples 6 years after dose 1. Anti-HPV-16/18 geometric mean titres (GMTs) were measured by enzyme-linked immunosorbent assay (ELISA), and were used to fit the modified power-law and piecewise models, predicting long-term immunogenicity. Serious adverse events (SAEs) were recorded. MAIN OUTCOME MEASURES: Anti-HPV-16/18 seropositivity rates and GMTs 6 years after dose 1. RESULTS: At 6 years after dose 1, all women were seropositive for anti-HPV-16 and $\geq 97\%$ were seropositive for anti-HPV-18 antibodies. GMTs ranged from 277.7 to 1344.6 EU/ml, and from 97.6 to 438.2 EU/ml, for anti-HPV-16 and anti-HPV-18, respectively. In all age groups, GMTs were higher (anti-HPV-16, 9.3-45.1-fold; anti-HPV-18, 4.3-19.4-fold) than levels associated with natural infection (29.8 EU/ml). A strong correlation between serum and CVS anti-HPV-16/18 levels was observed, with correlation coefficients of 0.81-0.96 (anti-HPV-16) and 0.69-0.84 (anti-HPV-18). Exploratory modelling based on the 6-year data predicted vaccine-induced anti-HPV-16/18 levels above natural infection levels for at least 20 years, except for anti-HPV-18 in the older age group (piecewise model). One vaccine-related and two fatal SAEs were reported. CONCLUSIONS: At 6 years after vaccination, immune responses induced by the HPV-16/18 AS04-adjuvanted vaccine were sustained in all age groups.

Einstein, M. H., M. J. Levin, A. Chatterjee, N. Chakhtoura, P. Takacs, G. Catteau, F. J. Dessy, P. Moris, L. Lin, F. Struyf and G. Dubin (2014). "**Comparative humoral and cellular immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18-45 years: follow-up through Month 48 in a Phase III randomized study.**" *Hum Vaccin Immunother* 10(12): 3455-3465.

We previously reported higher anti-HPV-16 and -18 immune responses induced by HPV-16/18 vaccine compared with HPV-6/11/16/18 vaccine at Month 7 (one month after completion of full vaccination series) in women aged 18-45 y in an observer-blind study NCT00423046; the differences of immune response magnitudes were maintained up to Month 24. Here we report follow-up data through Month 48. At Month 48, in according-to-protocol cohort for immunogenicity (seronegative and DNA-negative for HPV type analyzed at baseline), geometric mean titers of serum neutralizing antibodies were 2.0- to 5.2-fold higher (HPV-16) and 8.6- to 12.8-fold higher (HPV-18) in HPV-16/18 vaccine group than in HPV-6/11/16/18 vaccine group. The majority of women in both vaccine groups remained seropositive for HPV-16. The same trend was observed for HPV-18 in HPV-16/18 vaccine group; however, seropositivity rates in HPV-6/11/16/18 vaccine group decreased considerably, particularly in the older age groups. In the total vaccinated cohort (regardless of baseline serological and HPV-DNA status), anti-HPV-16 and -18 neutralizing antibody levels induced by HPV-16/18 vaccine were higher than those induced by HPV-6/11/16/18 vaccine. CD4+ T-cell response for HPV-16 and HPV-18 was higher in HPV-16/18 vaccine group than in HPV-6/11/16/18 vaccine group. Memory B-cell responses appeared similar between vaccine groups. Both vaccines were generally well tolerated. Overall, the higher immune response observed with the HPV-

16/18 vaccine was maintained up to Month 48. A head-to-head study incorporating clinical endpoints would be required to confirm whether the observed differences in immune response between the vaccines influence the duration of protection they provided.

Einstein, M. H., P. Takacs, A. Chatterjee, R. S. Sperling, N. Chakhtoura, M. M. Blatter, J. Lalezari, M. P. David, L. Lin, F. Struyf and G. Dubin (2014). **"Comparison of long-term immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18-45 years: end-of-study analysis of a Phase III randomized trial."** *Hum Vaccin Immunother* **10**(12): 3435-3445.

The observer-blind, randomized, age-stratified, head-to-head study (NCT00423046) comparing immunogenicity and safety of HPV-16/18 and HPV-6/11/16/18 vaccines in healthy women aged 18-45 y was completed. Five y after vaccination, in subjects from the Month 60 according-to-protocol cohort (seronegative and DNA negative for HPV type analyzed at baseline), serum neutralizing antibody (nAb) responses induced by HPV-16/18 vaccine remained 7.8-fold (18-26-y stratum), 5.6-fold (27-35-y stratum) and 2.3-fold (36-45-y stratum) higher than those induced by HPV-6/11/16/18 vaccine for HPV-16. For HPV-18, the fold differences were 12.1, 13.0 and 7.8, respectively. At Month 60, all (100%) subjects in HPV-16/18 vaccine group and the majority (95.7%-97.5%) in HPV-6/11/16/18 vaccine group were seropositive for HPV-16. For HPV-18, the majority (98.1%-100%) of subjects in HPV-16/18 vaccine group were seropositive; however, seropositivity rates in HPV-6/11/16/18 vaccine group decreased considerably (61.1%-76.9%) across the 3 age strata. In the total vaccinated cohort (received ≥ 1 dose regardless of baseline HPV serostatus and DNA status), geometric mean titers for anti-HPV-16 and anti-HPV-18 nAb were higher in HPV-16/18 vaccine group than in HPV-6/11/16/18 vaccine group. Based on the 5-y data, piece-wise and modified power-law models predicted a longer durability of nAb response for HPV-16/18 vaccine compared to HPV-6/11/16/18 vaccine. Beyond the differences apparent between the vaccines in terms of immunogenicity and modeled persistence of antibody responses, comparative studies including clinical endpoints would be needed to determine whether differences exist in duration of vaccine-induced protection.

Skinner, S. R., A. Szarewski, B. Romanowski, S. M. Garland, E. Lazcano-Ponce, J. Salmeron, M. R. Del Rosario-Raymundo, R. H. Verheijen, S. C. Quek, D. P. da Silva, H. Kitchener, K. L. Fong, C. Bouchard, D. M. Money, A. Ilancheran, M. E. Cruickshank, M. J. Levin, A. Chatterjee, J. T. Stapleton, M. Martens, W. Quint, M. P. David, D. Meric, K. Hardt, D. Descamps, B. Geeraerts, F. Struyf and G. Dubin (2014). **"Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study."** *Lancet* **384**(9961): 2213-2227.

BACKGROUND: Although adolescent girls are the main population for prophylactic human papillomavirus (HPV) vaccines, adult women who remain at risk of cervical cancer can also be vaccinated. We report data from the interim analysis of the ongoing VIVIANE study, the aim of which is to assess the efficacy, safety, and immunogenicity of the HPV 16/18 AS04-adjuvanted vaccine in adult women. **METHODS:** In this phase 3, multinational, double-blind, randomised controlled trial, we randomly assigned healthy women older than 25 years to the HPV 16/18 vaccine or control (1:1), via an internet-based system with an algorithm process that accounted for region, age stratum, baseline HPV DNA status, HPV 16/18 serostatus, and cytology. Enrolment was age-stratified, with about 45% of participants in each of the 26-35 and 36-45 years age strata and 10% in the 46 years and older stratum. Up to 15% of women in each age stratum could have a history of HPV infection or disease. The primary endpoint was vaccine efficacy against 6-month persistent infection or cervical intraepithelial neoplasia

grade 1 or higher (CIN1+) associated with HPV 16/18. The primary analysis was done in the according-to-protocol cohort for efficacy, which consists of women who received all three vaccine or control doses, had negative or low-grade cytology at baseline, and had no history of HPV disease. Secondary analyses included vaccine efficacy against non-vaccine oncogenic HPV types. Mean follow-up time was 40.3 months. This study is registered with ClinicalTrials.gov, number NCT00294047. FINDINGS: The first participant was enrolled on Feb 16, 2006, and the last study visit for the present analysis took place on Dec 10, 2010; 5752 women were included in the total vaccinated cohort (n=2881 vaccine, n=2871 control), and 4505 in the according-to-protocol cohort for efficacy (n=2264 vaccine, n=2241 control). Vaccine efficacy against HPV 16/18-related 6-month persistent infection or CIN1+ was significant in all age groups combined (81.1%, 97.7% CI 52.1-94.0), in the 26-35 years age group (83.5%, 45.0-96.8), and in the 36-45 years age group (77.2%, 2.8-96.9); no cases were seen in women aged 46 years and older. Vaccine efficacy against atypical squamous cells of undetermined significance or greater associated with HPV 16/18 was also significant. We also noted significant cross-protective vaccine efficacy against 6-month persistent infection with HPV 31 (79.1%, 97.7% CI 27.6-95.9) and HPV 45 (76.9%, 18.5-95.6]. Serious adverse events occurred in 285 (10%) of 2881 women in the vaccine group and 267 (9%) of 2871 in the control group; five (<1%) and eight (<1%) of these events, respectively, were believed to be related to vaccination. INTERPRETATION: In women older than 25 years, the HPV 16/18 vaccine is efficacious against infections and cervical abnormalities associated with the vaccine types, as well as infections with the non-vaccine HPV types 31 and 45. FUNDING: GlaxoSmithKline Biologicals SA.

Zhu, F., J. Li, Y. Hu, X. Zhang, X. Yang, H. Zhao, J. Wang, J. Yang, G. Xia, Q. Dai, H. Tang, P. Suryakiran, S. K. Datta, D. Descamps, D. Bi and F. Struyf (2014). "**Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese girls and women aged 9 to 45 years.**" *Hum Vaccin Immunother* **10**(7): 1795-1806.

Immunogenicity and safety of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine were evaluated in healthy Chinese females aged 9-45 years in 2 phase IIIB, randomized, controlled trials. Girls aged 9-17 years (ClinicalTrials.gov, NCT00996125) received vaccine (n = 374) or control (n = 376) and women aged 26-45 years (NCT01277042) received vaccine (n = 606) or control (n = 606) at months 0, 1, and 6. The primary objective was to show non-inferiority of anti-HPV-16 and -18 immune responses in initially seronegative subjects at month 7, compared with Chinese women aged 18-25 years enrolled in a separate phase II/III trial (NCT00779766). Secondary objectives were to describe the anti-HPV-16 and -18 immune response, reactogenicity and safety. At month 7, immune responses were non-inferior for girls (9-17 years) vs. young women (18-25 years): the upper limit of the 95% confidence interval (CI) for the geometric mean titer (GMT) ratio (women/girls) was below the limit of 2 for both anti-HPV-16 (0.37 [95% CI: 0.32, 0.43]) and anti-HPV-18 (0.42 [0.36, 0.49]). Immune responses at month 7 were also non-inferior for 26-45 year-old women vs. 18-25 year-old women: the upper limit of the 95% CI for the difference in seroconversion (18-25 minus 26-45) was below the limit of 5% for both anti-HPV-16 (0.00% [-1.53, 1.10]) and anti-HPV-18 (0.21% [-1.36, 1.68]). GMTs were 2- to 3-fold higher in girls (9-17 years) as compared with young women (18-25 years). The HPV-16/18 AS04-adjuvanted vaccine had an acceptable safety profile when administered to healthy Chinese females aged 9-45 years.

Luna, J., M. Plata, M. Gonzalez, A. Correa, I. Maldonado, C. Nossa, D. Radley, S. Vuocolo, R. M. Haupt and A. Saah (2013). "**Long-term follow-up observation of the safety, immunogenicity, and effectiveness of Gardasil in adult women.**" *PLoS One* **8**(12): e83431.

BACKGROUND: Previous analyses from a randomized trial in women aged 24-45 have shown the quadrivalent HPV vaccine to be efficacious in the prevention of infection, cervical intraepithelial neoplasia (CIN) and external genital lesions (EGL) related to HPV 6/11/16/18 through 4 years. In this report we present long term follow-up data on the efficacy, safety and immunogenicity of the quadrivalent HPV vaccine in adult women. **METHODS:** Follow-up data are from a study being conducted in 5 sites in Colombia designed to evaluate the long-term immunogenicity, effectiveness, and safety of the qHPV vaccine in women who were vaccinated at 24 to 45 years of age (in the original vaccine group during the base study [n = 684]) or 29 to 50 years of age (in the original placebo group during the base study [n = 651]). This analysis summarizes data collected as of the year 6 post-vaccination visit relative to day 1 of the base study (median follow-up of 6.26 years) from both the original base study and the Colombian follow-up. **RESULTS:** There were no cases of HPV 6/11/16/18-related CIN or EGL during the extended follow-up phase in the per-protocol population. Immunogenicity persists against vaccine-related HPV types, and no evidence of HPV type replacement has been observed. No new serious adverse experiences have been reported. **CONCLUSIONS:** Vaccination with qHPV vaccine provides generally safe and effective protection from HPV 6-, 11-, 16-, and 18-related genital warts and cervical dysplasia through 6 years following administration to 24-45 year-old women. **TRIAL REGISTRATION:** Clinicaltrials.govNCT00090220.

Castellsague, X., N. Munoz, P. Pitisuttithum, D. Ferris, J. Monsonego, K. Ault, J. Luna, E. Myers, S. Mallary, O. M. Bautista, J. Bryan, S. Vuocolo, R. M. Haupt and A. Saah (2011). "**End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age.**" *Br J Cancer* **105**(1): 28-37.

BACKGROUND: Previous analyses from a randomised trial in women aged 24-45 years have shown the quadrivalent human papillomavirus (qHPV) vaccine to be efficacious in the prevention of infection, cervical intraepithelial neoplasia (CIN), and external genital lesions (EGLs) related to HPV 6/11/16/18. In this report, we present end-of-study efficacy, safety, and immunogenicity data with a median follow-up time of 4.0 years. **METHODS:** We enrolled 3819 24-45-year-old women with no history of cervical disease or genital warts in the past 5 years. Women received quadrivalent vaccine or placebo at day 1, and at months 2 and 6. Ascertainment of CIN/EGL was accomplished through Pap testing, genital inspection, and cervicovaginal sampling (every 6 months). The main analysis was conducted in a per-protocol efficacy population (that received three doses, was naive to the relevant HPV types at day 1, and remained free of infection through month 7). Efficacy was also estimated in other naive and non-naive populations. **RESULTS:** Vaccine efficacy against the combined incidence of persistent infection, CIN/EGL related to HPV6/11/16/18 in the per-protocol population was 88.7% (95% CI: 78.1, 94.8). Efficacy for women who were seropositive and DNA negative for the relevant vaccine HPV type at the time of enrolment who received at least 1 dose was 66.9% (95% CI: 4.3, 90.6). At month 48, 91.5, 92.0, 97.4, and 47.9% of vaccinated women were seropositive to HPV 6/11/16/18, respectively. No serious vaccine-related adverse experiences were reported. **CONCLUSIONS:** The qHPV vaccine demonstrated high efficacy, immunogenicity, and acceptable safety in women aged 24-45 years, regardless of previous exposure to HPV vaccine type.

Einstein, M. H., M. Baron, M. J. Levin, A. Chatterjee, B. Fox, S. Scholar, J. Rosen, N. Chakhtoura, M. Lebacqz, R. van der Most, P. Moris, S. L. Giannini, A. Schuind, S. K. Datta and D. Descamps (2011). "**Comparison of the immunogenicity of the human papillomavirus (HPV)-16/18 vaccine and the HPV-6/11/16/18 vaccine for oncogenic non-vaccine types HPV-31 and HPV-45 in healthy women aged 18-45 years.**" *Hum Vaccin* **7**(12): 1359-1373.

Protection against oncogenic non-vaccine types (cross-protection) offered by human papillomavirus (HPV) vaccines may provide a significant medical benefit. Available clinical efficacy data suggest the two licensed vaccines (HPV-16/18 vaccine, GlaxoSmithKline Biologicals (GSK), and HPV-6/11/16/18 vaccine, Merck & Co., Inc.) differ in terms of protection against oncogenic non-vaccine HPV types -31/45. The immune responses induced by the two vaccines against these two non-vaccine HPV types (cross-reactivity) was compared in an observer-blind study up to Month 24 (18 mo post-vaccination), in women HPV DNA-negative and seronegative prior to vaccination for the HPV type analyzed (HPV-010 [NCT00423046]). Geometric mean antibody titers (GMTs) measured by pseudovirion-based neutralization assay (PBNA) and enzyme-linked immunosorbent assay (ELISA) were similar between vaccines for HPV-31/45. Seropositivity rates for HPV-31 were also similar between vaccines; however, there was a trend for higher seropositivity with the HPV-16/18 vaccine (13.0-16.7%) versus the HPV-6/11/16/18 vaccine (0.0-5.0%) for HPV-45 with PBNA, but not ELISA. HPV-31/45 cross-reactive memory B-cell responses were comparable between vaccines. Circulating antigen-specific CD4+ T-cell frequencies were higher for the HPV-16/18 vaccine than the HPV-6/11/16/18 vaccine (HPV-31 [geometric mean ratio [GMR] =2.0; p=0.0002] and HPV-45 [GMR=2.6; p=0.0092]), as were the proportion of T-cell responders (HPV-31, p=0.0009; HPV-45, p=0.0793). In conclusion, immune response to oncogenic non-vaccine HPV types -31/45 was generally similar for both vaccines with the exception of T-cell response which was higher with the HPV-16/18 vaccine. Considering the differences in cross-protective efficacy between the two vaccines, the results might provide insights into the underlying mechanism(s) of protection.

Einstein, M. H., M. Baron, M. J. Levin, A. Chatterjee, B. Fox, S. Scholar, J. Rosen, N. Chakhtoura, D. Meric, F. J. Dessy, S. K. Datta, D. Descamps and G. Dubin (2011). "**Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 vaccine and HPV-6/11/16/18 vaccine: follow-up from months 12-24 in a Phase III randomized study of healthy women aged 18-45 years.**" *Hum Vaccin* 7(12): 1343-1358.

In this observer-blind study (NCT00423046), women (N=1,106), stratified by age (18-26, 27-35, 36-45 y), were randomized (1:1) to receive the HPV-16/18 vaccine (Cervarix(R), GlaxoSmithKline Biologicals, Months 0, 1, 6) or the HPV-6/11/16/18 vaccine (Gardasil(R) Merck & Co., Inc., Months 0, 2, 6). Month 7 results were previously reported; we now report Month 24 results. In the according-to-protocol cohort for immunogenicity (seronegative and DNA-negative at baseline for HPV type analyzed), seropositivity rates of neutralizing antibodies (nAbs) [pseudovirion-based neutralization assay] were, across all age strata, 100% (HPV-16/18 vaccine) and 97.5-100% (HPV-6/11/16/18 vaccine) for HPV-16, and 99.0-100% (HPV-16/18 vaccine) and 72.3-84.4% (HPV-6/11/16/18 vaccine) for HPV-18. Corresponding geometric mean titers (GMTs) were 2.4-5.8-fold higher for HPV-16 and 7.7-9.4-fold higher for HPV-18 with the HPV-16/18 vaccine versus the HPV-6/11/16/18 vaccine; HPV-16 and HPV-18 GMTs were significantly higher with the HPV-16/18 vaccine than the HPV-6/11/16/18 vaccine (p< 0.0001) in the total vaccinated cohort (received >=1 vaccine dose, irrespective of baseline sero/DNA-status). Similar results were obtained using enzyme-linked immunosorbent assay (ELISA). Positivity rates and GMTs of antigen-specific IgG antibodies in cervicovaginal secretions (ELISA) were not significantly different between vaccines. At Month 24, CD4(+) T-cell responses for HPV-16 and HPV-18 were higher with the HPV-16/18 vaccine; memory B-cell response was higher for HPV-18 with the HPV-16/18 vaccine and similar between vaccines for HPV-16. Both vaccines were generally well tolerated. Although an immunological correlate of protection has not been defined, differences in the magnitude of immune response between vaccines may represent determinants of duration of protection.

Grant, L. A., E. F. Dunne, H. Chesson and L. E. Markowitz (2011). "**Considerations for human papillomavirus (HPV) vaccination of mid-adult women in the United States.**" *Vaccine* **29**(13): 2365-2370.

In the United States, human papillomavirus (HPV) vaccination is recommended for 11 or 12 year old girls, with catch-up vaccination through age 26 years. Data are available for women over the age of 26 years on immunogenicity for both quadrivalent and bivalent HPV vaccines and on efficacy for the quadrivalent HPV vaccine. If HPV vaccines are licensed for use in women over 26 years of age (mid-adult women), recommendations for this age group will need to be considered. This review summarizes vaccine efficacy and immunogenicity data in mid-adult women, and addresses epidemiologic data related to key questions for consideration of vaccine recommendations for women over age 26 years.

Zhu, F. C., C. G. Li, H. X. Pan, Y. J. Zhang, D. Bi, H. W. Tang and S. Datta (2011). "**Safety and immunogenicity of human papillomavirus-16/18 AS04-adjuvanted vaccine in healthy Chinese females aged 15 to 45 years: a phase I trial.**" *Chin J Cancer* **30**(8): 559-564.

Globally, about 70% of cervical cancers are associated with human papillomavirus (HPV)-16 or HPV-18 infection. A meta-analysis of epidemiologic studies in China showed that HPV was present in 98% of cervical cancer samples. The HPV-16/18 AS04-adjuvanted vaccine Cervarix has shown a high level of protection against HPV-16/18 infections and associated cervical lesions. This phase I trial (NCT00549900) assessed the safety, tolerability, and immunogenicity of the vaccine in Chinese. Thirty healthy Chinese females, aged 15 to 45 years with a median age of 29.5 years, received three doses of Cervarix in Months 0, 1, and 6. Safety was assessed via recording solicited local and systemic symptoms within 7 days and unsolicited symptoms within 30 days after each vaccination. Serious adverse events, new onset of chronic diseases, and other medically significant conditions were recorded throughout this trial. As an exploratory objective, HPV-16/18 antibody titers were determined by enzyme-linked immunosorbent assay in serum samples collected in Months 0 and 7. Pain at the injection site was the most frequently reported local symptom. Two subjects reported medically significant adverse events. Both cases were assessed as unrelated to vaccination by the investigator. In Month 7, 100% seroconversion was observed for both anti-HPV-16 and anti-HPV-18 with high geometric mean antibody titers. HPV-16/18 AS04-adjuvanted vaccine, evaluated for the first time in Chinese females, was generally well tolerated and immunogenic, as previously shown in global studies.

Castellsague, X., A. Schneider, A. M. Kaufmann and F. X. Bosch (2009). "HPV vaccination against cervical cancer in women above 25 years of age: key considerations and current perspectives." *Gynecol Oncol* **115**(3 Suppl): S15-23.

OBJECTIVE: Vaccination of young women (15-25 years of age) against human papillomavirus (HPV) has been shown to be very efficacious in preventing the development of moderate or severe cervical precancerous lesions associated with HPV-16 or -18. As the highest rates of new infections with high-risk (i.e., oncogenic) HPV types occur in the first years following sexual debut, most existing guidelines and recommendations advise on vaccinating young girls. We consider oncogenic HPV infection and the risk of developing cervical cancer in women over 25 years of age and whether they would also benefit from vaccination against HPV. **METHODS:** We reviewed all available literature on oncogenic HPV infection and the risk of developing cervical cancer in women over 25 years of age. **RESULTS:** HPV vaccination is likely to be beneficial to sexually active women due to their continuous risk of acquiring new HPV infections and of developing cervical intraepithelial neoplasia (CIN) and cervical cancer. Clinical trial data show that the HPV-16/18 AS04-adjuvanted vaccine is safe and immunogenic in women up to the age of 55 years, whilst preliminary data with the quadrivalent vaccine demonstrated evidence of safety, immunogenicity and high-level efficacy in women 24 to 45

years of age. HPV vaccination in women over 25 years of age is already approved in several countries, and these women are individually seeking advice on vaccination from healthcare professionals. The predicted reduction in cost benefit of vaccination with increasing age, however, is likely to limit the implementation of routine vaccination beyond the late 20s. CONCLUSION: The priority of routine vaccination programmes must be to target girls and young women, with catch-up programmes that extend to age 25/26 when resources allow. For sexually active women over the age of 25, HPV vaccination can be considered on an individual basis, as most will have the potential to benefit from vaccination.

Einstein, M. H., M. Baron, M. J. Levin, A. Chatterjee, R. P. Edwards, F. Zepp, I. Carletti, F. J. Dessy, A. F. Trofa, A. Schuind and G. Dubin (2009). "**Comparison of the immunogenicity and safety of Cervarix and Gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18-45 years.**" *Hum Vaccin* 5(10): 705-719.

This observer-blind study compared the prophylactic human papillomavirus (HPV) vaccines, Cervarix (GlaxoSmithKline) and Gardasil (Merck), by assessing immunogenicity and safety through one month after completion of the three-dose vaccination course. Women (n = 1106) were stratified by age (18-26, 27-35, 36-45 years) and randomized (1:1) to receive Cervarix (Months 0, 1, 6) or Gardasil (Months 0, 2, 6). At Month 7 after first vaccination, all women in the according-to-protocol cohort who were seronegative/DNA negative before vaccination for the HPV type analyzed had seroconverted for HPV-16 and HPV-18 serum neutralizing antibodies, as measured by pseudovirion-based neutralization assay (PBNA), except for two women aged 27-35 years in the Gardasil group who did not seroconvert for HPV-18 (98%). Geometric mean titers of serum neutralizing antibodies ranged from 2.3-4.8-fold higher for HPV-16 and 6.8-9.1-fold higher for HPV-18 after vaccination with Cervarix compared with Gardasil, across all age strata. In the total vaccinated cohort (all women who received at least one vaccine dose, regardless of their serological and DNA status prior to vaccination), Cervarix induced significantly higher serum neutralizing antibody titers in all age strata (p < 0.0001). Positivity rates for anti-HPV-16 and -18 neutralizing antibodies in cervicovaginal secretions and circulating HPV-16 and -18 specific memory B-cell frequencies were also higher after vaccination with Cervarix compared with Gardasil. Both vaccines were generally well tolerated. The incidence of unsolicited adverse events was comparable between vaccinated groups. The incidence of solicited symptoms was generally higher after Cervarix, injection site reactions being most common. However, compliance rates with the three-dose schedules were similarly high (>or= 84%) for both vaccines. Although the importance of differences in magnitude of immune response between these vaccines is unknown, they may represent determinants of duration of protection against HPV-16/18. Long-term studies evaluating duration of efficacy after vaccination are needed for both vaccines.

Munoz, N., R. Manalastas, Jr., P. Pitisuttithum, D. Tresukosol, J. Monsonego, K. Ault, C. Clavel, J. Luna, E. Myers, S. Hood, O. Bautista, J. Bryan, F. J. Taddeo, M. T. Esser, S. Vuocolo, R. M. Haupt, E. Barr and A. Saah (2009). "**Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial.**" *Lancet* 373(9679): 1949-1957.

BACKGROUND: Although the peak incidence of human papillomavirus (HPV) infection occurs in most populations within 5-10 years of first sexual experience, all women remain at risk for acquisition of HPV infections. We tested the safety, immunogenicity, and efficacy of the quadrivalent HPV (types 6, 11, 16, 18) L1 virus-like-particle vaccine in women aged 24-45 years. METHODS: Women aged 24-45 years with no history of genital warts or cervical disease were enrolled from community health centres, academic health centres, and primary health-care providers into an ongoing multicentre, parallel, randomised, placebo-controlled, double-blind study. Participants were allocated by computer-generated schedule to receive

quadrivalent HPV vaccine (n=1911) or placebo (n=1908) at day 1, and months 2 and 6. All study site investigators and personnel, study participants, monitors, and central laboratory personnel were blinded to treatment allocation. Coprimary efficacy endpoints were 6 months' or more duration of infection and cervical and external genital disease due to HPV 6, 11, 16, 18; and due to HPV 16 and 18 alone. Primary efficacy analyses were done in a per-protocol population, but intention-to-treat analyses were also undertaken. This study is registered with ClinicalTrials.gov, number NCT00090220. FINDINGS: 1910 women received at least one dose of vaccine and 1907 at least one dose of placebo. In the per-protocol population, efficacy against the first coprimary endpoint (disease or infection related to HPV 6, 11, 16, and 18) was 90.5% (95% CI 73.7-97.5, four of 1615 cases in the vaccine group vs 41/1607 in the placebo group) and 83.1% (50.6-95.8, four of 1601 cases vs 23/1579 cases) against the second coprimary endpoint (disease or infection related to HPV 16 and 18 alone). In the intention-to-treat population, efficacy against the first coprimary endpoint was 30.9% (95% CI 11.1-46.5, 108/1886 cases vs 154/1883 cases) and against the second coprimary endpoint was 22.6% (-2.9 to 41.9, 90/1886 cases vs 115/1883 cases), since infection and disease were present at baseline. We recorded no vaccine-related serious adverse events. INTERPRETATION: The quadrivalent HPV vaccine is efficacious in women aged 24-45 years not infected with the relevant HPV types at enrolment. FUNDING: Merck (USA).

Schwarz, T. F., M. Spaczynski, A. Schneider, J. Wysocki, A. Galaj, P. Perona, S. Poncelet, T. Zahaf, K. Hardt, D. Descamps and G. Dubin (2009). "**Immunogenicity and tolerability of an HPV-16/18 AS04-adjuvanted prophylactic cervical cancer vaccine in women aged 15-55 years.**" *Vaccine* 27(4): 581-587.

The immunogenicity and safety of an HPV-16/18 AS04-adjuvanted vaccine were assessed in women aged 26-55 years and compared with women aged 15-25 years in a Phase III, non-randomised, open-label, age-stratified study. Overall the vaccine was well tolerated and 100% seropositivity was achieved 1 month after the third dose in all age groups. There was a high correlation between HPV-16 and HPV-18 antibody levels (IgG) in cervicovaginal secretions and sera, regardless of age. The HPV-16/18 AS04-adjuvanted vaccine induces a robust and persistent immune response in women >26 years of age and generates antibodies that transudate through the cervix epithelium.

Summary Product Characteristics (SmPC) of Available Vaccines

SmPC of Gardasil 4vHPV: https://www.ema.europa.eu/en/documents/product-information/gardasil-epar-product-information_en.pdf

SmPC of Gardasil 9vHPV: https://www.ema.europa.eu/en/documents/product-information/gardasil-9-epar-product-information_en.pdf

SmPC of Cervarix: https://www.ema.europa.eu/en/documents/product-information/cervarix-epar-product-information_en.pdf

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5 - HPV prophylactic vaccines

IMMUNOGENICITY AND SAFETY OF A NINE-VALENT HUMAN PAPILLOMAVIRUS VACCINE IN WOMEN 27-45 YEARS OF AGE COMPARED WITH YOUNG WOMEN 16-26 YEARS OF AGE: AN OPEN-LABEL PHASE 3 TRIAL

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Background/Objectives: Clinical studies have demonstrated the efficacy of the nine-valent human papillomavirus (9vHPV; HPV 6/11/16/18/31/33/45/52/58) vaccine against infection and disease in women 16-26 years of age. We conducted a study comparing 9vHPV vaccine immunogenicity and safety in women 27-45 years of age vs. women 16-26 years of age.

Methods: Participants received 9vHPV vaccine on Day 1, Month 2 and Month 6. Blood was collected for immunogenicity testing by competitive Luminex immunoassay on Day 1 and Month 7. A distinct per-protocol immunogenicity population was assessed for each of the 9 HPV types. Geometric mean titers (GMTs) and seropositivity rates at Month 7 for anti-HPV 6/11/16/18/31/33/45/52/58 were summarized. The primary objective of the study was to demonstrate non-inferiority of anti-HPV 16/18/31/33/45/52/58 GMTs in women 27-45 years of age vs. women 16-26 years of age. A >2-fold decrease in immunogenicity had to be ruled out to demonstrate non-inferiority in women 27-45 years of age compared with women 16-26 years of age. The safety evaluation included injection-site and systemic adverse events (AEs) for 15 days after any vaccination and serious AEs during the entire study.

Results: 1212 participants were enrolled (570 women 16-26 years of age; 642 women 27-45 years of age); 1210 received at least one dose of 9vHPV vaccine. Anti-HPV 16/18/31/33/45/52/58 responses in adult women were non-inferior to young women at Month 7. Across these 7 HPV types, the GMT ratios ranged from 0.66-0.73; the lower bound of the 95% confidence interval of the GMT ratio ranged from 0.60-0.67. The non-inferiority criterion was met since the lower bound of the GMT ratios was >0.50 for each of the 7 HPV types. Seroconversion for each of the 9 HPV types was >99% in both age groups. The proportion of participants with injection-site AEs was similar in the older and younger age groups (85.5% vs. 87.9%, respectively). The proportion of participants with vaccine-related systemic AEs was also similar in the older and younger age groups (24.1% vs. 25.1%, respectively). No participants died during the study and there were no vaccine-related serious AEs; one participant discontinued from vaccination due to an AE that was not vaccine-related.

Conclusions: The 9vHPV vaccine regimen was highly immunogenic in women 16-45 years of age, resulting in non-inferior anti-HPV GMTs for HPV types 16/18/31/33/45/52/58 in women 27-45 years of age compared with women 16-26 years of age, and the 9vHPV vaccine was generally well tolerated in both age groups.

#0439

5 - HPV prophylactic vaccines

LONG-TERM EFFECTIVENESS OF THE 9-VALENT HUMAN PAPILLOMAVIRUS (9VHPV) VACCINE IN SCANDINAVIAN COUNTRIES

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Background/Objectives: A long-term follow-up (LTFU) extension (NCT02653118) of the pivotal efficacy study of the 9-valent human papillomavirus (9vHPV) vaccine in young women 16-26 years of age (NCT00543543) was initiated to assess effectiveness for up to 14 years total follow-up (approximately 4 years in the base study; 10 years in the LTFU study). We report data from an interim analysis conducted at 8 years post-vaccination.

Methods: Participants from Denmark, Norway, and Sweden, who received 9vHPV vaccine during the base study and provided consent, continued into the LTFU study. National health registries were used to assess those attending screening and diagnosed with cervical precancers and cancers. Tissues from histological confirmation of cervical pathology (biopsy and definitive therapy) were retrieved to be analyzed by polymerase chain reaction to detect HPV DNA and for pathology diagnosis adjudication. To assess effectiveness, the observed incidence of HPV16/18/31/33/45/52/58-related cervical intraepithelial neoplasia-2 (CIN2), CIN3, adenocarcinoma in situ (AIS), or cervical cancer ("CIN2 or worse") was compared with the estimated incidence rate in an unvaccinated cohort of similar age and risk level using a control chart method. Primary effectiveness analyses were conducted in the per-protocol effectiveness (PPE) population.

Results: Of 2223 participants from Denmark, Norway, or Sweden who received at least 1 dose of 9vHPV vaccine at the start of the base study, 2029 continued into the LTFU study. Among participants included in the PPE analyses (n=1799), the median effectiveness follow-up post-Dose 1 was 6.8 years (range: 0.5, 10.0). During the LTFU study period, among 1448 PPE population-eligible participants contributing 4084.2 person-years follow-up, no new cases of HPV16/18/31/33/45/52/58-related CIN2 or worse were observed as of the data cut-off date (Jan 1, 2018). Over at least 6 years of total follow-up post-9vHPV vaccine Dose 1, there were no signals observed in the control chart analysis that indicated waning of vaccine effectiveness in the PPE population.

Conclusions: The 9vHPV vaccine provides continued protection through at least 6 years following vaccination with a trend toward continued effectiveness for up to 8 years.

Session 2

HPV Immunological Dynamics at Mucosal and Systemic Level

A Pubmed search was performed with the following selection criteria **HPV Vaccine* AND Mucosal Immune***; **HPV Vaccine* AND Immunity AND Cervical Secretions** ; **HPV Vaccine* AND Antibodies AND Immune*** published in the last 10 years: 118 items were retrieved. References were imported in EndNote. Herein, a relevant manual selection of 9 publications between 2009-2019 based on title and abstract was made.

Pasmans, H., T. M. Schurink-Van't Klooster, M. J. M. Bogaard, D. M. van Rooijen, H. E. de Melker, M. J. P. Welters, S. H. van der Burg, F. R. M. van der Klis and A. M. Buisman (2019). "**Long-term HPV-specific immune response after one versus two and three doses of bivalent HPV vaccination in Dutch girls.**" **Vaccine.**

BACKGROUND: In view of further reduction of HPV vaccination schedules, gaining more insight into humoral and cellular immune responses after a single HPV vaccine is of great interest. Therefore, these responses were evaluated after different doses of the bivalent (2v) HPV-vaccine in girls. **METHODS:** Blood was collected yearly up to seven years post-vaccination with one-, two- or three-doses of the 2vHPV vaccine (N=890). HPV-type-specific IgG and IgA-antibody levels, IgG-isotypes and avidity indexes were measured by a virus-like-particle-based multiplex-immuno-assay for two vaccine and five non-vaccine HPV types. HPV-type-specific memory B-cell numbers- and T-cell cytokine responses were determined in a subpopulation. **RESULTS:** HPV-type-specific antibody concentrations were significantly lower in one- than in two- and three-dose vaccinated girls but remained stable over seven years. The lower antibody response coincided with reduced HPV-type-specific B- and T-cell responses. There were no differences in both the IgG subtypes and the avidity of the HPV16-specific antibodies between the groups. **CONCLUSIONS:** One-dose of the 2vHPV vaccine is immunogenic, but results in less B- and T-cell memory and considerable lower antibody responses when compared with more doses. Therefore, at least of some of girls receiving the one-dose of the vaccination might be at higher risk for waning immunity to HPV in the long-term.

Pattyn, J., S. Van Keer, W. Tjalma, V. Matheussen, P. Van Damme and A. Vorsters (2019). "**Infection and vaccine-induced HPV-specific antibodies in cervicovaginal secretions. A review of the literature.**" *Papillomavirus Res* **8**: 100185.

BACKGROUND: Human papillomavirus (HPV) infects and propagates in the cervical mucosal epithelium. Hence, in addition to assessing systemic immunity, the accurate measurement of cervical immunity is important to evaluate local immune responses to HPV infection and vaccination. This review discusses studies that investigated the presence of infection and vaccine-induced HPV-specific antibodies in cervicovaginal secretions (CVS). **METHODS:** We searched the two main health sciences databases, PubMed and the ISI Web of Science, from the earliest dates available to March 2019. From the eligible publications, information was extracted regarding: (i) study design, (ii) the reported HPV-specific antibody concentrations in CVS (and the associated serum levels, when provided), (iii) the CVS collection method, and (iv) the immunoassays used. **RESULTS:** The systematic search and selection process yielded 44 articles. The evidence of HPV-specific antibodies in CVS after natural infection (26/44) and HPV vaccination (18/44) is discussed. Many studies indicate that HPV-specific antibody detection in CVS is variable but feasible with a variety of collection methods and immunoassays. Most CVS samples were collected by cervicovaginal washing or wicks, and antibody presence was mostly determined by VLP-based ELISAs. The moderate to strong correlation between vaccine-induced antibody levels in serum and in CVS indicates that HPV vaccines generate antibodies that transudate through the cervical mucosal epithelium. **CONCLUSION:** Although HPV-specific antibodies have lower titres in CVS than in serum

samples, studies have shown that their detection in CVS is feasible. Nevertheless, the high variability of published observations and the lack of a strictly uniform, well-validated method for the collection, isolation and quantification of antibodies indicates a need for specific methods to improve and standardize the detection of HPV-specific antibodies in CVS.

Guevara, A., R. Cabello, L. Woelber, E. D. Moreira, Jr., E. Joura, O. Reich, C. Shields, M. C. Ellison, A. Joshi and A. Luxembourg (2017). "**Antibody persistence and evidence of immune memory at 5 years following administration of the 9-valent HPV vaccine.**" *Vaccine* **35**(37): 5050-5057.

BACKGROUND: The 9-valent HPV (9vHPV) vaccine was developed to prevent infection and disease related to 9 HPV types (HPV6/11/16/18/31/33/45/52/58) which cause approximately 90% of cervical cancers, HPV-related vulvar, vaginal and anal cancers, and genital warts worldwide. In a pivotal efficacy study, the 9vHPV vaccine prevented infection and disease due to the 9 vaccine types. Duration of protection remains to be determined. Vaccines that induce long-term protection are generally characterized by the generation of immune memory. The purpose of this report is to assess the persistence of HPV antibody response and existence of immune memory at 5 years post-vaccination. **METHODS:** A subset of subjects (N=150) who received 3 doses of 9vHPV vaccine at day 1, month 2 and month 6 in the pivotal efficacy study continued in a study extension and received a fourth dose of 9vHPV vaccine at month 60. Serum HPV antibody levels were measured pre-dose 4 and at 7 and 28 days post-dose 4 by competitive Luminex immunoassay. Adverse events were assessed using a vaccination report card. **RESULTS:** HPV antibodies induced following the 3-dose series of 9vHPV vaccine in the base study persisted through month 60 with seropositivity rates ranging from 77.5% to 100%. Geometric mean titers at 1 week and 1 month post-dose 4 were 1.25-4.10 and 1.65-4.88-fold higher, respectively, than levels observed 1 month following the completion of the three-dose primary series. Seropositivity rates were >99% and 100% at 1 week and 1 month post-dose 4, respectively. The fourth dose of 9vHPV vaccine was generally well tolerated. **CONCLUSIONS:** A three-dose regimen of the 9vHPV vaccine induced persistent HPV antibody response through 5 years post-vaccination. Administration of a fourth dose resulted in a strong anamnestic response to all 9 vaccine types. These findings suggest that the efficacy of the 9vHPV vaccine will be long lasting. Clinical Trials.gov Identifier: NCT00543543.

Wang, H. K., Q. Wei, Z. Moldoveanu, W. K. Huh, H. L. Vu, T. R. Broker, J. Mestecky and L. T. Chow (2016). "**Characterization of serum antibodies from women immunized with Gardasil: A study of HPV-18 infection of primary human keratinocytes.**" *Vaccine* **34**(27): 3171-3177.

The prevalent human papillomaviruses (HPVs) infect human epithelial tissues. Infections by the mucosotropic HPV genotypes cause hyperproliferative ano-genital lesions. Persistent infections by high-risk (HR) HPVs such as HPV-16, HPV-18 and related types can progress to high grade intraepithelial neoplasias and cancers. Prophylactic HPV vaccines are based on DNA-free virus-like particles (VLPs) composed of the major capsid protein L1 of HPV-16, -18, -6 and -11 (Gardasil) or HPV-16 and -18 (Cervarix). Sera from vaccinated animals effectively prevent HPV pseudovirions to infect cell lines and mouse cervical epithelia. Both vaccines have proven to be highly protective in people. HPV pseudovirions are assembled in HEK293TT cells from matched L1 and L2 capsid proteins to encapsidate a reporter gene. Pseudovirions and genuine virions have structural differences and they infect cell lines or primary human keratinocytes (PHKs) with different efficiencies. In this study, we show that sera and isolated IgG from women immunized with Gardasil prevent authentic HPV-18 virions from infecting PHKs, whereas non-immune sera and purified IgG thereof are uniformly ineffective. Using early passage PHKs, neutralization is achieved only if immune sera are added within 2-4h of infection. We attribute the timing effect to a conformational change in HPV virions, thought to occur upon initial binding to heparan sulfate proteoglycans (HSPG) on the cell surface. This

interpretation is consistent with the inability of immune IgG bound to or taken up by PHKs to neutralize the virus. Interestingly, the window of neutralization increases to 12-16h in slow growing, late passage PHKs, suggestive of altered cell surface molecules. In vivo, this window might be further lengthened by the time required to activate the normally quiescent basal cells to become susceptible to infection. Our observations help explain the high efficacy of HPV vaccines.

Tyler, M., E. Tumban and B. Chackerian (2014). "**Second-generation prophylactic HPV vaccines: successes and challenges.**" *Expert Rev Vaccines* **13**(2): 247-255.

The role of HPV as the causative factor in cervical cancer has led to the development of the HPV vaccines Gardasil and Cervarix. These vaccines effectively protect against two HPV types associated with 70% of cervical cancer cases. Despite this success, researchers continue to develop second-generation HPV vaccines to protect against more HPV types and allow increased uptake in developing countries. While a reformulated vaccine based on the current technology is currently in clinical trials, another strategy consists of targeting highly conserved epitopes in the minor capsid protein of HPV, L2. Vaccines targeting L2 induce broadly neutralizing antibodies, capable of blocking infection by a wide range of HPV types. Several vaccine designs have been developed to optimize the display of L2 epitopes to the immune system and to reduce the cost of manufacture and distribution. L2-based vaccines show considerable promise as a potential next-generation HPV vaccine.

Scherpenisse, M., M. Mollers, R. M. Schepp, C. J. Meijer, H. E. de Melker, G. A. Berbers and F. R. van der Klis (2013). "**Detection of systemic and mucosal HPV-specific IgG and IgA antibodies in adolescent girls one and two years after HPV vaccination.**" *Hum Vaccin Immunother* **9**(2): 314-321.

The bivalent HPV16/18 vaccine induces high antibody concentrations in serum while data about antibody responses in the cervix are limited. In this study, we investigated pre- and post-vaccination antibody responses against seven high-risk HPV types by detection of IgG and IgA HPV-specific antibodies in cervical secretion samples (CVS) and serum. From an HPV vaccine monitoring study CVS and serum samples were available (pre-vaccination (n = 297), one year (n = 211) and two years (n = 141) post-dose-one vaccination) from girls aged 14-16 y. The girls were vaccinated with the bivalent HPV vaccine at months 0, 1 and 6. CVS was self-sampled using a tampon. Samples were tested for HPV-specific antibodies (HPV16/18/31/33/45/52/58) by a VLP-based multiplex immunoassay. Post-vaccination, IgG and IgA antibody levels for HPV16/18 were detectable in CVS and amounted to 2% and 1% of the IgG and IgA antibody levels observed in serum, respectively. The antibody levels remained constant between one and two years after vaccination. The correlation between CVS and serum was similar for IgG and IgA vaccine-derived antibody levels for HPV16 (rs = 0.58, rs = 0.54) and HPV18 (rs = 0.50, rs = 0.55). Vaccine-derived IgG antibody levels against cross-reactive HPV types in CVS and in serum were highest for HPV45. No IgA cross-reactive antibody responses could be detected in CVS. Post-vaccination, HPV16/18 IgG and IgA antibodies are not only detectable in serum but also in CVS. The correlation of HPV16/18 IgG antibody levels between serum and CVS suggests that vaccine induced HPV antibodies transudate and/or exudate from the systemic circulation to the cervical mucosa to provide protection against HPV infections.

Stanley, M., L. A. Pinto and C. Trimble (2012). "**Human papillomavirus vaccines--immune responses.**" *Vaccine* **30 Suppl 5**: F83-87.

Prophylactic human papillomavirus (HPV) virus-like particle (VLP) vaccines are highly effective. The available evidence suggests that neutralising antibody is the mechanism of protection. However, despite the robust humoral response elicited by VLP vaccines, there is no immune correlate, no minimum level of antibody, or any other immune parameter, that predicts

protection against infection or disease. The durability of the antibody response and the importance of antibody isotype, affinity and avidity for vaccine effectiveness are discussed. Once infection and disease are established, then cellular immune responses are essential to kill infected cells. These are complex processes and understanding the local mucosal immune response is a prerequisite for the rational design of therapeutic HPV vaccines. This article forms part of a special supplement entitled "Comprehensive Control of HPV Infections and Related Diseases" Vaccine Volume 30, Supplement 5, 2012.

Frazer, I. H. (2010). **"Measuring serum antibody to human papillomavirus following infection or vaccination."** *Gynecol Oncol* **118**(1 Suppl): S8-11.

The family of human papillomaviruses (HPVs) includes more than 130 genotypes, many of which infect the genital tract, and these can be classified as low risk or high risk for induction of genital neoplasia. Two prophylactic vaccines are currently available for the prevention of genital HPV infection: a quadrivalent (Gardasil; Merck & Co. Inc) and a bivalent (Cervarix; GlaxoSmithKline) vaccine. Protection against HPV infection and associated disease is observed for at least 6.4 years following immunization with the bivalent vaccine and for at least 8.5 years with the HPV 16L1 virus-like particle of the quadrivalent vaccine. HPV vaccines induce robust immune memory, as evidenced by recall of responses after revaccination, suggesting that immunization will afford long-lasting protection. An immunological marker for ongoing protection from infection would provide information to help establish best-practice deployment of these vaccines. However, while HPV-specific antibody is likely the major mechanism of protection against HPV infection following immunization, available serological assays provide only a partial characterization of immune status, and no measured immune response has been shown to define immediate or future protection against HPV infection or associated disease. Future research efforts should therefore be directed towards correlating measures of virus-specific immune memory with continued protection against infection with the HPV types in the available vaccines, and towards determining the duration of cross-protection afforded by these vaccines against HPV types other than those incorporated in the vaccines.

Poppe, W. A., P. H. Simon and M. R. De Ridder (2010). **"Why consider human papillomavirus vaccination in older women?"** *Gynecol Obstet Invest* **70**(4): 237-243.

Preventive human papillomavirus (HPV) L1 vaccines are safe and efficient to prevent infection and lesions of vaccine-specific HPV types in women from 15 to 26 years, but also in older age groups. Clearly, public health funds are to be spent to organize programs for vaccination of young adolescents. Immunobridging studies and clinical trials have shown that HPV vaccines generate significantly higher plasma antibodies than following natural infections in women up to 55 years and prevent up to 90.5% (95% CI 73.7-97.5) vaccine-specific HPV infections and lesions in women aged 24-45 years who are HPV DNA-negative at the time of vaccination. However, data from clinical trials with HPV L1 vaccines in older women (older than 25 years) are still scarce compared to the amount of evidence from trials in women younger than 26 years. Information from large population-based studies indicates that older women remain at risk of infection by high-risk HPV and the risk of persistent high-risk HPV infection is significantly higher than in young women, leading to a higher risk of progressing disease and carcinoma. The natural history of HPV infection remains enigmatic as we do not know if the immune mechanisms that clear the HPV infection offer prolonged protection. On the contrary, some data indicate that seroconversion after a natural infection only partially protects against re-infection. Given the large proportions of adult men and women that change sexual partners, the protective effects of HPV L1 vaccines may offer an extra benefit against HPV-related genital diseases within a much shorter time period than after vaccination of prepubertal adolescents.

Session 3

Comprehensive Analysis of Challenges and Potential Benefits of HPV Vaccination of Adults.

A Pubmed search was performed with the following selection criteria: **HPV Vaccine* AND Transmission AND opportunities ; HPV AND Post Treatment AND Vaccination AND Women ; HPV Vaccine AND Recurrence AND CIN; HPV AND Transmission AND Modelling AND Adult population ; Human papillomavirus AND Modelling AND Prevention AND Vaccination** published in the last 10 years. In total 262 items were retrieved. References were imported in EndNote. Herein, a relevant manual selection of **11** publications between 2009-2019 based on title and abstract was made.

Velentzis, L. S., J. M. L. Brotherton and K. Canfell (2019). "**Recurrent disease after treatment for cervical pre-cancer: determining whether prophylactic HPV vaccination could play a role in prevention of secondary lesions.**" *Climacteric* **22**(6): 596-602.

Existing modalities can effectively treat high-grade cervical intraepithelial neoplasia (CIN) but around 7% of treated women will develop recurrence of CIN grade 2 or above within 2 years of treatment. Post-treatment surveillance is therefore required to detect residual or recurrent disease. Since the implementation of human papillomavirus (HPV) vaccination programs in high-income countries, significant reductions in high-grade CIN have been recorded in vaccinated cohorts who were predominantly HPV-naïve at vaccination. There is still debate as to the extent of potential benefit from vaccination for women previously infected with HPV, given that HPV incidence in women falls with age and previously cleared infection provides at least some protection against reinfection. Whilst vaccination-induced antibodies could prevent type-specific new infections, it is unclear whether vaccination could also prevent reactivation of latent, previously acquired infection and subsequent disease. A review of the available evidence suggests a potential reduction in risk of recurrent disease if women diagnosed and treated for CIN are offered prophylactic vaccines. New modeled analyses and, ideally, a prospectively designed randomized controlled trial in women treated and then randomized to vaccination or placebo would provide much-needed additional evidence to support the effectiveness and cost-effectiveness of offering vaccination to women after treatment for CIN.

Pieralli, A., C. Bianchi, N. Auzzi, M. G. Fallani, C. Bussani, M. Fambrini, G. Cariti, G. Scarselli, F. Petraglia and A. Ghelardi (2018). "**Indication of prophylactic vaccines as a tool for secondary prevention in HPV-linked disease.**" *Arch Gynecol Obstet* **298**(6): 1205-1210.

PURPOSE: To determine whether quadrivalent HPV vaccination is effective in reducing recurrent disease in women with a previous history of HPV disease. **METHODS:** All women under 45 years of age treated for HPV-linked disease and with negative HPV test, cytology and colposcopy 3 months after treatment were enrolled. Women were randomly assigned into two groups: a group that received HPV vaccine post treatment and a group that was only submitted to follow-up. Follow-up was performed every 6 months for a duration of at least 3 years. Kaplan-Meier curve was used to estimate the overall disease-free survival during the follow-up period. Statistical analysis was performed by Fisher's exact test. **RESULTS:** From November 2013 to October 2014, we enrolled a total of 178 women at Careggi University Hospital in Florence and at Azienda USL in Massa Carrara. 12 out of 89 patients in the non-vaccination group recurred (13.5%), while 3 out of 89 patients in the vaccination group recurred (3.4%). The Kaplan-Meier curves showed a statistically difference in the log rank test ($p = 0.0147$) for the overall disease-free survival in the study groups during follow-up. The rate of recurrence was significantly higher in the non-vaccination group, with a $p = 0.0279$ by Fisher

exact test. **CONCLUSION:** The introduction of anti-HPV vaccination during the follow-up post treatment for HPV-linked disease is recommended to reduce the risk of recurrence. The clinical implication of this could be very important to influence post-treatment management of HPV disease.

Hoffman, S. R., T. Le, A. Lockhart, A. Sanusi, L. Dal Santo, M. Davis, D. A. McKinney, M. Brown, C. Poole, C. Willame and J. S. Smith (2017). "**Patterns of persistent HPV infection after treatment for cervical intraepithelial neoplasia (CIN): A systematic review.**" *Int J Cancer* **141**(1): 8-23.

A systematic review of the literature was conducted to determine the estimates of and definitions for human papillomavirus (HPV) persistence in women following treatment of cervical intra-epithelial neoplasia (CIN). A total of 45 studies presented data on post-treatment HPV persistence among 6,106 women. Most studies assessed HPV persistence after loop excision (42%), followed by conization (7%), cryotherapy (11%), laser treatment (4%), interferon-alpha, therapeutic vaccination, and photodynamic therapy (2% each) and mixed treatment (38%). Baseline HPV testing was conducted before or at treatment for most studies (96%). Follow-up HPV testing ranged from 1.5 to 80 months after baseline. Median HPV persistence tended to decrease with increasing follow-up time, declining from 27% at 3 months after treatment to 21% at 6 months, 15% at 12 months, and 10% at 24 months. Post-treatment HPV persistence estimates varied widely and were influenced by patient age, HPV-type, detection method, treatment method, and minimum HPV post-treatment testing interval. Loop excision and conization appeared to outperform cryotherapy procedures in terms of their ability to clear HPV infection. This systematic review provides evidence for the substantial heterogeneity in post-treatment HPV DNA testing practices and persistence estimates.

Coskuner, E. R., T. A. Ozkan, A. Karakose, O. Dillioglugil and I. Cevik (2014). "**Impact of the quadrivalent HPV vaccine on disease recurrence in men exposed to HPV Infection: a randomized study.**" *J Sex Med* **11**(11): 2785-2791.

INTRODUCTION: Human papillomavirus (HPV) is one of the most common sexually transmitted infections and is the cause of several different diseases in men and women. Although little is known about HPV infection in men, they are also in the risk group of HPV infection and play an important role in transmitting the virus to women. **AIM:** To define the efficacy of the HPV vaccine through cross-immunization and its role in clearance of HPV infection, and to assess infection-associated factors in men. **METHODS:** This prospective randomized clinical study enrolled 171 evaluable men with genital warts between June 2009 and October 2013. After the initial treatment intervention, 91 patients were randomly assigned to receive HPV vaccine in three doses. Eighty patients were in the control (unvaccinated) group. One hundred-eleven men were single and 60 men were married. Patients who had previous treatment for pre-existing warts and medical disorders that needed chronic treatment or immunosuppression were not included in the randomization. Also 29 men with follow-up less than 12 months and incomplete vaccination were not included. **MAIN OUTCOME MEASURES:** The patients were assessed regarding age, condom use, marital status, number of visible genital warts, and smoking status. Post-treatment follow-up was monthly up to 12th month. **RESULTS:** Mean age was 34 +/- 7.6. One hundred fifteen patients were smokers. For the recurrence of warts, age, smoking, vaccination status were insignificant and marital status was significant in the univariable analysis; only marital status preserved significance (HR: 2.0 CI:1.29-3.12 P = 0.002) in the multivariable analysis including vaccination status, marital status, and smoking. **CONCLUSION:** Among the investigated factors vaccination status was not but marital status significantly influenced wart recurrence. Married men had more recurrences in our population. Larger multicenter

randomized clinical trials are lacking and seriously required to investigate the therapeutic effect of current quadrivalent HPV vaccine in genital warts.

Kang, W. D., H. S. Choi and S. M. Kim (2013). "Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2-3)?" *Gynecol Oncol* **130**(2): 264-268.

OBJECTIVES: This study was conducted to determine whether vaccination with the quadrivalent human papillomavirus (HPV) vaccine after loop electrosurgical excision procedure (LEEP) for high-grade cervical intraepithelial neoplasia (CIN2-3) is effective in preventing recurrence of CIN2-3. METHODS: Between August 2007 and July 2010, 737 patients aged 20-45 years who were diagnosed with CIN2-3 were treated by LEEP and followed. Three hundred and sixty patients were vaccinated with the quadrivalent HPV vaccine after LEEP (vaccination group), and 377 patients were followed without vaccination (non-vaccination group). The vaccination group received the first dose at 1 week after LEEP and the remaining two doses two and six months later. Post-LEEP follow-up was performed at 3, 6, 9, 12, 18, and 24 months during the first 2 years and yearly thereafter. RESULTS: Irrespective of causal HPV type, 36 (4.9%) patients developed recurrence. In the vaccination group (360 patients), 9 patients (2.5%) developed recurrence, whereas 27 patients (7.2%) in the non-vaccination group (377 patients) developed recurrence. In patients infected with HPV of 16 and/or 18 type, 5 patients (2.5%) in the vaccination group (197 patients) and 18 patients (8.5%) in the non-vaccination group (211 patients) developed recurrent disease related to vaccine HPV types (HPV 16 or 18 types) after LEEP ($P < 0.01$). Multivariate analysis showed that no vaccination after LEEP was an independent risk factor for recurrent CIN2-3 (HR=2.840; 95% confidence interval, 1.335-6.042; $P < 0.01$). CONCLUSIONS: Vaccination with the quadrivalent HPV vaccine after treatment may be considered in preventing recurrence of CIN2-3.

Canfell, K., J. J. Kim, S. Kulasingam, J. Berkhof, R. Barnabas, J. A. Bogaards, N. Campos, C. Jennett, M. Sharma, K. T. Simms, M. A. Smith, L. S. Velentzis, M. Brisson and M. Jit (2019). "HPV-FRAME: A consensus statement and quality framework for modelled evaluations of HPV-related cancer control." *Papillomavirus Res* **8**: 100184.

Intense research activity in HPV modelling over this decade has prompted the development of additional guidelines to those for general modelling. A specific framework is required to address different policy questions and unique complexities of HPV modelling. HPV-FRAME is an initiative to develop a consensus statement and quality-based framework for epidemiologic and economic HPV models. Its development involved an established process. Reporting standards have been structured according to seven domains reflecting distinct policy questions in HPV and cancer prevention and categorised by relevance to a population or evaluation. Population-relevant domains are: 1) HPV vaccination in pre-adolescent and young adolescent individuals; 2) HPV vaccination in older individuals; 3) targeted vaccination in men who have sex with men; 4) considerations for individuals living with HIV and 5) considerations for low- and middle-income countries. Additional considerations applicable to specific evaluations are: 6) cervical screening or integrated cervical screening and HPV vaccination approaches and 7) alternative vaccine types and alternative dosing schedules. HPV-FRAME aims to promote the development of models in accordance with an explicit framework, to better enable target audiences to understand a model's strength and weaknesses in relation to a specific policy question and ultimately improve the model's contribution to informed decision-making.

Simms, K. T., J. Steinberg, M. Caruana, M. A. Smith, J. B. Lew, I. Soerjomataram, P. E. Castle, F. Bray and K. Canfell (2019). "Impact of scaled up human papillomavirus vaccination and cervical screening

and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study." *Lancet Oncol* 20(3): 394-407.

BACKGROUND: Cervical screening and human papillomavirus (HPV) vaccination have been implemented in most high-income countries; however, coverage is low in low-income and middle-income countries (LMICs). In 2018, the Director-General of WHO announced a call to action for the elimination of cervical cancer as a public health problem. WHO has called for global action to scale-up vaccination, screening, and treatment of precancer, early detection and prompt treatment of early invasive cancers, and palliative care. An elimination threshold in terms of cervical cancer incidence has not yet been defined, but an absolute rate of cervical cancer incidence could be chosen for such a threshold. In this study, we aimed to quantify the potential cumulative effect of scaled up global vaccination and screening coverage on the number of cervical cancer cases averted over the 50 years from 2020 to 2069, and to predict outcomes beyond 2070 to identify the earliest years by which cervical cancer rates could drop below two absolute levels that could be considered as possible elimination thresholds—the rare cancer threshold (six new cases per 100 000 women per year, which has been observed in only a few countries), and a lower threshold of four new cases per 100 000 women per year.

METHODS: In this statistical trends analysis and modelling study, we did a statistical analysis of existing trends in cervical cancer worldwide using high-quality cancer registry data included in the Cancer Incidence in Five Continents series published by the International Agency for Research on Cancer. We then used a comprehensive and extensively validated simulation platform, Policy1-Cervix, to do a dynamic multicohort modelled analysis of the impact of potential scale-up scenarios for cervical cancer prevention, in order to predict the future incidence rates and burden of cervical cancer. Data are presented globally, by Human Development Index (HDI) category, and at the individual country level.

FINDINGS: In the absence of further intervention, there would be 44.4 million cervical cancer cases diagnosed globally over the period 2020-69, with almost two-thirds of cases occurring in low-HDI or medium-HDI countries. Rapid vaccination scale-up to 80-100% coverage globally by 2020 with a broad-spectrum HPV vaccine could avert 6.7-7.7 million cases in this period, but more than half of these cases will be averted after 2060. Implementation of HPV-based screening twice per lifetime at age 35 years and 45 years in all LMICs with 70% coverage globally will bring forward the effects of prevention and avert a total of 12.5-13.4 million cases in the next 50 years. Rapid scale-up of combined high-coverage screening and vaccination from 2020 onwards would result in average annual cervical cancer incidence declining to less than six new cases per 100 000 individuals by 2045-49 for very-high-HDI countries, 2055-59 for high-HDI countries, 2065-69 for medium-HDI countries, and 2085-89 for low-HDI countries, and to less than four cases per 100 000 by 2055-59 for very-high-HDI countries, 2065-69 for high-HDI countries, 2070-79 for medium-HDI countries, and 2090-2100 or beyond for low-HDI countries. However, rates of less than four new cases per 100 000 would not be achieved in all individual low-HDI countries by the end of the century. If delivery of vaccination and screening is more gradually scaled up over the period 2020-50 (eg, 20-45% vaccination coverage and 25-70% once-per-lifetime screening coverage by 2030, increasing to 40-90% vaccination coverage and 90% once-per-lifetime screening coverage by 2050, when considered as average coverage rates across HDI categories), end of the century incidence rates will be reduced by a lesser amount. In this scenario, average cervical cancer incidence rates will decline to 0.8 cases per 100 000 for very-high-HDI countries, 1.3 per 100 000 for high-HDI countries, 4.4 per 100 000 for medium-HDI countries, and 14 per 100 000 for low-HDI countries, by the end of the century.

INTERPRETATION: More than 44 million women will be diagnosed with cervical cancer in the next 50 years if primary and secondary prevention programmes are not implemented in LMICs. If high coverage vaccination can be implemented quickly, a substantial effect on the burden of disease will be seen after three to four decades, but nearer-term impact will require delivery of cervical screening to older cohorts who will

not benefit from HPV vaccination. Widespread coverage of both HPV vaccination and cervical screening from 2020 onwards has the potential to avert up to 12.5-13.4 million cervical cancer cases by 2069, and could achieve average cervical cancer incidence of around four per 100 000 women per year or less, for all country HDI categories, by the end of the century. A draft global strategy to accelerate cervical cancer elimination, with goals and targets for the period 2020-30, will be considered at the World Health Assembly in 2020. The findings presented here have helped inform initial discussions of elimination targets, and ongoing comparative modelling with other groups is supporting the development of the final goals and targets for cervical cancer elimination. FUNDING: National Health and Medical Research Council (NHMRC) Australia, part-funded via the NHMRC Centre of Excellence for Cervical Cancer Control (C4; APP1135172).

Velentzis, L. S., M. A. Smith, K. T. Simms, J. B. Lew, M. Hall, S. Hughes, S. Yuill, J. Killen, A. Keane, K. Butler, J. Darlington-Brown, H. Hui, J. M. L. Brotherton, R. Skinner, A. Brand, L. Roeske, S. Heley, J. Carter, D. Bateson, I. Frazer, S. M. Garland, R. Guy, I. Hammond, P. Grogan, M. Arbyn, P. E. Castle, M. Saville, B. K. Armstrong and K. Canfell (2019). "**Pathways to a cancer-free future: A protocol for modelled evaluations to maximize the future impact of interventions on cervical cancer in Australia.**" *Gynecol Oncol* **152**(3): 465-471.

OBJECTIVE: Australia's HPV vaccination and HPV-based cervical screening programs are changing the landscape in cervical cancer prevention. We aim to identify areas which can make the biggest further impact on cervical cancer burden. This protocol describes the first stage of a program of work called Pathways-Cervix that aims to generate evidence from modelled evaluations of interventions across the cervical cancer spectrum. METHODS: Based on evidence from literature reviews and guidance from a multi-disciplinary Scientific Advisory Committee (SAC), the most relevant evaluations for prevention, diagnosis and treatment were identified. RESULTS: Priority evaluations agreed by the SAC included: increasing/decreasing and retaining vaccination uptake at the current level; vaccinating older women; increasing screening participation; methods for triaging HPV-positive women; improving the diagnosis of cervical intraepithelial neoplasia (CIN) and cancer; treating cervical abnormalities and cancer; and vaccinating women treated for CIN2/3 to prevent recurrence. Evaluations will be performed using a simulation model, Policy1-Cervix previously used to perform policy evaluations in Australia. Exploratory modelling of interventions using idealised scenarios will initially be conducted in single birth cohorts. If these have a significant impact on findings then evaluations with more realistic assumptions will be conducted. Promising strategies will be investigated further by multi-cohort simulations predicting health outcomes, resource use and cost outcomes. CONCLUSIONS: Pathways-Cervix will assess the relative benefits of strategies and treatment options in a systematic and health economic framework, producing a list of 'best buys' for future decision-making in cervical cancer control.

Castanon, A., R. Landy, F. Pesola, P. Windridge and P. Sasieni (2018). "**Prediction of cervical cancer incidence in England, UK, up to 2040, under four scenarios: a modelling study.**" *Lancet Public Health* **3**(1): e34-e43.

BACKGROUND: In the next 25 years, the epidemiology of cervical cancer in England, UK, will change: human papillomavirus (HPV) screening will be the primary test for cervical cancer. Additionally, the proportion of women screened regularly is decreasing and women who received the HPV vaccine are due to attend screening for the first time. Therefore, we aimed to estimate how vaccination against HPV, changes to the screening test, and falling screening coverage will affect cervical cancer incidence in England up to 2040. METHODS: We did a data modelling study that combined results from population modelling of incidence trends, observable data from the individual level with use of a generalised linear model, and microsimulation of unobservable disease states. We estimated age-specific absolute risks of

cervical cancer in the absence of screening (derived from individual level data). We used an age period cohort model to estimate birth cohort effects. We multiplied the absolute risks by the age cohort effects to provide absolute risks of cervical cancer for unscreened women in different birth cohorts. We obtained relative risks (RRs) of cervical cancer by screening history (never screened, regularly screened, or lapsed attender) using data from a population-based case-control study for unvaccinated women, and using a microsimulation model for vaccinated women. RRs of primary HPV screening were relative to cytology. We used the proportion of women in each 5-year age group (25-29 years to 75-79 years) and 5-year period (2016-20 to 2036-40) who have a combination of screening and vaccination history, and weighted to estimate the population incidence. The primary outcome was the number of cases and rates per 100 000 women under four scenarios: no changes to current screening coverage or vaccine uptake and HPV primary testing from 2019 (status quo), changing the year in which HPV primary testing is introduced, introduction of the nine-valent vaccine, and changes to cervical screening coverage. FINDINGS: The status quo scenario estimated that the peak age of cancer diagnosis will shift from the ages of 25-29 years in 2011-15 to 55-59 years in 2036-40. Unvaccinated women born between 1975 and 1990 were predicted to have a relatively high risk of cervical cancer throughout their lives. Introduction of primary HPV screening from 2019 could reduce age-standardised rates of cervical cancer at ages 25-64 years by 19%, from 15.1 in 2016 to 12.2 per 100 000 women as soon as 2028. Vaccination against HPV types 16 and 18 (HPV 16/18) could see cervical cancer rates in women aged 25-29 years decrease by 55% (from 20.9 in 2011-15 to 9.5 per 100 000 women by 2036-40), and introduction of nine-valent vaccination from 2019 compared with continuing vaccination against HPV 16/18 will reduce rates by a further 36% (from 9.5 to 6.1 per 100 000 women) by 2036-40. Women born before 1991 will not benefit directly from vaccination; therefore, despite vaccination and primary HPV screening with current screening coverage, European age-standardised rates of cervical cancer at ages 25-79 years will decrease by only 10% (from 12.8 in 2011-15 to 11.5 per 100 000 women in 2036-40). If screening coverage fell to 50%, European age-standardised rates could increase by 27% (from 12.8 to 16.3 per 100 000 by 2036-40). INTERPRETATION: Going forward, focus should be placed on scenarios that offer less intensive screening for vaccinated women and more on increasing coverage and incorporation of new technologies to enhance current cervical screening among unvaccinated women. FUNDING: Jo's Cervical Cancer Trust and Cancer Research UK.

Easterly, C. W., F. Alarid-Escudero, E. A. Enns and S. Kulasingam (2018). "**Revisiting assumptions about age-based mixing representations in mathematical models of sexually transmitted infections.**" *Vaccine* **36**(37): 5572-5579.

BACKGROUND: Sexual mixing between heterogeneous population subgroups is an integral component of mathematical models of sexually transmitted infections (STIs). This study compares the fit of different mixing representations to survey data and the impact of different mixing assumptions on the predicted benefits of hypothetical human papillomavirus (HPV) vaccine strategies. METHODS: We compared novel empirical (data-driven) age mixing structures with the more commonly-used assortative-proportionate (A-P) mixing structure. The A-P mixing structure assumes that a proportion of sexual contacts - known as the assortativity constant, typically estimated from survey data or calibrated - occur exclusively within one's own age group and the remainder mixes proportionately among all age groups. The empirical age mixing structure was estimated from the National Survey on Sexual Attitudes and Lifestyles 3 (Natsal-3) using regression methods, and the assortativity constant was estimated from Natsal-3 as well. Using a simplified HPV transmission model under each mixing assumption, we calibrated the model to British HPV16 prevalence data, then estimated the reduction in steady-state prevalence and the number of infections averted due to expanding HPV vaccination from 12- through 26-year-old females alone to 12-year-old males

or 27- to 39-year-old females. RESULTS: Empirical mixing provided a better fit to the Natsal-3 data than the best-fitting A-P structure. Using the model with empirical mixing as a reference, the model using the A-P structure often under- or over-estimated the benefits of vaccination, in one case overestimating by 2-fold the number of infections prevented due to extended female catch-up in a high vaccine uptake setting. CONCLUSIONS: An empirical mixing structure more accurately represents sexual mixing survey data, and using the less accurate, yet commonly-used A-P structure has a notable effect on estimates of HPV vaccination benefits. This underscores the need for mixing structures that are less dependent on unverified assumptions and are directly informed by sexual behavior data.

Turner, H. C., I. Baussano and G. P. Garnett (2013). "**Vaccinating women previously exposed to human papillomavirus: a cost-effectiveness analysis of the bivalent vaccine.**" *PLoS One* 8(9): e75552.

Recent trials have indicated that women with prior exposure to Human papillomavirus (HPV) subtypes 16/18 receive protection against reinfection from the HPV vaccines. However, many of the original models investigating the cost effectiveness of different vaccination strategies for the protection of cervical cancer assumed, based on the trial results at that time, that these women received no protection. We developed a deterministic, dynamic transmission model that incorporates the vaccine-induced protection of women with prior exposure to HPV. The model was used to estimate the cost effectiveness of progressively extending a vaccination programme using the bivalent vaccine to older age groups both with and without protection of women with prior exposure. We did this under a range of assumptions on the level of natural immunity. Our modelling projections indicate that including the protection of women with prior HPV exposure can have a profound effect on the cost effectiveness of vaccinating adults. The impact of this protection is inversely related to the level of natural immunity. Our results indicate that adult vaccination strategies should potentially be reassessed, and that it is important to include the protection of non-naive women previously infected with HPV in future studies. Furthermore, they also highlight the need for a more thorough investigation of this protection.

EUROGIN 2019 ABSTRACT

#0225

5 - HPV prophylactic vaccines

Study of the impact of catch-up vaccination against papilloma virus on high-grade cervical dysplasia in France

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Background/Objectives: Cervical cancer is the 11th leading cause of cancer death in France. Human Papilloma Virus (HPV) are the main agents responsible for this disease. For the past 12 years, two vaccines have been available to prevent HPV infection and the development of precancerous lesions and cervical cancer. Population-based studies showed a reduced risk of cervical dysplasia in vaccinated young women in other countries. In case of high-grade cervical dysplasia, a surgical procedure by conization is the standard treatment, with potential impact on further pregnancies. We present here, the first results of the impact of catch-up vaccination on conization in France in a population based study.

Methods: We conducted a retrospective real-life cohort study on data collected prospectively by French National Health Insurance. Data collected prospectively and permanently included the demographic and care data of 1/97th of the French population. We extracted data from all women born between 1984 and 1991, corresponding to the catch-up population only at time of HPV vaccine implementation. We compared the conization rate between vaccinated and not vaccinated young women.

Results: The cohort consisted in 42 452 women. Vaccination coverage (at least one dose) was 9.8%. The coverage rate increased with time from vaccine implementation, from 0.5% in the 1984 cohort to 31% for the 1991 cohort. The conization rate was 1% for the entire cohort. The risk of conization between 19 and 30 years-old was reduced in the vaccinated group with a Hazard Ratio (HR) of 0.59 (95% CI[0.39-0.90]; p=0.043).

Conclusions: With a 10-year follow-up, HPV vaccination in catch-up population reduces the risk of conization between the ages of 19 and 30.

Session 4 **HPV Vaccination of High Risk Groups**

A Pubmed search was performed with the following selection criteria: **HPV AND Sex workers AND Vaccination; HPV Vaccination AND HIV** published in the last 10 years; altogether 477 items were retrieved. For the keyword search 'HPV Vaccination AND HIV', the articles were manually selected until 2017 . References were imported in EndNote. Herein, a relevant manual selection of **53** publications between based on title and abstract was made.

Diop-Ndiaye, H., K. Beiter, T. Gheit, A. Sow Ndoeye, A. Drame, S. McKay-Chopin, M. Tommasino, C. S. Bouh Boye, B. Sylla and C. T. Kane (2019). "**Human Papillomavirus infection in senegalese female sex workers.**" *Papillomavirus Res* **7**: 97-101.

OBJECTIVES: Several studies have documented the HPV genotypes in the Senegalese general population. The objective was to explore the HPV genotype distribution in Senegalese FSWs in order to assess the potential relevance of currently-available vaccines. **METHODS:** Vaginal swabs samples collected as part of the National Integrated Biological and Behavioral Survey in 14 regions throughout the country were randomly selected for HPV testing using bead-based multiplex genotyping (TS-MPG). **RESULTS:** Among the 436 FSW samples analyzed, the overall HPV prevalence was 79.8% (N=348), with 70.1% (N=244) cases presenting as multiple infections. High Risk HPV genotypes affecting at least 10% of FSWs included in order of decreasing frequency: 52, 16, 35, 51, 33, 31, 18, and 45. Sixty-seven (15.4%) FSWs were HIV positive and they were significantly more affected by HPV (94% vs 77%; $p < 0.01$) than seronegative FSWs as well as infections with multiple genotype. **CONCLUSION:** The present study indicates that FSW in Senegal experience a high burden of HPV infection with a high frequency of coinfection with HIV and multiple HPV genotypes. Public health interventions for this key population should include an earlier cervical dysplasia/cancer detection and preventative measures such as vaccination programs that must consider the HPV genotype distribution.

Ferre, V. M., D. K. Ekouevi, F. A. Gbeasor-Komlanvi, G. Collin, Q. Le Hingrat, B. Tchounga, M. Salou, D. Descamps, C. Charpentier and A. C. Dagnra (2019). "**Prevalence of human papillomavirus, human immunodeficiency virus and other sexually transmitted infections among female sex workers in Togo: a national cross-sectional survey.**" *Clin Microbiol Infect.*

OBJECTIVES: Sub-Saharan Africa is a region with high incidence of both human immunodeficiency virus (HIV) and cervical cancer. We conducted the first national study in Togo to assess prevalence of human papillomavirus (HPV), HIV and other sexually transmitted infections (STIs) among female sex workers (FSW). **METHODS:** A multicentric cross-sectional study was conducted among FSW recruited in hot spots (clubs, streets) in four Togolese cities. HPV and STIs were tested from cervical and anal swabs. HIV and syphilis were screened with rapid tests. **RESULTS:** In all, 310 FSW were recruited; HIV and cervical high-risk HPV (hrHPV) prevalence were 10.6% (33/310) and 32.9% (102/310), respectively. The most frequent hrHPV types were HPV58 (13.6%, 19/140), HPV35 (12.9%, 18/140), HPV31 (12.1%, 17/140) and HPV16 (10.7%, 15/140). Prevalence of hrHPV and multiple hrHPV infections showed higher rates in HIV-positive than in HIV-negative FSW (48.5% versus 31.0%, $p = 0.04$ and 21.2% versus 9.0%, $p = 0.03$; respectively). Prevalence of hrHPV was higher in cervical than anal swabs (34.1% versus 20.7%, $p = 0.0004$). High-risk HPV anal infections were more frequent among HIV-positive than HIV-negative FSW (51.9% versus 17.3%, $p = 2 \times 10^{-5}$). Concomitant anal and cervical hrHPV infections were present in 43.2% (41/95) of hrHPV-positive FSW. Overall prevalence in the cervix of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium* and *Trichomonas vaginalis* were 4.2%, 6.1%, 5.5% and 6.5%, respectively.

CONCLUSIONS: This first African study on paired cervical and anal samples showed a high prevalence of genital HPV infections with a rather high rate of concomitant HPV infections but low type concordance. We report an unusual distribution of hrHPV types. These findings highlight the critical need for implementation of a national HPV vaccination strategy.

Martinez-Gomez, X., A. Curran, M. Campins, L. Alemany, J. A. Rodrigo-Pendas, N. Borruel, X. Castellsague, C. Diaz-de-Heredia, F. A. Moraga-Llop, M. Del Pino and A. Torne (2019). **"Multidisciplinary, evidence-based consensus guidelines for human papillomavirus (HPV) vaccination in high-risk populations, Spain, 2016."** *Euro Surveill* **24**(7).

INTRODUCTION: Although human papillomavirus (HPV) routine vaccination programmes have been implemented around the world and recommendations have been expanded to include other high-risk individuals, current recommendations often differ between countries in Europe, as well as worldwide. **AIM:** To find and summarise the best available evidence of HPV vaccination in high-risk patients aiding clinicians and public health workers in the day-to-day vaccine decisions relating to HPV in Spain. **METHODS:** We conducted a systematic review of the immunogenicity, safety and efficacy/effectiveness of HPV vaccination in high-risk populations between January 2006 and June 2016. HPV vaccination recommendations were established with levels of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. **RESULTS:** A strong recommendation about HPV vaccination was made in the following groups: HIV infected patients aged 9-26 years; men who have sex with men aged 9-26 years; women with precancerous cervical lesions; patients with congenital bone marrow failure syndrome; women who have received a solid organ transplant or hematopoietic stem cell transplantation aged 9-26 years; and patients diagnosed with recurrent respiratory papillomatosis. **CONCLUSIONS:** Data concerning non-routine HPV vaccination in populations with a high risk of HPV infection and associated lesions were scarce. We have developed a document to evaluate and establish evidence-based guidelines on HPV vaccination in high-risk populations in Spain, based on best available scientific evidence.

Schim van der Loeff, M. F., A. Vorsters, E. Marra, P. Van Damme and A. Hogewoning (2019). **"Should female sex workers be offered HPV vaccination?"** *Hum Vaccin Immunother* **15**(7-8): 1544-1548.

Prophylactic vaccines are efficacious in preventing Human Papillomavirus (HPV) infection and subsequent cervical intraepithelial neoplasia (CIN), cervical cancer, other anogenital cancers, and anogenital warts. Female sex workers (SW) are at increased risk of acquiring sexually transmitted infections, including HPV. There are several reasons to offer HPV vaccination to SW: they are at high risk for HPV and often unvaccinated, and the immunogenicity of the vaccine is also excellent in previously HPV exposed women. Furthermore, women with disease caused by HPV may still benefit from vaccination. The efficacy of vaccinating mid-adult women (26-44 years old) against persistent HPV infection and CIN2+ is good. Although an SW may have been infected or exposed to HPV, she may not have been exposed to all vaccine-included hrHPV types. Vaccination induces mucosal immunity via the production of neutralizing antibodies on the surface of the female genital tract, thus preventing potential transmission to clients. Nevertheless, some considerations argue against offering vaccination to SWs. Current vaccines are only prophylactic and as such, do not affect current HPV infections. Women who have previously cleared HPV infections, may do so again and thus not need vaccination. Fewer SW might be naive to HPV-types than currently thought. HPV vaccination has probably no effect on latent infections. Vaccinating sometime after sexual debut could be too late, as infections have already occurred. Taken together, some data suggest that vaccination of SW may offer health benefits, also for the community, but sufficient evidence is lacking. In certain cases, HPV vaccination of SW may be recommended. Evidence-based,

public health decisions concerning vaccination of SW are challenging and could be facilitated with more research in this high-risk group.

Marra, E., N. Kroone, E. Freriks, C. L. van Dam, C. J. Alberts, A. A. Hogewoning, S. Bruisten, A. van Dijk, M. M. Kroone, T. Waterboer and M. F. Schim van der Loeff (2018). "**Vaginal and anal human papillomavirus infection and seropositivity among female sex workers in Amsterdam, the Netherlands: Prevalence, concordance and risk factors.**" *J Infect* **76**(4): 393-405.

BACKGROUND: We studied prevalence, risk factors and concordance of vaginal and anal HPV infection and L1 seropositivity among female sex workers (FSW) in Amsterdam. **METHODS:** In 2016, FSW aged ≥ 18 years having a sexually transmitted infections (STI) consultation were invited to participate. Participation entailed taking vaginal and anal self-swabs. Demographics and sexual behaviour data were collected. HPV DNA was analysed using the SPF10-PCR-DEIA-LiPA25-system-v1. Serum was tested for HPV L1 antibodies using multiplex serology assays. Determinants of vaginal and anal high risk HPV (hrHPV) infection and L1 seropositivity were assessed with logistic regression analyses. **RESULTS:** We included 304 FSW; median age was 29 years (IQR 25-37). Vaginal and anal hrHPV prevalence were 46% and 55%, respectively. HrHPV L1 seropositivity was 37%. Vaginal-anal hrHPV concordance was strong, but no significant association between vaginal or anal hrHPV infection and seropositivity was found. Having had anal sexual contact was not associated with anal hrHPV infection ($P = 0.119$). **DISCUSSION:** Vaginal and anal hrHPV prevalence is high among FSW in Amsterdam, the Netherlands. Promotion of HPV vaccination, preferably at the beginning of the sex (work) career, may be a useful prevention method against hrHPV infection and disease.

Loverro, G., E. Di Naro, A. M. Caringella, A. L. De Robertis, D. Loconsole and M. Chironna (2016). "**Prevalence of human papillomavirus infection in a clinic sample of transsexuals in Italy.**" *Sex Transm Infect* **92**(1): 67-69.

OBJECTIVES: Detectable human papillomavirus (HPV) DNA is the most common sexually transmitted infection. Reports on the prevalence of detectable HPV DNA among transsexuals (not sex workers) are scarce. The objective of the study was to determine the prevalence of detectable HPV DNA in a clinic sample of transsexuals and to assess the relationship between detectable HPV DNA and cytological outcomes. **METHODS:** Clinical samples (oral, anal, vaginal, cervicovaginal and penile scraped cells) from 35 transsexuals (surgically treated and surgically untreated) who attended the outpatient Clinic of Gender Identity Dysphoria of the Department of Obstetrics and Gynecology of Policlinico Hospital (Bari, Italy) were collected for cytological analysis and HPV DNA detection and typing. All enrolled subjects answered an anonymous structured questionnaire about their sexual habits. Serological status for other sexually transmitted diseases (hepatitis B virus (HBV), hepatitis C virus (HCV), HIV and syphilis) was also evaluated. **RESULTS:** HPV DNA was detected in 14 of 35 patients (40.0%). The prevalence of detectable HPV DNA was 38.2% (13/34) in tested anal samples, 9.1% (2/22) in vaginal samples and 8.3% (1/12) in penile samples. Oncogenic HPV genotypes have been detected in 93% of HPV-positive transsexuals. More than one-third (35.7%) of HPV-positive transsexuals were infected with at least one of the four vaccine-preventable genotypes, 6, 11, 16 and 18. **CONCLUSIONS:** The high rate of detectable HPV DNA by oncogenic types suggests that periodic cytological screening and clinical evaluation may be necessary since transsexuals are at high risk of anogenital cancer. Also promoting HPV vaccination in younger subjects may be advisable.

Menon, S., A. Wusiman, M. C. Boily, M. Kariisa, H. Mabeya, S. Luchters, F. Forland, R. Rossi, S. Callens and D. Vanden Broeck (2016). "**Epidemiology of HPV Genotypes among HIV Positive Women in Kenya: A Systematic Review and Meta-Analysis.**" *PLoS One* **11**(10): e0163965.

BACKGROUND: There is a scarcity of data on the distribution of human papillomavirus (HPV) genotypes in the HIV positive population and in invasive cervical cancer (ICC) in Kenya. This may be different from genotypes found in abnormal cytology. Yet, with the advent of preventive HPV vaccines that target HPV 16 and 18, and the nonavalent vaccine targeting 90% of all ICC cases, such HPV genotype distribution data are indispensable for predicting the impact of vaccination and HPV screening on prevention. Even with a successful vaccination program, vaccinated women will still require screening to detect those who will develop ICC from other High risk (HR) HPV genotypes not prevented by current vaccines. The aim of this review is to report on the prevalence of pHR/HR HPV types and multiple pHR/HR HPV genotypes in Kenya among HIV positive women with normal, abnormal cytology and ICC. **METHODS:** PUBMED, EMBASE, SCOPUS, and PROQUEST were searched for articles on HPV infection up to August 2nd 2016. Search terms were HIV, HPV, Cervical Cancer, Incidence or Prevalence, and Kenya. **RESULTS:** The 13 studies included yielded a total of 2116 HIV-infected women, of which 89 had ICC. The overall prevalence of pHR/HR HPV genotypes among HIV-infected women was 64% (95%CI: 50%-77%). There was a borderline significant difference in the prevalence of pHR/HR HPV genotypes between Female Sex workers (FSW) compared to non-FSW in women with both normal and abnormal cytology. Multiple pHR/HR HPV genotypes were highly prominent in both normal cytology/HSIL and ICC. The most prevalent HR HPV genotypes in women with abnormal cytology were HPV 16 with 26%, (95%CI: 23.0%-30.0%) followed by HPV 35 and 52, with 21% (95%CI: 18%-25%) and 18% (95%CI: 15%-21%), respectively. In women with ICC, the most prevalent HPV genotypes were HPV 16 (37%; 95%CI: 28%-47%) and HPV 18 (24%; 95%CI: 16%-33%). **CONCLUSION:** HPV 16/18 gains prominence as the severity of cervical disease increases, with HPV 16/18 accounting for 61% (95%CI: 50.0%-70.0%) of all ICC cases. A secondary prevention program will be necessary as this population harbors multiple pHR/HR HPV co-infections, which may not be covered by current vaccines. A triage based on FSW as an indicator may be warranted.

Vorstere, A., T. Cornelissen, E. Leuridan, J. Bogers, D. Vanden Broeck, I. Benoy, H. Goossens, N. Hens and P. Van Damme (2016). "**Prevalence of high-risk human papillomavirus and abnormal pap smears in female sex workers compared to the general population in Antwerp, Belgium.**" *BMC Public Health* **16**: 477.

BACKGROUND: Although female sex workers (FSWs) are a well-known high-risk group for Human Papillomavirus (HPV) infections, few tailored intervention programmes for HPV have been established worldwide. The lack of reliable data on the prevalence of HPV and related cervical lesions hampers the establishment of evidence-based intervention programmes. The objectives of this study were to describe the prevalence of high-risk Human Papillomavirus (hrHPV) infections and abnormal pap smears in FSWs compared to a control group in Antwerp, Belgium. **METHODS:** HPV genotyping and cytology data were analysed from routine Pap smear tests that were collected from both FSWs and the general population (1334 samples for each group) between June 2006 and June 2010. Within the laboratory database, all FSWs were matched 1:1 for age and testing date to determine the ORs of hrHPV genotypes, DNA and cytology outcome. **RESULTS:** The prevalence of hrHPV DNA in FSWs was 41.7 % compared to 19.8 % in the age-matched controls with an overall OR of 2.8 (95 % CI: 2.3-3.4). Significant differences were observed in all age groups, and the most significant differences were observed in the cohort under 21 years of age (prevalence of 64.4 % in FSWs versus 14.8 % in controls; OR 10.3 (95 % CI: 5.0-21.2). Significantly more cervical lesions were observed in FSWs, particularly in the 17- to 21-year old age group (OR for LSIL or HSIL: 10.3 (95 % CI: 3.2-33.8). In both groups, HPV 16 was the most prevalent at 12.1 and 6.6 % in the FSW and control groups, respectively. HPV 18 was the 8(th) and 7(th) most frequent genotype at 5.0 and 2.5 % in the FSW and control groups, respectively. **CONCLUSIONS:** FSWs have a significantly higher prevalence of hrHPV and more abnormal Pap smears than does the general population in

Antwerp, Belgium. The hrHPV prevalence in FSWs is similar to that reported in the literature. The need for tailored intervention programmes should be investigated further.

Hoang, H. T., A. Ishizaki, C. H. Nguyen, V. T. Tran, K. Matsushita, K. Saikawa, N. Hosaka, H. V. Pham, X. Bi, V. T. Ta, T. Van Pham and H. Ichimura (2013). "**Infection with high-risk HPV types among female sex workers in northern Vietnam.**" *J Med Virol* **85**(2): 288-294.

Vaccines against two high-risk human papillomavirus (HPV) types, HPV-16, and HPV-18, are in use currently, with high efficacy for preventing infections with these HPV types and consequent cervical cancers. However, circulating HPV types can vary with geography and ethnicity. The aim of this study was to investigate the prevalence of HPV types and the association between HPV types and abnormal cervical cytology among female sex workers in Northern Vietnam. Cervical swabs and plasma samples were collected from 281 female sex workers at two health centers in Hanoi and Hai Phong in 2009. The HPV L1 gene was amplified by PCR using original and modified GP5(+)/6(+) primers. Amplified PCR products were genotyped by the microarray system GeneSquare (KURABO) and/or clonal sequencing. Of the 281 women, 139 (49.5%) were positive for HPV DNA. Among the HPV-positive samples, 339 strains and 29 different types were identified. Multiple-type and high risk-type HPV infections were found in 85 (61.2%) and 124 (89.2%) women, respectively. The most common genotype was HPV-52, followed by HPV-16, HPV-18, and HPV-58. Abnormal cervical cytology was detected in 3.2% (9/281) of the women, and all of these samples were positive for HPV-DNA. Age \leq 25 years and infection with human immunodeficiency virus were associated positively with HPV infection among the women while ever smoking was associated negatively. These results show that HPV-52 is most prevalent among female sex workers in Northern Vietnam, most of whom had normal cervical cytology. This information may be important for designing vaccination strategies in Vietnam.

Hu, Y., H. Z. Qian, J. Sun, L. Gao, L. Yin, X. Li, D. Xiao, D. Li, X. Sun, Y. Ruan, D. F. Milam, S. W. Pan, Y. Shao and S. H. Vermund (2013). "**Anal human papillomavirus infection among HIV-infected and uninfected men who have sex with men in Beijing, China.**" *J Acquir Immune Defic Syndr* **64**(1): 103-114.

BACKGROUND: In light of China's unique ethnic and sociocultural context, and a marked rise in HIV prevalence among MSM, it is important to determine prevalence, genotypes and predictors of anal human papillomavirus (HPV) among HIV-infected and uninfected men who have sex with men (MSM) in Beijing, China. **METHODS:** In 2010-2011, we recruited MSM (age range 18-61; median 28 years) through peer volunteers, and collected demographic/behavioral information via interviewer-administrated questionnaires. Trained health workers collected anal swabs for HPV genotyping by PCR and blood samples for HIV/syphilis serologies. **RESULTS:** We obtained anal specimens from 212 HIV-infected and 459 HIV-uninfected participants. Among HIV-infected MSM, 82.1% were HPV-infected vs. 57.5% in HIV-uninfected ($p < 0.01$). HIV-infected men had the greatest likelihood of multiple types: 17.9% uninfected; 36.3% with one type; 36.8% with 2-3; 9.0% with ≥ 4 . Oncogenic HPV prevalence was higher among HIV-infected (61.3%) than uninfected participants (39.7%; $p < 0.01$). HIV-uninfected MSM reporting always using condoms during insertive anal intercourse (past 6 months) were less likely to be HPV-infected (OR=0.49, 95%CI: 0.31-0.77). Among HIV-uninfected MSM, HPV infection was associated with unprotected receptive anal intercourse (past 6 months; OR=1.92, 95%CI: 1.19-3.11) and being forced to have sex (previous year; OR=3.32, 95%CI: 1.10-10.0). Multivariable logistic analysis among HIV infected MSM suggested that unprotected oral intercourse (past 6 months) was associated with HPV (adjusted OR=2.12, 95%CI: 1.00-4.48). Syphilis occurred in 55.8% of HIV-infected/HPV-infected, 50.0% of HIV-infected/HPV-uninfected, 19.6% of HIV-uninfected/HPV-infected, and 13.0% of HIV-uninfected/HPV-uninfected MSM. **CONCLUSIONS:** HPV anal infections were

more common among HIV-infected than uninfected MSM in China, including oncogenic and multiple types. Unprotected oral and receptive anal sex were independently associated with HPV infection. Promotion of safer sex and HPV vaccination is strongly recommended among MSM.

Soochoo, M., M. Blas, G. Byraiah, C. Carcamo and B. Brown (2013). "**Cervical HPV Infection in Female Sex Workers: A Global Perspective.**" *Open AIDS J* 7: 58-66.

INTRODUCTION: Approximately 291 million women worldwide are HPV DNA carriers. Studies have indicated that having multiple sexual partners may lead to higher HPV transmission. Thus female sex workers (FSWs) may be at greater risk of infection compared to the general population. Herein we review publications with data on FSW cervical HPV test results. We also examine variations of HPV prevalence and risk behaviors by region. Knowledge of prevalent HPV types in FSWs may lead to improved prevention measures and assist in understanding vaccination in high-risk groups. **METHODS:** We conducted a review of the literature by searching PUBMED using the terms "prostitution" or "female sex workers", "human papillomavirus" or "HPV", and "prevalence" or "PCR" to find articles. We excluded studies without HPV testing or HPV type specific results, or unconventional HPV testing. **RESULTS:** A total of 35 peer-reviewed publications were included in our review. High risk HPV types 16 and 18 ranged from 1.1-38.9 per thousand in prevalence. In addition to high-risk HPV types, newer studies reported non-carcinogenic HPV types also of high prevalence. The most prevalent HPV types reported among FSWs included HPV 6 (11.5%), 16 (38.9%), 18 (23.1%), 31 (28.4%), 52 (32.7%), and 58 (26.0%). **CONCLUSIONS:** Female sex workers have an overall high prevalence of HPV infection of high-risk types as evident through various testing methods. FSWs are thought to be at increased risk of cervical cancer because of high HPV exposure. This highlights the need for HPV and cervical prevention campaigns tailored to FSWs.

Chikandiwa, A., P. T. Pisa, M. Sengayi, E. Singh and S. Delany-Moretlwe (2019). "**Patterns and trends of HPV-related cancers other than cervix in South Africa from 1994-2013.**" *Cancer Epidemiol* 58: 121-129.

BACKGROUND: HPV infection causes several cancers which include cervical, vaginal, vulval, penile and oropharyngeal cancer (OPC). Understanding the burden of HPV-related cancers is important for guiding cancer prevention and treatment interventions. **METHODS:** To inform policy, we analysed trends of age-standardised incidence (ASIR) and mortality (ASMR) rates for HPV-related head and neck (HNC) and anogenital cancers (AGC) in South Africa between 1994 and 2013. **RESULTS:** A total of 1 028 330 incident cancers and 617 044 cancer-related deaths were reported during the study period. The overall ASIR (-5.5%) and ASMR (-2.2%) for HNC declined, in part related to the anti-smoking legislation. In contrast, incidence (2.9%) and mortality (0.8%) rates for AGC increased with the rising HIV prevalence. ASIR for oral cavity cancer (OCC: -6.3%) and laryngeal cancer (LC: -11.3%) declined, including mortality associated with these cancers (OCC: -1.9%, and LC: -2.6%). However, oropharyngeal cancer showed a slower rate of decline in ASIR (-4.4%) and ASMR did not change. Compared to women, ASIR and ASMR for HNC were 3-fold higher among men. ASIR for both anal (7.5%) and vulval cancer (16.1%) increased. Median age at diagnosis of vulval cancer declined by 18 years (p-value = 0.01). Mortality rates for anal (3.9%) and vulval (2.6%) cancer increased. ASIR (-3.2%) and ASMR (-2.0%) for penile cancer declined. Rates for vaginal cancer did not change. **CONCLUSIONS:** Anal and vulval cancers have increased over the reporting period. There is need to continuously monitor trends of these cancers. Implementation of HPV vaccination could significantly reduce the burden of HPV-related cancers.

Bogaards, J. A., S. H. Mooij, M. Xiridou and M. F. Schim van der Loeff (2019). "**Potential effectiveness of prophylactic HPV immunization for men who have sex with men in the Netherlands: A multi-model approach.**" *PLoS Med* **16**(3): e1002756.

BACKGROUND: Men who have sex with men (MSM) are at high risk for anal cancer, primarily related to human papillomavirus genotype 16 (HPV16) infections. At 8.5 per 100,000 per year, the incidence rate of anal cancer among MSM is similar to that of cervical cancer among adult women in the Netherlands. However, MSM are not included in most HPV vaccination programs. We explored the potential effectiveness of prophylactic immunization in reducing anogenital HPV16 transmission among MSM in the Netherlands. **METHODS AND FINDINGS:** We developed a range of mathematical models for penile-anal HPV16 transmission, varying in sexual contact structure and natural history of infection, to provide robust and plausible predictions about the effectiveness of targeted vaccination. Models were informed by an observational cohort study among MSM in Amsterdam, 2010-2013. Parameters on sexual behavior and HPV16 infections were obtained by fitting the models to data from 461 HIV-negative study participants, considered representative of the local MSM population. We assumed 85% efficacy of vaccination against future HPV16 infections as reported for HIV-negative MSM, and age-specific uptake rates similar to those for hepatitis B vaccination among MSM in the Netherlands. Targeted vaccination was contrasted with vaccination of 12-year-old boys at 40% uptake in base-case scenarios, and we also considered the effectiveness of a combined strategy. Offering vaccine to MSM without age restrictions resulted in a model-averaged 27.3% reduction (90% prediction interval [PI] 11.9%-37.5%) in prevalence of anal HPV16 infections, assuming similar uptake among MSM as achieved for hepatitis B vaccination. The predicted reduction improved to 46.1% (90% PI 21.8%-62.4%) if uptake rates among MSM were doubled. The reductions in HPV16 infection prevalence were mostly achieved within 30 years of a targeted immunization campaign, during which they exceeded those induced by vaccinating 40% of preadolescent boys, if started simultaneously. The reduction in anal HPV16 prevalence amounted to 74.8% (90% PI 59.8%-93.0%) under a combined vaccination strategy. HPV16 prevalence reductions mostly exceeded vaccine coverage projections among MSM, illustrating the efficiency of prophylactic immunization even when the HPV vaccine is given after sexual debut. Mode of protection was identified as the key limitation to potential effectiveness of targeted vaccination, as the projected reductions were strongly reduced if we assumed no protection against future infections in recipients with prevalent infection or infection-derived immunity at the time of immunization. Unverified limitations of our study include the sparsity of data to inform the models, the omission of oral sex in transmission to the penile or anal site, and the restriction that our modeling results apply primarily to HIV-negative MSM. **CONCLUSIONS:** Our findings suggest that targeted vaccination may generate considerable reductions in anogenital HPV16 infections among MSM, and has the potential to accelerate anal cancer prevention, especially when combined with sex-neutral vaccination in preadolescence.

Rajendra Santosh, A. B., N. A. Christian, T. Jones, C. A. Thoms-Rodriguez, A. Condappa, T. Thompson, J. Pinkney, E. N. Barton and J. Lindo (2019). "**Molecular epidemiology of human papillomavirus genotypes in oral rinses from HIV-positive and HIV-negative Jamaican patients.**" *J Investig Clin Dent* **10**(1): e12365.

AIM: Human papillomavirus (HPV) has been reported to be associated with oral and oropharyngeal cancer. However, little information is available about the epidemiology of oral HPV infection in Jamaica. The purpose of the present study was to assess the prevalence of oral HPV strains using the oral rinse method in HIV and non-HIV Jamaican patients, as well as to determine the association of HPV with sexual practices, smoking, and alcohol use. **METHODS:** A cross-sectional study was conducted on patients attending The University of the West Indies Mona Dental Polyclinic and the Centre for HIV/AIDS Research and Education

Services. Salivary samples were tested through molecular analysis for 37 HPV genotypes using the linear array HPV genotyping test. A survey questionnaire was used to obtain demographic details, smoking history, alcohol practice, sexual practice, and history of HPV testing. RESULTS: The HPV prevalence was 8.65% in 18-64 y olds (N = 104), with a slight female predilection (55%). No high-risk HPV types were found. HPV-84 was the most common type in both HIV and non-HIV patients; 66.7% of HPV-positive participants reported that they had six or more lifetime sexual partners. CONCLUSION: The prevalence of oral HPV was similar to that in other countries. No statistically-significant relationship was observed between the prevalence of HPV and either the number of sexual partners, smoking, or alcohol history. A nationwide study on oral HPV detection might be helpful in developing a HPV vaccination policy in Jamaica.

Ong, J. J., S. Walker, A. Grulich, J. Hoy, T. R. H. Read, C. Bradshaw, M. Chen, S. M. Garland, A. Cornall, R. Hillman, D. J. Templeton, J. Hocking, B. Eu, B. K. Tee, E. P. F. Chow and C. K. Fairley (2019). **"Incidence, Clearance, and Persistence of Anal Human Papillomavirus in Men Who Have Sex With Men Living With Human Immunodeficiency Virus: Implications for Human Papillomavirus Vaccination."** *Sex Transm Dis* 46(4): 229-233.

BACKGROUND: Men who have sex with men living with human immunodeficiency virus have a high risk of anal cancer. We estimate the likely benefit of human papillomavirus (HPV) vaccination among participants of the Anal Cancer Examination study. METHODS: Anal swabs were collected for the detection and genotyping of anal HPV DNA by linear array (Roche Diagnostics) in this 2-year multicenter prospective cohort. We calculated the proportion of men, stratified by age, without detectable vaccine type-specific DNA. RESULTS: Overall, 255 men, with a median age of 50 years (interquartile range, 44-56 years) contributed 488.9 person-years of follow-up. After 2 years of follow-up, 149 (58%; 95% confidence interval [CI], 52-65) had at least 1 high-risk HPV (HRHPV), and 71 (28%, 95% CI, 22-34) had HPV types 16/18 detected. Assuming that DNA-negative men would receive vaccine protection, vaccination at baseline could potentially prevent HRHPV infection in 10.2% of men (95% CI, 6.8-14.6, 26 of 255) 2 years later from incident HRHPV covered by the bivalent and quadrivalent vaccine, and 29.4% of men (95% CI, 23.9-35.4, 75/255) from incident HRHPV covered by the nonavalent vaccine. CONCLUSION: Though there is high prevalence of anal HPV in men who have sex with men living with human immunodeficiency virus, there was also a high incidence of HRHPV vaccine types in the 2-year follow-up, indicating potential for prevention if these men were not previously infected with HPV vaccine types and were vaccinated at their baseline visit.

Chesson, H. W., E. Meites, D. U. Ekwueme, M. Saraiya and L. E. Markowitz (2019). **"Updated medical care cost estimates for HPV-associated cancers: implications for cost-effectiveness analyses of HPV vaccination in the United States."** *Hum Vaccin Immunother* 15(7-8): 1942-1948.

Estimates of medical care costs for cervical and other cancers associated with human papillomavirus (HPV) are higher in studies published in recent years than in studies published before 2012. The purpose of this report is (1) to review and summarize the recent cancer cost estimates and (2) to illustrate how the estimated cost-effectiveness of HPV vaccination might change when these recent cost estimates are applied. Our literature search yielded 6 studies that provided updated medical care cost estimates for 5 HPV-associated cancers. We found that applying the current cancer cost estimates had a notable impact on the estimated medical costs averted by HPV vaccination over an extended time frame (100 years), and a moderate impact on the estimated cost per quality-adjusted life year (QALY) gained by HPV vaccination. For example, for catch-up vaccination of teenagers and young adults, applying the more recent cancer costs reduced the estimated cost per QALY gained by about \$12,400. The cost studies we identified in our literature review are up-to-date and based on reliable data sources from United States settings, and can inform future studies of HPV vaccination

cost-effectiveness in the United States. However, careful consideration is warranted to determine the most appropriate cost values to apply.

Lacey, C. J. (2019). "**HPV vaccination in HIV infection.**" *Papillomavirus Res* **8**: 100174.

Persons with HIV are at increased risk of HPV infection, HPV disease, and HPV-related cancers compared to HIV negative persons. In persons with HIV, immune responses to vaccination are often sub-optimal, and while these improve with ART, they often remain lower and decline more rapidly than in HIV-negative individuals. Although the evidence base to support the immunogenicity of HPV vaccines in HIV + ve persons is reasonable, the evidence base to support the efficacy of HPV vaccines in HIV + ve individuals is inconsistent. There is one study in HIV + ve men who have sex with men (MSM) which showed no effect, and two other studies, one in HIV + ve women and one in HIV + ve adolescents that showed reduced effectiveness. All these effectiveness studies used Gardasil 4 (G4). Two studies in HIV + ve persons have shown superior immunogenicity of Cervarix (which uses a TLR4 agonist adjuvant) compared to G4. Studies of Hepatitis B vaccines in HIV + ve persons have shown that either (i) increased number of doses (ii) increased vaccine dose, or (iii) TLR agonist adjuvanted vaccines, all produce increased immunogenicity compared to standard vaccine regimes. Therefore, questions remain as to optimal HPV vaccine regimes in HIV and further clinical trials with different HPV vaccine regimes are needed.

Du, P. (2019). "**Human Papillomavirus Infection and Cervical Cancer in HIV+ Women.**" *Cancer Treat Res* **177**: 105-129.

Human papillomavirus (HPV) is the first identified necessary cause of human cancers and is associated with nearly 100% of all cervical cancers. Compared to the general female populations, HIV+ women have higher prevalence and incidence of cervical HPV infections, higher risks of persistent HPV infections and subsequent cervical intraepithelial lesions, and a higher incidence of cervical cancer. Although the wide use of combined antiretroviral therapy (cART) has improved the immune function and the longevity of HIV+ women, the incidence of cervical cancer in HIV+ women has not declined. For HIV+ women who follow routine cervical cancer screenings, their incidence of cervical cancer is comparable to that in HIV-negative women. Thus, adherence to the recommended cervical cancer screening is still critical for HIV+ women to prevent cervical cancer. Prophylactic HPV vaccines may also benefit HIV+ women, but prospective studies are needed to determine the effectiveness of HPV vaccination on reducing cervical cancer incidence in HIV+ women.

Stankiewicz Karita, H. C., K. Hauge, A. Magaret, C. Mao, J. Schouten, V. Grieco, L. F. Xi, D. A. Galloway, M. M. Madeleine and A. Wald (2019). "**Effect of Human Papillomavirus Vaccine to Interrupt Recurrence of Vulvar and Anal Neoplasia (VIVA): A Trial Protocol.**" *JAMA Netw Open* **2**(4): e190819.

Importance: Human papillomavirus (HPV), particularly HPV type 16, causes most anal and vulvar high-grade squamous intraepithelial lesions (HSIL), which are precursors to cancer. After initial treatment of HSIL, more than 30% of patients will have disease recurrence, with even higher recurrence among HIV-positive individuals and men who have sex with men. Recurrences can be debilitating and lead to significant morbidity and medical expense. Observational studies suggest a possible therapeutic benefit of the licensed HPV vaccines in reducing recurrent lesions in previously infected persons. Objective: To test whether the licensed prophylactic HPV vaccine (Gardasil-9) can reduce the risk of HSIL recurrence by 50% in previously unvaccinated individuals recently treated for anal or vulvar HSIL. Design, Setting, and Participants: This is a trial protocol for a randomized, double-blind, placebo-controlled, proof-of-concept clinical trial. Eligible participants are aged 27 to 69 at study start and have not received prior HPV vaccination, have had anal or vulvar HSIL diagnosed on or after January 1, 2014, and have no evidence of HSIL recurrence at screening. Persons infected with HIV are

eligible for the study provided they are receiving antiretroviral therapy. Target enrollment is 345 individuals. The primary outcome is time to histopathologically confirmed recurrence of HSIL. Differences in the risk for recurrence of HSIL will be evaluated using Cox proportional hazard models. Additional analyses include (1) frequency of HSIL recurrence; (2) role of HPV antibodies in deterring recurrence; (3) role of HPV persistence in recurrence, as measured by HPV genotype or HPV-16 variant lineage determined using swab samples collected at months 0, 18, and 36; and (4) incidence of adverse events. The study will be conducted at the University of Washington Virology Research Clinic from 2017 through 2022. Participants will be followed up for up to 36 months in the clinic, and up to 42 months by telephone. Discussion: Management of persistent or rapidly recurring anogenital HSIL remains challenging. Results from this study will provide evidence on whether incorporating the nonavalent HPV vaccine into routine care can decrease recurrence of anal and vulvar HSIL. Trial Registration: ClinicalTrials.gov identifier: NCT03051516.

Edelstein, M., N. Iyanger, N. Hennessy, D. Mesher, M. Checchi, K. Soldan, M. McCall, J. Nugent, J. Crofts, J. Lo, R. Gilson, K. Powell, M. Ramsay and J. Yarwood (2019). **"Implementation and evaluation of the human papillomavirus (HPV) vaccination pilot for men who have sex with men (MSM), England, April 2016 to March 2017."** *Euro Surveill* **24**(8).

BACKGROUND: Opportunistic human papillomavirus (HPV) vaccination for men who have sex with men (MSM) was piloted in sexual health clinics (SHC) in England between 2016 and 2018. AIM: to evaluate the pilot's first year (April 2016-March 2017) in terms of feasibility, acceptability, uptake, impact and equity and interpret the outcome in the context of wide HPV vaccination policy. METHODS: Attendance and uptake data from routine SHC surveillance datasets and a cross-sectional survey administered to individuals receiving the vaccine were analysed. RESULTS: Among 18,875 eligible MSM, 8,580 (45.5%) were recorded as having received one HPV vaccine dose, decreasing slightly with increasing age, and uptake was higher in rural than urban areas. Survey results suggested that of those receiving the first dose of HPV vaccine, 8% were new attendees and that among those, less than 11% attended just to receive the vaccine. Of those having their first HPV vaccination, 95% indicated they would like to receive the next vaccine doses at the same clinic and 85% of patients reported accessing other services when visiting SHC for the first dose of vaccine. CONCLUSION: An opportunistic HPV vaccination programme for MSM can be delivered in an acceptable and, as far as can be evaluated, equitable manner, without major disruption to SHC and HIV clinics.

Strong, C., H. Zou, N. Y. Ko, Y. L. Liang, W. W. Ku and C. W. Lee (2019). **"Prevalence and risk factors of anogenital human papillomavirus infection in a community sample of men who have sex with men in Taiwan: baseline findings from a cohort study."** *Sex Transm Infect*.

OBJECTIVES: Men who have sex with men (MSM) are a highly neglected population in the current recommendation of girls-only human papillomavirus (HPV) vaccination programmes in many countries. To better assess the cost effectiveness of HPV vaccination among men requires data on the prevalence of HPV infection in MSM using a community sample, which is still sparse in several regions. We examined the prevalence of and factors associated with anogenital HPV infection among MSM in Taiwan. METHODS: MSM 20 years of age and older were recruited from the community and social media in Taiwan in 2015-2016 and screened for HPV infection to detect 37 genotypes. MSM were seen at baseline and were/will be seen at 6, 12, 24 and 36 months. Men completed a questionnaire regarding their sexual experiences. Multivariable regression analyses were conducted to identify associated behavioural risk factors using the baseline data. RESULTS: A total of 253 MSM were recruited; 87% were below 35 years of age. Diagnosis of HIV was reported in 4% of men; just over 20% had three or more anal sex partners in the past year. The prevalence of any tested HPV type was 29.4% at the anal site and 11% at the penile site. One quarter of MSM were infected with

any of the 9-valent vaccine HPV types. Anal HPV detection was associated with having three or more receptive anal sex partners in the past year (adjusted odds ratio (aOR)=2.92, 95% CI 1.29 to 6.61) and having older sex partners (aOR=2.51, 95% CI 1.07 to 5.90). **CONCLUSIONS:** Our data provide the base to calculate the reproductive rate for HPV transmission in a low-risk community sample and cost-effectiveness to include men in HPV vaccination policies. Adding evidence from a community sample adds comprehensiveness for future estimates of disease transmission and vaccine effectiveness.

Pinto, L. A., T. J. Wilkin, T. J. Kemp, M. Abrahamsen, K. Isaacs-Soriano, Y. Pan, J. Webster-Cyriaque, J. M. Palefsky and A. R. Giuliano (2019). **"Oral and systemic HPV antibody kinetics post-vaccination among HIV-positive and HIV-negative men."** *Vaccine* **37**(18): 2502-2510.

Duration and functional aspects of the oral and systemic antibody responses following HPV vaccination in HIV-negative (HIV(-)) and HIV-positive (HIV(+)) men are not well characterized. Oral and systemic HPV-16 and HPV-18-specific antibody levels were evaluated over 18-months of follow-up, in HIV(+) and HIV(-) men. Sera and oral gargles from 147 HIV(-) men, ages 27-45 and 75 HIV(+) men, ages 22-61, who received 3-doses of quadrivalent HPV vaccine were tested for HPV-16 and HPV-18 antibodies at Day 1, Month 7 (1month post-dose 3), and Month 18 (12months post-dose 3) and HPV avidity (Day 1, and Month 7) using L1-VLP ELISA. All individuals seroconverted, regardless of HIV-status, following 3-doses of vaccine for HPV-16 and HPV-18. Serum HPV-16 and HPV-18 antibody geometric mean levels were >2-fold lower in HIV(+) compared to HIV(-) men at Month 7 (HPV-16: 808.5 versus 2119.8EU/mL, and HPV-18: 285.8 versus 611.6EU/mL, $p<0.001$) but not significantly different at Month 18 (HPV-16: 281.8 versus 359.7EU/mL, $p=0.145$, and HPV-18: 120.2 versus 93.4EU/mL, $p=0.372$). Post-vaccination, only oral HPV-16 antibody levels at Month 7 were significantly different between HIV(+) and HIV(-) men (127.7 versus 177.1EU/mg of IgG, $p=0.008$). Among baseline HPV-seronegative men, circulating levels of HPV-16 and HPV-18 antibodies were up to >3 fold lower in HIV(+) men, at Months 7 and 18. In contrast, levels of HPV-16 and HPV-18 antibodies after vaccination were not inferior in baseline HPV-seropositive, HIV(+) men. HPV-16 and HPV-18 avidity was lower among HIV(+) compared to HIV(-) men at Month 7 (HPV-16: 1.95M versus 2.12M, $p=0.027$; HPV-18: 1.50M versus 1.72M, $p<0.001$). Although differences in peak antibody levels were observed between HIV(+) and HIV(-) men following 3 doses of vaccine, plateau antibody levels were overall comparable, and avidity was relatively high for both groups. These data indicate that the vaccine induced antibody affinity maturation in both HIV(+) and HIV(-) men and will likely result in long-term protective immune responses.

Parisi, S. G., M. Basso, R. Scaggiante, S. Andreis, C. Mengoli, M. Cruciani, C. Del Vecchio, N. Menegotto, D. Zago, L. Sarmati, M. Andreoni and G. Palu (2019). **"Oral and anal high-risk human papilloma virus infection in HIV-positive men who have sex with men over a 24-month longitudinal study: complexity and vaccine implications."** *BMC Public Health* **19**(1): 645.

BACKGROUND: Few studies focused on longitudinal modifications over time of high-risk HPV (HR-HPV) at anal and oral sites in HIV+ men who have sex with men (MSM). **METHODS:** We described patterns and longitudinal changes of HR-HPV detection and the prevalence of HR-HPV covered by the nonavalent HPV vaccine (vax-HPV) at oral and anal sites in 165 HIV+ MSM followed in an Italian hospital. The samples were collected at baseline and after 24 months (follow-up). The presence of HPV was investigated with Inno-LiPA HPV Genotyping Extra II. **RESULTS:** Median age was 44 years (IQR 36-53), median CD4+ cell count at nadir was 312 cells/mm³ (IQR 187-450). A total of 120 subjects (72.7%) were receiving successful antiretroviral therapy (ART). At baseline and follow-up, the frequency of HR-HPV was significantly higher in the anal site (65.4% vs 9.4 and 62.4% vs 6.8%, respectively). Only 2.9% of subjects were persistently HR-HPV negative at both sites. All oral HR-HPV were single at baseline vs 54.6% at baseline at the anal site ($p = 0.005$), and all oral HR-HPV were single at

follow-up vs 54.4% at anal site at follow-up ($p = 0.002$). The lowest rate of concordance between the oral and anal results was found for HR-HPV detection; almost all HR-HPV positive results at both anal and oral sites had different HR-HPV. The most frequent HR-HPV in anal swabs at baseline and follow-up were HPV-16 and HPV-52. At follow-up at anal site, 37.5% of patients had different HR-HPV genotypes respect to baseline, 28.8% of subjects with 1 HR-HPV at baseline had an increased number of HR-HPV, and patients on ART showed a lower frequency of confirmed anal HR-HPV detection than untreated patients ($p = 0.03$) over time. Additionally, 54.6 and 50.5% of patients had only HR-vax-HPV at anal site at baseline and follow-up, respectively; 15.2% had only HR-vax-HPV at baseline and follow-up. **CONCLUSIONS:** We believe that it is important testing multiple sites over time in HIV-positive MSM. ART seems to protect men from anal HR-HPV confirmed detection. Vaccination programmes could reduce the number of HR-HPV genotypes at anal site and the risk of the first HR-HPV acquisition at the oral site.

Pasmans, H., T. M. Schurink-Van't Klooster, M. J. M. Bogaard, D. M. van Rooijen, H. E. de Melker, M. J. P. Welters, S. H. van der Burg, F. R. M. van der Klis and A. M. Buisman (2019). "**Long-term HPV-specific immune response after one versus two and three doses of bivalent HPV vaccination in Dutch girls.**" **Vaccine.**

BACKGROUND: In view of further reduction of HPV vaccination schedules, gaining more insight into humoral and cellular immune responses after a single HPV vaccine is of great interest. Therefore, these responses were evaluated after different doses of the bivalent (2v) HPV-vaccine in girls. **METHODS:** Blood was collected yearly up to seven years post-vaccination with one-, two- or three-doses of the 2vHPV vaccine (N=890). HPV-type-specific IgG and IgA-antibody levels, IgG-isotypes and avidity indexes were measured by a virus-like-particle-based multiplex-immuno-assay for two vaccine and five non-vaccine HPV types. HPV-type-specific memory B-cell numbers- and T-cell cytokine responses were determined in a subpopulation. **RESULTS:** HPV-type-specific antibody concentrations were significantly lower in one- than in two- and three-dose vaccinated girls but remained stable over seven years. The lower antibody response coincided with reduced HPV-type-specific B- and T-cell responses. There were no differences in both the IgG subtypes and the avidity of the HPV16-specific antibodies between the groups. **CONCLUSIONS:** One-dose of the 2vHPV vaccine is immunogenic, but results in less B- and T-cell memory and considerable lower antibody responses when compared with more doses. Therefore, at least of some of girls receiving the one-dose of the vaccination might be at higher risk for waning immunity to HPV in the long-term.

Mann, L. M., E. Llata, E. W. Flagg, J. Hong, L. Asbel, J. Carlos-Henderson, R. P. Kerani, R. Kohn, P. Pathela, C. Schumacher and E. A. Torrone (2019). "**Trends in the Prevalence of Anogenital Warts Among Patients at Sexually Transmitted Disease Clinics-Sexually Transmitted Disease Surveillance Network, United States, 2010-2016.**" *J Infect Dis* **219**(9): 1389-1397.

BACKGROUND: Approximately 90% of genital warts are caused by human papillomavirus (HPV) types 6 and 11. In the United States, HPV vaccination has been recommended for girls and women aged ≤ 26 years, and since 2011, for boys and men aged ≤ 21 years and for gay, bisexual, and other men who have sex with men (MSM) aged ≤ 26 years. **METHODS:** Data were obtained from 27 clinics participating in the STD Surveillance Network. Trends in the annual prevalence of anogenital warts (AGW) from 2010-2016 were described by sex and by the sex of sex partners. **RESULTS:** During 2010-2016, significant declines in the prevalence of AGW were observed in women aged < 40 years, men who have sex with women only (MSW) aged < 40 years, and MSM of all age categories. An inflection in trend in 2012 was noted for MSW aged 20-24 or 25-29 years and for MSM aged 20-24 years. **CONCLUSIONS:** The observed declines in the prevalence of AGW suggest that HPV morbidity is declining among populations attending STD clinics, including MSW, MSM, and women. Declines in younger age groups are

consistent with what would be expected following the implementation of HPV vaccination. However, declines were also observed in older age groups and are not likely to be the result of vaccination.

McClymont, E., M. Lee, J. Raboud, F. Coutlee, S. Walmsley, N. Lipsky, M. Loutfy, S. Trottier, F. Smaill, M. B. Klein, M. Harris, J. Cohen, M. H. Yudin, W. Wobeser and D. Money (2019). "**The Efficacy of the Quadrivalent Human Papillomavirus Vaccine in Girls and Women Living With Human Immunodeficiency Virus.**" *Clin Infect Dis* **68**(5): 788-794.

BACKGROUND: Human papillomavirus (HPV) vaccination is safe and efficacious in women without human immunodeficiency virus (HIV). Although good immunogenicity has been observed in women living with HIV (WLWH), efficacy data in this population are needed. METHODS: We enrolled 420 females aged ≥ 9 years (range, 9-65) living with HIV. Participants were to receive 3 doses of qHPV vaccine (0/2/6 months). The main endpoint was vaccine failure (ie, incident persistent qHPV infection, cervical intraepithelial neoplasia of grade 2 or higher [CIN2+], or genital warts). We compared these rates to published rates in vaccinated and unvaccinated women without HIV as well as unvaccinated WLWH. RESULTS: Among 279 eligible women, median follow-up was 2 years. In the intention-to-treat population, the incidence rate (IR) of persistent qHPV (HPV6/11/16/18) was 2.3 per 100 person-years (/100PY) (95% confidence interval [CI], 1.1-4.1), and IR of genital warts was 2.3/100PY (95% CI, 1.2-4.1). In the per-protocol efficacy population, IR of persistent qHPV was 1.0/100PY (95% CI, 0.3-2.6) and of genital warts was 1.0/100PY (95% CI, 0.3-2.5). No cases of CIN2+ occurred. Reported rates of qHPV-related infection and disease within vaccinated women without HIV, unvaccinated women without HIV, and vaccinated WLWH: 0.1 (95% CI, 0.02-0.03), 1.5 (95% CI, 1.1-2.0), and 1.2 (95% CI, 0.2-3.4) /100PY, respectively. The rate of persistent qHPV among vaccinated WLWH was lower than among unvaccinated WLWH (2.3 vs 6.0/100PY). CONCLUSIONS: Vaccinated WLWH may be at higher risk for vaccine failure than vaccinated women without HIV. However, overall rates of vaccine failure were low, and rates of persistent qHPV were lower than in unvaccinated WLWH.

Mpunga, T., M. Chantal Umulisa, V. Tenet, B. Rugwizangoga, D. A. Milner, Jr., C. Munyanshongore, D. A. M. Heideman, M. C. G. Bleeker, M. Tommasino, S. Franceschi, I. Baussano, T. Gheit, F. Sayinzoga and G. M. Clifford (2019). "**Human papillomavirus genotypes in cervical and other HPV-related anogenital cancer in Rwanda, according to HIV status.**" *Int J Cancer*.

The study aim was to describe human papillomavirus (HPV)-attributable cancer burden in Rwanda, according to anogenital cancer site, HPV type, age and HIV status. Tissue specimens of cervical, vulvar, vaginal, penile and anal cancer diagnosed in 2012-2018 were retrieved from three cancer referral hospitals and tested for high-risk (HR) HPV DNA. Cervical cancer represented the majority of cases (598 of 738), of which 96.0% were HR-HPV positive. HPV-attributable fractions in other cancer sites varied from 53.1% in 81 penile, through 76.7% in 30 vulvar, 83.3% in 24 vaginal, up to 100% in 5 anal cases. HPV16 was the predominant HR-HPV type in cervical cancer (55.0%), followed by HPV18 (16.6%) and HPV45 (13.4%). HPV16 also predominated in other cancer sites (60-80% of HR-HPV-attributable fraction). For cervical cancer, type-specific prevalence varied significantly by histology (higher alpha-9 type prevalence in 509 squamous cell carcinoma vs. higher alpha-7 type prevalence in 80 adenocarcinoma), but not between 501 HIV-negative and 97 HIV-positive cases. With respect to types targeted, and/or cross-protected, by HPV vaccines, HPV16/18 accounted for 73%, HPV31/33/45/52/58 for an additional 22% and other HR-HPV types for 5%, of HPV-attributable cancer burden, with no significant difference by HIV status nor age. These data highlight the preventive potential of the ongoing national HPV vaccination program in Rwanda, and in sub-Saharan Africa as a whole. Importantly for this region, the impact of HIV

on the distribution of causal HPV types was relatively minor, confirming type-specific relevance of HPV vaccines, irrespective of HIV status.

Cespedes, M. S., M. Kang, E. M. Kojic, T. Umbleja, C. Godfrey, J. Y. Webster-Cyriaque, R. Masih, C. Firnhaber, B. Grinsztejn, A. Saah, S. Cu-Uvin and J. A. Aberg (2018). "**Anogenital human papillomavirus virus DNA and sustained response to the quadrivalent HPV vaccine in women living with HIV-1.**" *Papillomavirus Res* **6**: 15-21.

OBJECTIVES: People living with HIV have increased Human Papillomavirus (HPV) related lesions and malignancies. We describe HPV DNA recovered from the cervix and anal canal, explore the effect of vaccination on HPV detection, and examine the durability of vaccine titers in women living with HIV-1 who were vaccinated with the quadrivalent HPV vaccine. **METHODS:** AIDS Clinical Trials Group A5240 was a prospective study of the quadrivalent HPV (qHPV) vaccine in 315 HIV-1 infected women in three CD4 strata (A: >350, B; 201-350, C: </=200 cells/mm³). Vaccine was administered at entry, week 8 and week 24. Cervical and anal HPV DNA specimens were collected at baseline, weeks 28 and 52; serum for antibody testing was obtained at baseline, weeks 28 and 72. **RESULTS:** Vaccine antibody titers decreased across all four HPV types at week 72 compared to week 28. Lower proportions of sustained seropositivity were observed in women with lower CD4 counts for all four vaccine types, with the lowest titers for HPV 18. Despite the decrease, the geometric mean titer levels were above the seroconversion cut-off levels for all types except HPV 18 in the lowest CD4 stratum. Of the 174 participants who had a negative baseline HPV 16 antibody and developed antibody response at week 28, 95%, 88%, and 86% retained seropositivity at week 72 in strata A, B, and C respectively. Lower antibody retention was observed in women with CD4 <200 compared to CD4>350 (p=0.016). Anal HPV detection was more prevalent compared to cervical detection at all visits. Among high risk types, type 52, 31, 16, 18 and 51 were the most common in the cervical compartment, while types 16, 35, 18, and 51 were the most prevalent in the anal canal at baseline (listed in the order of prevalence). Later detection of HPV not present at baseline was uncommon in either compartment. Serial recovery of HPV over time was more commonly observed in the anal canal. **CONCLUSION:** The qHPV vaccine elicits durable titer response above the seroconversion cut-off levels in HIV-infected women. However, the titer levels were substantially lower by Week 72, most noticeably in type 18. HPV DNA was detected more frequently in the anal canal. Detection of non-vaccine high risk HPV suggests a role for the nonavalent vaccine.

Cheng, S. H., K. S. Liao, C. C. Wang, C. Y. Cheng and F. Y. Chu (2018). "**Multiple types of human papillomavirus infection and anal precancerous lesions in HIV-infected men in Taiwan: a cross-sectional study.**" *BMJ Open* **8**(1): e019894.

OBJECTIVES: This study aimed to assess the relationship between infection with multiple human papillomavirus (HPV) types and abnormal anal cytology in HIV-infected men. **DESIGN:** An observational, cross-sectional study. **SETTING:** A regional referral hospital in Taiwan. **PARTICIPANTS:** In total, 714 HIV-infected men were enrolled between March 2011 and June 2016. Thin preparation anal Pap smears were interpreted according to the 2001 Bethesda System. Thirty-seven types of HPV were detected by reverse line blotting, including 13 oncogenic types and 24 non-oncogenic types. **OUTCOME MEASURES:** The relationship between anal HPV infection and abnormal anal cytology in people of Asian ethnicity and the coverage efficacy in HPV-vaccinated HIV-infected men. **RESULTS:** On anal cytology, 175 (24.5%) subjects had atypical squamous cells of undetermined significance (ASCUS) or higher grades of dysplasia, including 87 (49.7%) with ASCUS, 73 (41.7%) with low-grade squamous intraepithelial lesions (LSILs) and 15 (8.6%) with high-grade squamous intraepithelial lesions (HSILs). A higher proportion of subjects with those without LSIL/HSIL (93.1% vs 67.3%, P<0.0001) had multiple HPV types. The odds of having LSIL/HSIL increased with an increasing

number of HPV types: the ORs ranged from 1 for no HPV types to 6.96 (95% CI 2.38 to 20.37) for more than five types (Ptrend <0.0001). Multivariate logistic regression analysis showed a significant association between LSIL/HSIL and the number of HPV genotypes present (OR 1.20; 95% CI 1.02 to 1.42, P<0.05). HPV types covered by the nonavalent HPV vaccine (types 6/11/16/18/31/33/45/52/58) were detected in 70.1% of the patients in this study. CONCLUSIONS: The odds of having anal LSIL/HSIL are approximately seventimes greater in HIV-infected men with than without six or more types of HPV. Multiple HPV types in HIV-infected patients deserves aggressive follow-up, and HPV vaccination programme require scaling up.

Easterly, C. W., F. Alarid-Escudero, E. A. Enns and S. Kulasingam (2018). "**Revisiting assumptions about age-based mixing representations in mathematical models of sexually transmitted infections.**" *Vaccine* **36**(37): 5572-5579.

BACKGROUND: Sexual mixing between heterogeneous population subgroups is an integral component of mathematical models of sexually transmitted infections (STIs). This study compares the fit of different mixing representations to survey data and the impact of different mixing assumptions on the predicted benefits of hypothetical human papillomavirus (HPV) vaccine strategies. METHODS: We compared novel empirical (data-driven) age mixing structures with the more commonly-used assortative-proportionate (A-P) mixing structure. The A-P mixing structure assumes that a proportion of sexual contacts - known as the assortativity constant, typically estimated from survey data or calibrated - occur exclusively within one's own age group and the remainder mixes proportionately among all age groups. The empirical age mixing structure was estimated from the National Survey on Sexual Attitudes and Lifestyles 3 (Natsal-3) using regression methods, and the assortativity constant was estimated from Natsal-3 as well. Using a simplified HPV transmission model under each mixing assumption, we calibrated the model to British HPV16 prevalence data, then estimated the reduction in steady-state prevalence and the number of infections averted due to expanding HPV vaccination from 12- through 26-year-old females alone to 12-year-old males or 27- to 39-year-old females. RESULTS: Empirical mixing provided a better fit to the Natsal-3 data than the best-fitting A-P structure. Using the model with empirical mixing as a reference, the model using the A-P structure often under- or over-estimated the benefits of vaccination, in one case overestimating by 2-fold the number of infections prevented due to extended female catch-up in a high vaccine uptake setting. CONCLUSIONS: An empirical mixing structure more accurately represents sexual mixing survey data, and using the less accurate, yet commonly-used A-P structure has a notable effect on estimates of HPV vaccination benefits. This underscores the need for mixing structures that are less dependent on unverified assumptions and are directly informed by sexual behavior data.

Giuliani, M., A. Latini, M. Colafigli, M. Benevolo, F. Rollo, M. Zaccarelli, E. Giuliani, D. Moretto, A. Giglio, G. Rezza, A. Cristaudo and M. G. Dona (2018). "**Vaccine-preventable anal infections by human papillomavirus among HIV-infected men who have sex with men.**" *Future Microbiol* **13**: 1463-1472.

AIM: HIV-infected men who have sex with men (MSM) show the highest prevalence of anal HPV infection. Anal prevalence of the HPVs targeted by the quadrivalent HPV vaccine (4vHPV) and nonavalent HPV vaccine (9vHPV) was estimated in this population. MATERIALS & METHODS: Anal specimens were collected from HIV-infected MSM attending a sexually transmitted infection/HIV center. Specimens were analyzed using the Linear Array HPV Genotyping Test. RESULTS: A total of 49.5 and 71.2% of the 313 enrolled MSM harbored at least one of the 4vHPV and 9vHPV types, respectively. A significantly decreasing trend was observed for the prevalence of both 4vHPV ($p = 0.04$) and 9vHPV types ($p < 0.001$) across age classes. CONCLUSION: A substantial proportion of HIV-infected MSM do not harbor a current

anal infection with vaccine-preventable HPVs. The potential benefit of the 4vHPV versus 9vHPV vaccination in these subjects, including older MSM, should be investigated.

Bacik, L. C. and C. Chung (2018). "**Human papillomavirus-associated cutaneous disease burden in human immunodeficiency virus (HIV)-positive patients: the role of human papillomavirus vaccination and a review of the literature.**" *Int J Dermatol* **57**(6): 627-634.

Human papillomavirus (HPV) infection is related to the development of cutaneous squamous cell carcinoma, oropharyngeal carcinoma, and anogenital malignancies. Patients infected with human immunodeficiency virus (HIV) have impaired cell-mediated immunity, placing them at risk for more prolonged infection with a greater likelihood of disease expression. This presents important implications for screening and treatment of HPV in the HIV patient population. The use of prophylactic vaccines directed against HPV has been a promising clinical development, though the immunogenicity of these vaccines in the immunocompromised host and in patients with previously established HPV infections has not been well established. In this review, we describe the pathogenesis and epidemiology of HPV-related cutaneous malignancies in patients with HIV. We outline the current guidelines and recent advances in the field of HPV vaccination. It is our hope that increasing awareness of the HPV-related HIV comorbidities will lead to developments in preventative medicine capable of reducing the burden of these diseases. We recognize the importance of prevention as a primary defense against disease and hope that this article organizes and disseminates recent findings in the field of HPV-associated comorbidities in the HIV population.

Lazcano-Ponce, E., J. Salmeron, A. Gonzalez, B. Allen-Leigh, L. Leon-Maldonado, C. Magis, C. Aranda-Flores, C. Conde-Gonzalez, A. J. Portillo-Romero, E. Yunes-Diaz, L. Rivera-Rivera, G. Vargas, A. G. Nyitray and A. R. Giuliano (2018). "**Prevention and control of neoplasms associated with HPV in high-risk groups in Mexico City: The Condesa Study.**" *Salud Publica Mex* **60**(6): 703-712.

OBJECTIVE: To evaluate the effectiveness of a combined strategy of human papillomavirus virus (HPV) vaccination and high-risk HPV screening to reduce the occurrence of anogenital and oropharyngeal neoplasms among men who have sex with men, people with HIV, homeless people, transgender women, female sex workers and rape victims. MATERIALS AND METHODS: This mixed methods study evaluates the effectiveness of a combined vaccination-screening strategy to reduce HPV prevalence/incidence and occurrence of cervical intraepithelial neoplasms grade 2+ and/or anal intraepithelial neoplasms grade 2+, using Kaplan-Meier. The time-to-event method will evaluate time from positive results for specific anogenital HPV to incidence of anogenital lesions containing that HPV type. RESULTS: People vaccinated against HPV and screened for HPV as a primary test will have lower prevalence and incidence of HPV infection and consequently lower frequency of HPV-related anogenital and oropharyngeal lesions. CONCLUSIONS: This study will generate scientific evidence on effectiveness of a combined vaccination-screening strategy to reduce the burden of HPV-associated neoplasms.

Lin, C., S. Franceschi and G. M. Clifford (2018). "**Human papillomavirus types from infection to cancer in the anus, according to sex and HIV status: a systematic review and meta-analysis.**" *Lancet Infect Dis* **18**(2): 198-206.

BACKGROUND: Data on carcinogenicity of human papillomavirus (HPV) types in the anus are needed to inform anal cancer prevention through vaccination and screening. This is particularly the case for people infected with HIV, who are at an increased risk of anal cancer. METHODS: We did a systematic review of studies published from January, 1986, to July, 2017, in MEDLINE, Embase, and the Cochrane Library on anal HPV infection, without any language restrictions. Eligible studies reported type-specific HPV prevalence by strata of cytopathological or histopathological anal diagnosis, sex, and HIV status. Data requests were

made to authors when necessary. We did a meta-analysis of type-specific HPV prevalence across the full spectrum of anal diagnoses, from normal cytology to anal cancer. We assessed the main outcome of type-specific HPV prevalence ratios [PR], calculated across strata of anal diagnoses, gender, or HIV status, by use of generalised linear models. FINDINGS: 95 studies were identified from the search, published between 1992-2017, from which 18 646 individuals fulfilled the criteria for inclusion in the analyses: 8534 people with normal cytology, 5730 with low-grade lesions, 2024 with high-grade lesions, and 2358 with anal cancer. HPV prevalence varied in normal cytology from 42% in HIV-negative women to 76% in HIV-positive men and, for each diagnosis, was higher in individuals who were HIV positive than those who were HIV negative. HPV16 positivity increased with diagnosis severity, being the only HPV type accounting for more HPV infection in anal cancer than normal cytology, both in individuals who were HIV negative (PR 5.0, 95% CI 3.8-6.6, $p < 0.0001$) and those who were HIV positive (2.3, 1.9-2.7, $p < 0.0001$). HPV16 positivity increased even between high-grade lesions and anal cancer, whereas other high-risk HPV types accounted for high proportions of low-grade or high-grade lesions but their prevalence decreased in anal cancer. However, HPV16 was less frequent in HIV-positive than HIV-negative anal cancer, both in men (PR 0.8, 95% CI 0.7-0.9, $p < 0.0001$) and women (0.8, 0.6-1.0, $p = 0.063$), and in HIV-positive versus HIV-negative high-grade lesions in women (0.6, 0.5-0.9, $p = 0.0077$). Type-specific attribution of the non-HPV16 fraction of HIV-positive anal cancer is hindered by a high prevalence of multiple HPV infections. INTERPRETATION: HPV16 is by far the most carcinogenic HPV type in the anus, with enrichment of HPV16 even from high-grade lesions to anal cancer, both in individuals who are HIV negative and those who are HIV positive. Nevertheless, the fraction of anal cancer attributable to HPV16 is smaller in the HIV-positive population. FUNDING: International Agency for Research on Cancer.

Medina-Laabes, D. T., E. L. Suarez-Perez, H. M. Guiot, C. Munoz, V. Colon-Lopez, M. Tirado-Gomez and A. P. Ortiz (2018). "**Human Papillomavirus Correlates With Histologic Anal High-Grade Squamous Intraepithelial Lesions in Hispanics With HIV.**" *J Low Genit Tract Dis* **22**(4): 320-325.

OBJECTIVE: To estimate the magnitude of association between anal infection with high-risk human papilloma virus (HR-HPV) types and severity of biopsy-confirmed histopathological anal squamous intraepithelial lesions (SILs) among a clinic-based sample of HIV-infected adults in Puerto Rico. METHODS: This cross-sectional study analyzed data from medical records of adult patients who visited a specialized anal neoplasia clinic from June 2015 to December 2017 ($n = 239$); sociodemographics, behavioral risk factors, medical history, clinical data, and pathology reports were collected. The magnitude of association between anal HR-HPV and severity of anal SIL, adjusted for potential confounders, was assessed using a multinomial logistic model. RESULTS: A 78.7% of patients had anal HR-HPV infection, 43.9% had histopathological low-grade SIL (LSIL), and 37.7% had histopathological high-grade SIL (HSIL). The prevalence of anal HR-HPV infection was 63.6% among patients with no anal SIL, 70.5% for those with LSIL and 95.6% for those with HSIL. After adjusting for different predictors, patients with anal HR-HPV infection were more likely to have HSIL (odds ratio, 11.0; 95% confidence interval, 3.2-37.2) than those without anal HR-HPV infection, whereas no significant excess was observed for LSIL (odds ratio, 1.4; 95% confidence interval, 0.6-3.1). CONCLUSIONS: This study showed a strong association between anal HR-HPV infection and HSIL. Likewise, a high prevalence of anal HR-HPV infection and presence of anal SIL was observed among HIV-infected individuals. Our result highlights the importance of screening for anal HR-HPV infection and anal SIL and optimizing strategies for HPV vaccination in HIV-infected individuals.

Nadarzynski, T., H. Smith, D. Richardson, S. Bremner and C. Llewellyn (2018). "**Men who have sex with men who do not access sexual health clinics nor disclose sexual orientation are unlikely to receive the HPV vaccine in the UK.**" *Vaccine* **36**(33): 5065-5070.

BACKGROUND: Men who have sex with men (MSM) are recommended the Human Papillomavirus (HPV) vaccination due to their higher risk of genital warts and anal cancer. PURPOSE: To examine HPV vaccine acceptability amongst MSM in the UK. METHODS: Using advertisements via Facebook, MSM were recruited to an online survey measuring motivations for HPV vaccination. Logistic regression was performed to identify predictors of HPV vaccine acceptability. RESULTS: Out of 1508 MSM (median age=22, range: 14-63years) only 19% knew about HPV. Overall, 55% of MSM were willing to ask for the HPV vaccine and 89% would accept it if offered by a healthcare professional (HCP). Access to sexual health clinics (SHCs) [OR=1.82, 95% CI 1.29-2.89], the disclosure of sexual orientation to a HCP [OR=2.02, CI 1.39-3.14] and HIV-positive status [OR=1.96, CI 1.09-3.53] positively predicted HPV vaccine acceptability. After receiving information about HPV, perceptions of HPV risk [OR=1.31, CI 1.05-1.63], HPV infection severity [OR=1.89, CI 1.16-3.01], HPV vaccination benefits [OR=1.61, CI 1.14-3.01], HPV vaccine effectiveness [OR=1.54, CI 1.14-2.08], and the lack of perceived barriers to HPV vaccination [OR=4.46, CI 2.95-6.73] were also associated with acceptability. CONCLUSIONS: Although nearly half of MSM would not actively pursue HPV vaccination, the vast majority would accept the vaccine if recommended by HCPs. In order to achieve optimal uptake, vaccine promotion campaigns should focus on MSM who do not access SHCs and those unwilling to disclose their sexual orientation.

Ong, J. J., S. Walker, A. Grulich, J. Hoy, T. R. H. Read, C. Bradshaw, M. Chen, S. M. Garland, R. Hillman, D. J. Templeton, J. Hocking, B. Eu, B. K. Tee, E. P. F. Chow and C. K. Fairley (2018). "**Incidence, Clearance and Persistence of Anal HPV in Men who Have Sex with Men Living with HIV: Implications for HPV Vaccination.**" *Sex Transm Dis*.

BACKGROUND: Men who have sex with men (MSM) living with HIV have a high risk of anal cancer. We estimate the likely benefit of HPV vaccination amongst participants of the Anal Cancer Examination (ACE) study. METHODS: Anal swabs were collected for the detection and genotyping of anal HPV DNA by Linear Array (Roche Diagnostics) in this two-year multicentre prospective cohort. We calculated the proportion of men, stratified by age, without detectable vaccine-type-specific DNA. RESULTS: Overall, 255 men, with a median age of 50 years (IQR 44-56) contributed 488.9 person-years of follow-up. After two years of follow up, 149 (58%, 95% CI:52-65) had at least one high-risk HPV (HRHPV), and 71 (28%, 95% CI:22-34) had HPV types 16/18 detected. Assuming that DNA negative men would receive vaccine-protection, vaccination at baseline could potentially prevent HRHPV infection in 10.2% of men (95% CI:6.8-14.6, 26/255) two years later from incident HRHPV covered by the bivalent and quadrivalent vaccine, and 29.4% of men (95% CI:23.9-35.4, 75/255) from incident HRHPV covered by the nonavalent vaccine. CONCLUSION: Though there is high prevalence of anal HPV in MSM living with HIV, there was also a high incidence of HRHPV vaccine types in the two-year follow up indicating potential for prevention if these men were not previously infected with HPV vaccine types and were vaccinated at their baseline visit.

Soe, N. N., J. J. Ong, X. Ma, C. K. Fairley, P. M. Latt, J. Jing, F. Cheng and L. Zhang (2018). "**Should human papillomavirus vaccination target women over age 26, heterosexual men and men who have sex with men? A targeted literature review of cost-effectiveness.**" *Hum Vaccin Immunother* **14**(12): 3010-3018.

BACKGROUND: Human papillomavirus (HPV) vaccination for young women up to age 26 is highly cost-effective and has been implemented in 65 countries globally. We investigate the cost-effectiveness for HPV vaccination program in older women (age > 26 years), heterosexual men and men who have sex with men (MSM). METHOD: A targeted literature review was

conducted on PubMed for publications between January 2000 and January 2017 according to the PRISMA guidelines. We included English-language articles that reported the incremental cost-effectiveness ratio (ICER) of HPV vaccination programs for women over age 26, heterosexual men, and MSM and identified the underlying factors for its cost-effectiveness. RESULTS: We included 36 relevant articles (six, 26 and four in older women, heterosexual men and MSM, respectively) from 17 countries (12 high-income (HICs) and five low- and middle-income (LMICs) countries). Most (4/6) studies in women over age 26 did not show cost-effectiveness (\$65,000-192,000/QALY gained). Two showed cost-effectiveness, but only when the vaccine cost was largely subsidised and protection to non-naïve women was also considered. Sixteen of 26 studies in heterosexual men were cost-effective (ICER = \$19,600-52,800/QALY gained in HICs; \$49-5,860/QALY gained in LMICs). Nonavalent vaccines, a low vaccine price, fewer required doses, and a long vaccine protection period were key drivers for cost-effectiveness. In contrast, all four studies on MSM consistently reported cost-effectiveness (ICER = \$15,000-\$43,000/QALY gained), particularly in MSM age < 40 years and those who were HIV-positive. Countries' vaccination coverage did not significantly correlate with its per-capita Gross National Income. CONCLUSION: Targeted HPV vaccination for MSM should be next priority in HPV prevention after having established a solid girls vaccination programme. Vaccination for heterosexual men should be considered when 2-dose 4vHPV/9vHPV vaccines become available with a reduced price, whereas targeted vaccination for women over age 26 is unlikely to be cost-effective.

Ortiz, A. P., E. A. Engels, G. M. Noguera-Gonzalez, V. Colon-Lopez, M. Soto-Salgado, A. Vargas, M. Machin and M. S. Shiels (2018). "**Disparities in human papillomavirus-related cancer incidence and survival among human immunodeficiency virus-infected Hispanics living in the United States.**" *Cancer* **124**(23): 4520-4528.

BACKGROUND: Human papillomavirus (HPV) causes 10% of cancers among human immunodeficiency virus (HIV)-infected people in the United States. Because Hispanics are disproportionately affected by the HIV epidemic and by infection-related cancers, this study compared incidence rates for HPV-related cancers and survival between Hispanics and non-Hispanic whites (NHWs) and non-Hispanic blacks (NHBs) in the HIV-infected US population. METHODS: Based on data from the HIV/AIDS Cancer Match Study, standardized incidence ratios (SIRs) were used to estimate cancer risk in HIV-infected Hispanics and the general US Hispanic population. Among HIV-infected people, cancer rates were compared with incidence rate ratios (IRRs), and survival was compared with hazard ratios between Hispanics and NHWs and NHBs. RESULTS: Five hundred two HPV-related cancers occurred in 864,067 person-years of follow-up among HIV-infected Hispanics. Except for oropharyngeal cancer, the risk of HPV-related cancers was higher among HIV-infected Hispanics than in the general population (SIR range, 3.59 [cervical cancer] to 18.7 [anal cancer in men]). Among HIV-infected females, Hispanics had higher cervical cancer rates than NHWs (IRR, 1.70; 95% confidence interval [CI], 1.19-2.43) but lower vulvar cancer rates than NHWs (IRR, 0.40; 95% CI, 0.24-0.67) and NHBs (IRR, 0.62; 95% CI, 0.41-0.95). Among HIV-infected males, Hispanics had higher penile cancer rates than NHWs (IRR, 2.60; 95% CI, 1.36-4.96) but lower anal cancer rates than NHWs (IRR, 0.54; 95% CI, 0.46-0.63) and NHBs (IRR, 0.65; 95% CI, 0.56-0.77). Among HIV-infected Hispanics, 5-year survival was greater than 50% across HPV-related cancer types, with no major differences by racial/ethnic group. CONCLUSIONS: HIV-infected Hispanics have an elevated risk for HPV-related cancers. Similarly to the general population, HIV-infected Hispanics have higher rates of cervical and penile cancer than NHWs and NHBs. HPV vaccination should be promoted among HIV-infected individuals to reduce the burden of HPV-related cancers.

Tan, N., M. Sharma, R. Winer, D. Galloway, H. Rees and R. V. Barnabas (2018). **"Model-estimated effectiveness of single dose 9-valent HPV vaccination for HIV-positive and HIV-negative females in South Africa."** *Vaccine* **36**(32 Pt A): 4830-4836.

BACKGROUND: Women in sub-Saharan Africa have high dual burden of HPV and HIV infections, which can interact to increase cervical cancer (CC) risk. The 9-valent HPV (9vHPV) vaccine has high demonstrated effectiveness against HPV types causing 90% of CC. Additionally, one dose of the 9vHPV vaccine has the potential to achieve greater coverage at lower costs than a two-dose schedule. However, the potential impact of single-dose 9vHPV vaccine accounting for HPV-HIV interactions has not been estimated. **METHODS:** We adapted a dynamic HIV transmission model to include HPV acquisition and CC pathogenesis and projected the impact of a single dose 9vHPV preadolescent vaccination in KwaZulu-Natal, South Africa. We report health impacts of HPV vaccination separately for HIV-positive women stratified by HIV treatment and CD4 count and HIV-negative women. **RESULTS:** At 90% coverage of females age 9 years with 80% lifelong vaccine efficacy, single dose HPV vaccination was projected to reduce CC incidence by 74% and mortality by 71% in the general female population at 70 years after the start of the vaccination program. Age-standardized CC incidence and mortality reductions were comparable among HIV-negative women, HIV-positive women, and HIV-positive women on ART. Health benefits were reduced when assuming waning protection at 10, 15 and 20 years after vaccination. **DISCUSSION:** Single dose 9vHPV vaccination is projected to avert substantial CC burden in South Africa and similar high HIV prevalence settings. Health benefits were comparable across all female subpopulations stratified by HIV status, CD4 count, and ART status.

Thompson, A. B., S. E. Gillespie, M. B. Mosunjac, S. A. Hussen, L. C. Flowers and A. F. Camacho-Gonzalez (2018). **"Prevalence of Anal Squamous Intraepithelial Lesions in HIV-1-Infected Young Men Who Have Sex With Men and Transwomen."** *J Low Genit Tract Dis* **22**(4): 340-347.

OBJECTIVE: Anal cancer rates are increasing among HIV-infected persons. Although an efficacious human papillomavirus (HPV) vaccine is available, HPV vaccination rates remain low. Therefore, providers perform anal cancer screening, but there is no consensus on the optimal methods or timing of screening. This study was performed to determine the prevalence of and factors associated with anal squamous intraepithelial lesions in sexually active HIV-infected young men who have sex with men and transgender women. **MATERIALS AND METHODS:** We performed a single-center, retrospective study of sexually active HIV-infected young men who have sex with men and transgender women aged 13 to 24 years at an HIV clinic in Atlanta GA from 2009 to 2016. We used analysis of variance and chi tests of independence to evaluate bivariate associations and identify demographic, behavioral, and clinical risk factors. **RESULTS:** Of 314 subjects with a mean (SD) age of 20.4 (2.1) years at initial anal cytology testing, 5% had completed the HPV vaccine series at or before the time that cytology was obtained. Ninety-five percent of the anal cytology tests obtained were abnormal, and 72 (29%) of those subjects returned for diagnostic testing either by intraoperative biopsy or high-resolution anoscopy. Fifty-seven percent of those who underwent biopsy had histologic high-grade squamous intraepithelial lesions including 2 cases of carcinoma in situ. A history of greater than 20 lifetime sexual partners was associated with abnormal histology (probability < 0.001, $p = .017$). **CONCLUSIONS:** Our study highlights the value of early, standardized screening to avoid missing anal dysplasia or cancer, particularly in unvaccinated persons with high numbers of sexual partners.

Ucciferri, C., M. Tamburro, K. Falasca, M. L. Sammarco, G. Ripabelli and J. Vecchiet (2018). **"Prevalence of anal, oral, penile and urethral Human Papillomavirus in HIV infected and HIV uninfected men who have sex with men."** *J Med Virol* **90**(2): 358-366.

Aims of the study were to evaluate Human Papillomavirus (HPV) and type-specific prevalence in four anatomical sites in HIV infected men who have sex with men (MSM) compared with HIV uninfected MSM. Participants were recruited among the attendees of Infectious Diseases Clinics in Central Italy. A trained medical practitioner collected by interview sociodemographic data and information on medical history, sexual behavior, and drug use. Swabs from anal canal, oral cavity, urethral mucosa, and coronal sulcus were tested for HPV DNA and genotyping. Ninety MSM were enrolled, 45 subjects within each group. Overall, 48.9% MSM were HPV positive and prevalence was higher in HIV infected men (60.0% vs 37.8%, $P = 0.035$). HPV at multiple anatomic sites occurred in 59.1% MSM, with 34.1% and 22.7% at two and three sites, respectively. Prevalence of anal, coronal sulcus, oral, and urethral HPV was 96.3%, 37%, 21.6%, and 18.5% in HIV infected MSM, and 70.6%, 70.6%, 29.4%, and 23.5% among HIV uninfected. A similar proportion of HIV infected and uninfected MSM (59.2% and 58.8%) carried at least one high-risk genotype. Prevalence of types covered by nonavalent vaccine was 77.8% in HIV infected compared with 82.3% in HIV uninfected MSM. HPV 58 and 16 were mostly detected in HIV positive (43.7% and 31.2%) and negative MSM (50.0% and 40.0%). HPV detection rate underlined the high vulnerability of MSM to acquire multisite infections, characterized by various genotype combinations. Since nonavalent vaccine could have prevented 80% of HPV infections, study findings support the implementation of vaccination programs among MSM.

Valanikas, E., K. Dinas and K. Tziomalos (2018). "**Cancer prevention in patients with human immunodeficiency virus infection.**" *World J Clin Oncol* 9(5): 71-73.

Cancer is a leading cause of death in patients with human immunodeficiency virus (HIV) infection. With the advent of antiretroviral treatment, the risk of AIDS-defining cancers declined but the ageing of this population resulted in the emergence of other common cancers, particularly lung and hepatocellular cancer. Accordingly, screening programs similar to the general population should be implemented in patients with HIV infection. Vaccination against common oncogenic viruses is also essential. However, rates of cancer screening and vaccination against HPV and HBV are considerably low in this population, highlighting a pressing need to educate patients and healthcare professionals about the importance of cancer preventive measures in these vulnerable patients.

Wheldon, C. W., E. M. Daley, E. R. Walsh-Buhi, J. A. Baldwin, A. G. Nyitray and A. R. Giuliano (2018). "**An Integrative Theoretical Framework for HPV Vaccine Promotion Among Male Sexual Minorities.**" *Am J Mens Health* 12(5): 1409-1420.

The objective of the current study was to quantify the behavioral intentions of young adult male sexual minorities (MSM) to initiate human papillomavirus (HPV) vaccination and test an integrative model of HPV vaccine decision making. Participants were 575 MSM who were residing in the United States and were between ages 18 and 26 years. Standard direct and indirect measures of attitudes, perceived norms, and perceived behavioral control were employed to explain variation in behavioral intention. Additional background factors-such as concealment of one's sexual identity, suspicion of health care provider competence in LGBT health issues, perceived threat, and information orientation-were also included in the model. The final model fit the data well and identified a set of salient attitudinal and control beliefs as the strongest determinants of intention ($R^2 = .38$). Perceived threat and information orientation were positively correlated with HPV-related beliefs. Perceived threat was higher among men infected with HIV and lower among men in monogamous relationships. Self-efficacy, as an indirect measure of perceived behavioral control, was inversely related to the general tendency to conceal aspects of one's sexual orientation and a suspicion of health care providers. Bisexual identified men were more likely to conceal their sexual orientation and be more suspicious of health care providers. In this study, a number of modifiable determinants

of HPV vaccine intentions-both psychosocial and environmental-were identified and have implications for targeted and tailored behavioral interventions to promote HPV vaccination among MSM.

Wigfall, L. T., S. A. Bynum, H. M. Brandt, N. Sebastian and M. G. Ory (2018). "**HPV-Related Cancer Prevention and Control Programs at Community-Based HIV/AIDS Service Organizations: Implications for Future Engagement.**" *Front Oncol* **8**: 422.

Background: People living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and, men who have sex with men (MSM) are disproportionately affected by genital warts and cancers caused by human papillomavirus (HPV). We assessed community-based HIV/AIDS service organizations' (ASOs) staff awareness, knowledge, attitudes, and beliefs about HPV and effective cancer prevention tools, namely HPV vaccination, Pap, and HPV tests. The potential engagement of ASO staff in future efforts to reduce the disproportionate burden of genital warts and HPV-related cancers among HIV-positive women and MSM was explored. Methods: In May-June 2016, staff were recruited from three ASOs located in the South United States Census region-a geographical area disproportionately affected by HIV/AIDS. Participants completed a 30-min self-administered, 118-item paper and pencil survey about HPV and cancer. Data analysis was conducted using Stata/SE 14.2. Results: ASO staff (n = 30) were 83% non-Hispanic Black, 40% lesbian/gay, and worked with people living with HIV for an average of 11.4 +/- 7.7 years. All reported hearing of HPV and 77% had heard of the HPV vaccine (n = 23). While all knew HPV can cause cervical cancer, only 67% knew HPV can cause anal cancer. Most (61%) thought the HPV vaccine could prevent cervical cancer. Fewer (39-48%) thought the HPV vaccine could prevent anal, oral, penile, vaginal, and vulvar cancers. All were willing to encourage MSM and female clients to talk to a healthcare provider about HPV vaccination. Almost all were willing to promote HPV vaccination to clients (91-95%) and navigate clients to adult safety net HPV vaccine providers (86-95%). More than half (59-67%) thought they could positively influence their MSM and female clients' HPV vaccine decision-making. Conclusion: HPV vaccination and the Pap and HPV tests are effective cancer prevention tools that can reduce the disproportionate burden of genital warts and HPV-related cancers among HIV-positive women and MSM. Engaging ASO staff in cancer prevention efforts may increase HPV vaccination rates and early detection of HPV-related cancers among HIV-positive women and MSM. Exploring ASOs as community-based settings for promoting effective cancer prevention tools may foster opportunities to reduce the disproportionate burden of genital warts and HPV-related cancers among HIV-positive women and MSM.

Wilkin, T. J. (2018). "**Human papillomavirus-related malignancies in HIV infection: anal and oropharyngeal cancers.**" *Top Antivir Med* **26**(3): 85-88.

Human papillomavirus (HPV)-related cancers, including anal cancer and oropharyngeal cancer, occur more frequently in individuals living with HIV infection than in the general population. Strategies for prevention among individuals with HIV infection include HPV vaccination, anal cancer screening programs, and early initiation of antiretroviral therapy (ART). HPV vaccination is not yet optimally used; a stronger and more persistent effort is needed to increase vaccination rates. Although anal cancer screening is not recommended by all authorities, there is at least some evidence that screening and treatment of anal high-grade squamous intraepithelial lesions may prevent progression to cancer. However, more definitive evidence is needed. Early initiation of ART reduces the risk of infection-related cancers, with some evidence of benefit in preventing HPV-associated cancer in individuals with HIV infection. This article summarizes a presentation by Timothy J. Wilkin, MD, MPH, at the IAS-USA continuing education program held in Los Angeles, California in April 2018.

Wilkin, T. J., H. Chen, M. S. Cespedes, J. T. Leon-Cruz, C. Godfrey, E. Y. Chiao, B. Bastow, J. Webster-Cyriaque, Q. Feng, J. Dragavon, R. W. Coombs, R. M. Presti, A. Saah and R. D. Cranston (2018). **"A Randomized, Placebo-Controlled Trial of the Quadrivalent Human Papillomavirus Vaccine in Human Immunodeficiency Virus-Infected Adults Aged 27 Years or Older: AIDS Clinical Trials Group Protocol A5298."** *Clin Infect Dis* 67(9): 1339-1346.

Background: Adults living with human immunodeficiency virus (HIV) are at increased risk for anal and oropharyngeal cancer caused by human papillomavirus (HPV). The efficacy of HPV vaccines in this population is unknown. Methods: In this phase 3, double-blind, randomized, controlled trial, we assigned HIV-infected adults aged ≥ 27 years to the quadrivalent HPV (types 6, 11, 16, 18) vaccine or placebo (1:1) stratified by sex and presence of anal high-grade squamous intraepithelial lesions on biopsy (bHSIL). The primary endpoint was vaccine efficacy against incident persistent anal infection with quadrivalent vaccine types or single detection at the final visit that were not present at baseline. Secondary endpoints included vaccine efficacy for anal bHSIL after week 52, persistent oral HPV infection. Results: A total of 575 participants were randomized. The Data and Safety Monitoring Board stopped the study early due to futility. Vaccine efficacy was 22% (95.1% confidence interval [CI], -31%, 53%) for prevention of persistent anal infection or single detection at the final visit, 0% (95% CI -44%, 31%) for improving bHSIL outcomes and 88% (95.1% CI 2%, 98%) for preventing persistent oral HPV infection, but was 32% (95.1% CI -80%, 74%) for 6-month persistent oral HPV infection or single detection at the final visit. Conclusions: These results do not support HPV vaccination of HIV-infected adults aged ≥ 27 years to prevent new anal HPV infections or to improve anal HSIL outcomes. However, our data suggest a role for prevention of oral HPV infections, but this finding should be confirmed in future studies. Clinical Trials Registration: NCT01461096.

Orlando, G., S. Bianchi, M. M. Fasolo, F. Mazza, E. R. Frati, G. Rizzardini, A. Matteelli, N. Zanchetta, A. Amendola and E. Tanzi (2017). **"Cervical Human Papillomavirus genotypes in HIV-infected women: a cross-sectional analysis of the VALHIDATE study."** *J Prev Med Hyg* 58(4): E259-e265.

Introduction: Primary-prevention by prophylactic vaccination against HPV-related cancers and HPV-based screening programs are based on HPV-type distribution in immunocompetent individuals. HIV-infected women are at high risk of invasive HPV-disease sustained by a broader range of HPV-types and have higher multi-type infection rates than immunocompetent hosts. Methods: This is a cross-sectional analysis of High Risk HPV (HR HPV) type distribution in 805 HIV+ women (HIW) compared with a control group of 1402 immunocompetent HIV- women (SPW) enrolled in the VALHIDATE study in order to define HPV type-specific distribution according to cytology. Results: HIW had a 3.8, 3.6, and 2.7 times higher risk of atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL) and high grade squamous intraepithelial lesion (HSIL) than SPW respectively. HPV-DNA prevalence was 28.4% in HIW and 11.81% in SPW ($p < 0.0001$). The prevalence of infection increased from normal cytology to HSIL both in HIW (from 21.45% to 90.91%) and SPW (from 9.54% to 75%). The OR for women with normal cytology of having a positive HPV-DNA test result of was 2.6 times higher in HIW than in SPW. The cumulative prevalence of HPV-16/18 in HSIL is much lower in HIW (36.4+/-28.4) than SPW (62.5+/-33.5). Conclusions: A higher prevalence of infection and broader HPV type distribution were observed in HIV+ women compared to the general population. More than 60% of HSIL lesions of HIW patients are caused by single or multi-type infections from non-HPV16/18 HPVs. The potential 9v-HPV vaccine coverage could be even higher than that expected for the general population given the wide panel of HPV-types observed in the HSIL of HIV+ women.

Pankam, T., S. J. Kerr, N. Teeratakulpisan, P. Rodbamrung, R. Wongkanya, S. Keelawat, K. Ruangritchankul, P. Hongchookiat, R. Watanapokasin and N. Phanuphak (2017). **"Human**

papillomavirus in anal biopsy tissues and liquid-based cytology samples of HIV-positive and HIV-negative Thai men who have sex with men." *Papillomavirus Res* 3: 149-154.

BACKGROUND: Men who have sex with men (MSM) are at high risk of developing human papillomavirus (HPV)-related anal cancer. We compared HPV genotypes in anal tissues (Bx) and anal liquid-based cytology fluid (LBC) from HIV-positive and HIV-negative MSM. METHODS: Bx (32 normal, 41 low-grade squamous intraepithelial lesions (LSIL) and 22 high-grade squamous intraepithelial lesions (HSIL)), along with LBC from the same visit, were selected from 61 HIV-positive and 34 HIV-negative MSM who enrolled into a prospective cohort in Bangkok, Thailand. HPV genotyping was performed on Bx and LBC. RESULTS: Any HPV and high-risk HPV (HR-HPV) prevalence were 63.2% and 60.0% in Bx and 71.6% and 62.1% in LBC, respectively. HIV-positive MSM had higher rates of HR-HPV genotypes detection (70.5% vs. 47.1%, $p=0.03$) in LBC than HIV-negative MSM. HPV16 (27%) was the most common HR-HPV found in HSIL tissue. In HIV-positive MSM, the frequency of HR-HPV detection increased with histopathologic grading in both Bx and LBC samples. HSIL was associated with the presence of any HR-HPV (OR 7.6 (95%CI 1.8-31.9); $P=0.006$) in LBC and in Bx (OR 5.6 (95%CI 1.4-22.7); $P=0.02$). CONCLUSIONS: Our data strongly support the integration of HR-HPV screening on LBC samples, along with HPV vaccination, into an anal cancer prevention program.

Saunders, C. L., C. Meads, G. A. Abel and G. Lyratzopoulos (2017). "**Associations Between Sexual Orientation and Overall and Site-Specific Diagnosis of Cancer: Evidence From Two National Patient Surveys in England.**" *J Clin Oncol* 35(32): 3654-3661.

Purpose To address gaps in evidence on the risk of cancer in people from sexual minorities. Patients and Methods We used data from 796,594 population-based English General Practice Patient Survey responders to explore the prevalence of self-reported diagnoses of cancer in the last 5 years among sexual minorities compared with heterosexual women and men. We analyzed data from 249,010 hospital-based English Cancer Patient Experience Survey responders with sexual orientation as a binary outcome, and International Classification of Diseases, Tenth, Revision, diagnosis as covariate-38 different common and rarer cancers, with breast and prostate cancer as baseline categories for women and men, respectively-to examine whether people from sexual minorities are over- or under-represented among different cancer sites. For both analyses, we used logistic regression, stratified by sex and adjusted for age. Results A diagnosis of cancer in the past 5 years was more commonly reported by male General Practice Patient Survey responders who endorsed gay or bisexual orientation compared with heterosexual men (odds ratio [OR], 1.31; 95% CI, 1.15 to 1.49; $P < .001$) without evidence of a difference between lesbian or bisexual compared with heterosexual women (OR, 1.14; 95% CI, 0.94 to 1.37; $P = .19$). For most common and rarer cancer sites (30 of 33 in women, 28 of 32 in men), the odds of specific cancer site diagnosis among Cancer Patient Experience Survey respondents seemed to be independent of sexual orientation; however, there were notable differences in infection-related (HIV and human papillomavirus [HPV]) cancers. Gay or bisexual men were over-represented among men with Kaposi's sarcoma (OR, 48.2; 95% CI, 22.0 to 105.6), anal (OR, 15.5; 95% CI, 11.0 to 21.9), and penile cancer (OR, 1.8; 95% CI, 0.9 to 3.7). Lesbian or bisexual women were over-represented among women with oropharyngeal cancer (OR, 3.2; 95% CI, 1.7 to 6.0). Conclusion Large-scale evidence indicates that the distribution of cancer sites does not vary substantially by sexual orientation, with the exception of some HPV- and HIV-associated cancers. These findings highlight the importance of HPV vaccination in heterosexual and sexual minority populations.

Poynten, I. M., S. N. Tabrizi, F. Jin, D. J. Templeton, D. A. Machalek, A. Cornall, S. Phillips, C. K. Fairley, S. M. Garland, C. Law, A. Carr, R. J. Hillman and A. E. Grulich (2017). "**Vaccine-preventable anal human papillomavirus in Australian gay and bisexual men.**" *Papillomavirus Res* 3: 80-84.

OBJECTIVE: HPV causes ~90% of anal cancer and HPV16 is the type most commonly associated with anal cancer. Gay and bisexual men (GBM) are at greatly increased risk. We investigated patterns of vaccine-preventable anal HPV in older GBM. **METHODS:** The Study of the Prevention of Anal Cancer (SPANAC) is an ongoing, prospective cohort study of HIV-positive and HIV-negative Australian GBM. Participants completed questionnaires and underwent an anal swab for HPV genotyping using Roche Linear Array. We analysed baseline data from SPANAC by HPV type, mean number of types, stratified by age and HIV status. **RESULTS:** Anal HPV results from 606 (98.2%) of 617 participants (median age 49 years, 35.7% HIV-positive) showed 525 (86.7%) had ≥ 1 HPV type and 178 (29.4%) had HPV16. Over one third of participants (214, 35.3%) had no nonavalent vaccine-preventable types detected. Two (0.3%) participants had all quadrivalent types and none had all nonavalent vaccine types. HIV-positive participants ($p < 0.001$) and younger participants ($p = 0.059$) were more likely to have more vaccine-preventable HPV types detected. **CONCLUSION:** Anal HPV was highly prevalent in this largely community-based GBM cohort. Vaccine-preventable HPV16 was detected in approximately one third of participants. These findings suggest that the potential efficacy of HPV vaccination of older GBM should be explored.

Tian, T., P. Mijiti, H. Bingxue, Z. Fadong, A. Ainiwaer, S. Guoyao, Z. Zhanlin, Y. Mahan, T. Xiaoqin, G. Zheng and D. Jianghong (2017). "Prevalence and risk factors of anal human papillomavirus infection among HIV-negative men who have sex with men in Urumqi city of Xinjiang Uyghur Autonomous Region, China." *PLoS One* **12**(11): e0187928.

BACKGROUND: Infection with human papillomavirus (HPV) is the most common sexually transmitted infection among men who have sex with men (MSM). Study on prevalence and risk factors of anal HPV infection among HIV-negative MSM in Northwestern China was rare. **METHODS:** We performed a cross-sectional study of HPV prevalence using anal swab specimens among HIV-negative MSM in Urumqi city of Xinjiang Uyghur Autonomous Region, China between April 1st and October 30th in 2016. Prevalence of any anal HPV infection, high-risk and low-risk HPV infection was estimated. Risk factors associated with any anal HPV infection was analyzed using univariate and multivariate logistic regression models. **RESULTS:** Among 538 potential participants, 500 (92.9%) were recruited in this study. The genotyping results of anal HPV infection were available for all. Of them, 259 (51.8%), 190 (38.0%) and 141 (28.2%) were positive for at least one of the targeted 37 HPV genotypes, high-risk HPV genotypes, and any low-risk HPV genotypes. The most prevalent anal HPV genotype was HPV 6 (11.8%), followed by HPV 16 (11.2%), HPV 11 (10.8%), HPV 51 (7.0%) and HPV 18 (5.4%). Among those infected with at least one of the targeted 37 anal HPV genotypes, 75 (29.0%), 155 (59.8%) and 191 (73.7%) were infected with 2-valent, quadrivalent and 9-valent HPV vaccine-covered genotypes. Receptive anal intercourse in the past year was the only predictor of any anal HPV infection in multivariate logistic regression model. **CONCLUSION:** Prevalence of any anal HPV infection and high-risk HPV infection among HIV-negative MSM in Urumqi city of Xinjiang is high. The majority of genotypes detected in our study were covered by quadrivalent and 9-valent HPV vaccines. Regular anal exams and early HPV vaccination among MSM may be considered in future HPV prevention programs in Xinjiang, China.

Session 5

LIMITATIONS AND ELIMINATION GOALS

This session includes content from WHO SAGE October 2019 Meeting

HPV vaccines in females over 25 years

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Trusted evidence.
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Key findings

In females aged 25 years and over there was

- Low-certainty evidence of little to no difference in HPV 16 or 18-related CIN2+ for 2- or 4-valent HPV vaccine compared to placebo
- Low-certainty evidence of little to no difference in HPV 6, 11, 16, or 18-related CIN2+ or condyloma for 4-valent HPV vaccine compared to placebo
- Moderate-certainty evidence of reduced HPV 16 or 18-related persistent infection for 2- or 4-valent HPV vaccine compared to placebo
- Moderate-certainty evidence of reduced HPV 6, 11, 16, or 18-related persistent infection for 4-valent HPV vaccine compared to placebo
- High-certainty evidence of significantly higher GMTs and higher rate of seroconversion for HPV 16 and 18 with 2-valent HPV vaccine compared with control (hepatitis B) vaccine at 7 months follow-up
- Low-certainty evidence of significantly higher GMTs for HPV 16 and 18 with 2-valent HPV vaccine compared with 4-valent HPV vaccine at 7 months to 5 years follow-up
- Low-certainty evidence of little to no difference in rate of seropositivity to HPV 16 at 7 months to 5 years follow-up between 2-valent HPV vaccine and with 4-valent vaccine.
- Low-certainty evidence of significantly higher rate of seropositivity for HPV 18 with 2-valent HPV vaccine compared with 4-valent HPV vaccine at 1 to 5 years follow-up.

Abstract

Background

Human papilloma virus (HPV) is the most common viral infection of the reproductive tract and causes a range of conditions in females and males, including precancerous lesions that may progress to cancer. In this Target Update, we review and analyse evidence for the protection afforded by prophylactic HPV vaccines in women over 25 years.

Objectives

To evaluate the efficacy and immunogenicity of HPV vaccines in females over 25 years.

Search methods

We updated a previous review performed by Cochrane Response in 2016, searches were conducted for this update from June 2016 to August 2018, and all relevant studies regardless of language or publication status were screened. We searched the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE (PubMed); EMBASE (OVID). We searched the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov, to identify ongoing trials. We searched the reference lists of relevant systematic reviews published within the search dates. We contacted the pharmaceutical industry for any potential relevant study through the WHO Initiative for Vaccines Research Department (IVR).

Selection criteria

Randomised controlled trials (RCTs) were eligible for inclusion. The studies in this document focus on the comparisons of HPV vaccine versus placebo, no vaccine, or control vaccine, and HPV vaccine versus other HPV vaccine in females over 25 years.

Data collection and analysis

Two review authors independently assessed trial eligibility and risk of bias and extracted data. Rate ratios (RR) with 95% confidence intervals (CI) were calculated for binary outcomes reported as rates. For continuous data, where GMTs were reported, we calculated the data as mean differences (95% CI) on the log scale and re-expressed as ratio of GMTs.

Main Results

We included five RCTs (China3, Italy2, Multinational12, Multinational13, and USA8). China3 compared 2-valent vaccine with hepatitis B vaccine (control vaccine) in 1202 females aged 26 to 45 years. Italy2 compared 2-valent HPV vaccine versus no vaccine in 832 females aged 25 years. Multinational12 compared 3 doses 4-valent vaccine to placebo in 3819 females aged 24 to 45 years old, Multinational13 compared 3 doses 4-valent vaccine to placebo in 5752 females aged over 25 years, and USA8 compared 3 doses 2-valent to 3 doses 4-valent HPV vaccine in women aged 18 to 45 years old, we present here the subset of 1106 females aged 27 to 45 years.

No randomised studies were identified that reported data on the efficacy or immunogenicity of the 9-valent HPV vaccine, or that compared different intervals between doses in females aged > 25 years.

The risk of bias was low for China3, Multinational12, and Multinational13. Italy2 and USA8 were considered at unclear risk of selection bias because randomisation and allocation concealment methods were not clearly reported, and Italy2 at high risk of performance bias since the study was not blinded.

2-valent or 4-valent HPV vaccine versus placebo or no vaccine in women over 25 years – clinical outcomes

Italy2, Multinational12, and Multinational13 reported clinical outcomes at 30 months to 7 years follow-up.

For the outcome HPV 16 or 18-related cervical intraepithelial neoplasia, grade 2 and above (CIN2+) there was low-certainty evidence of little to no difference between 2- or 4-valent HPV vaccine versus placebo in women over 24 years old at up to 7 years follow-up in the intention-to-treat (ITT) analysis (RR 0.74, 95% CI 0.52 to 1.05, 9121 participants, 2 RCTs). In the per protocol analysis HPV vaccines (2-valent and 4-valent) showed a significant beneficial effect compared to placebo reducing HPV 16 or 18-related CIN2+ by 84% at up to 7 years follow-up (RR 0.16, 95% CI 0.04 to 0.73, 6836 participants, 2 RCTs).

For the outcomes of HPV 6, 11, 16, or 18-related CIN2+ and HPV 6, 11, 16, or 18-related condyloma, there was low-certainty evidence of little to no difference between 4-valent vaccine and placebo in 24-45-year old women at a mean of 3.8 years follow-up in both the ITT and per protocol analyses.

For the outcome of persistent HPV infection there was moderate-certainty evidence that 2- or 4-valent HPV vaccine reduced persistent infection caused by HPV 16 or 18 in women over 24 years old compared with placebo at up to 7 years follow-up in both the ITT (RR 0.17, 95% CI 0.10 to 0.29, 7327 participants, 2 RCTs) and per protocol analyses. There was moderate-certainty evidence that 4-valent HPV vaccine reduced persistent infection caused by HPV 6, 11, 16 or 18 in 24-45-year old women compared with placebo at a mean of 3.8 years follow-up in both the ITT (RR 0.52, 95% CI 0.42 to 0.65, 3769 participants, 1 RCT) and per protocol analyses.

For the outcome of HPV 16 or 18-related infection there was very low-certainty evidence of little to no difference

between 2-valent vaccine and no vaccine in 25-year old women at 30 months follow-up.

2-valent HPV vaccine versus control vaccine in women over 25 years – immunogenicity outcomes

China3 reported immunogenicity outcomes at 7 months (one month after last vaccine dose) follow-up.

There was high-certainty evidence that 2-valent vaccine increased GMTs for HPV 16 and 18 when compared with placebo (means of 6439.8 EU/mL (HPV 16) and 3563.3 EU/mL (HPV 18) in the vaccine group). Seroconversion for HPV 16 and 18 was 100% and 99% respectively (high-certainty evidence).

2-valent HPV vaccine versus 4-valent HPV vaccine in women over 25 years – immunogenicity outcomes

USA8 reported immunogenicity outcomes at 7 months to 5 years follow-up.

There was low-certainty evidence that 2-valent vaccine increased GMTs for HPV 16 and 18 when compared with 4-valent HPV vaccines in 27 to 45-year old females at 7 months to 5 years follow-up. For HPV 16 seropositivity there was low-certainty evidence of little to no difference between 27 to 45-year old women that received 2-valent or 4-valent HPV vaccine at 7 months to 5 years follow-up. For HPV 18 seropositivity there was low-certainty evidence of little to no difference between 27 to 45-year old women that received 2-valent or 4-valent HPV vaccine at 7 months to 1 year follow-up; for 27-35-year old women there was a higher rate of seropositivity with 2-valent vaccine from 1 to 5 years follow-up, and for 36-45-year old women there was

a higher rate of seropositivity with 2-valent vaccine from 1.5 to 5 years follow-up.

Implications and conclusions

There was no difference between 2-valent or 4-valent HPV vaccine and control on HPV 6, 11, 16, or 18-related CIN2+ or condyloma in women over the age of 25. In a per protocol analysis of women who received all three doses of HPV vaccine, the 2-valent and 4-valent HPV vaccines prevented HPV 16 or 18-related CIN2+ compared to control at up to 7 years follow-up. There was moderate certainty evidence of a benefit with 2-valent or 4-valent HPV vaccines to prevent HPV 6, 11, 16, or 18-related persistent infection compared to control.

There was evidence of higher HPV 16 and 18-related GMTs and seropositivity with the 2-valent compared to the 4-valent vaccine at up to 5 years follow-up.

Summary of Findings: 2-valent or 4-valent HPV vaccine versus placebo or no vaccine in women over 25 years – clinical outcomes

Participants: Females aged 25 years and older (HPV serostatus mixed at baseline)

Setting: Australia, Canada, Colombia, France, Germany, Italy, Mexico, the Netherlands, Peru, Philippines, Portugal, Russia, Singapore, Spain, Thailand, the UK, and the USA

Comparison: 2-valent HPV vaccine (3-doses (Day 0, Month 1, Month 6)) or 4-valent HPV vaccine (3-doses (Day 0, Month 2, Month 6)) versus placebo (vaccine adjuvant) or no vaccine

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) N° of participants & studies	Certainty of the evidence (GRADE)
		Placebo or no vaccine	2- or 4-valent HPV vaccine		
CIN2+ associated with HPV 16/18 follow up: up to 7 years	There is low-certainty evidence that females receiving HPV vaccine had little to no difference in incidence of CIN2+ associated with HPV 16 or 18 compared to females receiving placebo	16 per 1,000	12 per 1,000 (8 to 17)	RR 0.74 (0.52 to 1.05) * 9121 participants in 2 RCTs	⊕⊕⊕ LOW ¹
CIN2+ associated with HPV 6/11/16/18 follow up: 3.8 years (mean)	There is low-certainty evidence that females receiving 4-valent HPV vaccine had little to no difference in incidence of CIN2+ associated with HPV 6, 11, 16, or 18 compared to females receiving placebo	14 per 1,000	11 per 1,000 (6 to 20)	RR 0.77 (0.44 to 1.37) † 3769 participants in 1 RCT	⊕⊕⊕ LOW ²
Persistent infection with HPV 16/18 follow up: up to 7 years	There is moderate-certainty evidence that females receiving HPV vaccine had a lower incidence of persistent HPV 16 or 18 infection than females receiving placebo	46 per 1,000	8 per 1,000 (5 to 13)	RR 0.17 (0.10 to 0.29) ‡ 7327 participants in 2 RCTs	⊕⊕⊕ MODERATE ³
Persistent infection with HPV 6/11/16/18 follow up: 3.8 years (mean)	There is moderate-certainty evidence that females receiving HPV vaccine had a lower incidence of persistent HPV 6, 11, 16, or 18 infection than females receiving placebo	112 per 1,000	58 per 1,000 (47 to 73)	RR 0.52 (0.42 to 0.65) § 3769 participants in 1 RCT	⊕⊕⊕ MODERATE ³
Infection HPV 16 follow up: 30 months	There is very low-certainty evidence that females receiving 2-valent HPV vaccine had little to no difference in HPV 16 infection compared to females receiving no vaccine	67 per 1,000	32 per 1,000 (13 to 76)	RR 0.47 (0.19 to 1.12) 618 participants in 1 RCT	⊕⊕⊕ VERY LOW ^{1,4}
Infection HPV 18 follow up: 30 months	There is very low-certainty evidence that females receiving 2-valent HPV vaccine had little to no difference in HPV 18 infection compared to females receiving no vaccine	14 per 1,000	16 per 1,000 (4 to 63)	RR 1.14 (0.29 to 4.52) 618 participants in 1 RCT	⊕⊕⊕ VERY LOW ^{2,4}
Condyloma HPV 6/11/16/18 follow up: 3.8 years (mean)	There is low-certainty evidence that females receiving 4-valent HPV vaccine had little to no difference in condyloma associated with HPV 6, 11, 16, or 18 compared to females receiving placebo	6 per 1,000	4 per 1,000 (1 to 9)	RR 0.58 (0.23 to 1.48) 3769 participants in 1 RCT	⊕⊕⊕ LOW ²

CI= confidence interval; CIN2+= cervical intraepithelial neoplasia, grade 2 and above; HPV= human papilloma virus; RR= risk ratio; RCT= randomised controlled trial

*ITT analysis. The per protocol analysis showed a significant beneficial effect with HPV vaccine (RR 0.16 (95% CI 0.04 to 0.73), 6836 participants, 2 RCTs). † ITT analysis. The per protocol analysis also showed no significant beneficial effect with HPV vaccine (RR 0.17 (95% CI 0.02, 1.38), 3222 participants, 1 RCT). ‡ ITT analysis, the per protocol analysis also showed a significant beneficial effect with HPV vaccine (RR 0.11 (0.06 to 0.20), 6651 participants, 2 RCTs) § ITT analysis, the per protocol analysis also showed a significant beneficial effect with HPV vaccine (RR 0.11 (0.05 to 0.21), 3222 participants, 1 RCT) || ITT analysis, the per protocol analysis also showed no significant beneficial effect with HPV vaccine (RR 0.07 (0.00 to 1.17), 3222 participants, 1 RCT)

¹ Downgraded two levels for imprecision: few events and 95% CIs include both no effect and benefit for HPV vaccine

² Downgraded two levels for imprecision: few events and 95% CIs include both benefit for both HPV vaccine and placebo as well as no effect

³ Downgraded one level for imprecision: few events

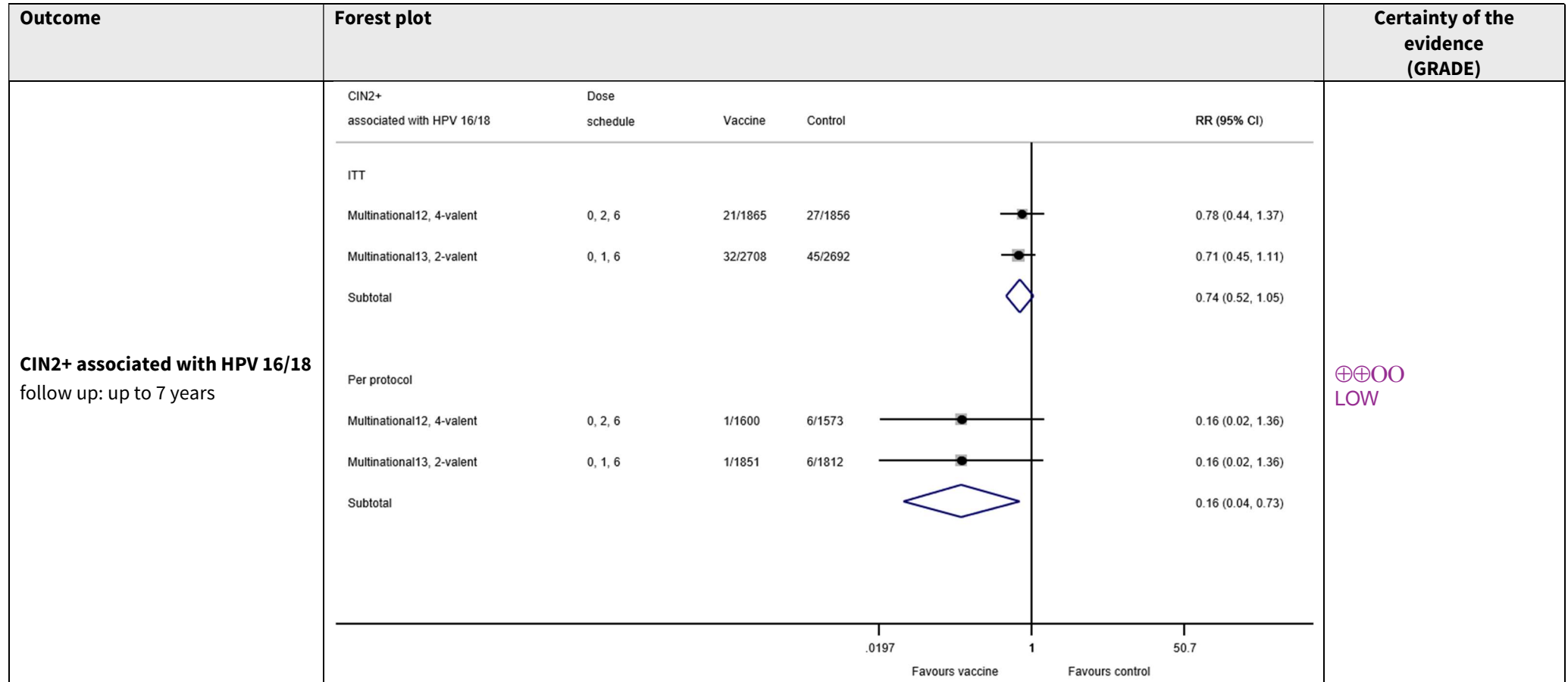
⁴ Downgraded one level for risk of bias: randomization and allocation concealment methods were not clearly reported; the study was not blinded to participants and study personnel

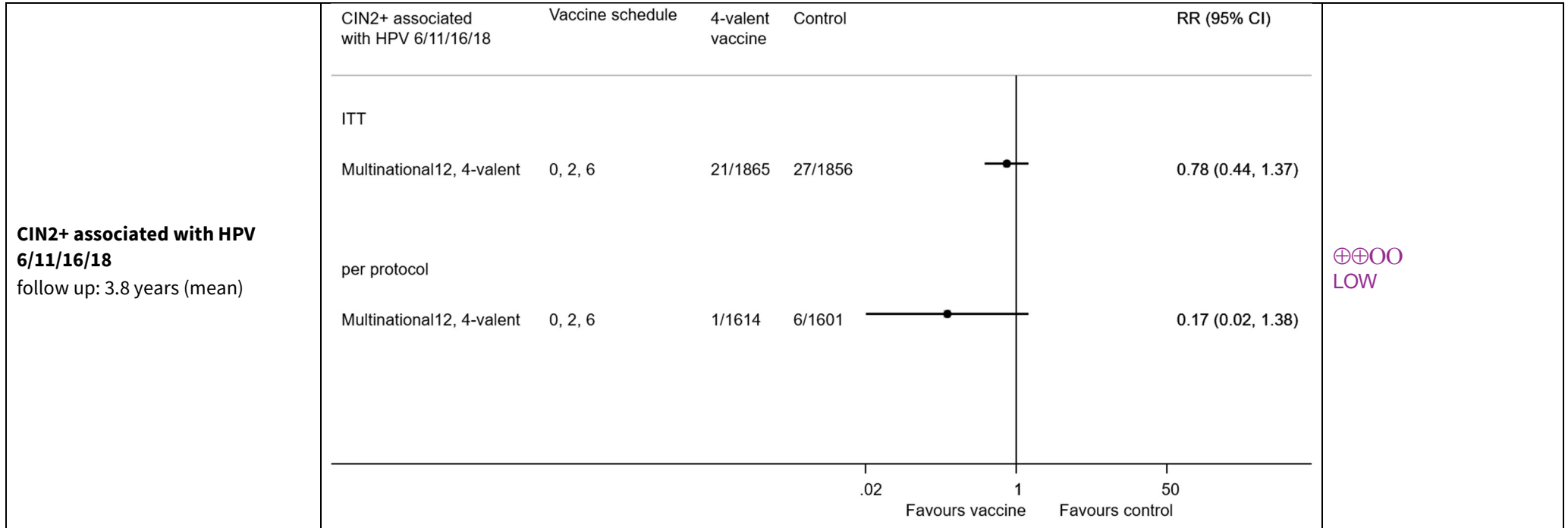
Forest plot: 2-valent or 4-valent HPV vaccine versus placebo or no vaccine in women over 25 years – clinical outcomes

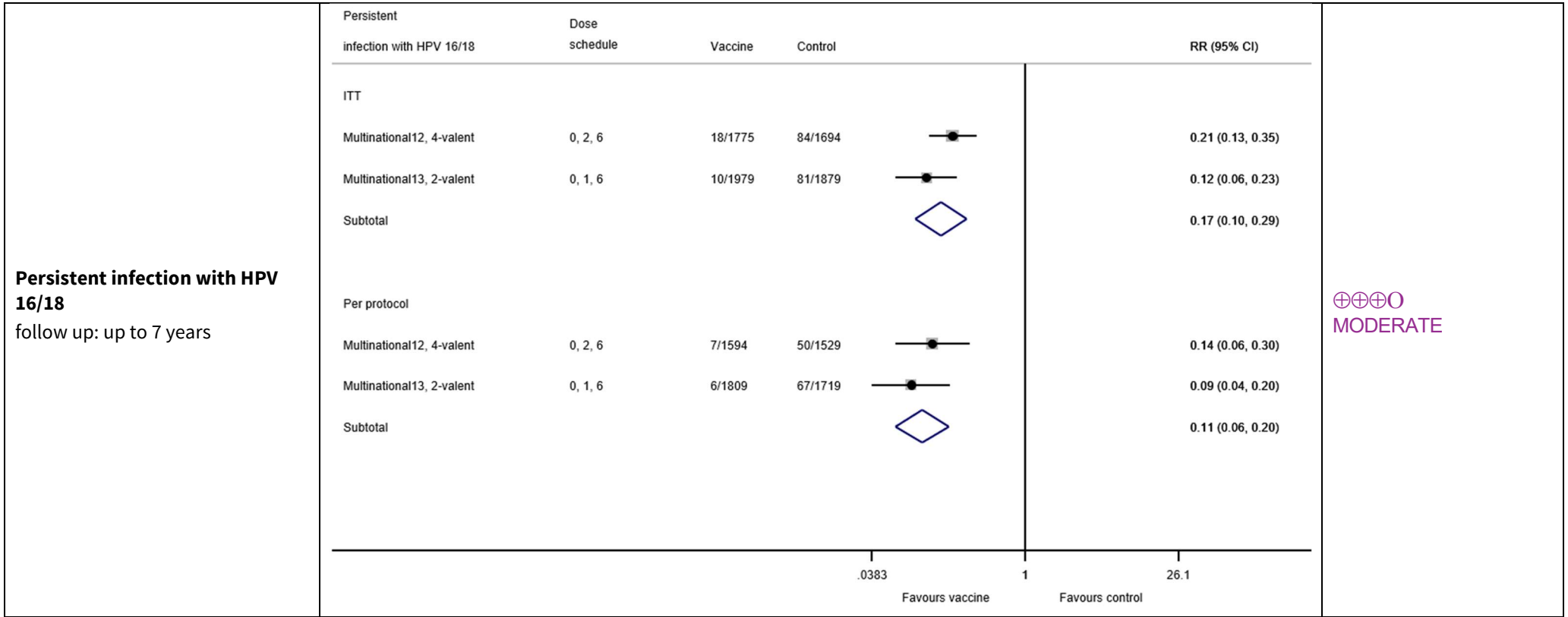
Participants: Females aged 25 years and older (HPV serostatus mixed at baseline)

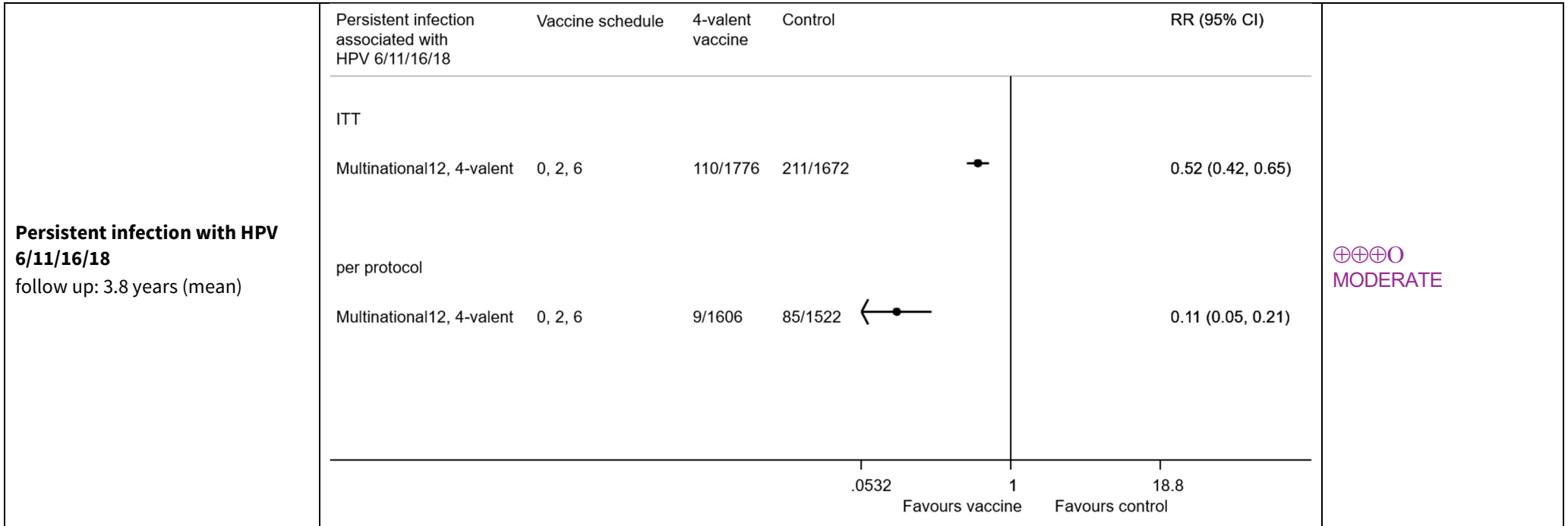
Setting: Australia, Canada, Colombia, France, Germany, Italy, Mexico, the Netherlands, Peru, Philippines, Portugal, Russia, Singapore, Spain, Thailand, the UK, and the USA

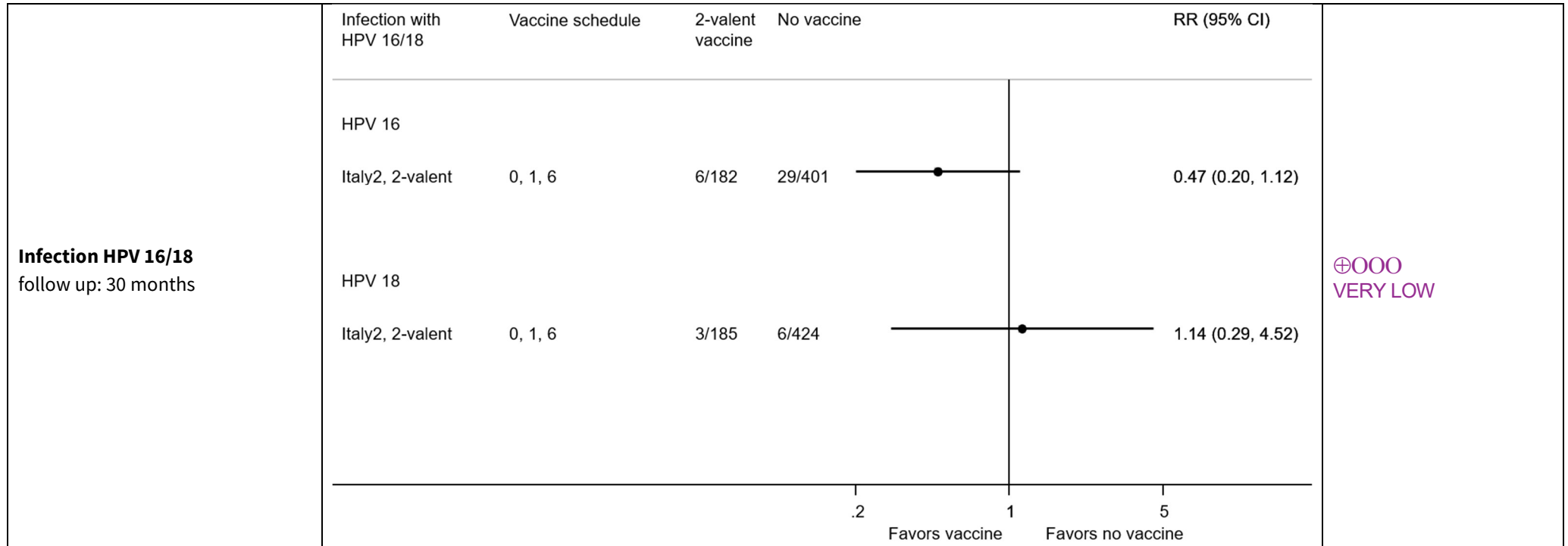
Comparison: 2-valent HPV vaccine (3-doses (Day 0, Month 1, Month 6)) or 4-valent HPV vaccine (3-doses (Day 0, Month 2, Month 6)) versus placebo (vaccine adjuvant) or no vaccine

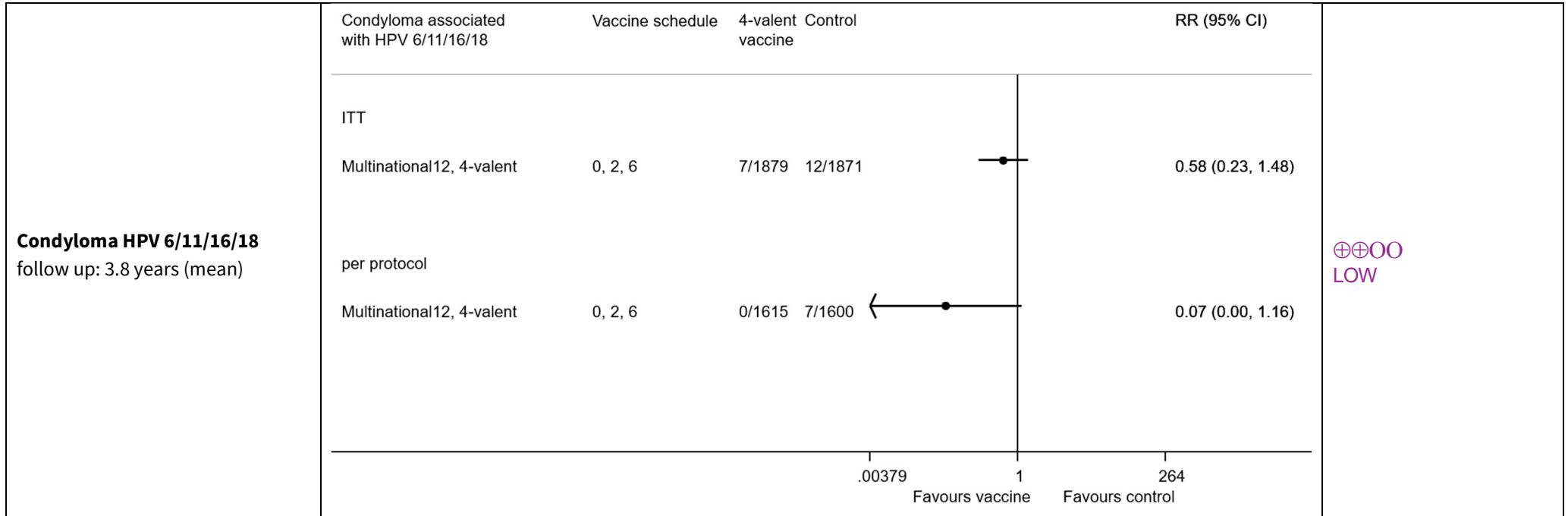












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CI= confidence interval; CIN2+= cervical intraepithelial neoplasia, grade 2 and above; HPV= human papilloma virus; RR= risk ratio

Summary of Findings: 2-valent HPV vaccine versus control vaccine in women over 25 years – immunogenicity outcomes

Participants: 26 to 45-year old females (HPV seronegative at baseline)

Setting: China

Comparison: 2-valent HPV vaccine (3-doses (Day 0, Month 1, Month 6)) versus control vaccine (Hepatitis B vaccine)

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) N° of participants & studies	Certainty of the evidence (GRADE)
		Control (Hep B) vaccine	2-valent HPV vaccine		
GMTs for HPV 16 follow up: 7 months	There is high-certainty evidence that 26-45-year old women receiving 2-valent HPV vaccine had higher GMTs for HPV 16 and HPV 18 than those receiving Hepatitis B control vaccine	Mean: 12.1 EU/mL	Mean: 6439.8 EU/mL	Ratio of GMTs 532.2 (473.1 to 598.7) 1197 participants in 1 RCT	⊕⊕⊕⊕ HIGH
GMTs for HPV 18 follow up: 7 months		Mean: 8.7 EU/mL	Mean: 3563.3 EU/mL	Ratio of GMTs 409.6 (365.7 to 458.7) 1197 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 16 follow up: 7 months	There is high-certainty evidence that 26-45-year old women receiving 2-valent HPV vaccine had a higher rate of seroconversion to HPV 16 and HPV 18 than those receiving Hepatitis B control vaccine	19% (67/344)	100% (345/345)	RR 5.10 (4.12 to 6.32) 689 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 18 follow up: 7 months		34% (135/401)	99% (363/365)	RR 2.95 (2.57 to 3.39) 766 participants in 1 RCT	⊕⊕⊕⊕ HIGH

CI= confidence interval; GMT= Geometric mean titre; HPV= human papilloma virus; EU= ELISA units; RCT= randomised controlled trial; RR= risk ratio

Forest plot: 2-valent HPV vaccine versus control vaccine in women over 25 years – immunogenicity outcomes

Participants: 26 to 45-year old females (HPV seronegative at baseline)

Setting: China

Comparison: 2-valent HPV vaccine (3-doses (Day 0, Month 1, Month 6)) versus control vaccine (Hepatitis B vaccine)

Outcome	Forest plot					Certainty of the evidence (GRADE)
GMTs for HPV 16 and 18 follow up: 7 months	HPV 16	2-valent, mean (95% CI)	Control (HepB), mean (95% CI)	Ratio of GMTs (95% CI)	Timepoint	⊕⊕⊕⊕ HIGH
	China3	6439.8 (6039.8, 6866.3)	12.1 (11, 13.4)	532.2 (473.1, 598.7)	Month 7	
	HPV 18	2-valent	Control (HepB)	Ratio of GMTs (95% CI)	Timepoint	
	China3	3563.3 (3310, 3836)	8.7 (8, 9.5)	409.6 (365.7, 458.7)	Month 7	
Seroconversion for HPV 16 and 18 follow up: 7 months	Serotype Study	Vaccine schedule	2-valent vaccine	Control (Hep B vaccine)	RR (95% CI)	⊕⊕⊕⊕ HIGH
	HPV 16					
	China3	0, 1, 6	345/345	67/344	5.10 (4.12, 6.32)	
	HPV 18					
China3	0, 1, 6	363/365	135/401	2.95 (2.57, 3.39)		
.5 1 10						
Favours vaccine Favours control						

CI= confidence interval; GMT= Geometric mean titre; HPV= human papilloma virus; RR= risk ratio

Summary of Findings: 2-valent HPV vaccine versus 4-valent HPV vaccine in women over 25 years – immunogenicity outcomes

Participants: 27 to 45-year old females (HPV sero-status mixed at baseline)

Setting: USA

Comparison: 2-valent HPV vaccine (3-doses (Day 0, Month 1, Month 6)) versus 4-valent HPV vaccine (3-doses (Day 0, Month 2, Month 6))

Outcome		Plain language summary	Absolute effect		Relative effect (95% CI) N° of participants & studies	Certainty of the evidence (GRADE)
			4-valent HPV vaccine	2-valent HPV vaccine		
GMTs for HPV 16 in 27-35-year olds	follow up: 7 months	There is low-certainty evidence that 27-35-year old women receiving 2-valent HPV vaccine had higher GMTs for HPV 16 than those receiving 4-valent vaccine at 7 months to 5 years follow-up*	Mean: 4958.4 EU/mL	Mean: 23907.9 EU/mL	Ratio of GMTs 4.82 (3.44 to 6.75) 175 participants in 1 RCT	⊕⊕⊕⊕ LOW ¹²
	follow up: 60 months		Mean: 346.4 EU/mL	Mean: 1925.3 EU/mL	Ratio of GMTs 5.56 (3.07 to 10.07) 72 participants in 1 RCT	
GMTs for HPV 16 in 36-45-year olds	follow up: 7 months	There is low-certainty evidence that 36-45-year old women receiving 2-valent HPV vaccine had higher GMTs for HPV 16 than those receiving 4-valent vaccine at 7 months to 5 years follow-up*	Mean: 7634.4 EU/mL	Mean: 17301.5 EU/mL	Ratio of GMTs 2.27 (1.60 to 3.22) 179 participants in 1 RCT	⊕⊕⊕⊕ LOW ¹²
	follow up: 60 months		Mean: 764.9 EU/mL	Mean: 1784.5 EU/mL	Ratio of GMTs 2.33 (1.28 to 4.24) 93 participants in 1 RCT	
GMTs for HPV 18 in 27-35-year olds	follow up: 7 months	There is low-certainty evidence that 27-35-year old women receiving 2-valent HPV vaccine had higher GMTs for HPV 18 than those receiving 4-valent vaccine at 7 months to 5 years follow-up*	Mean: 1043.0 EU/mL	Mean: 9501.6 EU/mL	Ratio of GMTs 9.11 (6.33 to 13.11) 212 participants in 1 RCT	⊕⊕⊕⊕ LOW ¹²
	follow up: 60 months		Mean: 74.4 EU/mL	Mean: 967.2 EU/mL	Ratio of GMTs 13.00 (7.53 to 22.46) 90 participants in 1 RCT	
GMTs for HPV 18 in 36-45-year olds	follow up: 7 months	There is low-certainty evidence that 36-45-year old women receiving 2-valent HPV vaccine had higher GMTs for HPV 18 than those receiving 4-valent vaccine at 7 months to 5 years follow-up*	Mean: 1438.8 EU/mL	Mean: 9845.5 EU/mL	Ratio of GMTs 6.84 (4.83 to 9.70) 201 participants in 1 RCT	⊕⊕⊕⊕ LOW ¹²
	follow up: 60 months		Mean: 105.3 EU/mL	Mean: 816.6 EU/mL	Ratio of GMTs 7.75 (4.56 to 13.19) 106 participants in 1 RCT	
Seropositivity for HPV 16 in 27-35-year olds	follow up: 7 months	There is low-certainty evidence that 27-35-year old females receiving 2-valent HPV vaccine had little to no difference in ratio of seropositivity for HPV 16 compared to those receiving 4-valent HPV vaccine at 7 months to 5 years follow-up*	100% (85/85)	100% (90/90)	RR 1.00 (not estimable) 175 participants in 1 RCT	⊕⊕⊕⊕ LOW ¹²
	follow up: 60 months		97% (28/29)	100% (43/43)	RR 1.04 (0.95 to 1.14) 72 participants in 1 RCT	
	follow up: 7 months	There is moderate-certainty evidence that 36-45-year old females receiving 2-valent HPV vaccine had little	100% (83/83)	100% (96/96)	RR 1.00 (not estimable) 179 participants in 1 RCT	

Seropositivity for HPV 16 in 36-45-year olds	follow up: 60 months	to no difference in ratio of seropositivity for HPV 16 compared to those receiving 4-valent HPV vaccine at 7 months to 5 years follow-up*	96% (45/47)	100% (46/46)	RR 1.04 (0.97 to 1.12) 93 participants in 1 RCT	⊕⊕○○ LOW ¹²
Seropositivity for HPV 18 in 27-35-year olds	follow up: 7 months	There is low-certainty evidence that 27-35-year old females receiving 2-valent HPV vaccine had little to no difference in ratio of seropositivity for HPV 18 compared to those receiving 4-valent HPV vaccine at 7 months, but a higher rate of seropositivity with 2-valent vaccine from 1 to 5 years follow-up*	98% (99/101)	100% (102/102)	RR 1.02 (0.99 to 1.05) 203 participants in 1 RCT	⊕⊕○○ LOW ¹²
	follow up: 60 months		61% (22/36)	98% (53/54)	RR 1.61 (1.23 to 2.09) 90 participants in 1 RCT	⊕⊕○○ LOW ¹²
Seropositivity for HPV 18 in 36-45-year olds	follow up: 7 months	There is low-certainty evidence that 36-45-year old females receiving 2-valent HPV vaccine had little to no difference in ratio of seropositivity for HPV 18 compared to those receiving 4-valent HPV vaccine at 7 to 12 months, but a higher rate of seropositivity with 2-valent vaccine from 1.5 to 5 years follow-up*	100% (91/91)	100% (110/110)	RR 1.00 (not estimable) 201 participants in 1 RCT	⊕⊕○○ LOW ¹²
	follow up: 60 months		75% (38/51)	100% (55/55)	RR 1.34 (1.14 to 1.58) 106 participants in 1 RCT	⊕⊕○○ LOW ¹²

CI= confidence interval; GMT= Geometric mean titre; HPV= human papilloma virus; EU= ELISA units; RCT= randomised controlled trial; RR= risk ratio

* See forest plot for all timepoints, including 7 months, 1 year, 1.5 years, 2 years, 3 years, 4 years, and 5 years

¹ Downgraded one level for risk of bias: randomization and allocation concealment methods were not clearly reported

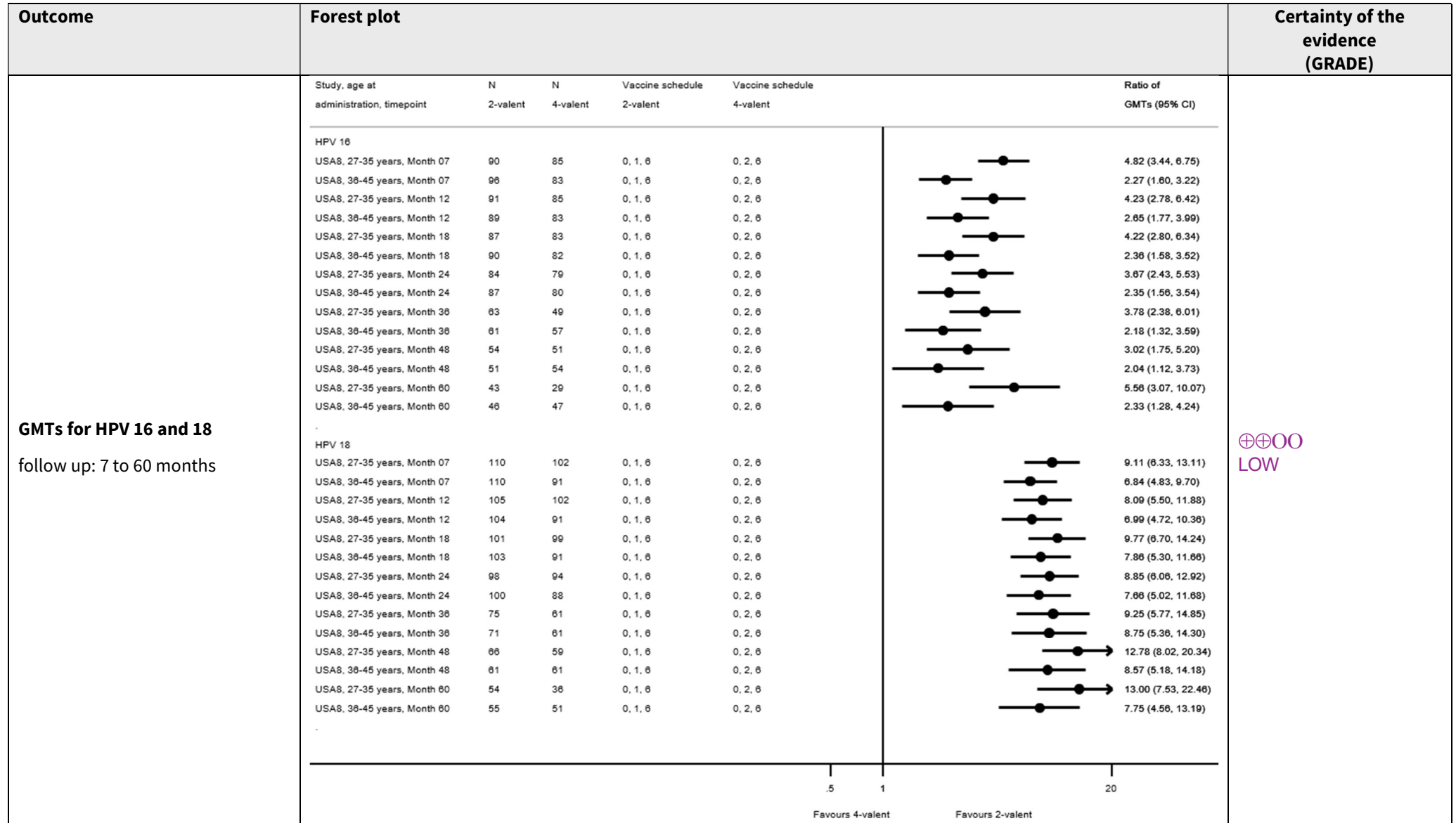
² Downgraded one level for imprecision: few participants

Forest plot: 2-valent HPV vaccine versus 4-valent HPV vaccine in women over 25 years – immunogenicity outcomes

Participants: 27 to 45-year old females (HPV serostatus mixed at baseline)

Setting: USA

Comparison: 2-valent HPV vaccine (3-doses (Day 0, Month 1, Month 6)) versus 4-valent HPV vaccine (3-doses (Day 0, Month 2, Month 6))



Seropositivity for HPV 16 and 18 follow up: 7 to 60 months	HPV 16	2-valent	4-valent	RR (95% CI)	Timepoint	⊕⊕⊕⊕ LOW
	USA8, 27-35 years	90/90	85/85	RR 1.00 (not estimable)	Month 7	
	USA8, 36-45 years	96/96	83/83	RR 1.00 (not estimable)	Month 7	
	USA8, 27-35 years	91/91	84/85	1.01 (0.98, 1.05)	Month 12	
	USA8, 36-45 years	89/89	83/83	RR 1.00 (not estimable)	Month 12	
	USA8, 27-35 years	87/87	82/83	1.01 (0.98, 1.05)	Month 18	
	USA8, 36-45 years	90/90	82/82	RR 1.00 (not estimable)	Month 18	
	USA8, 27-35 years	84/84	77/79	1.03 (0.98, 1.07)	Month 24	
	USA8, 36-45 years	87/87	80/80	RR 1.00 (not estimable)	Month 24	
	USA8, 27-35 years	63/63	49/49	RR 1.00 (not estimable)	Month 36	
	USA8, 36-45 years	61/61	57/57	RR 1.00 (not estimable)	Month 36	
	USA8, 27-35 years	54/54	49/51	1.04 (0.97, 1.11)	Month 48	
	USA8, 36-45 years	50/51	53/54	1.00 (0.95, 1.05)	Month 48	
	USA8, 27-35 years	43/43	28/29	1.04 (0.95, 1.14)	Month 60	
	USA8, 36-45 years	46/46	45/47	1.04 (0.97, 1.12)	Month 60	
	HPV 18	2-valent	4-valent	RR (95% CI)	Timepoint	
	USA8, 27-35 years	102/102	99/101	1.02 (0.99, 1.05)	Month 7	
	USA8, 36-45 years	110/110	91/91	RR 1.00 (not estimable)	Month 7	
	USA8, 27-35 years	104/105	92/102	1.20 (1.03, 1.17) *	Month 12	
	USA8, 36-45 years	104/104	90/91	1.01 (0.98, 1.04)	Month 12	
USA8, 27-35 years	101/101	74/99	1.34 (1.19, 1.50) *	Month 18		
USA8, 36-45 years	102/103	79/91	1.14 (1.05, 1.24) *	Month 18		
USA8, 27-35 years	98/98	68/94	1.38 (1.22, 1.56) *	Month 24		
USA8, 36-45 years	99/100	68/88	1.28 (1.14, 1.44) *	Month 24		
USA8, 27-35 years	75/75	43/61	1.42 (1.20, 1.67) *	Month 36		

	USA8, 36-45 years	69/71	45/61	1.32 (1.13, 1.54) *	Month 36	
	USA8, 27-35 years	66/66	34/59	1.73 (1.39, 2.15) *	Month 48	
	USA8, 36-45 years	59/61	44/61	1.34 (1.14, 1.58) *	Month 48	
	USA8, 27-35 years	53/54	22/36	1.61 (1.23, 2.09) *	Month 60	
	* Statistically significant difference between 2-valent and 4-valent HPV vaccine					

CI= confidence interval; GMT= Geometric mean titre; HPV= human papilloma virus; EU= ELISA units; RR= risk ratio

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GLOBAL MARKET STUDY

HPV

Key Takeaways

- Twelve years after the first HPV vaccine registration, less than half of WHO Member States have introduced HPV vaccine into the routine national immunization schedule. Introductions are lowest in Gavi 73 countries and non-Gavi, non-PAHO middle-income countries (MICs)
- Supply is currently insufficient to meet demand and some countries have or will have to postpone introductions
- WHO issued a call for action towards global cervical cancer elimination in May 2018 which, through national introductions in all countries and increased coverage, is estimated to increase total demand for HPV vaccines by at least 100M doses over the next 10 years
- To meet the expected increase in demand due to the cervical cancer elimination initiative, sizeable increases in supply will be required. Constraints are expected until at least 2024, assuming the base case supply scenario. This timing may change depending on selected vaccination strategies and investment decisions of current manufacturers, as well as on the timing of the three programs in advanced stage of clinical development
- Meeting the projected demand volumes required for multi-age cohort (MAC) introductions (9–14 years of age), as per WHO recommendation, will remain especially problematic in large countries, as well as meeting additional demand generated by implementing gender-neutral HPV vaccination
- Affordability of HPV vaccines in non-Gavi MICs is a barrier which needs to be addressed to encourage introduction

QUICK STATS

NUMBER OF VACCINE SUBTYPES¹

3

TOTAL NUMBER OF MANUFACTURERS²

2

2018 ESTIMATED GLOBAL SUPPLY

~30 million doses (maximum)

2018 ESTIMATED GLOBAL DEMAND

~30 million doses (supply constrained)

2017 REPORTED PRICE PER DOSE (RANGE)

US \$4.50–\$154.28

Purpose & Background

Several countries across regions and income groups have notified WHO of constraints to their access of HPV vaccines. The issue of affordability has also been raised, particularly by non-Gavi MICs. Following the announcement of a call for action towards global elimination of cervical cancer by the WHO Director General in May 2018, increasing introduction and coverage of HPV vaccine worldwide will be key. Working to understand current and future global trends and drivers of supply and demand, this study aims to address the current and expected constraints and to serve as an important resource for the development of the cervical cancer elimination strategy.

Market Highlights

As of May 2018, 81 countries (42% of UN Member States, corresponding to 25% of target population) had introduced HPV into the national routine immunization schedule.³ Despite carrying the greatest share of disease burden⁴, LICs and MICs are lagging in the introduction of HPV vaccine. To date, the majority of the countries have self-procured HPV vaccines (74% in 2017).

Currently, three HPV vaccine sub-types are available on the market: GSK's Cervarix (HPV2), using the proprietary AS04 adjuvant, and Merck's Gardasil (HPV4) and Gardasil 9 (HPV9), both using alum adjuvant. Merck's two products are also commercialized by two licensors (Instituto Butantan in Brazil and Sinergium Biotech in Argentina). Distribution agreements exist

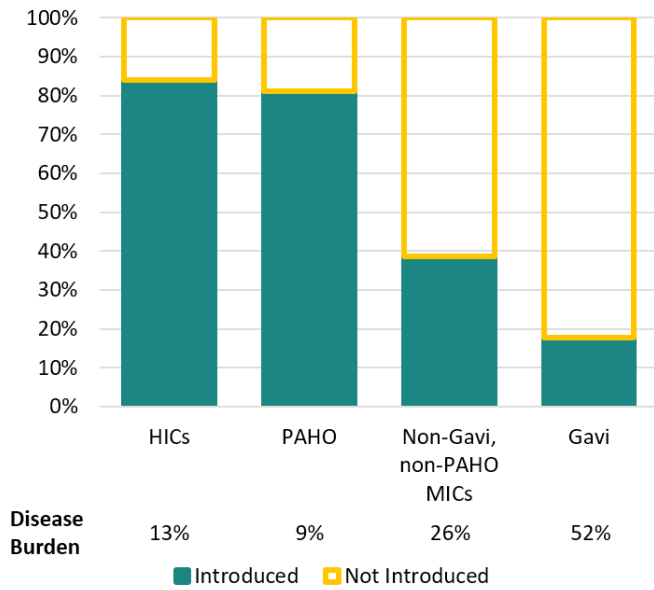
¹ Vaccine Subtypes differentiate by the antigen content of the various HPV vaccines, in this case there are three distinct vaccine sub-types available on the market: HPV2 (16,18), HPV4 (6,11,16,18) and HPV9 (6,11,16,18,31,33,45,52,58)

² This number indicates only the companies that have full manufacturing capacity, and does not include licensed companies providing a portion of the manufacturing process or distributors that simply commercialize the product in some locations

³ WHO/IVB Database, as of 15 May 2018

⁴ HPV cases (all cancers), women. Source: IARC, Globocan data, 2012

FIG. 1: HPV INTRODUCTION STATUS AND DISEASE BURDEN BY COUNTRY GROUP



in various countries. Current available evidence suggests that the three licensed HPV vaccines have relatively similar effectiveness in preventing cervical cancer.⁵

Estimated market share (volume) are as follows: HPV4: 52%, HPV9: 25% (increasing by 7% over 2016), HPV2: 21%.⁶ Though HPV vaccines make up only ~1% of the global vaccine market by volume, they account for ~15% of global market value (per 2017 MI4A estimates).

Global Demand

Based on the analysis of historical procurement data (2013–2017) and country introduction plans, as well as of key drivers of demand, a global demand forecast for HPV vaccine has been developed for the period 2018–2030. Base demand is estimated to be 55M doses in 2019, reaching ~100M doses in 2025 and stabilizing at ~110M annual doses from 2028 onward. Increased demand in 2019 and 2020 is driven largely by planned Gavi-supported MAC campaigns.⁷ Future projected introductions in China and India (estimated for 2021+) will drive the most significant increases in demand, representing ~1/3 of the market by 2030.

This report evaluated demand scenarios (see Figure 2) around the potential impact for 2019–2030 of a cervical cancer elimination strategy⁸ (additional ~100–250M doses depending on strategy⁹ chosen), a possible 1-dose schedule recommendation¹⁰ (a decrease of up to 250M doses), and potential for more countries to adopt a gender-neutral immunization policy (an additional 135M doses). Rapid implementation of MAC campaigns or increased country adoption of gender-neutral immunization policies will result in the

⁵ WHO HPV Position Paper, May 2017

⁶ 2% of the market share is unknown (due to lack of procurement data from a small number of countries) and is believed to be split between HPV2 and HPV4

⁷ 48 Gavi-supported countries are forecasted to conduct MACs in the next 10 years – only planned Gavi MACs are included in the base demand forecast

⁸ HPV vaccine introductions across the globe with all countries reaching at least 80% coverage by 2030

⁹ Two elimination strategies were modeled: 1. No additional MACs and 2. MACs for five age cohort in all new introduction countries (2018-2030)

¹⁰ Studies are ongoing to assess the level of protection provided by the administration of a single dose of the HPV vaccines. Preliminary results are expected by 2021/2022

greatest increase in future demand.

Global Supply

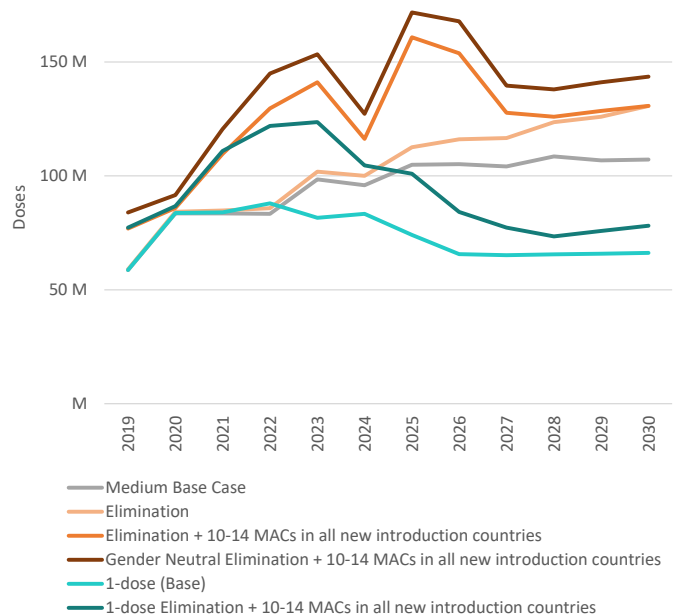
Consultations with manufacturers and experts, as well as a review of publicly available information on HPV vaccines, provides the basis for an assessment of the current and future global supply of HPV vaccine.

Increases in capacity are currently under consideration by the existing manufacturers; however, the required lead time will delay the availability of additional doses to the beginning of the next decade. At the same time, any increase in allocation of manufacturing capacity to HPV9 (versus HPV4) will result in decreases in total output, given the higher requirements to produce a nonavalent vaccine compared to a quadrivalent one.

Three products are currently in advanced clinical development: two HPV2 vaccines from Inovax and Shanghai Zerun Biotech, both in Phase III, and one HPV4 vaccine from Serum Institute of India currently entering Phase II. All use alum-based adjuvants. The success, timing and capacity of these pipeline vaccine efforts will have an important impact on the health of the HPV vaccine market.

The base projection foresees a threefold increase in available supply

FIG. 2: COMPARISON OF BASE CASE DEMAND AND SCENARIOS



over five years (range 2–6X) – from the approximately 30M doses available for 2018 – and a more than fivefold increase over 10 years.

Demand-Supply Balance

Currently, supply is insufficient to fully meet existing demand.¹¹ This imbalance is forecasted to grow and remain problematic for the short/mid-term due to an increased number of countries planning introductions, including MAC campaigns. Only from 2024 onward is supply expected to support demand (with tight management and careful planning) as per the base case demand and supply scenarios. However, routine demand alone, excluding all MAC campaigns, can be supported starting from 2020 with careful management of country introductions.

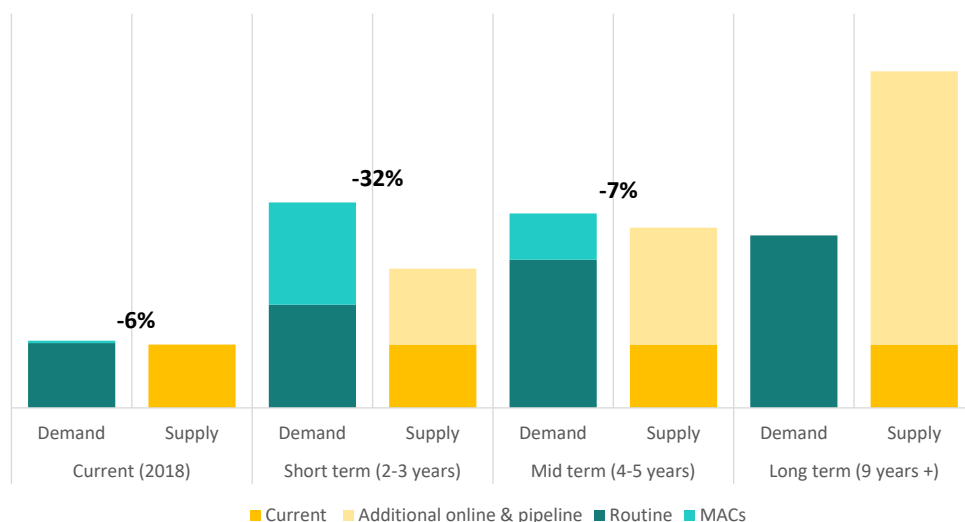
Aggressive capacity increases and faster product development in the context of the call for action to cervical cancer elimination could lead to a sufficient supply to support demand – inclusive of five age cohort

MAC campaigns from 2022. Immunization partners are in active discussions with manufacturers to expedite all activities that can improve the supply situation.

Several risk factors may alter the forecasted balance:

- Timely materialization and size of production capacity increases
- Time to market and size of available supply of pipeline products (domestic and global)¹²
- Use of HPV9 and impact on total supply availability
- Extension of immunization to boys
- Evidence on the level of protection from a single dose of HPV vaccine
- Implementation of MACs by countries and selected target age groups
- Timelines of country introductions and uptake speed

FIG. 3: DEMAND-SUPPLY BALANCE OVER TIME¹³



Price

Reported price per dose¹⁴ of HPV vaccines is tiered by procurement method and income group, with Gavi (UNICEF Supply Division [SD]) and PAHO Revolving Fund (RF) paying the lowest median prices, at \$4.55 and \$9.15, respectively. The non-Gavi MIC (UNICEF- and self-procuring) median prices for both HPV2 and HPV4 are ~3X the Gavi price while HICs pay ~7X the Gavi price. Between 2016 and 2017, the

price per dose of HPV vaccine products generally remained stable or decreased slightly.

Both Merck and GSK have made price commitments to countries transitioning out of Gavi support; nevertheless approximately five of these countries are no longer eligible for these commitments.¹⁵ Affordability remains a concern for non-Gavi MICs, some of which reported paying higher prices than HICs (see Figure 4).

¹¹ To account for stock dynamics in countries, this analysis considers supply as sufficient – even if still tight – when it exceeds demand by at least 10%

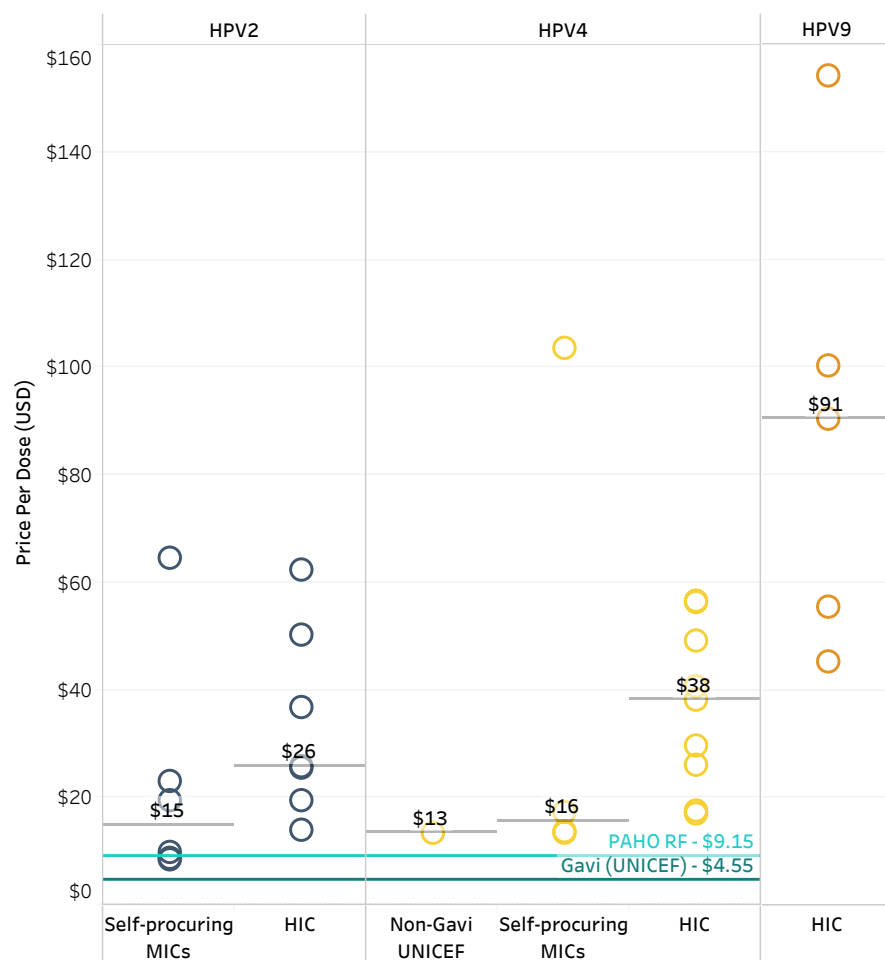
¹² Regulatory aspects should be taken into account

¹³ Base case – Brazil, Argentina, China, and India excluded

¹⁴ Source: WHO JRF 2018 data

¹⁵ For details of price commitments, see MI4A factsheet on vaccine pricing for Gavi-transitioning countries: http://www.who.int/immunization/programmes_systems/procurement/v3p/platform/module2/en/

FIG. 4: 2017 PRICE PER DOSE FOR HPV, BY PRODUCT



Methodology & Data Sources

MI4A Technical Advisory Group of Experts:

MI4A benefits from the expertise of a standing advisory group for input, review and validation of market analyses. The group includes members from regional Technical Advisory Groups on immunization, UNICEF SD, PAHO RF, Gavi, the Bill & Melinda Gates Foundation, JSI, and WHO SAGE, along with manufacturers (DCVMN and IFPMA) and independent experts.

Demand Resources:

Historical procurement: WHO MI4A V3P/JRF (2013–2017) and UNICEF SD (2014–2017). Planned/projected country introductions: WHO JRF, Gavi Operational Forecast, and Global Vaccine Market Model (GVMM) Demand Module. Regional historical coverage: Brotherton & Bloem, 2017 and Bruni, et al., 2016.

Supply Resources:

MI4A annual data collection from manufacturers, high-level validation of output of analysis with studies from Gavi, CHAI and BMGF, bilateral discussions with manufacturers on capacity drivers and pricing prospects, review of clinical trials information, review of Cost of Goods (COGs) available studies, review of manufacturing processes documentation (e.g. EMA), analysis of vaccine products registration.

Pricing: WHO MI4A V3P/JRF (2017 data)

Areas for Action

Careful coordination and investments are required to enhance supply availability towards global cervical cancer elimination goals:

1. WHO will continue to share its understanding of global supply and demand to inform immunization strategies and the design of the Cervical Cancer Elimination Strategy as well as enhance dialogue on global needs across HPV vaccine market segments to improve supply allocation
2. WHO will explore opportunities to increase supply flexibility through application of available scientific evidence
3. WHO will inform continued efforts to increase supply availability and synchronize regulatory efforts
4. In particular, WHO will enhance information sharing with countries to inform product choices with available scientific evidence and explore opportunities for clearer understanding of country product preferences
5. WHO aims to identify non-Gavi, non-PAHO MICs where affordability is the major barrier to introduction and explore opportunities for improvements

Other Useful Public Resources

This global study complements market analysis performed by UNICEF SD and Gavi for specific market segments:

- UNICEF SD HPV Supply and Demand Update (2018): https://www.unicef.org/supply/files/HPV_2_Status_Update.pdf
- Gavi HPV Roadmap Public Summary (2017): <https://www.gavi.org/about/market-shaping/supply-and-procurement-roadmaps/>

For more information, contact:
vaccinesupply@who.int

Part 3: Bibliography of Speakers

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