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Prevalence of Human papillomavirus among women following HPV vaccine introduction; a systematic review

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3. This dissertation is my own work.

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Acknowledgements

My sincere gratitude goes to my supervisors Leila Abdullahi and Associate Professor Mark Engel for their tenacity and guidance throughout the writing process. I would not have made it without them.

I dedicate this work to the short but full life of my daughter Caitlin Rebecca Kandi.

This work would not have been possible without the University of Cape Town school of Public health accepting me into their programme, I would like to take the opportunity to commend the value the institution keeps adding to the world.

Abstract

Part A of the thesis is a protocol. The protocol outlines the background and the process of the research. The aim was to explore Human papillomavirus (HPV) prevalence among women following HPV vaccine introduction; the side effects and vaccination coverage. The vaccination coverage was measured as proportion of females who have received the recommended dose of the vaccine in a study. The protocol follows the PRISMA guidelines.

Part B is the thesis is an extensive literature review that explains the background, HPV vaccines currently available, HPV prevalence in the world, HPV vaccine implementing countries and considers the gaps in HPV vaccines literature.

Part C of the thesis is a manuscript presented in the format suitable for Plos One journal submission. The background of the research is summarised and the methods and results are presented and discussed.

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List of abbreviations

CBA:	Control Before and After
CDC:	Centres for Disease Control and Prevention
CI:	Confidence Interval
CINAHL:	Cumulative Index of Nursing and Allied Health Literature
DNA:	Deoxyribonucleic acid
EPI:	Expanded Programme on Immunisation
GAVI:	Global Alliance for Vaccines and immunization
GRADE:	Grading of Recommendations, Assessment, Development and Evaluation
HPV:	Human papillomavirus
ITS:	Interrupted Time Series
L1:	Major capsid protein
L2:	Minor capsid protein
LMIC:	Low and middle-income countries
MeSH:	Medical Sub Headings
PATH:	Vaccine Resources Library (http://www.path.org/),
RCTs:	Randomised Controlled Trials
UNICEF:	United Nations Children's Funds
WHO:	World Health Organisation

PART A: Protocol

1. Background

HPV is the most common, viral infection of the reproductive tract world-wide (1).The most common HPV types globally are HPV 16 and 18 which are strongly associated with the development of cervical cancer in women. In both men and women HPV types 6 and 11 are also common and strongly associated with genital warts (2). Although a majority of the HPV infections resolve on their own, constant infection may result in developing a disease (2). HPV has to be present in a cervical cancer diagnosis, HPV infections are therefore necessary for the development of cervical pre-cancer and cancer (3). Cervical cancer is also the second most frequently diagnosed cancer in women globally and more so in developing countries (3).

Currently there are three vaccines recommended to prevent HPV related diseases, all three vaccines can be used in women but two are recommended for men (2), (4). All three licensed vaccines namely Gardasil, a quadrivalent vaccine; Cervarix, a bivalent vaccine and Gardasil, a 9 valent vaccine, cover at least two of the high risk HPV types 16 and 18. By 2014, 58 countries had introduced HPV vaccine in their national immunisation programme for girls (2). The World Health Organisation (WHO) recommends HPV vaccines be part of routine vaccinations for girls from the age of nine to thirteen years (2). Routine HPV vaccination covering more high risk types is said to be more effective in preventing cancer and less subject to variations in different regions (5).

The introduction of a vaccine against human papillomavirus (HPV) has therefore been widely acknowledged as one of the greatest health care developments for women in recent years (6). Incidences of HPV related diseases caused by vaccine HPV types are projected to decrease in populations that have received the vaccine,

the biggest beneficiary being women, who have borne the brunt of HPV diseases over the years. As it stands, population studies are showing a decrease in vaccine type HPV prevalence among young girls since the vaccine was introduced (5). Many deaths will therefore be averted as a result of the vaccine as globally cervical cancer is estimated to cause 7.5% of all female cancer deaths, in 2012 alone an estimated 266 000 globally deaths were from cervical cancer (2). The adjusted HPV prevalence globally among women with normal cytological findings was estimated to be 11.7%, according to a 5 continent meta-analysis (6).

Female adolescents are the recommended target population for the vaccine (1). Particularly in young women, it has been found that the risk for HPV infection is mainly heightened soon after sexual debut; the peak prevalence of 24% has been observed in young women younger than 25 years (2). Extensive uptake of current HPV vaccines by young women could therefore reduce cervical cancer and mortality by roughly two-thirds (5).

Evaluation of vaccine coverage has shown a big gap between developed and developing countries (6). A pooled analysis estimated from 2006 until 2014 has reported that 118 million women have been reached by vaccine programmes globally; however only 1% were from low-income or lower-middle-income countries (6). It is not surprising therefore that only a few developing countries to date are said to have undertaken national vaccination programmes (5). The highest HPV vaccination coverage in young women by 2014 was in developed countries where 32.9% had been vaccinated, on the contrary developing countries had a coverage of 2.7% (7). Vaccination coverage of at least 50% is estimated to reduce prevalence of HPV 16 and 18 by 68%, and reduction in anogenital warts by 61%. In low medium income countries, the introduction of vaccination on a large scale has so far been

limited or non-existent because vaccines were deemed too expensive (7). In Africa, where vaccination programmes are scant, the Global Alliance for Vaccines and immunisation (GAVI) has supported HPV vaccine rollout in support of HPV vaccination strategies in Africa (4).

The review will be of potential interest in several areas globally. The review data will be used to help to inform the importance of HPV vaccination among the recommended age in a future national vaccination programme. On the other hand, in developed countries where the vaccine coverage remains high, this study will shed light on remaining questions about the indirect impacts of current and future HPV vaccines. The population effectiveness of HPV vaccines is currently an active area of research; therefore, we plan to review the currently available evidence on the effect of HPV vaccine uptake among female adolescents to prevent HPV infection.

2. Objectives

To evaluate the effect of HPV vaccine uptake among female adolescents to prevent HPV infection

3. Methods

3.1 Criteria for considering studies for this review

3.1.1 Types of studies

Randomised controlled trials (RCTs), cohort studies, control before and after (CBA), interrupted time series (ITS) and cross-sectional studies.

3.1.2 Types of participants

Females older than 9 years who received HPV vaccine.

- ➢ 9 years of age is selected since it's the recommended start age to receive vaccine at the adolescent phase. There is no maximum age limit.
- ➢ Adolescents are defined as individuals aged 9 to 13 years; eligible for WHO-recommended vaccines (2).

3.1.3 Types of interventions

Recommended HPV vaccines; quadrivalent vaccine, bivalent vaccine and 9valent vaccine.

3.1.4 Types of outcome measures

Primary outcomes

Incidence or prevalence of HPV infection (proportion of females who developed HPV infection following vaccination).

Secondary outcomes

1. Vaccination coverage (the proportion of females who have received the recommended dose of the vaccine in a study)
2. Cross protection Cost of the intervention.
3. Adverse events following immunisation.
4. Adverse effects of the intervention.

3.2 Search methods for identification of studies

3.2.1 Search strategy

We will develop a comprehensive search strategy to search both published and unpublished articles, with no restrictions on language or publication date. The strategy will include Medical Sub Headings (MeSH) and free-text terms relating to HPV vaccination uptake literature globally and will be adapted to suit each individual database using applicable controlled vocabulary.

3.2.2 Electronic searches

The peer reviewed articles in the following electronic databases will be screened: PubMed, Cochrane Central Register of Controlled Trials, Scopus, Web of Science, World Health Organisation Library Information System (WHOLIS), Africa Wide and Cumulative Index of Nursing and Allied Health Literature (CINAHL). We will search websites and databases for grey materials like WHO (http://www.who.int/), Global Alliance for Vaccine and Immunisation (GAVI) (http://www.gavialliance.org/), United Nations Children's Funds (UNICEF) (http://www.unicef.org/), Program for Appropriate Technology in Health (PATH) Vaccine Resources Library (http://www.path.org/), US Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/), The communication initiative network (http://www.comminit.com/), http://www.nyam.org/library, http://www.opengrey.eu/, http://www.eldis.org/, Immunisation basics (http://www.immunizationbasics.jsi.com/Index.html). Reference lists of relevant reviews and all eligible papers will also be searched for relevant studies.

4. Data collection and analysis

4.1 Selection of studies

Two authors will independently screen abstracts and titles identified in the search results for eligible studies. The full text of studies that are eligible will be retrieved for assessment. Two of the authors reviewing the study will each independently apply inclusion criteria to the retrieved studies. Differences will be resolved through consensus between the two review authors. A third author's opinion will be sought if consensus is not reached.

4.2 Data extraction and management

Two review authors will independently carry out data extraction using a standardized data extraction form. Disagreements will be resolved by consensus and the third author will be required if necessary to help resolve the issues. Prior to use, the extraction form will be piloted on at least four studies identified randomly from the list of included studies. The data extraction will include the following eligibility criteria:

1. Study setting
2. Study design
3. Type of participants
4. Vaccine type
5. Details of outcome

4.3 Assessment of risk of bias in included studies

We will employ the quality assessment tool for evaluating prevalence studies as suggested by Hoy and colleagues and adapted by Werfalli and colleagues (8),(9).

The quantitative scoring system to the Risk of Bias criteria allocates four points for external validly and six points for internal validity. The scoring system tool categorises high risk studies as those with an overall score of 0-5 points, moderate risk as 6-8 and low risk > 8 points. Two review authors will apply the risk of bias criteria and we will discuss any disagreements through discussion and consensus, with the mediation of a third review author if required.

4.4 Dealing with missing data

Where necessary, the authors of the studies will be contacted for missing data. If the authors are not able to respond, the available data will be used and it will be stated that there are studies with missing data in the review.

4.5 Assessment of heterogeneity

If any variation in study results is experienced due to differences in the type of intervention, the type of setting, study design and risk of bias, we will describe in detail the variation. The result will not be pooled in case of substantial variation rather we will summarise in a narrative format (9). Statistical heterogeneity between study results will be assessed using the chi-squared test of homogeneity using a 10% level of significance cut off. The I^2 statistic will be used where values of 25% reflect low heterogeneity, 50% medium heterogeneity and 75% reflect high heterogeneity.

4.6 Assessment of reporting biases

In order to assess risk of publication bias, we will use funnel plot to examine asymmetry provided there are 10 or more studies included. When we find evidence of small study effects we will consider publication bias as a possible explanation. A

sensitivity analysis will be undertaken if plots suggest treatment effects may not be from a symmetric distribution.

5. Data synthesis

Data synthesis will comprise of two steps. The first step will be about identifying data sources, documenting the numerators and denominators that will be used for calculating prevalence. The second step is the use of the Freeman-Tukey double arcsine transformation to stabilise the variance of study prevalence using Stata® (version 13.1). The stabilisation of variance will help minimise influence from studies with outliers before the data is pooled together. Stratification of the data will be done by study design and samples sizes.

5.1 Subgroup analysis and investigation of heterogeneity

Subgroup analyses may be conducted if possible, taking into account but not limited to age of target population, vaccine given, setting of the studies and country income status.

5.2 Subgroup analysis

Where sufficient data are available, we will conduct subgroup analyses, which will explore the effects of vaccine given, setting of the studies and country income status. We will use the subgroup differences to test for subgroup interactions. Sensitivity analysis will be carried out to determine if the study designs, study period or publication type have an impact on the results of the meta-analysis.

6. Assessing the of quality of evidence

The basic principles of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach will be used to assess the

certainty of evidence of the included studies (10) We will set out the main findings of the assessment across studies in 'Summary of findings' tables prepared using GRADE profiler software (11). We will GRADE the evidence as high, moderate, low or very low (10). High certainty evidence implies that "further research is very unlikely to change our confidence in the estimate of effect". Moderate certainty evidence means that "further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate". Evidence is considered of low certainty if "further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate", and very low certainty if "we have very little confidence in the effect estimate" (12).

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8. Appendices

8.1 Appendix 1: Search strategy

PubMed search		
Subject	**Search term**	**Items found**
HPV prevalence following HPV vaccination in women	Search ((((((Human papillomavirus) AND Human papillomavirus[MeSH Terms)))) AND Human papillomavirus vacci*) AND ((Following OR after OR result OR impact))) AND ((Girls OR adolescent girls OR young women OR women))) AND ((Prevalence OR Incidence OR frequency OR distribution))	86
Prevalence	Search (Prevalence OR Incidence OR frequency OR distribution)	3894961
Women	Search (Girls OR adolescent girls OR young women OR women)	2527388
Following	Search (Following OR after OR result OR impact)	6004645
HPV Vaccine	Search Human papillomavirus vacci*	1949
HPV	Search (Human papillomavirus) AND Human papillomavirus[MeSH Terms))	27705

8.2 Appendix2: Data extraction form

Review title	
Study ID (e.g. Muusha 2016)	

A. General Information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Reference citation	
Study author contact details	
Publication type *(e.g. full report, abstract, letter)*	
References of potentially eligible studies from the reference list	
Notes:	

B. Study characteristics

Study Characteristics	Eligibility criteria	Location in text
Vaccine and disease targeted	Cervarix-bivalent vaccine, Gardasil- quadrivalent vaccine, Gardasil - 9valent vaccine, for HPV vaccination	
Setting	Studies in any country	
Study design	Randomised controlled trials (RCTs), cohort studies, control before and after (CBA), interrupted time series (ITS) and cross-sectional studies	
Participants	Women from the age of 9 years and above	
Types of outcome measures	<u>Primary outcome:</u> Incidence or prevalence of HPV infection (proportion of females who received the recommended dose of the vaccine in a study).	
	<u>Secondary outcomes:</u> 1. Vaccination coverage (the proportion of females who have received the recommended dose of the vaccine in a study)	

	2. Cost of the intervention	
	3. Adverse events following immunisation.	
	4. Adverse effects of the intervention.	
Results	Prevalence/incidence	
INCLUDE EXCLUDE		
Reason for exclusion		
Notes:		

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

C. Characteristics of study included

Methods

	Descriptions as stated in report	Location in text
Aim of study		
Study design		
Start date		
End date		
Length of participation		
Informed consent obtained	Yes No Unclear	
Ethical approval obtained for study	Yes No Unclear	
Notes:		

Participants

	Description as stated in paper	**Location in text**
Setting		
Sample size		

Inclusion criteria		
Exclusion criteria		
Method/s of recruitment of participants		
Selection method (e.g. convenience sampling)		
Age		
Notes		

Outcome measures

Primary outcome: Prevalence of HPV infection following vaccination

Sample Size	Withdrawals and exclusions	Sample size analysed	Number of HPV types analysed	Numerator Denominator	**Prevalence**
Note:					

Secondary outcomes

	Description as stated in report	Location in text or source
Vaccine type		
HPV types covered		
Country		
Vaccination coverage		
Adverse effects of the intervention		
Adverse events following vaccination		

Cost of the intervention		
Notes:		

Discussion

	Descriptions as stated in report/paper
Key conclusions of study authors	
Study limits as reported by authors	
Notes	

Appendix 3: Risk of Bias for Prevalence Studies

External validity	**(1 = agree; 0= disagree)**
1. Was the study's target population a close representation of the national population in relation to relevant variables?	1 0
Support for judgment:	
2. Was the sampling frame a true or close representation of the target population? Yes No Unclear	1 0
Support for judgment:	
3. Was some form of random selection used to select the sample, or was a census undertaken?	1 0
Support for judgment:	
4. Was the likelihood of nonresponse bias minimal?	
Internal validity	**(1 = agree; 0= disagree)**
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	1 0
Support for judgment:	
5. Were data collected directly from the subjects (as opposed to a proxy)?	1 0
Support for judgment:	
6. Was an acceptable case definition used in the study?	1 0
Support for judgment:	
7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	1 0

Support for judgment:	
8. Was the same mode of data collection used for all subjects?	1 0
Support for judgment:	
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	1 0
Support for judgement	
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	1 0
Support for judgement	
Notes	

PART B: Literature Review

1. Origins of HPV

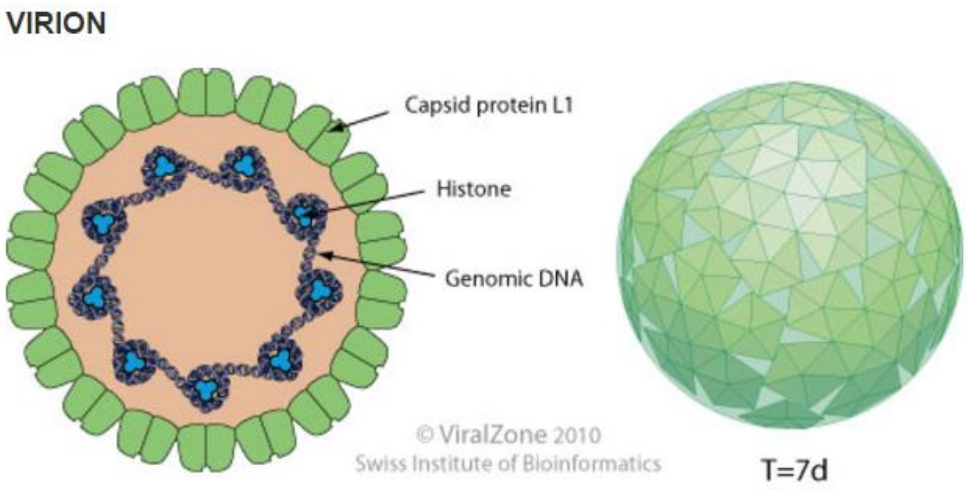
HPVs have evolved over millions of years to promulgate in a variety of animal species which include humans, the viruses are thought to have been linked to changes in the epithelium of their host in the first reptiles approximately 350 million years ago (1,2) . Viruses that evolve gradually with their hosts are known to be harmless and as such most HPV infection in humans resolve on their own, many HPVs therefore exist commensally within the human body and are not associated with disease(1,3,4).

2. Biology of HPV and types

HPVs are generally small of diameter 50-60nm, they are non-enveloped containing doubled strand closed circles of Deoxyribonucleic Acid (DNA) genome with approximately 8000 base pairs(1,4). Once infection is in the host cell nucleus, the virus survives as an independent episome; the life cycle of the virus however is facilitated by a chain of viral and host interactions which directs virion production, viral transcription and clearance of the majority of infections (5). The virus is protected by a capsid formed by two late proteins, Major Capsid Protein (L1) and Minor Capsid Protein (L2) structural proteins (1,6).

The HPV genome is divided into three regions; the first is a noncoding upstream regulatory region which regulates the transcription of certain viral genes known as E6 and E7; the second region consists of six open reading frames which encodes structural proteins involved in viral replication and oncogenesis; the third region is responsible for encoding L1 and L2 structural proteins.

Figure 1: The structure of HPV.



(Adapted from Swiss Institute of Bioinformatics, Viral Zone. - Available http://viralzone.expasy.org/5?outline=all_by_species

As such, there are over 200 types papillomaviruses which have been identified and sequenced of which more than 150 are HPVs and over 100 are involved in human disease (1,2,7,8). The HPV types that cause disease are cutaneotropic, affecting the outer bodily skin, whereas other types are mucosotropic , affecting the skin the covers the internal organs such as cervix or mouth; there are however HPV types that can be found both in the cutaneous and mucosotropic layer (2). The various groups HPV types are found are tabled below;

Table 1: HPV group and type

HPV group	HPV type
Cutaneotropic	1, 4, 5, 8, 41, 48, 60, 63 and 65
Mucosotropic	6, 11, 13, 44, 55, 16, 31, 33, 35, 52, 58, 67, 18, 39, 45, 59, 68, 70, 26, 51, 69, 30, 53, 56, 66, 32, 42, 34, 64, 73, 54
Cutaneotropic & mucosotropic	2, 3, 7, 10, 27, 28, 29, 40, 43, 57, 61, 62 and 72

Cutaneous infections in humans are known to cause warts, cysts and skin cancer while mucosotropic HPV types are known to cause condyloma acuminatum, focal epithelial hyperplasia, cervical neoplasia and cervical cancer, anogenital cancers including and head and neck cancer.

3. Epidemiology aspects of HPV infection

Although many HPV types resolve on their own and are harmless, those that cause diseases have warranted the extensive study of HPV over the years. Of the over 100 HPV types that are known to cause human disease, over 40 are thought to infect the genital tract (4,8). Specifically in women, HPV types that infect the female genital tract are known to cause precancerous and cancerous lesions of the cervix, condyloma acuminate and cancers of the lower genital tract (8). The most significant disease caused by HPV, cervical cancer, was first hypothesised by Italian physician to cause cancer linked with sexual behaviour (5). Infection by HPV is therefore basically a sexually transmitted disease, this has already been established. Risks of HPV infection are, early sexual debut, high number of sexual partners, sexual contacts with high risk individuals. In cervical cancer, factors such as genetic

predisposition, frequency of reinfection, coinfection with more than one HPV type, hormone levels and intertypic genetic variation with the HPV type itself have influence of the ability to clear an HPV infection (2) In light of HPV and women, it is therefore important to dwell more on HPV and cervical cancer which is the fourth most common cancer in women worldwide and the leading cause of cancer deaths among women in developing countries (3,9)

4. HPV and cervical cancer

In the development of cervical cancer, HPV DNA is required for the development of cervical cancer; over 90-100% of cervical cancer specimens have HPV (2,10) . This causal relationship was established in the 1990s, where molecular technology was able for the first time to provide evidence on the causal role of some HPV types in the development of cervical cancer (10). Of the HPV types that have been linked to cervical cancer, HPV 16,18,45 and 31 would explain approximately 80% of the cases, this information has been instrumental in the development of vaccines to prevent cervical cancer (2). HPV 16, 18, 45 and 31 as cancer causing agents will be beneficial in this systematic review, in the analysis of vaccine type prevalence as well as cross protective types. In fact, the associations between HPV and cervical cancer are noted as the highest ever in cancerology (2). Cervical cancer is initiated when HPV infects the cervical epithelium during mainly sexual intercourse, and despite many young people getting infected at sexual debut, it has been established that many of these infections do not develop into cervical cancer. Following the infection of the cervix, if there is persistent infection, cellular dysregulation will occur resulting in the formation of high grade cervical intraepithelial neoplasia; following this process would be the development of invasive cervical cancer. Throughout this process, the host immune system plays an vital role in the clearance or persistence

of infection as well as host genetic factors, cellular genetic changes and co-carcinogens (7).

That said, it is important to highlight that HPV infection is a necessary but not sufficient cause for infection. Acting in concert with high risk HPV types are additional factors such as sexual activity; the fact that a woman has a greater risk of getting infected if she has multiple sexual partners, or a partner of someone with many sexual partners; early sexual debut as well as previous infection with other sexually transmitted infections plays a role (7).

Cervical cancer can thus be termed as a rare disease of a common infection because the development of cervical cancer itself takes a long time, usually decades (10-20 years), this presents a unique opportunity to intervene (6,7). The development of cervical cancer is ultimately dependent of the vivacity of the host immune system, women with a good immune system are able to clear HPV infection as 90% of the lesions regress naturally within 12 to 36 months (2). The importance of a strong immune system in the clearance of HPV has been shown in some studies looking at women living with HIV/AIDS, in immune compromised individuals, infection with high risk HPV types and their persistence is much more common than in immune competent individuals (3,7). This development is of particular importance for developing countries where HIV prevalence and incidence is high, hence the risk of women in these regions to develop cervical cancer is indeed high. The greatest risk of HPV infection is said to occur during metaplastic activity, which is, during puberty, at first pregnancy; however, despite the risk and infections occurring more frequently in younger ages, cervical cancer is common in older women as it has been proven to take years to develop. In light of this information, treatment and vaccination efforts can be age specific.

One of the important risk factors in cervical cancer development is persistent infection, especially when an infection is detected more than once every six months. The risk of developing cervical cancer with HPV 16 and 18 respectively is higher than other HPV types. HPV 16 in particular has been shown to reach higher viral loads compared to other HPV types and correlate with increased severity of cervical cancer, many studies have shown worldwide that HPV 16 and 18 are most prevalent (7,11,12). A significant factor that has been noted in HPV variants is how they vary geographically, for instance, five HPV 16 variants have been defined for Europe, Asia, Asian-American and African; as such Asian American variants are thought to have increased oncogenic virility compared to European as a result of increased transcriptional activity (11,13). In light of this evidence, HPV vaccinations currently available will be instrumental in ensuring countries are able to prioritise most fitting vaccine types for their country considering the most prevalent HPV types.

Other cervical cancer risk factors are non-viral factors such as already postulated weak immune system due to not only HIV AIDS but conditions such as renal transplantation, increase risk of acquisition and progression of cervical cancer. The use of contraceptives, especially on a long-term basis; smoking, number of births a woman has had and genetic inheritance are also key factors in the development of cervical cancer.

5. HPV and other diseases

Aside from cervical cancer, HPV is implicated to cause 20-90% of squamous carcinomas of the anus, oropharynx, vulva and vagina; in anal cancers, HPV type 16 and 18 are responsible for an estimated 90% of the cancers and 40% of vulva cancers (3). The median infection time necessary for anogenital warts to develop in women is 5-6 months; anogenital warts are however not easy to treat and in some rare instances become malignant (14,15). HPV 6 and 11 are known to cause a rare condition called recurrent respiratory papillomatosis where warts develop on the larynx or any other part of the respiratory tract; this condition usually affects children, in rare instances this disease may be passed on to babies during childbirth.

Numerous other diseases are caused by HPV, some of the prominent diseases affecting women will be mentioned in this section. Approximately 90% of anogenital warts are caused by HPV types 6 and 11 and in a systematic review the worldwide prevalence of anogenital warts was said to be between 0,13% to 0,20% (14). Worldwide the incidence of warts ranges from 160 to 280 per 100 000; in women to be precise, the incidence of warts is higher than in men, with a median age of 120,5 per 100 000 (14). By region new anogenital warts incidence for North America ranged from 101 to 205 per 100 000 population, Europe ranged from 118 to 170 per 100 000 population and in Asia 204 per 100 000 population (25–27). Anogenital warts are said to be extremely infectious, as 65% of people with an infected companion develop anogenital warts within 3 weeks and 8 months (28)

Options to treat anogenital warts are available but are known to have high recurrent rates after treatment (29–31). The available options for treatment include home

based (podofilox and imiquimod) as well as physician based chemical treatments (podophyllin, trichloracetic acid, interferon, green tea extract) there are also ablative treatments (cryotherapy, surgical removal, laser treatment) (14,32). In addition to the available options, there are preventative options in the form of the quadrivalent vaccine which has demonstrated efficacy in preventing the HPV types 6 and 11 related anogenital warts (33).

6. Diagnosis and treatment options for HPV and cervical cancer

Screening and treatment for preinvasive cancer of the cervix is very effective in averting advancement to cervical cancer(16). Cytology and visual inspection with acetic acid are the main methods of cervical cancer screening; visual inspection is a popular method used in low resource countries. Early detection of precancerous changes is detected through screening at peak ages of cervical cancer incidence; the screenings allow for the detection of any changes which may lead to the disease (6). Tests that are based on HPV DNA are used and performed on cervical or vaginal swabs; a microscopic examination of the exfoliated cells detects changes in the cervical epithelium.

HPV infections can be treated by tissue destructive methods as there is no virus specific treatment. Cryotherapy, surgical excision of the affected tissue, excision by cone biopsy are some of the methods used to treat precancerous lesions. In addition, radiotherapy, brachytherapy, radical surgery and chemotherapy can be effectively used to treat cancer, especially when disease is still localised (6). Even though these options are effective, developing countries have been unable to consistently apply then so as to reap the benefits, the cost of some of the options have been too high for some developing countries with competing health

interests(6,12); vaccination is another option that has be added to the cocktail of current interventions whose promise we hope to further illuminate in this study

7. HPV Vaccines

There are currently 3 vaccines licenced for distribution worldwide; that is, a quadrivalent vaccine, bivalent vaccine and nonavalent vaccine, all the vaccines focus on the oncogenic HPV genotypes. First to be licenced was the quadrivalent vaccine in 2006, the vaccine aims to protect against HPV 6, 11, 16 and 18; in 2007 the bivalent vaccine was introduced, protecting against HPV types 16 and 18 and most recently in 2014 the nonavalent vaccine was approved by the FDA which focuses of protecting against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. All the vaccines are recommended to be administered before sexual debut as this maximises vaccine effectiveness (3,17). HPV vaccines have been found to be most effective in people who have not been previously exposed to the HPV virus. Targeting older populations poses a risk of wasting resources as this population has most likely been exposed to the HPV virus which reduces the HPV vaccine's effectiveness(3). The reason why HPV vaccination is more effective in uninfected individuals than those infected, is still the subject of debate, Schiller theorises that the HPV vaccine works in uninfected individuals because of the high antigen dosage and method of administration which target the blood stream (18). When compared with the HPV vaccine, an individual's immune system's response to HPV infection is considered to be weak. It is argued that the HPV natural immune system is not bolstered by high virus dosage so as to activate strong immunity, the natural HPV exposure to the immune system is usually of low dose and also because HPV infections are limited to epithelial surfaces (18).

The quadrivalent vaccine is injected intramuscularly and contains purified viral proteins meaning that they do not have live biological products or viral DNA. The vaccine is created using yeast substrate and includes amorphous aluminium hydroxyphosphate sulphate, each the vaccine contains HPV-6 L1 protein, HPV-11 L1 protein, HPV-16 L1 protein and HPV-18 L1 protein which gets absorbed onto the adjuvant (3,19). The second dosage of the vaccine follows the first in the second month and the last vaccine at six months. The vaccine is indicated for use in females and males from the age of 9 years to prevent premalignant genital and anal lesions, cervical and anal cancers and anogenital warts (3). The bivalent vaccine is injected intramuscularly, also contains purified viral proteins for the two HPV types. Prefilled syringes or vials are used as a single or two dose with the second dose given after one month of the first and third at six months (6). The vaccine dose of 0.5 ml contains HPV-16 protein, HPV 18 LI protein absorbed into and adjuvant system containing aluminium hydroxide and monophosphotyl lipid (6). The vaccine is indicated for use in girls of the ages 9 years to prevent genital lesions cervical cancer related to HPVs 16 and 18. In resource constrained settings however, the recommendation is that girls under the age of 15 receive the 2-dose schedule with a 6-month interval between first dose, if the interval between first dose is less than 5 months, a third dose is recommended but only in immunocompromised (16). This recommendation is based on studies that have shown little difference between immune response in those who received 2 or 3 dose schedules, in countries with limited resources, opting for the two-dose schedule would therefore be cost effective (20,21).

The nonavalent vaccine is also a non-infectious, virus-like particle which can be injected intramuscularly the vaccination is recommended be initiated from age 9 to 26 years, it is recommended to be administered in a 3-dose schedule with the second dose following the first at two months and the third dose at six months (3).

Currently the bivalent and quadrivalent vaccine have been used in many settings, in the studies analysed, there was no study reporting nonavalent use. Since the nonavalent vaccine was approved in 2014, it makes sense that it will take a while until any HPV prevalence studies associated with national rollout will come after a few years.

8. Impact and cost effectiveness of the vaccines

All vaccines are expected to reduce incidence of HPV16 and 18 thereby preventing cervical cancer and cervical adenocarcinoma related to HPV 16 and 18 as well as other cancers related to the HPV types such as head and neck cancer or anal cancer (6). Mortality reductions are expected to benefit low and middle-income countries (LMICs) as they have limited screening, hence vaccine coverage and duration will be critical in determining vaccine impact assuming that efficacy is high. Vaccination is expected to reduce lifetime risk of cervical cancer by 35 to 80%; in the Global alliance for vaccines and immunisation eligible countries with coverage of 70%, over a million women's lives are expected to be saved (6). In a systematic review considering global cost effectiveness of the HPV vaccine, 25 of 26 studies concluded that vaccinating young girls is likely to be most cost effective, especially when done in resource constrained settings where there is limited coverage of cervical cancer prevention and control measures (22)

9. HPV in the world and its overall prevalence, mortality and morbidity

80% of women in the world will at some point in their life get an HPV infection, of the women who will get infected, 10% will harbour cervical HPV types at any given time, arguably in another meta-analysis, the percentage of women estimated to carry HPV 16 and 18 DNA worldwide is 32% (12,23,24) Based on a 5 continental meta-analysis, women with normal cytological findings had an adjusted HPV prevalence of 11, 7% with a 95% CI of 11,6% to 11,7% and a study by de Sanjose et.al looking at worldwide HPV prevalence showed women with normal cytology to have 10.4% prevalence with a 95% CI of 10.2 to 10,7% (11,12). Worldwide, women between the age of 15 and 25 years stand the highest risk of HPV infection while older women stand the highest risk of developing cervical cancer(11,24).

In one study HPV prevalence in Africa was found to be 22.1%, while another reported HPV prevalence in Africa ranging between 7% to 60% with over half of the studies having a prevalence less than 20%; regionally in Africa the highest HPV prevalence according to the 5 continental analysis was Sub-Saharan Africa, where the adjusted prevalence was found to be 24% (11,12,24). Africa thus far has the highest HPV prevalence with each study examined worldwide. It also goes without saying that Sub-Saharan Africa, the Caribbean and Latin America account for the highest incidence rates of cervical cancer, most of the cervical cancer deaths however occur in India, with approximately 123000 new cases diagnosed a year with more than 67000 women dying from the disease (25). Compared to the rest of the world, in the 5 continental meta-analysis, Africa's HPV prevalence was followed by Latin America and the Caribbean with 16,1%; Eastern Europe with 14,2% and South East Asia with 14% (11). Asia seems to generally have low HPV prevalence, this was also highlighted in the de Sanjose et.al meta-analysis where Asia's HPV

prevalence was found to be 8% with a 95% CI of 7,5% to 8,4%(12). In the 5 continental meta-analysis, when HPV prevalence was considered by country, prevalence would range between 1, 6% to 41, 9%, there was a huge variation which speaks to the inequality in the distribution of resources in countries, this is also evident among regions where LMICs have the highest prevalence of HPV. That said, high risk regions for cervical cancer are East African countries, Melanasia, Southern African countries and middle Africa; the lowest cervical cancer rates were found to be in Australia and Western Asia(11). HPV types that were found common worldwide in the 5 continental meta-analysis were HPV types 16, 18, 52, 31, 58, 39, 51, and 56 , these types are also responsible for 90% cancerous cells; the most frequent HPV types worldwide however were found to be HPV 16 and 18 and it has been so since 1940 (3,11). Considering age specific HPV distribution by region, in a systematic review done considering age specific prevalence worldwide, HPV prevalence constantly peaked in women younger or 25 years old, decreasing afterwards with age(24). In the study, Central and South America and Africa's age curves showed an additional increase of HPV prevalence in women 45 years and older, this second and most pronounced peak is thought to reflect differences in sexual behaviour across regions, or reactivation of latent HPV infections in older women (12,24).

Compared to uninfected women, the risk of developing squamous cell carcinoma of the cervix increases by approximately 400 times when the HPV type of infection is HPV 16 and 250 times higher is HPV type is 18 (3) Despite these alarming odds, the chance of a women living in less developed regions to develop cervical cancer is as small as 2%, this is because infection with HPV does not always lead to cancer as infections are short lived, furthermore, infection persists only in a small percentage of

women infected with high risk HPV types , which may progress to pre cancer and an even smaller number into cervical cancer.

As highlighted before, less developed regions have the highest prevalence of HPV, this prevalence accounts for more than 80% of cervical cancers in the regions. In developing regions, cervical cancer accounts for 12% of all female cancer mortalities (3). Mortality however differs by different regions, it is estimated mortality rates vary 18 fold between regions, with less than 2 deaths per 100 000 women in industrialised countries and greater that 20 per 100 000 in some developing countries (26).

The WHO position paper proposes that HPV vaccines need to be introduced as part a coordinated and comprehensive strategy to prevent cervical cancer and related diseases, the strategy will include educating general masses around behaviours that lower risks, training of health workers, and giving women information about screening, diagnosis and treatment about cancer and related lesions (3). HPV vaccination is recommended by WHO for girls aged 9 to 13 years (16).

That said, the implementation of HPV vaccines began in 2006 mainly targeting young girls of ages 10-14 years. According to cervical cancer action, 69 countries as of June 2017 have implemented HPV vaccination on a national scale while 38 countries have implemented pilot programmes; the continents that have introduced most of the national HPV vaccination are North America, South America, Europe, and Australia while Africa has mostly implemented pilot programs (38).

High income countries have thus had the advantage of resources and finance needed to implement vaccination so early on, while LMICs have had to depend on donor funding and pilot projects to implement, this despite that the biggest need is in

middle to low income countries. LMICs face unique challenges in rolling out HPV vaccination. These comprise health system challenges which include cost and delivery logistics, socio cultural resistance around fear of infertility, as well as lack of political will to invest in HPV vaccination against other pressing priority health issues such as AIDS treatment (39,40).

A systematic review has estimated that worldwide, not less than 118 million people have been targeted for vaccination by a vaccination program between 2006 and 2014; of the targeted population 62 million is said to be the primary target, the numbers are said to only represent 3,5% of females globally; 82% of the HPV vaccination targeted population was from developed regions while 18% from the less developed regions (41) High income countries have nevertheless shown vaccination coverage of less than 50% as a result of some countries that are underperforming such as France and United States of America. In developing countries, however, coverage levels in the few countries that implemented were higher; considering the 21 demonstration projects from 14 countries, HPV vaccination uptake rate was 88.7% (41).

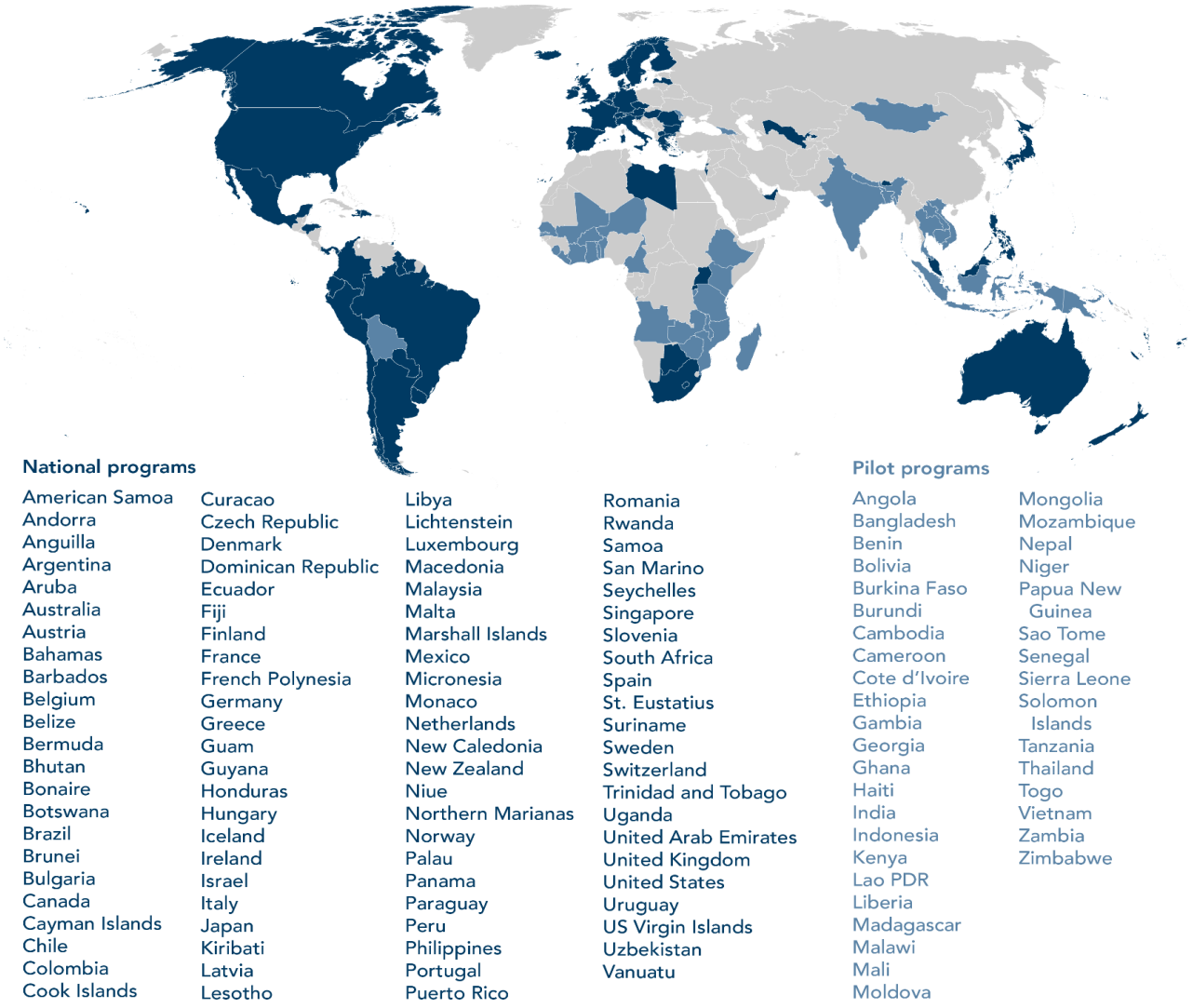
10. HPV prevalence in Africa

Africa has the highest HPV prevalence compared to other continents, and thus specific focus will be in zooming into the HPV prevalence and current HPV vaccination progress in this continent. In Africa, the most prevalent HPV type according to a 5 continental meta-analysis is HPV 16, which has a prevalence of 3,5% the highest among other oncogenic types(11). Based on a systematic review done on African women with normal cytological findings the most prevalent HPV types identified included HPV 16, which was the most prevalent HPV type followed

by 52,35,18,58,51,45,31,53 and 56 in descending order and the age group with the highest HPV prevalence was the 25-34 years age group with 50,5% prevalence (27). When infection was considered by region, Southern Africa had the highest HPV prevalence with a prevalence of 57,3%, followed by East Africa with 42,2%, Western Africa with 27,8% and the lowest in Northern Africa where there was a 12,8% HPV prevalence (27) It is also imperative to highlight that HPV 16 and 18 in women with normal cytology was higher in Sub Saharan women compared to other regions with a prevalence of 9.9% and 5.8% respectively; this is much higher the continental average as indicated in the 5 continental meta-analysis where HPV 16 had a 3,5% prevalence(11,27).

Sub-saharan Africa therefore clearly has the biggest burden to reduce infection in the prevalence of cervical cancer causing HPV types 16 and 18, the effort by South Africa in using bivalent vaccine in its national rollout is one testament to this reality(27,28). Screening programs have especially been difficult to implement in Sub Saharan Africa as a result of competing interests, more so vaccination. HIV AIDS has been on the priority agenda for many sub-Saharan Africa countries, cervical cancer and screening therefore just had to take a back seat(29). HPV surveys in some sub Saharan African countries have shown a prevalence of 40% in Mozambique, 44% in Zimbabwe, 34% in Tanzania and in 44,3% in Kenya(30).

Figure 2: Global progress in HPV vaccination



(31)"Source: Cervical Cancer Action."

Vaccine demonstration projects in India, Peru, Uganda and Viet Nam from 2008 until 2010 using the Expanded Programme on Immunisation (EPI) and using WHO guidelines showed high coverage of the HPV vaccine in Viet Nam of 98.6% (25). A caveat about EPI data is its unreliability, when compared to surveys, routine administrative reports often overestimate coverage levels. The reliability of EPI data is compromised by service providers often report crude coverage instead of valid coverage, poor data quality, weak information systems and service providers

intentionally inflating numbers (32,33). In South Africa, where cervical cancer is the second most common form of cancer in women and transects with high HIV/AIDS prevalence, a recently rolled out national immunisation programme is showing high uptake of the vaccine. In the demonstration project prior to national rollout of vaccination there was a more than 96% vaccine uptake; this level of uptake has been consistently shown in countries such as Bolivia and Uganda where uptake was over 90%. (34). 47 million women are estimated to have been vaccinated against HPV with a full dose through various immunisation programs by 2015, representing 1,5% of the total female population (35) HPV coverage of 70% is regarded as the threshold for cost effectiveness, whilst coverage by at least 50% in a meta-analysis resulted in 68% reduction on HPV types 16 and 18 and reduced anogenital warts by 61%(35).

More than any other cancer, cervical cancer shows a striking global health inequality, the impact has been illuminated in developing countries, it is therefore imperative that focus is on how developing countries can use various strategies to implement vaccination as well as look at their challenges. In the WHO position paper of 2014, they suggest that HPV vaccine be implemented using approached that are compatible with their delivery infrastructure and cold chain capacity, affordable and cost effective as well as sustainable, and are most likely to achieve the highest possible coverage(3). Consideration in the implementation of HPV vaccination will need to consider affordability, cost effectiveness, cultural acceptability, political will and support from the public(36). Policy makers also need to consider the disease burden, health care infrastructure and the ability to initiate and sustain vaccination programs; this is already problematic in developing countries where health resources continue to be very limited considering the need.

All countries have a national immunisation program delivering vaccines funded by the government of the country. In developing countries however, the lead in the roll out of HPV vaccination was led by GAVI an organisation in support of vaccination globally. Success with GAVI implementation has already been seen in the hepatitis B vaccine in over 40 countries where there was improved coverage, financing, infrastructure and information systems (37). The GAVI HPV vaccine programme has 48 countries which it has identified as eligible for HPV vaccine introduction with the assistance of GAVI financing, all these countries are in developing countries. GAVI Alliance support has seen national rollout of HPV vaccine in Uganda, Bolivia, Guyana, Honduras, Sri Lanka, Uzbekistan and Rwanda; Rwanda was the first African country to implement HPV vaccination, which had already implemented a successful demonstration project (38). GAVI Alliance as of 2017 has also seen to the implementation of 28 demonstration programmes in the eligible countries (38)

Low and middle income countries face social cultural barriers mainly due to the fact that it is a vaccine against STI something which holds as taboo and has connotations of promiscuity for many; health system barriers as a result of insufficient infrastructure and human resources; political barriers as a result of lack of political will and investment, competing health priorities and the involvement of stakeholders(39) A study in Mali regarding attitudes towards HPV vaccination interestingly found out that 59% of the women in their study would need consent from their male counterparts in order to be vaccinated(40)

As a result, there is no prevalence data following vaccination from developing countries, in the developing countries, many countries as illustrated have implemented but however, few studies have been done to monitor vaccine prevalence following implementation. Countries that benefited in early rollout of HPV

vaccination like the United States and Australia are producing encouraging results of HPV vaccination. In this systematic review from the data collected in the studies monitoring HPV prevalence after vaccination, the hope is to add to evidence, a more comprehensive outlook on the performance of HPV vaccination thus far.

11. Summary and conclusion of the literature review

HPV is a common sexually transmitted infection with the highest prevalence among women during sexual debut. HPV is well known to cause among other diseases cervical cancer and certain HPV strains can be targeted by vaccines to ameliorate cervical cancer and genital warts. HPV vaccines have been available on the market since 2006 and a number of developed countries have already implemented national vaccination programs with varying coverages and successes.

Reviews considering developing countries especially Africa are therefore much needed. National HPV vaccination data in developing countries in scarce and most developing countries are yet to introduce a national HPV vaccination programme. Vaccination coverages in developing countries have however been more promising than current coverages seen in developed countries. Developing countries will therefore have a unique opportunity to maximise the benefits of the HPV vaccine among their populations. Developing countries have the most need for the vaccine due to highest HPV prevalence and cervical cancer mortalities being recorded in the regions. The HPV has been out of reach for most developing countries because of high vaccine costs and competing health interests. We therefore undertake a systematic review on HPV prevalence following HPV vaccination in women around the world. The review will add onto the active area of research around HPV

vaccination impact as well as hopefully inform clinical practice and policy in countries yet to implement national HPV vaccination programmes.

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Prevalence of Human papillomavirus among women following HPV vaccine introduction; a systematic review.

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List of abbreviations

CBA:	Control Before and After
CDC:	Centers for Disease Control and Prevention
CI:	Confidence Interval
GAVI:	Global Alliance for Vaccines and immunization
HPV:	Human papillomavirus
ITS:	Interrupted Time Series
MeSH:	Medical Sub Headings
RCTs:	Randomised Controlled Trials
UNICEF:	United Nations Children's Funds
WHO:	World Health Organisation

Prevalence of Human papillomavirus among women following HPV vaccine introduction; a systematic review.

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Abstract

Background: Worldwide efforts have been made by some countries to offer HPV vaccination since its introduction in 2006. Population effectiveness of HPV vaccines is presently an active area of research. We review available evidence on the effectiveness of HPV vaccine uptake among young women to prevent HPV infection.

Methods: A comprehensive search of published and grey literature was conducted in several electronic databases using a pre-defined search strategy related to HPV prevalence following vaccination. The database searches were complemented by hand-searches of reference lists of eligible studies. Data were extracted onto a purpose-designed data extraction form, pooled in a meta-analysis and stratified by continent considering vaccine type, cross protective and (high/low) risk HPV types as subgroups.

Results: Our search yielded 1680 studies, of which thirteen met with our inclusion criteria (8332 vaccinated women aged 12 to 34 years from across the world). The pooled HPV (comprising types 6, 11, 16 and 18) prevalence among young vaccinated women was 7% (95% Confidence Interval (CI): 5% to 9%, 13 studies, n=8,332). The 13 studies were conducted across 3 continents: HPV prevalence for North America was 5% (95% CI: 3% to 7%, 9 studies, n=5781, age range =13 to 34); Europe, 14% (95% CI: 9% to 18%, 3 studies, n=2213, age range =13 to 29) and Australia 5% (95% CI: 3% to 8%, 1 study, n=5781, age range=13 to 34). Of the studies which reported the effect of vaccination on other non-vaccine HPV type prevalence (known as cross protective types)HPV (31, 33, 45, 51 & 58), the overall pooled cross protective HPV prevalence was 9% (95% CI: 6% to 12%, 4 studies, n=3081 age range=13 to 29), by continent North America had 14% (95% CI: 12 to

17%, 1 study, n=753 age range=14 to 24), Europe 7% (95% CI: 6 to 8%, 2 studies, n=1990, age range=13 to 29) and Australia with 8% (95% CI: 5% to 11%, 1 study, n=338 age range=18 to 26).

Conclusion: This study showed an HPV prevalence of 7% in women vaccinated against HPV types 6, 11, 16 and 18, which represents a substantial difference to the 22% HPV prevalence in non-vaccinated women. There is however, still a dearth of information on vaccinated women and HPV prevalence, highlighting the need for further studies in this area.

Strengths and limitation of this review

- The review comprehensively searched multiple databases and bibliographies. We had no language restrictions.
- We were stringent in the selection of studies as far as vaccination status was concerned. Studies considering HPV prevalence in unvaccinated women were excluded.
- A variety of methods was utilised in collecting data across the studies. However, some of the study participants were not representative of the general population. Caution therefore, needs to be considered when using these results to make inferences or conclusions about prevalence of certain populations.

Keywords: Human papillomavirus, HPV prevalence, HPV vaccine type, Women

1. Background

The introduction of a vaccine against the types of human papillomavirus (HPV) which are linked to most cases of cervical cancer, is widely considered to be one of the greatest health care developments for women in recent years (1,2). Cervical cancer is currently the fourth most frequently diagnosed cancer in women globally and more so in developing countries where it is the leading cause of cancer mortality, in Sub-Saharan Africa it is the leading cause of all cancer deaths in women (3–5). Although a majority of the HPV infections resolve on their own, constant infection may result in developing a disease (3,6). Globally the most common HPV types which are strongly associated with the development of cervical cancer are HPV 16 and 18 (3,7,8). HPV has to be present in a cervical cancer diagnosis, HPV infections particularly high-risk types are necessary for the development of cervical pre-cancer and cancer. HPV types 6 and 11 are known to cause genital warts, in both women and men (9,10).

Advancements in HPV prevention have to date resulted in the development of vaccines targeting high risk HPV types, with the most recent vaccine targeting 9 HPV types, HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 (11,12). Currently there are three vaccines recommended to prevent HPV related diseases, namely quadrivalent, bivalent and nonavalent vaccine; all three vaccines can be used in women but only two are also recommended for use in men (3,11) . Table 1 shows vaccines currently available.

Table 1: HPV vaccine available

	Formulation	**HPV type**	**Year approved**
1	Quadrivalent	6,11,16 and 18	2006
2	Bivalent	16 and 18	2009
3	Nonavalent	6, 11, 16, 18, 31, 33, 45, 52, and 58	2014

All the vaccines cover at least two of the high risk HPV types 16 and 18 (3,11,13). The vaccines have also been proven to have cross protection on HPV types 31,33,45,51 and 58. HPV vaccination progress has been slow, especially for developing countries; by 2017, 64 countries, mainly in developed countries had introduced HPV vaccination into their national immunisation programme (14).

The risk for HPV infection begins soon after sexual debut with the peak prevalence of 24% observed in young women under 25 years. The World Health Organisation (WHO) therefore recommends HPV vaccines be part of routine vaccinations for girls from nine to thirteen years of age (3). Extensive uptake of current HPV vaccines by young women could therefore potentially reduce cervical cancer and mortality by roughly two-thirds (15). In addition, routine HPV vaccination covering more high risk types would be more effective in preventing cancer and less subject to variations in different regions (16).

Incidences of HPV-related diseases caused by vaccine HPV types are projected to decrease in populations that have received the vaccine, especially in women (15). To date, population studies are showing a decrease in vaccine type HPV prevalence among young girls since the vaccine was introduced (15,17). Many deaths will therefore be averted because of the HPV vaccine introduction. Globally cervical cancer is estimated to cause 7.5% of all female cancer deaths. In 2012 alone an estimated 266 000 globally deaths were from cervical cancer (3). The adjusted HPV prevalence globally among women with normal cytological findings was estimated to be 11.7%, according to a 5 continent meta-analysis, but most of the high risk HPV prevalence was identified in developing countries where HPV prevalence in Africa was found to be highest at 22.1% (8).

Assessment of vaccine coverage currently shows a gap between developing and developed countries, therefore, cervical cancer has been said to be a health condition that is indicative of health inequalities in the world (8,15). Developing countries are indeed lagging behind with HPV vaccination despite having the most need; in a pooled analysis of data from 2006 to 2014, it is reported that 118 million women have been reached by vaccine programmes globally; however only 1% were from low-income or lower-middle-income countries (8). A few demonstration projects have been implemented in developing countries. The demonstration projects show high vaccine coverage when compared with developed countries despite developed countries having implemented national vaccination programmes.

Based on good coverage in the demonstration projects in developing countries, there is much hope for vaccine benefits once developing countries are able to rollout national HPV vaccination. It has been further highlighted that by 2014, the highest HPV vaccination coverage was in young women from developed countries where 32.9% had been vaccinated; on the contrary developing countries had a coverage of 2.7% (18). Vaccination coverage of at least 50% is estimated to reduce prevalence of HPV 16 and 18 by 68%, and reduction in anogenital warts by 61% (16). In developing countries the introduction of vaccination on a large scale has so far been limited because, amongst other reasons, vaccines were deemed too expensive (18). Vaccination programmes in developing countries are scant and the few implemented were demonstration projects spearheaded by the Global Alliance for Vaccines and immunization (GAVI) (2).

We undertook a systematic review to determine the prevalence of HPV following HPV vaccination in women. The review will be of potential interest in a number of

areas globally, especially developing countries which are yet to adopt national HPV vaccination. The review data could be used to help to inform the importance of HPV vaccination among the recommended age range in a future national vaccination programme. While developing countries benefit from overall, developed countries on the other hand, could also still benefit from this study by highlighting some remaining questions about the indirect impacts of current and future HPV vaccines. The population effectiveness of HPV vaccines is an active area of research; we therefore review the currently available evidence on HPV vaccine uptake among women to prevent HPV infection.

1.1 Objective

The review seeks to assess the prevalence of HPV following HPV vaccination in women.

2 Methods

This systematic review employed scientific techniques and guidelines. The protocol was published in the PROSPERO International Prospective Register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017058845), registration number CRD 42017058845.

2.1 Criteria for considering studies for this review

The review considered studies using the following study designs: randomised controlled trials (RCTs), cohort studies, control before and after (CBA), interrupted time series (ITS) and cross-sectional studies.

Studies were excluded if;

1. They did not report HPV prevalence in vaccinated women.
2. Studies did not specify prevalence by gender in the vaccinated.
3. Studies were duplicates.

2.2 Types of participants

The review only considered studies reporting HPV prevalence of females older than 9 years who had received HPV vaccine. The age of 9 years is selected since it is the recommended starting age to receive HPV vaccine in the adolescent phase. There is no maximum age limit. The participants could be from any part of the world.

2.3 Types of interventions

To date three HPV vaccines are available; all the recommended HPV vaccines (quadrivalent, bivalent, and nonavalent vaccines) are considered as intervention, any HPV vaccine is therefore considered as intervention. Vaccines may have been administered intramuscularly or otherwise within a variation of intervals in recommended doses (3,11)

2.4 Types of outcome measures

2.4.1 Primary outcomes

Proportion of females who developed HPV infection following vaccination.

2.4.2 Secondary outcomes

- Vaccination coverage, that is, the proportion of females who have received the recommended dose of the vaccine in a study.
- Prevalence of cross protective HPV types following HPV vaccination

2.5 Search methods for identification of studies

We developed a comprehensive search strategy to search for both published and unpublished articles, with no restrictions on language or publication date. The strategy included Medical Subject Headings (MeSH) and free-text terms relating to HPV vaccination uptake globally. The strategy was adapted to suit each individual database using applicable controlled vocabulary. The imported articles from various search results were managed with the Mendeley referencing software (Copyright © 2009-2013 Mendeley Ltd).

2.5.1 Electronic searches

In this review, the following peer reviewed electronic databases were searched for eligible studies: PubMed, Cochrane Central Register of Controlled Trials, Scopus, Web of Science, World Health Organisation Library Information System (WHOLIS), Africa Wide and Current Nursing and Allied Health Literature (CINAHL). In addition, we also searched websites and databases for grey materials like World Health Organisation (WHO) (http://www.who.int/), United Nations Children's Funds (UNICEF) (http://www.unicef.org/), Global Alliance for Vaccine and Immunisation (GAVI), (http://www.gavialliance.org/), US Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/), Program for Appropriate Technology in Health (PATH) Vaccine Resources Library (http://www.path.org/)The communication initiative network (http://www.comminit.com/), http://www.nyam.org/library, http://www.opengrey.eu/ and http://www.eldis.org/, Immunisation basics (http://www.immunizationbasics.jsi.com/ Index.html). Reference lists of relevant reviews and all eligible papers were also searched for relevant studies. Both published and unpublished studies were considered in the search.

2.6 Data collection and analysis

2.6.1 Selection of studies

Two authors (PM, LA) independently screened abstracts and titles identified in the search results for eligible studies. The full-text of studies that were eligible for inclusion were retrieved for assessment. Two (LA, PM) authors reviewed the studies independently and applied inclusion criteria to the retrieved studies. Differences were resolved through consensus between the two review authors. A third author's (ME) opinion was sought when consensus was not reached.

2.6.2 Data extraction and management

Two review authors (PM, LA) independently carried out data extraction using a purpose designed data extraction form. Disagreements were resolved by consensus and a third author resolved the issues. Prior to use, the extraction form was piloted on at least four studies identified randomly from the list of included studies. The data collected included the study setting (country the study was undertaken), the study design, the type of participants, in this case women, vaccine type and details of outcome which includes prevalence of HPV in vaccinated women.

2.7 Assessment of risk of bias in included studies

We employed the quality assessment tool for evaluating prevalence studies as suggested by Hoy and adapted by Werfalli and colleagues (19,20). The quantitative scoring system of the Risk of Bias criteria allocates four points for external validly and six points for internal validity. Each of 10 domains are given a score of "1" if free of bias and "0" if bias is deemed to be present. The scoring system tool categorises high-risk studies as those with an overall score of 0-5 points, moderate risk as 6-8 and low risk > 8 points. Two review authors (PM, LA) applied the risk of bias criteria

and discussed any disagreements through discussion and consensus, with the mediation of a third review (ME) when required. Table 2 shows the assessment criteria used.

Table 2: Assessment criteria quality score

External validity	**Point**
1. Was the study's target population a close representation of the national population in relations to relevant variables	1
2. Was the sampling frame a true or close representation of the target population?	1
3. Was some form of random selection used to select the sample, or was a census undertaken?	1
4. Was the likelihood of non-response bias minimal?	1
Internal validity	
1. Were data collected directly from the participants (as opposed to a proxy)?	
2. Was an acceptable case definition used in the study?	1
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	1
4. Was the same mode of data collection used for all participants?	1
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	1
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	1

Table 3 shows the risk assessment scale. Moderate risk means that “further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate” (20). Evidence is considered of low certainty if “further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate”, and very low certainty if “we have very little confidence in the effect estimate”(21).

Table 3: Risk assessment scale

Quality scale	Points
Low risk	>8 points
Moderate risk	6-8 points
High risk	0-5 points

2.8 Dealing with missing data

Where essential, the authors of the studies were contacted to obtain missing data. In this review most of the studies were clear, one study however was not clear and the author was contacted for clarification.

2.9 Assessment of heterogeneity

Variation in study results due to differences in the type of intervention, the type of setting and study design and risk of bias, are described to assess the extent of variation between studies included in the systematic review. Statistical heterogeneity between study results was assessed using the chi-squared test of homogeneity with a 10% level of significance cut off. The I^2 statistic was used with values of 25% reflecting low heterogeneity, 50% medium heterogeneity and 75% high heterogeneity.

2.10 Data synthesis

Data synthesis comprised two steps. The first, was to identifying data sources, documenting the numerators and denominators that were used for calculating prevalence. The second step used the Freeman-Tukey double arcsine transformation to stabilise the variance of study prevalence using Stata® (version 13.1). The stabilisation of variance helps to minimise influence from studies with outliers before the data is pooled together. Stratification of the data was done by continent and HPV type.

2.11 Ethics

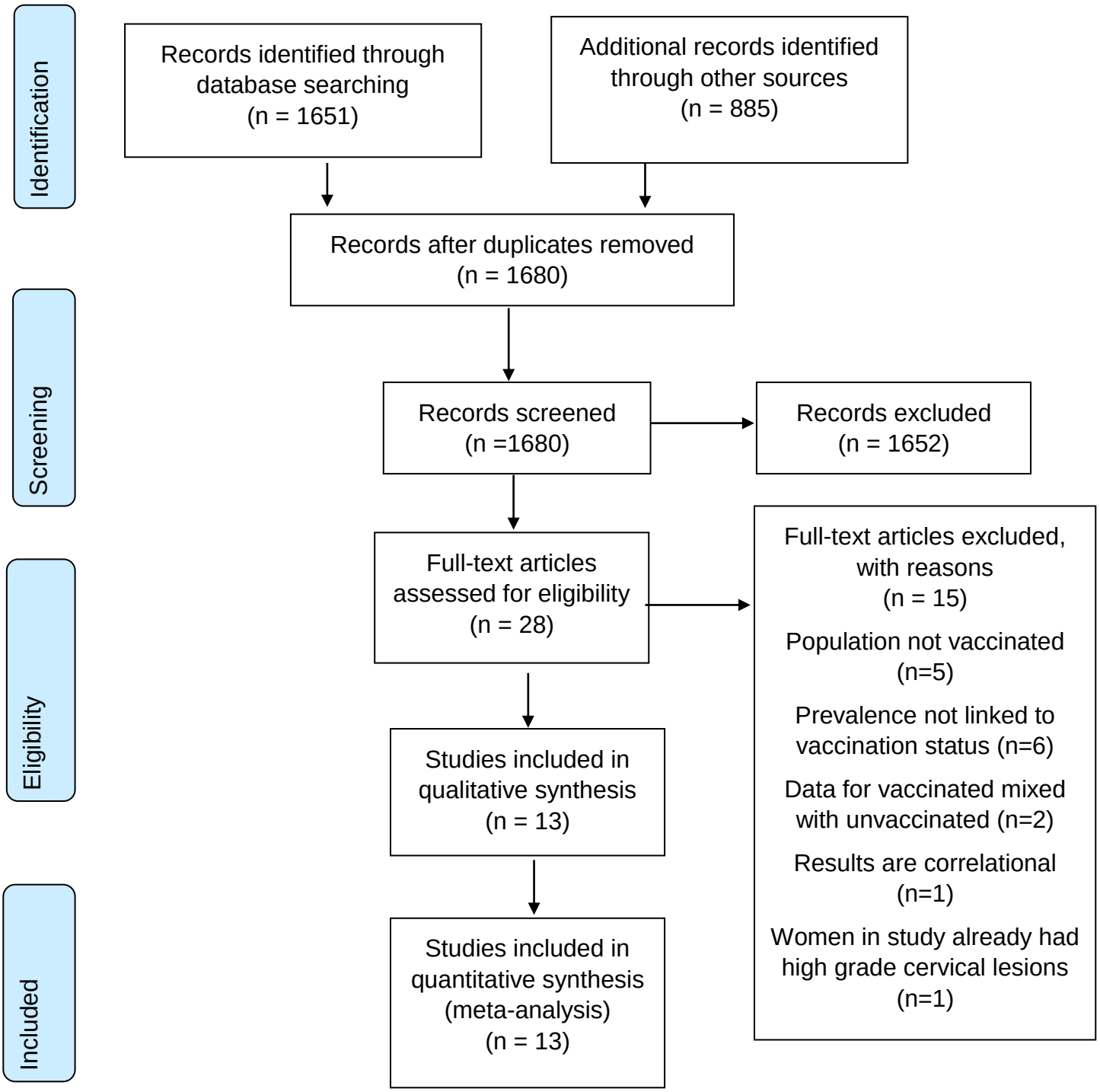
Ethical clearance was obtained from the Health Research committee from the University of Cape Town. This however was not a formal ethical review as systematic reviews draw on publicly available data.

3. Results

3.1 Description of studies

We retrieved, in total 2536 records, of which 1651 were from electronic published databases, 885 from the grey literature, hand searches and conference proceedings. After removing 856 duplicate records, 1680 remained from which 1652 were excluded based on title and abstract. The full-text records for the remaining 28 studies were obtained for detailed evaluation after which, a further 15 records were excluded for various reasons (not having a vaccinated population or, lack of clarity between prevalence of vaccinated and unvaccinated and correlational data). Finally, 13 studies met with our inclusion criteria. Studies excluded are listed with reasons in table 5. Only studies which showed clear numerators and denominators were included. Figure 1 shows the PRISMA flow diagram for the search results.

Figure 1: PRISMA Flow diagram



3.2 Characteristics of included studies

Table 4 provides a summary of the studies included in this review. The most common study design was cross sectional (10 studies, n=4839) (22–31) followed by randomised controlled trials (2 studies, n=3418) (32,33) and a single cohort study (n=75) (34). The age of participants ranged from 12 to 34 years. The studies were conducted in the United States of America (7 studies), Scotland (2 studies), Costa Rica (2 studies), Germany (1 study) and Australia (1 study).

The 13 studies reported HPV prevalence following vaccination from 2004 to 2013.The studies reported on vaccine HPV types HPV (6, 11, 16 and 18), cross protective HPV type (31, 33, 45, 51 & 58) prevalence, high risk HPV type (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 & 68) prevalence and overall HPV prevalence. No study had yet analysed the impact of the nonavalent vaccine on HPV prevalence in women as it was recently licenced in 2014.

Ten studies (22–24,27,28,30–33) had a follow up sample representative of the originally vaccinated population while the remaining three (26,29,34) studies had samples not representative of the population.

Table 4: Summary of included findings

Study ID	Country	Study design	HPV vaccine type	Post vaccine prevalence HPV (6, 11, 16 & 18)	§HPV vaccine coverage	Sample size - follow up	Sample size - original	Age range	Period
North America									
Brogly 2014	USA	Cross sectional design	Quadrivalent Vaccine	3%	NS	96	235	21-30 years	2011-2012
Cummings 2012	USA	Cohort	Quadrivalent Vaccine	5%	NS	75	75	20-29 years	2010
Guo 2015	USA	Cross sectional design	Quadrivalent Vaccine	7%	21%	177	878	18-25 years	2007-2012
Herrero 2013	USA	Randomised Controlled Trial	Bivalent Vaccine	2%	NS	2910	7466	13–26 years	2004-2005
Markowitz 2016	USA	Cross sectional design	Quadrivalent Vaccine	2%	51%	753	753	16–24 years	2009-2012
Kahn 2012	USA	Cross sectional design	Quadrivalent Vaccine	6%	NS	409	409	20-21 years	2009-2010
Kuhs 2014	Costa Rica	Randomised Controlled Trial	Bivalent Vaccine	6%	NS	508	7466	14-34 years	NS
Schlecht 2012	USA	Cross sectional design	Quadrivalent Vaccine	10%	NS	513	645	10-24 years	NS
Tarney 2016	USA	Cross sectional design	Quadrivalent Vaccine	4%	32%	340	1526	13-17 years	2007-2012
Cameron 2016	Scotland	Cross sectional design	Bivalent Vaccine	10%	90%	1016	5765	14-17 years	2009-2013
Delere 2014	Germany	Cross sectional design	Both quadrivalent and bivalent	14%	NS	223	787	20-25 years	2010-2012
Kavanagh 2014	Scotland	Cross sectional design	Bivalent Vaccine	17%	90%	974	4679	22-29 years	2009-2012
Tabrizi 2012	Australia	Cross sectional design	Quadrivalent Vaccine	5%	55%	338	404	19-26 years	2011-2012

ID, Identification; *NS, Not Sated*

§ HPV vaccine coverage is defined as the proportion of women vaccinated in the eligible population

Table 5: Excluded studies

Study ID	Reason for exclusion for exclusion
Brown 2009	No HPV prevalence data despite the population having been vaccinated for HPV. The focus was on cross-protective efficacy of the quadrivalent vaccine,
Chow 2015	The study does not show separate data for vaccinated participants.
Dunne 2015	The study does not show separate data for vaccinated participants despite mentioning that there was a low HPV prevalence in vaccinated participants
Fischer 2016	The study does not specify whether participants were vaccinated. It makes assumptions that certain age groups may have been vaccinated.
Hariri 2012	The paper describes HPV type distribution in US women aged 18–39 years reported to the HPV-IMPACT monitoring system with a diagnosis of CIN2+ during 2008–2009, prior to wide scale HPV vaccine introduction.
Konopnicki 2016	The population not vaccinated, the study aimed to analyse the high-risk HPV genotype distribution in a cohort of HIV-positive women and to estimate the potential protection offered by the different HPV vaccines.
Liu 2016	There was no HPV prevalence data following vaccination. The study describes the frequencies of adverse events following HPV vaccination among Alberta females
Merckx 2014	The study presents analysis of correlational data that is not linked to vaccination registration
Mesher 2015	The study only considers pre- vaccination and post vaccination prevalence without distinguishing those who had received vaccination in the post vaccine period.
Mesher 2016	The study only considers pre- vaccination and post vaccination prevalence without distinguishing those who had received vaccination in the post vaccine period.
Osborne 2015	The population included vaccinated and unvaccinated individuals, prevalence reported did not distinguish between vaccinated and unvaccinated.
Powell 2012	The study included women who had already been advanced cervical lesions meaning they had already been pre- exposed to high risk HPV types
Tota J.E 2016	The study explores the potential for type replacement, evaluating natural HPV type competition in unvaccinated females.
Uhnoo 2014	The study followed HPV prevalence in Southern Sweden from 2008 to 2013 but did not report specifically in vaccinated women.
Veldhuijzen 2015	The study does not clearly distinguish vaccinated women from unvaccinated. The study reports the age- and type-specific distribution of screen detected incident high-risk HPV infections among participants of two large European population based screening trials over the course of two screening rounds.

3.3 Assessment of risk of bias in included studies

No study was deemed as having a high risk of bias. Three studies were of low risk, and ten of moderate risk bias (Table 6).

Two studies (32,33), indicated randomised sampling, while for the remaining studies the sampling method was not randomised. Since HPV testing requires vaginal swab samples or a cytological test obtained from individuals in order to make a diagnosis, all studies were collected directly from participants instead of a proxy and response bias was minimal as only one of 13 studies showed likelihood of response bias.

An acceptable case definition was used in all studies; all studies indicated using a reliable instrument to measure the parameter of interest; all studies clearly indicated HPV data from women of the ages 12 years and above; all studies used a consistent mode of data collection for all subjects. Given the risk of bias in the studies reviewed, although minimal, caution should be exercised in interpreting the outcome.

Table 6: Risk Assessment

Study ID	Internal Validity				External validity							
	Risk of bias 1	Risk of bias 2	Risk of bias 3	Risk of bias 4	Risk of bias 1	Risk of bias 2	Risk of bias 3	Risk of bias 4	Risk of bias 5	Risk of bias 6	Total quality score	Risk of bias
Brogly 2014	−	+	−	+	+	+	+	+	+	+	**8**	**moderate risk**
Cameron 2016	−	+	−	+	+	+	+	+	+	+	**8**	**moderate risk**
Cummings 2012	+	−	−	+	+	+	+	+	−	−	**6**	**moderate risk**
Delere 2014	−	+	−	+	+	+	+	+	+	+	**8**	**moderate risk**
Guo 2015	+	+	−	−	+	+	+	+	+	−	**7**	**moderate risk**
Herrero 2013	−	+	+	+	+	+	+	+	+	+	**9**	**low risk**
Kahn 2012	−	−	−	+	+	+	+	+	+	+	**7**	**moderate risk**
Kavanagh 2014	+	+	−	+	+	+	+	−	+	+	**8**	**moderate risk**
Kuhs 2014	−	+	+	+	+	+	+	+	+	−	**8**	**moderate risk**
Markowitz 2016	+	+	−	+	+	+	+	+	+	+	**9**	**low risk**
Schlecht 2012	−	−	−	+	+	+	+	+	+	+	**7**	**moderate risk**
Tabrizi 2012	−	+	−	+	+	+	+	+	+	+	**8**	**moderate risk**
Tarney 2016	+	+	+	+	+	+	+	+	+	−	**9**	**low risk**

Table 6 shows risk of bias assessment for each individual study; 0-5 high risk of bias; 6-8 moderate risk of bias; >8 Low risk of bias.

Symbol + represents 1 point indicating no bias while the − symbol represents 0 indicating bias in the study.

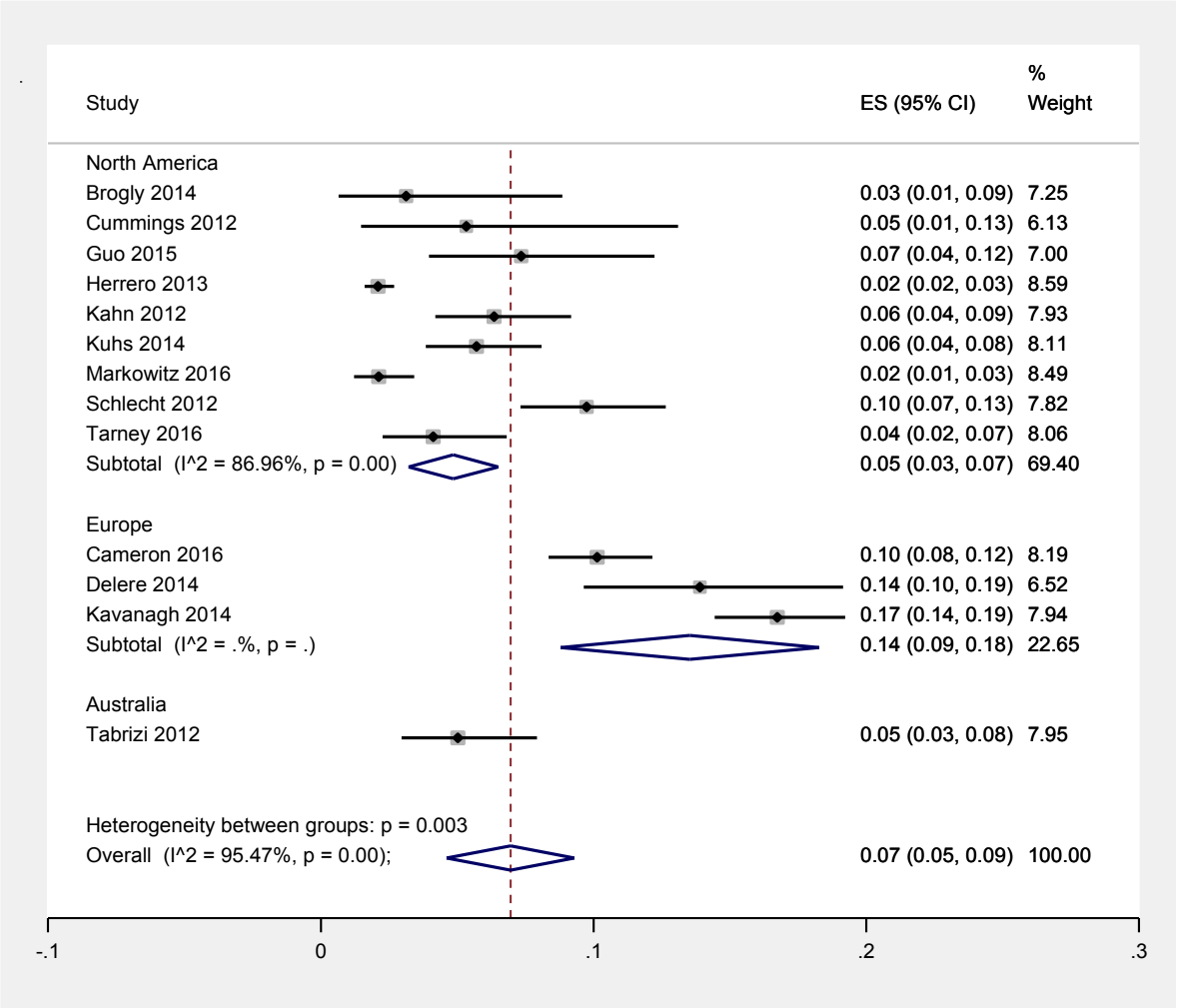
4. Quantitative data synthesis

4.1 Prevalence of vaccine type HPV (6, 11, 16 & 18)

Thirteen studies with 8332 women vaccinated with the quadrivalent, bivalent or a combination of both vaccines, were analysed. HPV prevalence was 7% (95% CI: 5% to 9%, 13 studies, n=8332) for all the women who were vaccinated; test for heterogeneity, I^2 =95,5% (Figure 2).

Subgroup analysis by continent indicates a prevalence in North America of 5% (95% CI: 3% to 7%, studies=9, n=5781) Europe, 14% (95% CI: 9 % to 18%, 3 studies, n=2213) and Australia, 5% (95% CI: 3% to 8%, 1 study, n=338).

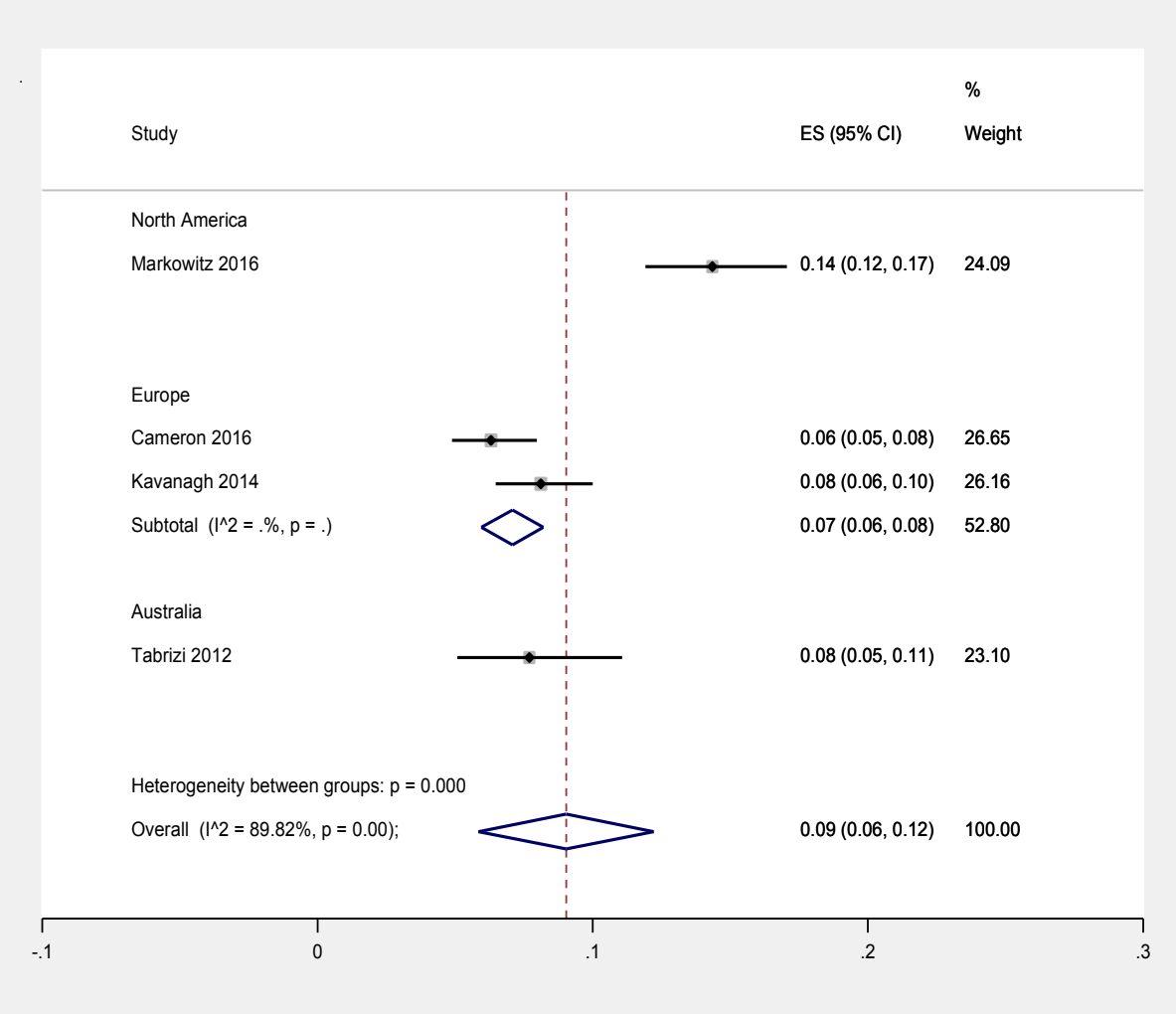
Figure 2: HPV prevalence by continent: Vaccine types (HPV 6, 11, 16 & 18)



4.2 HPV prevalence with cross protective HPV types (31, 33, 45, 51 & 58)

Four studies with 3081 women were tested for HPV prevalence by HPV cross protective types (HPV 31, 33, 45, 51 & 58) (Figure 3). Overall, cross protective type HPV prevalence was 9% (95% CI: 6% to 12%, 4 studies, n=3081) in the women vaccinated; test for heterogeneity, I^2 =89, 8%), North America had a statistically significant higher prevalence when compared to Europe or Australia. North America had a prevalence of 14% (95% CI: 12% to 17%, 1 study, n=753), Europe, 7% (95% CI: 6% to 8%, 2 studies, n=1990) and Australia, 8% (95% CI: 5% to 11%, study=1, n=338).

Figure 3: HPV prevalence by continent: Cross protective types (31, 33, 45, 51 & 58)

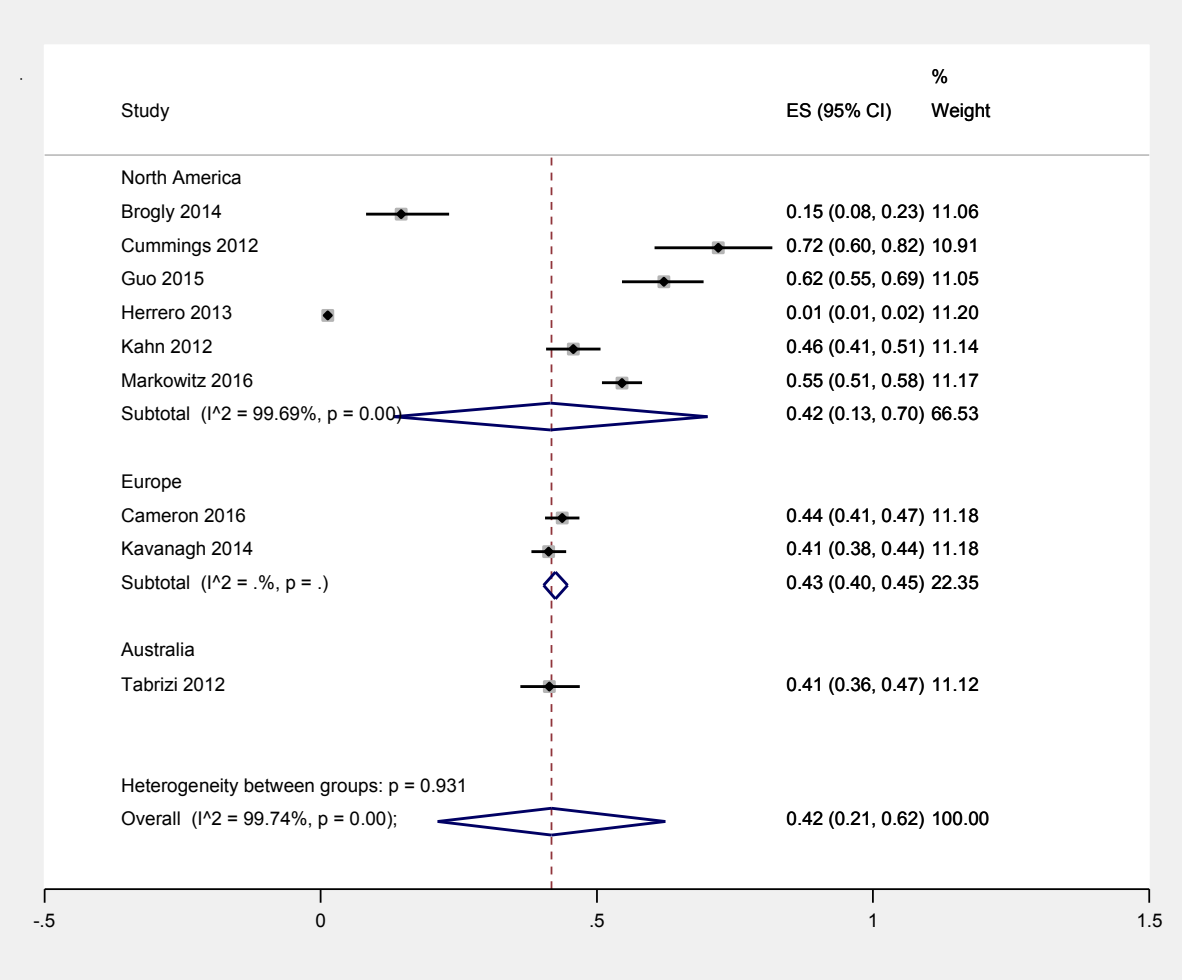


4.3 HPV prevalence by non-vaccine any HPV risk type

Nine studies report prevalence by non-vaccine HPV types in vaccinated women (Figure 4). The pooled estimate shows a prevalence of 46% (95% CI: 21% to 71%,9 studies, n=6784), test for heterogeneity, I^2=99,8%.

When considered by continent, prevalence in North America was 43% (95% CI: 13% to 73%, 6 studies, n=4420), Europe, 56% (95% CI: 54% to 58%, 2 studies, n=1990) and Australia, 46% (95% CI: 41% to 52%, 1 study, n=338).

Figure 4: HPV prevalence by continent: non-vaccine any HPV risk type

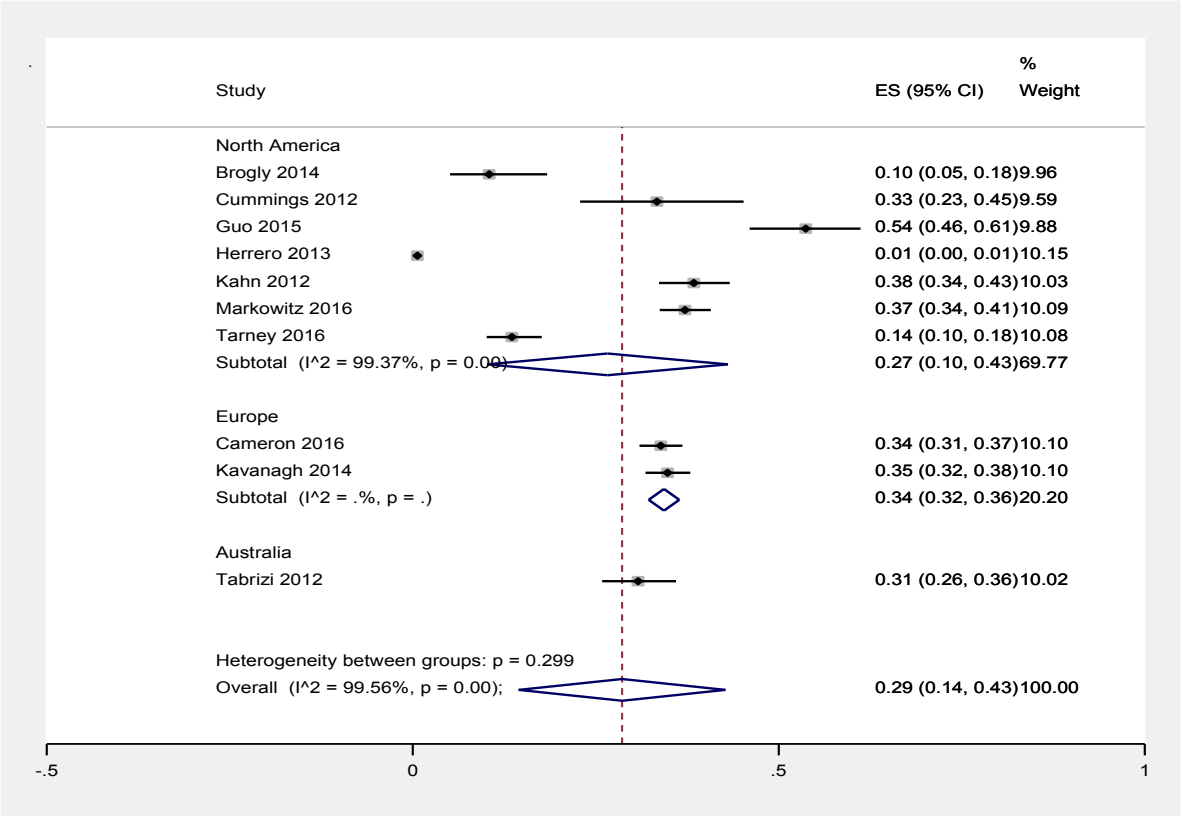


4.4 HPV prevalence by high risk non-vaccine HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 & 68),

Figure 5 shows prevalence by high risk non-vaccine HPV types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 & 68); these are HPV types considered as high risk for disease but not currently covered by the vaccines administered in the studies in this review. Ten studies with 7088 women reported high risk non-vaccine HPV prevalence, and our pooled analysis found an overall estimated prevalence of 29% (95% CI: 14% to 43%, 10 studies, n = 7088); test for heterogeneity, I^2 =99,6%.

When prevalence was considered by continent, North America had 27% (95% CI: 10% to 43%, 7 studies, n=4760), Europe had 34% (95% CI: 32% to 36%, 2 studies, n=1990); Australia 31% (95% CI: 26% to 36%, 1 study, n=338).

Figure 5: HPV prevalence by continent: High risk non-vaccine HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 & 68)

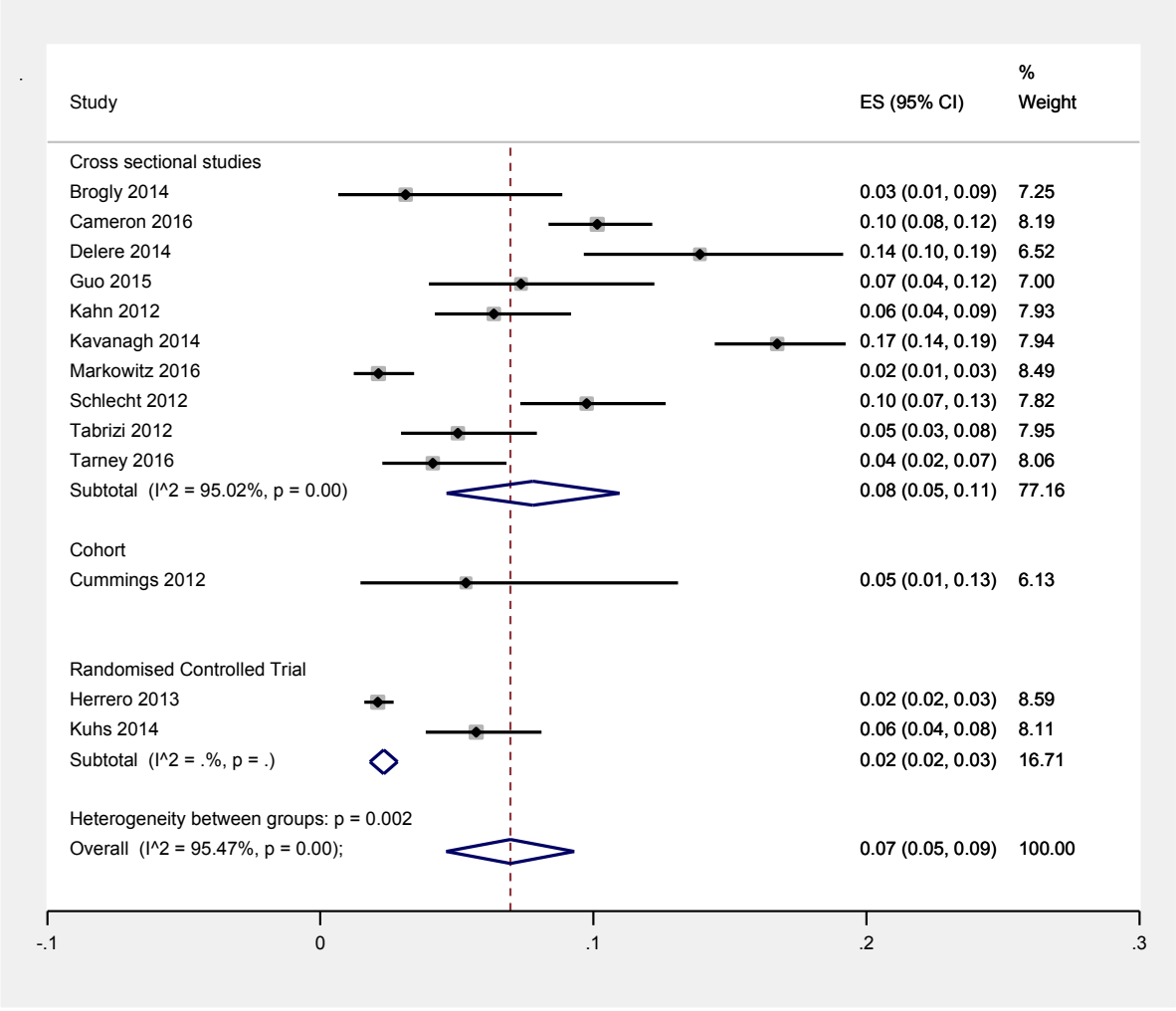


4.5 HPV (6, 11, 16 and 18) prevalence by study design

We considered HPV vaccine type prevalence by study design, 13 studies with 8332 vaccinated young women were analysed (Figure 6).

Cross sectional studies had a prevalence 8% (95% CI: 5% to 11%, 10 studies, n=4839); Cohort studies 5% (95% CI: 1% to 13%, 1 study, n=75) and RCT 6% (95% CI: 4% to 8%, 2 studies, n=3418)

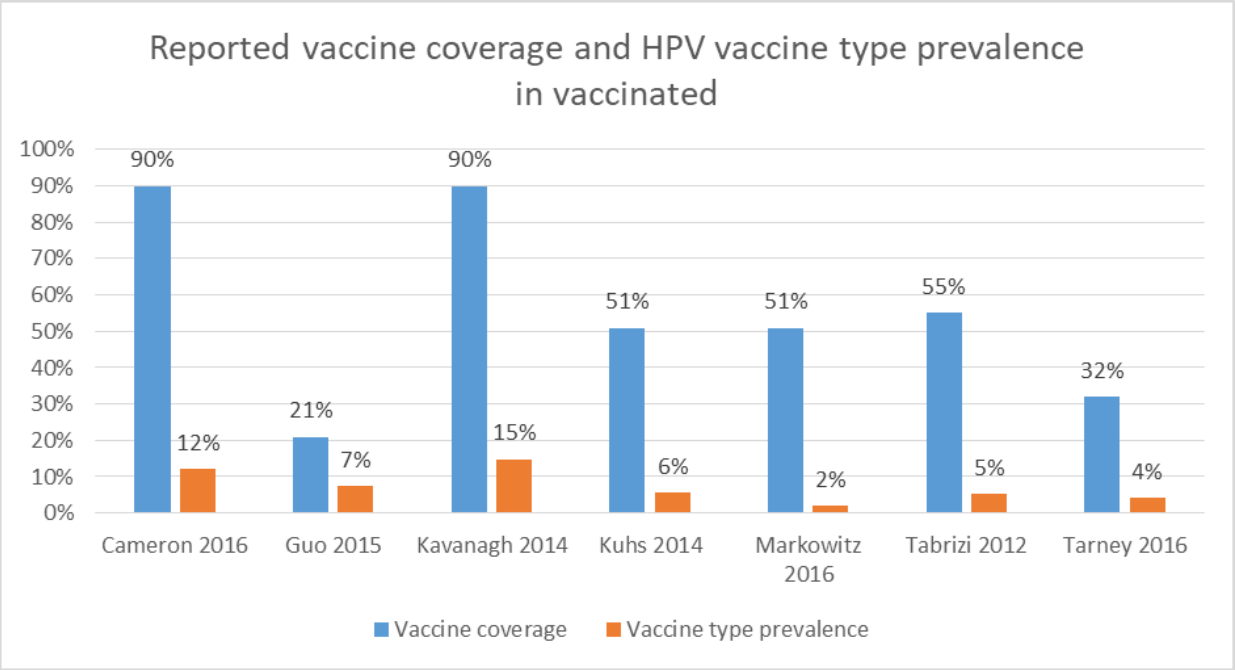
Figure 6: HPV Prevalence (6, 11, 16 & 18) by study design



4.6 HPV vaccine coverage

A limited number of studies reported on HPV vaccine coverage. Figure 7 considers vaccination coverage versus vaccine type HPV prevalence following vaccination.

Figure 7: Vaccine coverage and HPV (6, 11, 16 and 18) prevalence



Vaccination coverage varied widely across studies, the lowest coverage reported is 21% while the highest is greater than 90%. The highest vaccine type prevalence was in a study that reported the highest HPV vaccine coverage whilst the lowest HPV vaccine type prevalence of 2% was reported in a study that had 51% coverage.

Five of the seven studies which reported on vaccine coverage met with the minimum suggested threshold of 50% (16). Prevalence of HPV in the studies ranged from 17% to 25%. The remaining studies with vaccination coverage of 21% and 32% respectively nevertheless compared favourably in terms of HPV prevalence. We suspect that these data are insufficient from which to draw conclusions on the correlation between coverage and prevalence.

Our original intention was to evaluate cost of intervention, adverse events following immunisation and, adverse effects of the intervention; however, we found no data in the included studies to allow for this.

5. Discussion and conclusion

The HPV vaccine development has been hailed as a major advancement of women's health. Since the vaccine was first introduced in 2006, the world has been waiting to see its impact on HPV infection and, subsequent cervical cancer. However, cervical cancer usually develops in the third decade of life, meaning that the impact of HPV vaccination will only be accurately measured 30 years after vaccine introduction. In the meantime, a good measure of the vaccine effectiveness and a good proxy for cervical cancer are high risk HPV types known to cause cancer. Thus far many studies have been conducted considering HPV vaccination in the population following HPV vaccination.

This review found a pooled HPV prevalence of 7% amongst women, globally, vaccinated with HPV 6,11,16,18 subtypes. At a continental level the prevalence was higher in Europe at 14% when compared with North America or Australia where HPV vaccine coverage was 59% and 73% respectively. High income countries account for approximately 70% of the vaccinated population worldwide and have globally achieved less than 50% coverage (16). HPV vaccination coverage could therefore have had minimal impact on HPV prevalence. HPV prevalence in unvaccinated women within the 34 years and younger age band was previously reported to be as high as 21%, this age band is reported have the highest prevalence (35). When

compared to the pre-HPV vaccine study our study shows a reduction in HPV prevalence as a result of vaccination.

This review, to our knowledge the first of its kind, represents a comprehensive attempt at synthesising available data on HPV prevalence in vaccinated women; multiple databases were searched with no language restrictions and, employing stringent inclusion criteria. However, we acknowledge several limitations that could have impacted on this review. Participants were influenced by study design, for example, all RCTs did not have a representative sample. Some studies used samples taken from women attending regular gynaecological tests which may have influenced HPV prevalence in that women going for gynaecological tests could already have existing symptoms indicative of HPV-related infections.

All 13 studies had the age group required in our inclusion criteria of ten years or older. Of studies initially considered, fifteen were removed as they did not meet inclusion criteria in that, despite measuring vaccine prevalence following vaccination, they did not specifically measure prevalence in women who were vaccinated. A further study was excluded from analysis despite being considered eligible as the women had advance cervical lesions which already meant pre-exposure to high risk HPV types.

In the analysis we looked at vaccine coverage and study designs in relation to vaccine type prevalence. It is interesting that high vaccine coverage reported did not always translate to low vaccine type prevalence. Analysis by study design also interestingly revealed that HPV vaccination is effective even under non-RCT conditions where follow up is more stringent.

HPV vaccination has been proven to have cross protective abilities for vaccine types (HPV 31, 33, 45, 51 & 58). Studies reporting on cross protective HPV types together showed a prevalence of 9%; the sample size was 3081 women. One study included in our analysis reported prevalence of cross protective types having reduced from 13% before vaccination to 6% following vaccination (24). There is still some debate around HPV vaccine on the non-vaccine types; however most studies report moderate to high significance in reduction while one large study in the USA saw no evidence in reduction of cross protective types, explained to possibly be as a result of low vaccine coverage (17,36,37).

We also considered HPV prevalence of high risk HPV subtypes not included amongst those incorporated into the vaccines. The pooled estimate of 29% for this subgroup was significantly higher than the 7% amongst recipients of the HPV vaccine against subtypes 6, 11, 16 and 18. Of note, one of the studies pooled for the analysis reported a prevalence of 54% (24).

HPV prevalence in vaccinated women by non-vaccine any HPV risk types was 42%. Our results contrasts greatly to those reported of in meta-analysis results of world HPV prevalence, found to be much less at 10,1% (7). This may be because our analysis, included a narrow age band from 12 – 34 years old; this age group is likely to have the highest prevalence since sexual debut is a risk factor for HPV infection leading to a HPV peak prevalence in young women (6). The prevalence in our study remained considerably higher when considering the continental breakdown; North America 42% compared to 4,7% and Europe 43% compared to 14,2% (7).

As part of our secondary outcomes we sought to assess the cost of interventions and adverse events following immunisation and adverse effects of the intervention.

None of the articles that fit our selection criteria reported this information as a result we will not be reporting on them.

The findings for this review provides world-wide a snapshot of vaccination performance in possibly reducing diseases such as cervical cancer. This information will be useful to policy makers and implementers on issues around cost effectiveness, priority age groups and vaccines to use. It is necessary to still continue monitoring HPV incidences in vaccinated populations especially in countries where vaccine coverage is high, developing countries are said to be doing better in vaccine coverage than developed countries whose data contribute to this study. HPV prevalence in developing countries will likely to change if high coverage persists, thus it will be interesting to see the direction prevalence will take.

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Supplementary materials

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	61
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	65
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	67
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	70
METHODS			

Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	70
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	71
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	73
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	73
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	73
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	75

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Reports of systematic reviews and meta-analyses must include a completed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist and flow diagram to accompany the main text. Blank templates are available here:

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