



## Table of Contents

{Placeholder for title page} .....	<b>Error! Bookmark not defined.</b>
Table of Contents .....	2
{Placeholder for abbreviations} .....	4
{Placeholder for acknowledgements} .....	5
ABSTRACT: .....	6
Background: .....	6
Methods: .....	6
Results: .....	6
Conclusions: .....	7
INTRODUCTION .....	8
AIMS & OBJECTIVES .....	11
Aim: .....	11
Objectives: .....	11
Methods, search strategy and inclusion criteria .....	12
Overview of the Systematic Literature Search .....	12
Search of the Literature Indexed by MEDLINE and EMBASE .....	13
Indexed Database Search Results .....	13
Search Strategy .....	13
Additional databases .....	16
Grey Literature Search .....	16
Inclusion Criteria .....	16
Exclusion Criteria .....	17
Selection of Eligible Studies .....	18
Title and Abstract Screening .....	18
Full-text Screening .....	18
Data Abstraction Strategy .....	19
RESULTS .....	20
Overview of Results .....	20
Study Characteristics .....	20
Quality assessment .....	21
Study Perspective: .....	24
Single or Multi-Country .....	24
Country, Funding and Authorship .....	24
Interventions and Comparators .....	25
Outcome Measure .....	27
Cost Effectiveness thresholds .....	28
Time Horizon .....	28
Health States .....	28
Geographical distribution of study sources .....	28
Model input Parameters .....	29

Vaccine Coverage .....	30
Vaccine Efficacy.....	30
Vaccine duration .....	30
Sensitivity analyses .....	30
Summary of cost-effectiveness results.....	32
DISCUSSION .....	34
CONCLUSION.....	38
REFERENCES .....	39
Appendix A .....	41
Data Extraction Tables .....	41
Appendix B .....	<b>Error! Bookmark not defined.</b>
CARE Form.....	<b>Error! Bookmark not defined.</b>
Appendix C .....	<b>Error! Bookmark not defined.</b>
Letter of ethics .....	<b>Error! Bookmark not defined.</b>

## **Abbreviations**

HPV –Human Papillomavirus

ICER- Incremental Cost Effectiveness Ratio

QALYs-Quality Adjusted Life Years

DALYs-Disability Adjusted Life Years

LYS-Life Years Saved

LLD-Life years lived with Disability

SSA-Sub-Saharan Africa

LMIC-Low and Middle Income Countries

HEED-Health Economic Evaluation Database

Econ.lit.-Economics Literature

PRISMA-Preferred, reporting Items for Systematic Reviews and Meta Analysis

FMOH-Federal Ministry of Health

WHO-World Health Organisation

DNA-Deoxyribonucleic Acid

GDP-Gross Domestic Product

LSHTM-London School of Hygiene and Tropical Medicine

NIMR-National Institute of medical research

MITU-Mwanza Intervention Trial Unit

GAVI-Global Alliance for Vaccine and Immunisation

VIA-Visual Inspection with Acetic Acid

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## **ABSTRACT:**

### **Background:**

Cancers are emerging public health problems in developing countries like Nigeria accounting for over 85% of total global burden. Cervical Cancer is one of the most prevalent types of Cancer in Women globally; HPV infection is associated with cervical cancers. The most commonly associated subtypes are HPV-6, HPV-11, HPV-16, and HPV-18. Globally, several countries are implementing HPV vaccination programmes with the aim of preventing the development of cervical cancers in Women as young as 12 years of age. This study sought to investigate the economic evaluation of implementing HPV vaccination in Nigeria. Outcome of study is expected influence policy by advising relevant stakeholders on the socioeconomic impact of implementing HPV vaccination in Nigeria.

### **Methods:**

A comprehensive systematic literature review was conducted to identify English language articles relevant to the economic evaluation of human papillomavirus vaccines in low- and middle-income countries published up to July 2014. MEDLINE, EMBASE, Health Economic Evaluation Database (HEED), Econ Lit, and the grey literature were all searched which yielded 831 abstracts. All of these were reviewed in stages using predetermined inclusion and exclusion criteria studies were eventually included for the study.

### **Results:**

All studies established the dominance of vaccination over every other competing alternative using the ICER as the threshold against GDP per capita. Vaccine price and discount rate were found to be most influential on ICER, other factors such as Cervical Cancer incidence, Death rate from other causes, Health related quality of life weights, and coverage and duration of protection were found to be influential on ICER. Vaccination of preadolescent girls was cost effective at a vaccine price ranging from \$10-\$25 per vaccinated girl resulting in mean reduction of a lifetime cancer risk from 40%-50% in most settings in the SSA.

## **Conclusions:**

Implementation of HPV vaccination is potentially cost effective in Nigeria; this implies a huge savings in prospective cost of treating cervical cancer and other HPV related diseases. This study provides a scope for Government to improve on its stewardship and accountability in health systems management by publicly funding the vaccination and treatment of HPV related conditions and creating an effective platform for research and development in the context of documentation of quality cost data, healthcare resource use, and clinical effectiveness data. Pharmaceutical companies are to be more responsible with making prices of vaccine affordable to users and Donors to show more commitment.

## INTRODUCTION

Human Papilloma virus (HPV) is the commonest sexually transmitted infection with over 100 subtypes. The virus is the causative agent of all carcinoma of the cervix with the subtypes 16 & 18 identified as the most common causing 70% of infections across the globe (Fesenfeld, Hutubessy, & Jit, 2013). Globally, HPV is a prevailing public health concern and the principal cause of cervical, anal, penile and vulva carcinoma, anogenital warts and respiratory papillomatosis (Insinga, Dasbach, Elbasha, Puig, & Reynales-Shigematsu, 2007). Roughly half a million infections and more than 270,000 deaths from cervical carcinoma have been ascribed to HPV (Goldie et al., 2007). Cervical carcinoma is the second most prevalent form of carcinoma affecting women resulting in about 493,000 new diagnosis and 274,000 deaths each year with more than 80% mortality occurring in developing world (Agosti & Goldie, 2007). Sadly, a mortality rate as high as 90% is anticipated by the year 2020 in the developing world (Agosti & Goldie, 2007). Over 80% cases of cancer are fatal in low and middle income countries (Fesenfeld et al., 2013). In Sub-Saharan Africa (SSA), cervical carcinoma is the commonest form of carcinoma among women. An estimated age adjusted prevalence of 31/100,000 women and with regional disparity of 42.7/100,000 in East Africa, 38.2/100,000 in Southern Africa, 28/100,000 in Central Africa and 29/100,000 in Western Africa. (Louie, de Sanjose, & Mayaud, 2009). It is the predominant cause of life years lost to cancer in developing countries. Paucity in incidence data, general knowledge and lack of political will to deal with the scourge have been reported to be responsible for the poor attention it has received from policy makers. (Louie et al., 2009).

Nigeria is Africa's most populous nation with an estimated 170 million inhabitants with an average life expectancy at birth of 53 years in males and 55 years in females, Probability of dying between age 15 & 60 years in males is 371/100,000 and 346/100,000 in females, total healthcare cost per capita is \$161. Total expenditure on health is 6.1% of GDP. (WHO bulletin, 2014.) Carcinoma is an emerging public health concern in Nigeria. 100,000 new cancer cases are diagnosed annually in Nigeria with the propensity to rise even higher in years to come. Cancer prevalence has been estimated to be 90.7/100,000 and 100.9/100,000, and the deaths

rate 72.7/100,000 and 76,000/100,000 among Nigerian Women & Men respectively. (Omolar, 2011). There is currently no organised cancer prevention program in Nigeria, which has a population of over 170 million people, more than 40 million who are women in their reproductive age (15-49). Majority of these women are at risk of developing cervical cancer, which is the most common gynaecological cancer in Nigeria. The incidence of cervical cancer, which is reportedly on the increase, is estimated to be about 25/100,000 (Omolar, 2011). Healthcare costs associated with managing ill health in Nigeria often involve catastrophic expenditure, particularly for cancer-related treatment. Therefore, it is possible that a vaccination-based preventative healthcare programme could provide substantial economic benefits to both the Nigerian Government and society.

This systematic literature review aims to review economic evaluation literature relevant to the implementation of HPV vaccine in Nigeria. There is paucity of literature on the epidemiology of human papilloma virus infection in Nigeria. Although, certain epidemiological studies have been conducted in a few states in South-western Nigeria. Currently, there is no national initiative or policy on prevention and treatment of existing cases of HPV and the resulting cancer. (Omolar, 2011). It is worthy of note that, several economic evaluations have been undertaken in developed countries which show that implementation of HPV vaccination in these countries is cost effective (Fesenfeld et al., 2013). Conversely, these approaches are prohibitively expensive to adopt in a poor resource context like Nigeria. (Louie et al., 2009). Despite its ability to control HPV infection, the HPV vaccine is not affordable and accessible to the target population in need in a resource poor setting like Nigeria where healthcare financing is often catastrophic. However, it is plausible to say that, for the HPV vaccine to achieve significant prevention of HPV infection and subsequently, the associated cancer, Government would need to step in and coordinate a national response by incorporating HPV vaccination into the national immunisation program. (Louie et al., 2009). The World Health Organisation (WHO) has suggested that an economic evaluation is conducted before the implementation of the vaccination program in any country. This is to evidently establish its feasibility in the context of cost and effectiveness in the context in question. (Fesenfeld et al., 2013). WHO endorses a

bivalent vaccine (Cervarix) against HPV 16 & 18 infections and a quadrivalent vaccine against HPV 16, 18, 6 & 11 (Fesenfeld et al., 2013).

Giving the palpable burden of cervical cancer in Nigeria as reflected in the preceding statistics, it is essential to undertake a systematic review of the cost effectiveness of implementing HPV vaccination in SSA with a view to leveraging on the transferability of the outcome to make a case for investment in HPV vaccination in Nigeria. It is expected that the outcome of this study would provide convincing evidence to health policy makers, international donors, healthcare professionals and every other relevant stakeholder on the need to invest in the implementation of HPV vaccination in Nigeria to alleviate the huge burden of cervical cancer and its associated catastrophic healthcare cost.

## **AIMS & OBJECTIVES**

### **Aim:**

To determine the cost effectiveness of implementing a quadrivalent HPV vaccine in Nigeria.

### **Objectives:**

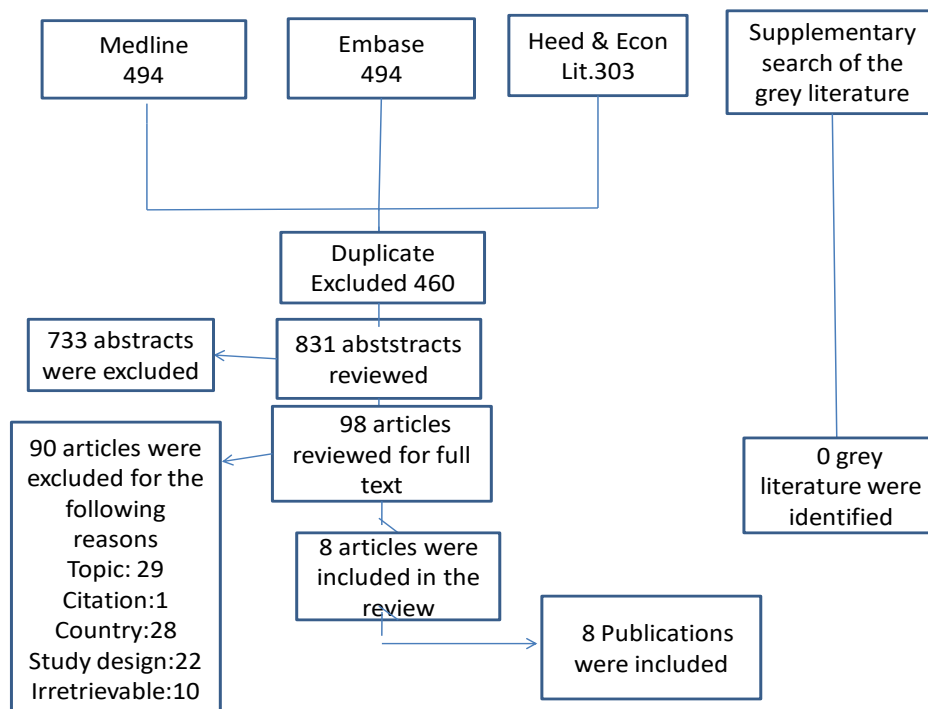
- To assess if it is cost-effective to purchase quadrivalent HPV vaccine to decrease the incidence of cervical cancers in Nigeria.
- To assess the organisational feasibility of implementing an HPV vaccine in Nigeria
- To assess the cost effectiveness of the WHO recommended pilot program for quadrivalent HPV vaccine.
- To make recommendations to health policy makers on the need to prioritise cervical cancer prevention in Nigeria.
- To contribute to the body of knowledge.

## Methods, search strategy and inclusion criteria

### Overview of the Systematic Literature Search

I systematically reviewed MEDLINE EMBASE, Health Economic Evaluation Database (HEED) and EconLit for published economic evaluation articles of HPV vaccination strategies in sub-Saharan African countries. To be considered for inclusion in the systematic review, articles had to be cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, cost-minimization analysis, cost-consequence analysis, budget impact analysis or cost analysis of HPV vaccination. **Error! Reference source not found.** presents a summary of our literature search strategy and results derived from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

**Figure 1. Study selection flow chat**



## Search of the Literature Indexed by MEDLINE and EMBASE

### Indexed Database Search Results

The MEDLINE, EMBASE, HEED and EconLit-indexed database search yielded 1,291 publications (494 from MEDLINE, 494 from EMBASE, and 303 from HEED and EconLit combined), with some overlap between the databases. After removing duplicate articles (those indexed on both MEDLINE and EMBASE), there were 831 unique publications. The abstracts of these 831 publications were examined manually applying the set of inclusion criteria described below. Following this process, 98 were selected for full-text retrieval in order to examine them further for potential inclusion in the review. I anticipated that a subset of these 98 articles would be included in the review once all the publications were examined in full text.

### Search Strategy

I reviewed MEDLINE-indexed publications using the following search strategy. The limits for this search included abstracts only, humans, and English language.

Topic		Search Algorithm	Hits
1	Disease	"human papillomavirus"[Title/Abstract] OR "human papilloma	40,608
	string	virus"[Title/Abstract] OR hpv*[Title/Abstract] OR papilloma[Title/Abstract] OR papillomavirus[Title/Abstract]	

Topic	Search Algorithm	Hits
2	<p>Economic evaluation string</p> <p>"economic evaluation"[tiab] OR "cost-benefit analysis"[tiab] OR "cost benefit"[tiab] OR "cost-consequence analysis"[tiab] OR "cost consequence"[tiab] OR "cost analysis"[tiab] OR "cost-effectiveness"[tiab] OR "cost effectiveness"[tiab] OR "cost utility"[tiab] OR "cost-utility"[tiab] OR "cost-minimisation"[tiab] OR "cost-minimization"[tiab] OR "cost minimisation"[tiab] OR "cost minimization"[tiab] OR "cost savings"[tiab] OR "cost saving"[tiab] OR "cost-saving"[tiab] OR "cost-savings"[tiab] OR "pharmaceutical economics"[tiab] OR "budget impact"[tiab] OR "econometric"[tiab] OR "markov"[tiab] OR "discrete event simulation"[tiab] OR "decision analysis"[tiab] OR (("model"[tiab] OR "models"[tiab] OR "modeling"[tiab] OR "modelling"[tiab]) AND ("cost"[tiab] OR "costs"[tiab] OR "economic"[tiab] OR "economics"[tiab]))</p>	113,278
3	1 AND 2	635
4	<p>Reviews string</p> <p>review NOT (systematic OR "meta analysis" OR (indirect OR mixed AND "treatment comparison")) OR editorial/pt OR letter/pt OR note/pt OR "short survey"/pt</p>	41,037
5	3 NOT 4	635
6	<p>Limits string</p> <p>Limits: Abstracts available; humans; English language</p>	494

\*\*\* The search was limited to not include non-systematic reviews.

I also reviewed EMBASE-indexed publications using the following search strategy. The limits for this search included abstracts only, humans, and English language.

Topic	Search Algorithm	Hits
-------	------------------	------

Topic		Search Algorithm	Hits
1	Disease string	'human papillomavirus':ab,ti OR 'human papilloma virus':ab,ti OR hpv:ab,ti OR papilloma:ab,ti OR papillomavirus:ab,ti	47,685
2	Economic evaluation string	'economic evaluation':ab,ti OR 'cost-benefit analysis':ab,ti OR 'cost benefit':ab,ti OR 'cost-consequence analysis':ab,ti OR 'cost consequence':ab,ti OR 'cost analysis':ab,ti OR 'cost-effectiveness':ab,ti OR 'cost effectiveness':ab,ti OR 'cost utility':ab,ti OR 'cost-utility':ab,ti OR 'cost-minimisation':ab,ti OR 'cost-minimization':ab,ti OR 'cost minimisation':ab,ti OR 'cost minimization':ab,ti OR 'cost savings':ab,ti OR 'cost saving':ab,ti OR 'cost-saving':ab,ti OR 'cost-savings':ab,ti OR 'pharmaceutical economics':ab,ti OR 'budget impact':ab,ti OR 'econometric':ab,ti OR 'markov':ab,ti OR 'discrete event simulation':ab,ti OR 'decision analysis':ab,ti OR (('model':ab,ti OR 'models':ab,ti OR 'modeling':ab,ti OR 'modelling':ab,ti) AND ('cost':ab,ti OR 'costs':ab,ti OR 'economic':ab,ti OR 'economics':ab,ti))	143,236
3		1 AND 2	843
4	Reviews string	review NOT (systematic OR 'meta analysis' OR (indirect OR mixed AND 'treatment comparison')) OR editorial:it OR letter:it OR note:it OR 'short survey':it	4,764,423
5		3 NOT 4	632
6	Limits string	Limits: Abstracts available; humans; English language	494

\*\*\* The search was limited to not include non-systematic reviews.

## Additional databases

Topic		Search Algorithm	Hits
		'human papillomavirus':ab,ti OR 'human papilloma	
1	Disease string	virus':ab,ti OR hpv:ab,ti OR papilloma:ab,ti OR papillomavirus:ab,ti	N/A
2	Limits string	Title and abstract	303

## Grey Literature Search

I searched the 'grey' literature (material that can be referenced but is not published in peer-reviewed, MEDLINE, EMBASE, HEED or EconLit-indexed medical journals) for any documents assessing the economic evaluation articles of HPV vaccination strategies in sub-Saharan African countries. Papers identified were screened using the same inclusion criteria as for the identified indexed database journals:

- World Health Organization (WHO): [www.who.int](http://www.who.int)
- Federal Ministry of Health Nigeria (FMOH): [www.health.gov.ng](http://www.health.gov.ng)

No additional articles were identified from the grey literature searches.

## Inclusion Criteria

### *i. Topic*

- Only studies reporting on HPV vaccination were considered.

### *ii. Patient population*

- Female individuals who received vaccination against HPV infection.

### *iii. Country*

- All countries, from sub-Saharan Africa: Angola, Benin, Boswana, Burkina faso, Burundi, Cape verde, Cameroun, Central African Republic, Chad, Comoros, Congo Democratic Republic, Cote d'Voire, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagaster, Malawi, Mali,

Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra-leone, Somalia, South Africa, South Sudan, Sudan, Swaziland, Tanzania, Togo, Uganda, Zambia and Zimbabwe.

iv. *Study design*

- Economic evaluations including cost-benefit analyses, cost-effectiveness analyses, cost-utility analyses, systematic reviews of economic evaluations.

v. *Year of study*

- There were no date limitations applied.

vi. *Languages*

- Only publications in English were considered.

## **Exclusion Criteria**

vii. *Topic*

- Studies not reporting on HPV vaccination.

viii. *Patient population*

- Studies not evaluating female patients who received vaccination against HPV infection.

ix. *Country*

- Countries other than the sub-Saharan countries.

x. *Study design*

- Case studies
- Case–control studies
- Case series
- Cross-sectional studies
- Editorials
- *In vitro*, animal, fetal, molecular, genetics and pharmacokinetics/pharmacodynamics studies

- Letters to the editor
- Narrative reviews
- Observational studies (without an economic evaluation component)
- Opinion pieces
- RCTs (without an economic evaluation component)

*xi. Year of study*

- There were no date limitations applied.

*xii. Languages*

- Studies published in any other language apart from English

## **Selection of Eligible Studies**

### **Title and Abstract Screening**

Initial screening of publications for potential inclusion in the review was based on their titles and abstracts. I reviewed the selected articles for inclusion in the systematic review according to the pre-defined inclusion and exclusion criteria. For abstracts that were deemed relevant, or those that could not be excluded because of inadequate information during this initial screen, the related full-text articles were retrieved and reviewed.

### **Full-text Screening**

The second stage of screening involved scrutiny of the full-text of articles, when title and abstract screening was insufficient for making the inclusion or exclusion decision. I reviewed the full-texts of the identified abstracts using the same inclusion/exclusion criteria. For each excluded study, a specific reason for exclusion was documented. Quality assessment:

Quality assessment was performed on all included studies not to ascertain eligibility but to assess the methodological quality of the included studies in the context of their strengths and weaknesses. Table 1. Shows summary of the quality assessment performed.

### **Data Abstraction Strategy**

Following perusal of all the included studies, I developed a data abstraction form in Microsoft Word® (2007) format specifically for this project based on understanding of their individual methods and general idea. Economic evaluation outcomes considered for inclusion in the systematic review were then abstracted for each study included at the full-text screening stage. To ensure the quality and consistency of data abstraction, the abstraction form was piloted using a sample of studies considered relevant for inclusion in the review. During this pilot phase, differences in interpretation or potential ambiguities were identified, and necessary modifications were made to the data abstraction template before abstraction of data commenced.

# RESULTS

## Overview of Results

A systematic review of the economic evaluation of human papillomavirus (HPV) Vaccine implementation in Nigeria was conducted, which mainly seeks to establish if it would be cost effective to implement human papillomavirus vaccine in Nigeria. The results of this economic evaluation are presented in the following format:

- An overview of the models used in the literature review
- Model characteristics focusing on the following parameters:
  - Geographical settings
  - Time horizons
  - Health states
- The following methodological characteristics of the models were identified:
  - Interventions and comparators
  - Analysis of perspectives
  - Model input parameters
  - Sensitivity analyses
- Finally, I elucidated more on the results of each of the models by geographical setting

## Study Characteristics

831 Titles and abstract of published articles were searched using the prepared search algorithm. Following stages of comprehensive reviews of abstracts and full text articles using the predefined exclusion and inclusion criteria, this exercises yielded 8 articles eligible for economic evaluation of HPV in Sub-Saharan African Countries. **See appendix A.** showing key characteristics of the selected articles.

A total of 8 published economic evaluation literature which met the inclusion criteria were identified and reviewed (Campos et al., 2012) (Goldie et al., 2008) (Hutubessy et al., 2012) (Jit, Brisson, Portnoy, & Hutubessy, 2014) (Kim, Campos, O'Shea, Diaz, & Mutyaba, 2013) (Quentin et al., 2012) (Sinanovic et al., 2009) (Tracy, Schluterman, Greene, Sow, & Gaff, 2014).

**Quality assessment**

{Placeholder for summary of quality assessment}

**Table 1.** Shows summary of quality assessment performed on all the included studies.

Quality question	Campos et al. 2012	Goldie et al. 2008	Hutubessy et al. 2012	Jit et al. 2014	Kim et al. 2013	Quentin et al. 2012	Sinanovic et al. 2009	Tracy et al. 2014
Answer (Y/N)								
Was a well-defined question posed in answerable form?	Y	Y	Y	Y	Y	Y	Y	Y
Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?	Y	Y	Y	Y	Y	Y	Y	Y
Was the effectiveness of the programme or services established?	Y	Y	Unclear	Y	Y	Y	Y	Y
Were all the important and relevant costs and consequences for each alternative identified?	Y	Y	Y	Y	Y	Y	Y	Y
Were costs and consequences measured accurately in appropriate physical units	Y	Y	N	Y	Y	Y	Y	Y

<b>Were the cost and consequences valued credibly?</b>	Y	Y	Not Clear	Y	Y	Y	Y	Y
<b>Were costs and consequences adjusted for differential timing?</b>	N	Y	Y	Y	Y	N	N	Y
<b>Was an incremental analysis of costs and consequences of alternatives performed?</b>	Y	Y	Y	Y	Y	Y	Y	Y
<b>Was allowance made for uncertainty in the estimates of costs and consequences?</b>	Y	Y	N	Y	Y	Y	Y	Y
<b>Did the presentation and discussion of study results include all issues of users?</b>	Y	Y	Y	Y	Y	Y	Y	Y

## **Study Perspective:**

Four (4) studies were conducted from the societal perspective (Goldie et al., 2008)(Kim et al., 2013)(Quentin et al., 2012)(Tracy et al., 2014), two (2) conducted from the payer's perspective (Hutubessy et al., 2012)(Jit et al., 2014) and two (2) other studies were conducted from both societal and payer's perspectives (Campos et al., 2012)(Sinanovic et al., 2009).

## **Model Type:**

Three (3) studies conducted economic evaluation using simulation model (Campos et al., 2012)(Goldie et al., 2008)(Kim et al., 2013) One (1) other study did not use any models (Hutubessy et al., 2012) and four other studies reported the use of the following model types in their economic evaluation:

- Papillomavirus Rapid Interface for Modeling and Economics (PRIME) (Jit et al., 2014)
- Markov Model (Sinanovic et al., 2009)
- Non Compartmental Mathematical Model (Tracy et al., 2014)
- Incremental cost Model (Quentin et al., 2012).

## **Single or Multi-Country**

Four (4) of the Eight (8) included studies undertook a multi-country study of economic evaluation of HPV in the target region; the remaining four (4) studies undertook a single country study in the target region. However, it is worthy of note almost all multi-country studies were sponsored by international organizations such as the Global Alliance for Vaccine and Immunization (GAVI), World Health Organization and certain private Donor organizations such as Bill and Melinda Foundation etc.

## **Country, Funding and Authorship**

The focus of most included studies, both single and multi-country was on low-income countries, which also includes all countries in the sub-Saharan Africa. Although two (2) of the studies undertook an extensive economic evaluation of HPV in Low and Middle income countries, but has focused mainly on low-income countries to be eligible for this review. However, it is worth of

note that researchers who are primarily based in High income setting mostly used model-based assumptions or some raw data wherever available to report studies authored on all studies conducted on low resource settings such as the sub-Saharan African countries. Poor or lack of quality data, funding and technical capacity to undertake economic evaluation studies are thought to be responsible for this trend.

## Interventions and Comparators

Economic evaluation of HPV vaccination in adolescent girls age (9-13years) was investigated by all included studies. One (1) study investigated the possibility of vaccinating adolescent girls plus screening at age 30 or older. Four (4) studies investigated the cost effectiveness of vaccination of adolescent girls compared to no vaccination. One (1) study investigated cost effectiveness of age-based compared to class-based HPV vaccination of adolescence girls. Two (2) other studies investigated cost effectiveness of screening alone compared to vaccination and screening of adolescent girls. Finally, one (1) study investigated the impact of adolescent HPV vaccine in rural and urban area. It is pertinent to note that all studies investigated the economic evaluation of HPV vaccination of adolescent girls as either a new intervention or an additional intervention to an existing preventative program. Table 2 below shows Interventions and comparators used in the models.

Table 2. Interventions and Comparators used in the models

Study	Intervention and Comparators
<b>Campos et al 2012.</b>	<p>. HPV (16/18) vaccination of pre-adolescent girls.</p> <p>Screening of adult Women using HPV DNA testing or Visual inspection with acetic acid (VIA).</p> <p>Preadolescent not vaccination followed by screening at older ages.</p>
<b>Goldie et al 2008</b>	<p>Economic evaluation of health and economic consequences expected with HPV 16, 18 vaccinations of young adolescent girls. Compared</p>

	to no vaccination.
<b>Hutubessy et al 2012</b>	Phased HPV vaccination over a five-year period of a cohort of adolescent school girls.
<b>Jit, M., et al 2014</b>	Cost effectiveness and health effect of Vaccination of girls against HPV before sexual debut compared to doing nothing.
<b>Kim j . j et al 2013</b>	Cost effectiveness of HPV -16/18 vaccination compared to no vaccination
<b>Quentin et al 2012</b>	Cost effectiveness of age-based vaccination versus Class- based vaccination.
<b>Sinanovic, E., et al. 2009</b>	Current strategy of screening within the National cervical cancer- screening programme compared to vaccination of 12-year old girls followed by screening.
<b>Tracy, J. K., et al. 2014.</b>	Impact of adolescent HPV vaccine in urban and rural areas of Mali.

The results of the studies fall into the flowing categories of intervention compared:

- Vaccination versus Screening
- Screening alone
- Vaccination Vs screening at older age

- Vaccination Vs nothing
- Vaccination + Screening Vs Screening alone

## **Outcome Measure**

Outcome measures used in the studies are briefly described below:

- Disability Adjusted Life Years (DALYs): This is a composite of Year Life Lost due to sudden death and years lived with disability from injuries and diseases i.e. (DALYs = YLD + YLL). It is the most frequently used type of economic evaluation outcome in middle and low income countries, varying opinions exist concerning its use, as some experts are sceptical about its validity(Grosse, Lollar, Campbell, & Chamie, 2009).
- Quality Adjusted Life Years (QALYs): An economic evaluation outcome measure that measures the impact of an intervention on quality and quantity of life in relation to other competing alternatives. Commonly used in high income countries, but sometimes used in low and middle income settings(Whitehead & Ali, 2010).
- Incremental Cost Effectiveness Ratio (ICER): This is a measure of the difference in costs (C1-C2) and effects (E1-E2) of competing alternatives. It informs health policy makers on the most cost effective intervention to invest in healthcare giving the limited resources available(Econ, 2009)

All the included studies except one(1)(Tracy et al., 2014) used Incremental Cost Effectiveness Ratio(ICER) as their outcome measure. The ICER value is measured against a country's Gross Domestic Product (GDP) per capita to determine the cost effectiveness of a particular health program. It is advised by the WHO's commission on microeconomics that a vaccination program with an ICER less than a country's GDP is cost effective. Other outcomes used include the Year life saved(YLS) used by five studies(Campos et al., 2012)(Goldie et al., 2008)(Kim et al., 2013)(Sinanovic et al., 2009)(Tracy et al., 2014) and Disability Adjusted Life Years(DALYs) was used by (Goldie et al., 2008)(Jit et al., 2014)(Kim et al., 2013).

## **Cost Effectiveness thresholds**

All of the included studies established cost effectiveness of HPV vaccination of adolescent girls by using the incremental Cost Effectiveness ratio( ICER)of the HPV vaccine as the threshold against a country's Gross Domestic Product (GDP) per capita. This is in congruent with the suggestion of WHO's Commission on microeconomics and health that an ICER per Quality Adjusted Life Years(QALYs) gained below a country's GDP per capita is very cost effective(Sinanovic et al., 2009). It may not be plausible to confirm that a cost effectiveness threshold based on a country's GDP is a true reflection of willingness to pay and its affordability from the societal and payer's perspective respectively(Fesenfeld et al., 2013).

## **Time Horizon**

Six(6) included Studies specified their time horizon(Campos et al., 2012)(Goldie et al., 2008)(Jit et al., 2014)(Kim et al., 2013)(Sinanovic et al., 2009)(Tracy et al., 2014) and Two (2) did not (Quentin et al., 2012)(Hutubessy et al., 2012), four(4) out of those that specified their time horizon were lifetime (Campos et al., 2012)(Goldie et al., 2008)(Jit et al., 2014)(Kim et al., 2013)(Sinanovic et al., 2009)(Tracy et al., 2014)and Two studies specified 0-85 years and 50 years' time horizon respectively(Sinanovic et al., 2009)(Tracy et al., 2014). Lifetime horizon is the most frequently reported in all the studies.

## **Health States**

Six(6) included specified different health states studied in their studies(Campos et al., 2012)(Goldie et al., 2008)(Jit et al., 2014)(Kim et al., 2013)(Sinanovic et al., 2009)(Tracy et al., 2014).Two (2) did not report health state(Hutubessy et al., 2012)(Quentin et al., 2012). Health states in the reported studies mostly start with HPV infection and terminate at death due to cancer.

## **Geographical distribution of study sources**

All the eight (8) published articles selected for review reported on economic evaluation of HPV in Sub-Saharan Africa Country, Developing countries and GAVI-eligible countries. Studies are individualized itemized below base on their sources:

Six(6) studies (Campos et al., 2012)(Kim et al., 2013)(Hutubessy et al., 2012)(Quentin et al., 2012)(Sinanovic et al., 2009)(Tracy et al., 2014) reported exclusively on countries in SSA

region. Two(2) other countries reported on developing countries and GAVI-eligible countries(Goldie et al., 2008)(Jit et al., 2014).

## Model input Parameters

Sources of input that used in conducting the economic evaluation studies that used models vary greatly, although generally data were extracted from previously published studies, local or international health organization or research agency. **Table 3.** Below shows study and sources of input parameters.

Study	Source of input parameter
(Campos et al., 2012)	Kenya:De Vuyst,2003,Mozambique: Castellsague, 2001,Tanzania: Mayaud, 2001.  Uganda: Castellsague, 2001,Zimbabwe: Castellsauge, 2001,Kenya:de vuyst 2008.  Mozambique: Castellsague, 2008; Naucier, 2004,Tanzania: Bosch, 1995; TerMeulen, 1992,Uganda: Bosch,1995;Odida,2008,Zimbabwe: Stanczuk, 2003
(Goldie et al., 2008)	S.J Goldie et al.
(Hutubessy et al., 2012)	Survey of local cost, Ministry of health and Social Welfare, World Health Organisation and GAVI alliance estimate 2011
(Jit et al., 2014)	WHO, World Bank and The international agency for research on cancer.
(Kim et al., 2013)	J.J kim at al/Vaccine 31S(2013) F60-F72.  Globocan,United Nations world population prospect 2008 data and 2009 WHO life tables
(Quentin et al., 2012)	Mwanza Intervention Trial Unit (MITU), London school of hygiene and tropical medicine (LSHTM) and National Institute for Medical Research (NIMR

(Sinanovic et al., 2009)	Medical research council and actuarial society of South Africa. Prices of screening tests were obtained from local manufacturers
(Tracy et al., 2014)	J.K Tracy et al.

### **Vaccine Coverage**

Of all the Eight(8) included studies ,four(4) assumed that 3-doses of HPV vaccination coverage of adolescent girls would be 70% or greater(Campos et al., 2012)(Goldie et al., 2008)(Kim et al., 2013)(Hutubessy et al., 2012).whilst the other four (4) studies did not report on any assumptions made with regards to vaccination coverage.

### **Vaccine Efficacy**

Only one(1) of the included studies reported 100% vaccine efficacy against HPV 16 & 18(Kim et al., 2013)The rest of the study did not report any assumptions made about HPV vaccine efficacy(Campos et al., 2012)(Goldie et al., 2008)(Hutubessy et al., 2012)(Jit et al., 2014)(Quentin et al., 2012)(Sinanovic et al., 2009)(Tracy et al., 2014).

### **Vaccine duration**

Of all the eight(8) included studies four (4) assumed vaccine lifelong protection against HPV 16 and 18(Campos et al., 2012)(Kim et al., 2013)(Jit et al., 2014)(Tracy et al., 2014)and the other four(4) studies did not report lifelong protection against the vaccine(Goldie et al., 2008)(Hutubessy et al., 2012)(Quentin et al., 2012)(Sinanovic et al., 2009).

### **Sensitivity analyses**

Sensitivity analyses of uncertain parameters were explored to determine their impact on ICER by all the included studies except one(Hutubessy et al., 2012) who did not report if sensitivity analysis was explored. One of the studies explored univariate and multivariate sensitivity analysis specifically(Quentin et al., 2012).Two studies reported that cost of vaccine and discount rate were the most influential parameters on ICER(Kim et al., 2013)(Sinanovic et al., 2009)(Fesenfeld et al., 2013) in his systematic review of the cost effectiveness of HPV vaccine in Low and Middle income countries also reported that vaccine cost was an influential parameter in all the studies he explored. The following parameters were mostly explored in most studies:

- Cost of vaccine
- Vaccine Efficacy, coverage and duration of protection
- Discount rate
- Cervical Cancer incidence
- Death rate from other causes
- Health related quality of life weights

**Table 4. Shows details of sensitivity analysis explored and the list of parameters explored.**

Study	Sensitivity analysis	Outcome Reported
<b>Campos et al 2012.</b>	Vaccine efficacy, coverage and duration of protection, influence of screening coverage, test performance and loss of follow up and assumptions.	<b>ICER:</b> Cost per Life Year saved (YLS).
<b>Goldie et al 2008</b>	One-way sensitivity analysis on the ICER /DALYs	<b>ICER:</b> Cost per Disability adjusted life years( DALYs)and cost per life year saved(YLS)
<b>Hutubessy et al 2012</b>	Not reported	Incremental cost
<b>Jit, M., et al 2014</b>	Cancer incidence.  Overall results of sensitivity analysis of key parameters were robust to adjustments to any of the key parameters.	<b>ICER:</b> Cost per Disability adjusted life years(DALYs)
<b>Kim j . j et al 2013</b>	Discount rate, coverage rate, vaccine efficacy and Vaccine cost	<b>ICER:</b> Cost per life year saved(LYS),Cancer cases

		averted and Disability adjusted life years(DALYs)
<b>Quentin et al 2012</b>	Univariate and multivariate sensitivity analysis were performed using the high cost and low cost assumptions	<b>ICER:</b> Cost per fully immunised girl.
<b>Sinanovic, E., et al. (2009)</b>	Screening coverage, Vaccine efficacy  Vaccine coverage, Delivery options, Death -rate from other causes  Discount rate for both cost and benefits  Health-related quality of life weights.	<b>ICER:</b> Cost per quality adjusted life years (QALYs) and cost per Year life saved (YLS).
<b>Tracy, J. K., et al. 2014.</b>	Variation in cervical cancer occurrence without vaccination and impact of vaccination on undiscounted life years lost from cervical cancer.  Different values of sexual mixing the projected life years gained through vaccination.	Life year saved.

## Summary of cost-effectiveness results

All the eight (8) included studies reviewed for economic evaluation of HPV vaccination of the adolescent female concluded that vaccination would be cost effective even at a cost ranging from \$10-\$25 per vaccinated girls (Campos et al., 2012) (Goldie et al., 2008) (Jit et al., 2014) (Kim et al., 2013) (Quentin et al., 2012) (Sinanovic et al., 2009) (Tracy et al., 2014). Although one study did not clearly report the cost effectiveness of the vaccine (Hutubessy et al., 2012). Most studies reported that the ICER is sensitive to vaccine cost, discount rate and GDP per capita. The ICER is a more informative numerical value which informs more of the needed cost to gain a DALYs, QALYs or YLS.



## DISCUSSION

This systematic review sought to evaluate the implementation of HPV vaccine in Nigeria. The burden of cervical cancer in Nigeria and sub-Saharan Africa at large is eminently amenable to vaccination of preadolescent girls before their sexual debut with three doses of HPV 16 & 18 vaccine at coverage of 70% or over against every benchmark as revealed by this systematic review. The eight studies included for review has four multi-country and four single country studies this allows far reaching representation of relevant studies from relevant contexts. Four of the eight studies conducted their economic evaluation from the societal perspective, two conducted from the payer's perspective whilst the last two conducted from both societal and payer's perspectives this shows that the studies were conducted for different relevant perspectives to reflect costs to Government and the society. A cost to Government or payers alone would not be a true reflection of cost of vaccination and treatment of cervical cancer to the society. Three(3) studies conducted their economic evaluation using simulation models, four(4) studies conducted their economic evaluation using four different models namely: Papillomavirus Rapid Interface for Modeling and economics(PRIME)(Jit et al., 2014), Markov Model(Sinanovic et al., 2009), Non Compartmental Mathematical Model (Tracy et al., 2014), Incremental cost Model (Quentin et al., 2012). One(1) other study did not use any models.

The model-based assumptions used for studies on sub-Saharan African countries by researchers who are mostly based in high income countries is explainable by the lack of or poor data quality available in these region and technical capacity to undertake economic evaluation studies. All the eight included studies investigated economic evaluation of HPV vaccination in adolescent girls but with different comparators .i.e. alternative intervention being measured against vaccination. Studies investigated economic evaluation of HPV vaccination of adolescence girls against no vaccination, vaccination plus screening, screening alone, and certain intra-vaccination program comparisons based on age, class or settlements. All studies established the dominance of vaccination over every other competing alternative. This outcome further strengthens argument for investment in vaccination program over other competing alternatives. Using the ICER as the threshold against GDP per capita in agreement with the

World Health Organization's Commission on Microeconomics and Health that advised that intervention with an ICER, less than a country's GDP per capita should be considered very cost effective. All studies used ICER as the effectiveness threshold in their economic evaluation. (Fesenfeld et al., 2013) Opined that this may not be a true reflection of a country's willingness to pay and affordability from the payer's and societal perspectives.

Almost all studies had time horizons, four studies specified a lifetime horizon whilst two studies had 85 and 50 years' time horizon. However, two other studies did not specify their time horizons. Time horizons are specifically significant in economic evaluation studies. Almost all studies except two specified different health states studied in their models, Health states normally begins with HPV infection and terminates in death due to cancer. All studies included investigated economic evaluation of HPV vaccination of adolescent girls in sub-Saharan African countries. Data for modeling were mostly retrieved from already published articles; local data, international health organization and research agencies adjustment were made to risk adjust for uncertainties resulting from data quality or availability in all studies reviewed. Assumptions were made concerning vaccine coverage and efficacy and lifelong immunity, 70% vaccine coverage at three doses with 100% efficacy these were all necessary to model development. Although only one study reported 100% vaccine efficacy these parameters were consistently explored in sensitivity analysis to assess if they had any influence on ICER of HPV vaccination of adolescent girls.

Vaccine price and discount rate were found to be the most influential parameters when sensitivity analysis were explored to account for certain parameter uncertainties and end ensure robustness of the models. (Fesenfeld et al., 2013) also reported the dominance of vaccine cost in influencing ICER over every other parameters explored in his systematic review. (Jit et al., 2014) in his systematic review specifically reported the dominance influence of vaccine price and discount rate on ICER with variation in the incidence of cancer mildly influencing ICER in Nigeria. This study found that, despite the widely reported cost effectiveness of HPV vaccination of adolescent girls in almost every income settings all across the world, Consideration has to be

given to vaccine price, affordability and willingness to pay in that context. It was found in this study that HPV vaccination of adolescent girls at \$10 per vaccinated girls would be very cost effective in almost every settings in the world with particular emphasis being laid on low resource settings with no existing national preventative program. This study further revealed the cost effectiveness of HPV vaccination of adolescent girls even at vaccine price ranging from \$10-\$25 per vaccinated girls. It is plausible to deduce that HPV vaccination of preadolescent girls can be cost effective, if vaccine prices were affordable relative to Nigeria's purchasing power. Mean reduction in lifetime cancer risks was reported to be below 40% (Goldie et al., 2008) This can certainly be improved upon.

This findings are in agreement with those previously reported in (Fesenfeld et al., 2013) Unfortunately in Nigeria, pre-adolescent and adolescent girls are not routinely included in national immunization program in Nigeria against HPV 16 & 18. Poor documentation, data quality and lack of technical capability to undertake economic evaluation has precluded policy makers to appreciate the burden of cancer resulting from HPV infection and consequently making it a public health priority by giving it a legitimate attention and combating the scourge. GAVI alliance in 2008, made a giant stride by enlisting HPV vaccine as one of its highly prioritized vaccines for implementation. Provided vaccine is subsidized by GAVI, it could achieve a coverage of over 80% in the region (SSA) and this result has a positive implication for Nigeria, being one of the countries in the region (Louie et al., 2009).

Despite its limitations, the outcome of this study would play a pivotal role in informing the policy makers, donors, GAVI and every other key stakeholder on the need to place HPV vaccination of preadolescent girls on top of the policy agenda. This study is also expected to avert the burden of cervical cancer, loss of income due to illness, risk of children being orphaned due to untimely maternal mortality and the consequent catastrophic cost of treatment incurred by patients and their Families giving the fact that, healthcare cost in Nigeria is largely out of pocket with no universal health coverage to offer some form of financial protection. It is expected that, the

generalisability of this study should be leveraged upon by implying its outcome for Nigeria. The outcome of this study can make an astute case for investment in vaccination of preadolescent girls' vaccination Nigeria. It is worthy of note that this Study is not devoid of several limitations as listed below:

- Only English languages abstract were included, certain relevant studies may have been reported in other languages.
- Only one researcher reviewed studies. As such, there may have been an element of subjectivity during the study selection process.
- Data extraction was undertaken by only the researcher, this might not have given room for a balanced opinion.
- Included studies may not be without risk of bias and reporting bias
- Some studies were irretrievable as they were to be purchased or full text not found

## **CONCLUSION**

Nigeria is faced with a huge burden of cervical cancer and its economic, its socio-economic implications transcend the society .healthcare cost associated with treating cervical cancer is often catastrophic, and this predisposes patients and their families to serious financial hardship and poverty. There is an eminent lack of Government attention and priority for the scourge of cervical cancer. This lethargy is as a result several factors ranging from Government's political will to poor or lack of incidence data to reflect the true prevalence of the disease.HPV 16 & 18 have been identified as the most virulent oncogenic subtype of HPV causing 70% of cervical cancer, The introduction of HPV vaccination presents a prospect for alleviating the prevalence of HPV infection and cervical cancer.

Several economic evaluation studies conducted in high, middle and low-income countries have been able to establish the cost effectiveness of the vaccine. This study has revealed that it is potentially cost effective to implement HPV vaccination of preadolescent girls in Nigeria; this implies a huge savings in prospective cost of treating cervical cancer and other HPV related diseases. This study provides a scope for Government to publicly fund the vaccination and treatment of HPV related conditions; Pharmaceutical companies are to be more responsible with making prices of vaccine affordable. Donors to show more commitment to this course and public to engage in vaccination programs when available. Further studies may be undertaking to fashion out the best approach to ensuring accountability in the Nigeria's health system. This is expected to facilitate adequate and quality documentation country specific cost data, healthcare resource use, and clinical effectiveness data.

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<http://www.who.int/countries/nga/en/>

**Appendix A**  
**Data Extraction Tables**

Source			Study Characteristics								
Reference	Country & Setting	Objective	Intervention	Date of Analysis & Currency	Patient Population	Type of Economic Evaluation & Type of Analysis	Health States or Events	Source of Data Used in the Model	Time Horizon & Perspective	Assumptions used in the model	Outcomes Measure and Sensitivity Analyses
Campos et al 2012.	Kenya Mozambique Tanzania Uganda Zimbabwe	<p>To inform and guide policy makers.</p> <p>To evaluate the value of alternative cervical cancer prevention strategies.</p> <p>To explore the comparative performance of, and potential synergies between primary and secondary prevention strategies.</p>	<p>1. HPV (16/18) vaccination of pre-adolescent girls.</p> <p>2. Screening of adult Women using HPV DNA testing or Visual inspection with acetic acid(VIA)</p> <p>3. Preadolescent vaccination followed by screening at older ages.</p>	2005 (Intl.Dollars)	Preadolescent girls before age 12 and older women at ages (35, 40 and 45).	<p>Cost Effectiveness analysis (CEA) and Incremental cost effectiveness analysis</p> <p>CEA, ICER</p> <p>Sensitivity analysis</p> <p>Computer-based simulation model</p>	<p>1. HPV infection state</p> <p>2. Grade of cervical epithelia neoplasm</p> <p>3. Stage of cancer.</p>	<p>Cost: Kenya: De Vuyst, 2003 Mozambique: Castellsague, 2001. Tanzania: Mayaud, 2001. Uganda: Castellsague, 2001. Zimbabwe: Castellsague, 2001.</p> <p>Efficacy and safety:</p> <p>Epidemiology: Kenya: de vuyst 2008.</p> <p>Mozambique: Castellsague, 2008; Naucle, 2004. Tanzania: Bosch, 1995; Ter Meulen, 1992. Uganda: Bosch, 1995; Odida, 2008 Zimbabwe: Stanczuk, 2003.</p> <p>Utilities:</p> <p>Mortality:</p>	<p>Lifetime</p> <p>Societal and payer's perspectives.</p>	<p>Study Assumed 70% of the target population was vaccinated with first dose of the vaccination or screening.</p> <p>Assumed target population were vaccinated prior to age 12.</p> <p>Assumed vaccine provided full lifelong protection against (HPV 16/18) for girls being vaccinated with all three doses.</p> <p>Assumed two doses provided 90% and 1 dose provided 30% lifelong protection</p> <p>Assumed same day treatment of women who tested positive to screening and are therefore eligible for cryosurgery.</p> <p>Assumed that patients not eligible for cryosurgery would be eligible for onward referral to a secondary facility for further clinical investigation and treatment.</p> <p>Assumed screening of women was undertaken during the first visit and the second visit was for collection of screening result. (HPV DNA testing) for a two-visit strategy.</p> <p>Women were eligible for cryosurgery if tested positive following screening on first visit.</p> <p>Assumed the choice of screening modalities, frequency and number of visits depends on the contextual factors.</p>	<p>Incremental cost effectiveness ratio (ICER) &amp; year life saved (YLS) were the outcomes used.</p> <p>Sensitivity analyses were explored on uncertain parameters such as (Vaccine efficacy, coverage and duration of protection, impact of screening coverage, test performance and loss of follow up) and assumptions were undertaken.</p> <p><b>RESULT:</b></p> <p>HPV vaccination and cervical screening were analysed under optimistic assumptions (70% coverage, lifelong immunity).</p> <p>In adolescent girls, vaccination conferred in range (36-45% reduction lifetime risk of cancer.</p> <p>The most effective strategy was the combination of vaccination and once in a lifetime HPV DNA testing, screening at age 35 (which conferred 43-51%).</p> <p>Women above age 30, would benefit most from the one-visit HPV DNA testing Strategy. As this has been identified as the most effective strategy for this group.</p> <p>Visual inspection acetic (VIA) once in a lifetime was identified as the least effective strategy on the effectiveness strata.</p> <p>Screening undertaken three times in a lifetime with one-visit HPV DNA testing attenuated the risk of cancer from 27% to 34%.</p> <p>Screening of pre-adolescence target plus one-visit HPV DNA testing at age 35 was established to be associated with ICER ranging from \$740 (Tanzania) - \$2090 (Kenya).</p> <p>Cost per vaccinated girl alone was found to be more expensive and less cost effective as it approached \$50 than screening alone, Although an exception is the two-visit HPV DNA testing in Uganda with the ICER of \$1240 per YLS.</p> <p>At a cost of \$200/vaccinated girl (\$54 per dose of vaccine), adolescence vaccination followed by screening using one-visit HPV DNA testing at age 35 was associated with an ICER ranging from \$5610 (Tanzania, Uganda) to (\$15000-Kenya).</p> <p>Provided HPV DNA testing is available, it is</p>

											<p>more effective with lower cost effectiveness ratio than VIA (Visual inspection acetic) with ICER ranging from &amp;450(One visit HPV testing once in a lifetime-Tanzania) to \$1860(Two-visit HPV testing once in a lifetime –Kenya)/YLS.</p> <p>It was found that, HPV 16/18 vaccination at 70% coverage of girls between age 9-12 is expected to reduce the lifetime cancer risk by approx.40%, even with attrition rates of 15% between doses.</p> <p>A 50% attenuation of cancer risk is expected in girls who received vaccination with subsequent screening with HPV DNA testing at least once per lifetime.</p>
Goldie et al (2008)	Global Alliance for vaccine Immunisation (GAVI)-eligible countries (e.g. Nigeria,Ghana ,Uganda ,Kenya etc)	To advice Policy makers, Financial Coordination mechanism (GAVI) and potential donors on information on cost effectiveness and financial cost requirement by these stakeholders.	Economic evaluation of health and economic consequences expected with HPV 16, 18 vaccinations of young adolescent girls. Compared to no vaccination.	2005 intl dollar.(I\$)	Birth Cohort of 9-year old girls tracked throughout their lifetimes. Not previously infected with the HPV infection.	Micro- simulation model of HPV infection and cervical Cancer.CEA.	Birth Cohort of 9-year old girls tracked throughout their lifetimes. Comparing health and cost outcomes with or without HPV vaccination.	Cost: S.J Goldie et al.  Utility: S .J Goldie et al.	Lifetime Societal perspective.	<p>1. The model assumed that the average mean time frame between development of invasive cancer and death is 6 years. Ratio of death rate to incidence approximately.80 percent</p> <p>3. Cancer detected because of symptoms in population that are not screened is all at regional and distant stages.</p> <p>4. Model also Assumed 70% Coverage.</p>	<p>Disability Adjusted Life years (DALYs) YLS and ICER.</p> <p>One-way sensitivity analysis exploring the impact of uncertain parameter on ICER /DALYs.</p> <p>Result: At average rate of 70% coverage in all GAVI eligible countries in which countries in sub-Saharan Africa belong, Vaccination of young adolescent girls against HPV 16 and 18 could avert close to three million deaths from cervical cancer over the lifetime of a 10-birth cohort.</p> <p>In Nigeria, Ghana, and some other GAVI eligible countries, mean reduction in lifetime risk of cancer is under 40%, in Uganda and Kenya the mean reduction in lifetime risk of cancer is above 50%.</p> <p>13 averted deaths per 1000 girls vaccinated from all the GAVI eligible countries.</p> <p>17 averted deaths per 1000 girls vaccinated from all high risk areas of the GAVI eligible countries.</p> <p>Vaccination was cost effective for all GAVI eligible countries at \$10 cost per vaccinated girls using the per capital GDP threshold.</p> <p>Cost per DALYs averted was less than \$100 in 49 out of the 72 GAVI eligible countries.</p> <p>Cost per DALYs averted was less than \$200 for 59 countries whilst taking into account country-specific assumptions.</p>

											<p>It was concluded</p> <p>Provided high coverage of adolescent girls is feasible and vaccine costs are lowered, HPV 16, 18 could be very cost- effective even in the poorest countries and provide comparable value to other competing vaccination programs.</p>
Hutubessy et al (2012)	Tanzania	To present the purpose, definitions, methods, data sources and assumptions behind the generic World Health Organisation (WHO) Cervical Cancer Prevention and Control Costing (C4P) tool to assist the Low Middle Income Country (LMIC) in planning and costing their nationwide HPV vaccination program using Tanzania as a case study and result from Tanzania was to be used in piloting the tool.	Phased HPV vaccination over a five-year period of a cohort of adolescent school girls.	3% discount rate.	Adolescent school girls aged 9-13 years.	Incremental cost	N/A	Cost Data: Survey of local cost, Ministry of health and Social Welfare, World Health Organisation and GAVI alliance estimate 2011.	Payer's perspective	<p>Assumed that no additional costs for cold chain would be required for HPV vaccination introduction.</p> <p>Vaccine would be in over three years, 3 regions the first year, 10 regions the second year and all 26 regions in 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> year.</p> <p>Girls enrolled in primary 4 are a proxy of 10-year old girls.</p> <p>Four visits would be made to each school for orientation and to reach all the girls.</p> <p>No additional cost for the cold chain would be required.</p> <p>Transport bringing the HPV</p> <p>HPV vaccine to the facility would be integrated into the existing EPI vaccines.</p> <p>The coverage for girls aged 10 is 85%, 77% and 65% in the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> rounds respectively, Vaccine wastage is 5%, a buffer stock of 15% is maintained.</p> <p>The price per dose is US\$5 based on the price offered by the GAVI.</p> <p>The health worker spends half a day at each school and receives outreach per diem.</p> <p>The transport cost for the health worker from the health facility to and from the school cost an average of US \$ 6.30.</p> <p>Vaccines would be donated during the first three years, but the Ministry of Health and Social Welfare (MOHSW) will pay for syringes, receivers, clearance,</p>	<p>Incremental cost.</p> <p>Over 5 years the cost of introducing HPV vaccine program that delivers three doses of vaccine to girls at school via phased national introduction is estimated to be US \$9.2M (Excluding vaccine cost) and US \$ 31.5M (including vaccine cost) assuming a vaccine price of US \$5.</p> <p>The most important cost of service delivery is social mobilization cost and Information, Education and Communication cost (IEC) and service delivery operation costs.</p> <p>Concluded that countries are faced with initial costs to fund critical pre-introduction activities, as well as incremental system costs to deliver the vaccines on an ongoing basis.</p> <p>Financial delivery costs of nationwide HPV vaccination are higher than those of infants vaccine and can be substantial in resource poor settings since it requires</p> <p>Build up of new delivery channels.</p>

										storage and transport of the vaccines to the health facility.	
Jit, M., et al 2014	179 countries including low and middle-income countries. Low and middle-income countries in focus.	To address the knowledge gap and support evidence based vaccine introduction in countries without economic assessment s of HPV vaccine.  To	Cost effectiveness and health effect of Vaccination of girls against HPV before sexual debut compared to doing nothing.	2011 US \$	12-year old girls before sexual debut.	Papillomavirus Rapid Interface for modelling and Economics Model(PRIME) CEA	Cervical cancer and death.	Cost Data: WHO, World Bank, The international agency for research on cancer.	Lifetime. Payer's perspective  0% or 6% discount rates.	No changes to methods of cervical cancer screening or uptake occur during the time horizon of the model.  Vaccine provided lifelong protection.	DALYS, ICER.  Sensitivity analysis of the following uncertain parameters were explored: -Cancer incidence -Overall results of sensitivity analysis of key parameters were robust to adjustments to any of the key parameters.  <b>RESULT:</b> For all 72 countries in a published study of GAVI-eligible countries, Vaccination of 58million 12-year old girls, in 179 countries 69000 cases,420,000 deaths during their lifetime mostly in LMIC at a net cost of US \$4 Billion. HPV vaccination was very cost effective, with every DALYs averted costing less than the GDP per head. Introduction of HPV vaccine in countries without national HPV at present would prevent substantially more cases of cervical cancer than in countries with such programs. Although disparity has narrowed since 2012.According to forecasts, by the year 2070 GAVI alliance –funded vaccination could prevent 200,000 cases of cervical cancers and 100,000 deaths in some of the highest burden countries.  <b>CONCLUSION:</b> Vaccination is likely to be very cost effective in most countries and cost effective in almost every country in the world. Goldie and Colleagues assessed the cost effectiveness of HPV vaccination in 72 low-income countries. Their result also agreed with the overall conclusion that HPV vaccination is likely to be very cost effective in most part of the world.  This study as they also concluded that vaccination is likely to be very cost effective in most part of the world.
Kim j. j et al (2013)	48 Sub-Saharan Africa Countries.	To project the health benefits, financial requirements and cost effectiveness of HPV vaccination and screening.	Cost effectiveness of HPV -16/18 vaccination compared to no vaccination.	2005 I\$  Discount rate 3%	Birth cohort of pre-adolescent girls aged 9 prior to sexual debut.	CEA, Excel-based model(Simulation model)	HPV infection, precancer and invasive cancer.	J.J kim at al/Vaccine 31S(2013) F60-F72. Globocan,United Nations world population prospect 2008 data,2009 WHO life tables	lifetime Societal perspective	70% vaccination coverage at 100% lifelong efficacy. Lifelong protection against HPV 16/18	YLS, DALYs, Cancer cases averted and ICER.  Sensitivity Analysis of the following were explored: -Discount rate - influence of uncertain inputs and

		To provide decision makers with the information on health and economic benefits of alternative strategies.									<p>assumptions on result.( eg lower coverage rate, vaccine efficacy,</p> <p>-Vaccine cost was varied considerably over a range of \$5-\$360 per vaccinated girl to reflect uncertainty in those costs estimates and as well as heterogeneity of prices for all components across different settings.</p> <p><b>RESULT:</b></p> <p>At a cost price of I\$25 per vaccinated girl(I\$5 per dose ,the price offered by the vaccine manufacturer to GAVI) the ICER of HPV vaccination remained less than the per capital GDP of most countries.</p> <p>For all Countries, ICER increased as the vaccine cost increased.</p> <p>Large variation in health benefits across countries attributable to differential cancer rates, population size and demographic age structure.</p> <p>Variation in financial cost also influenced by population size.</p> <p>At a vaccine cost of I\$5(0.55 per I\$5 (\$0.55 per dose)Per vaccinated girl, HPV vaccination was cost saving in 38 sub-Saharan Africa countries.</p> <p>Using Nigeria as an example, Vaccine cost and discount rates were the most influential parameters explored in sensitivity analysis. Variation incidence of cancer moderately influenced the ICER.</p> <p>Using the empirically calibrated model from South Africa and Uganda, in both settings,screening with Visual Inspection Acetic (VIA) once per lifetime, or the traditional three times per lifetime cytology screening were found to be less effective and with higher ICER when compared to the HPV DNA two-visit screening and three times per life time.</p> <p>HPV DNA three times per lifetime provided 25% cancer incidence reduction over a lifetime in Uganda and South Africa.</p> <p>Vaccination of pre-adolescent girls alone cancer reduction increased to 46.4% in SA and 51.5 in Uganda.</p> <p>HPV DNA three times per lifetime +</p>
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											<p>Vaccination of pre-adolescent girls 59.7% in SA and 63.7% in Uganda.</p> <p>Health gain was high from preadolescent vaccination against HPV 16/18 were quite high for the region overall. However, large disparities exist across countries.</p> <p>Depending on estimated cancer incidence, population age</p> <p>At US\$25 purchasing power parities per vaccinated girl, the cost per life year saved (LYS), DALYs averted would be below the per capital income in these countries.</p>
Quentin et al (2012)	Nwanza region Tanzania	To estimate the cost of school-based HPV vaccination Project in three districts in Mwanza.Tanzania and to model incremental scale-up cost of a regional vaccination program.	Cost effectiveness of age-based vaccination vs Class –Based vaccination	N/A	4,211 cohort of schools girls: Class-based (Class 6 of primary school in 2010) and Age-based (Girls born in 1998).	Cost analysis, Incremental cost modelling.	N/A	Cost data were obtained for the financial departments of the following organisations: Mwanza Intervention Trial Unit (MITU), London school of hygiene and tropical medicine (LSHTM) and National Institute for Medical Research (NIMR).	Societal perspective  3% discount rate	HPV vaccines would be delivered through the Extended Program on Immunisation (EPI).	<p>ICER.</p> <p>Sensitivity Analysis:</p> <p>Univariate and multivariate sensitivity analysis were performed using the high cost and low cost assumptions</p> <p>RESULT:</p> <p>Model of a scale up regional HPV vaccination program estimates that cost per fully immunised girl would be US\$26 when including the vaccine price per dose US\$5.</p> <p>Results of previous cost effectiveness suggest that HPV vaccine at US\$25 per fully immunised girl would be very cost effective in all countries of eastern Africa.</p> <p>Cost estimates suggest that the vaccine can be delivered at cost that would make HPV vaccination a very cost effective intervention.</p> <p>Potentially, delivering HPV vaccines together with other cost effective school-based health interventions and a reduction in vaccine price below US\$5 would lead to lower costs and higher cost effectiveness.</p> <p>I\$5 (\$0.55 per dose) Per vaccinated girl, HPV vaccination was cost saving in 38 sub-Saharan Africa countries.</p> <p>Using Nigeria as an example, Vaccine cost and discount rates were the most influential parameters explored in sensitivity analysis.</p> <p>Variation incidence of cancer moderately influenced the ICER.</p> <p>Using the empirically calibrated model from South Africa and Uganda, in both settings,screening with VIA once per lifetime, or the traditional three times per lifetime cytology screening were found to be less effective and with higher ICER when compared to the HPV DNA two-visits screening and three times per life time.</p>

											<p>HPV DNA three times per lifetime provided 25% cancer incidence reduction over a lifetime in Uganda and South Africa.</p> <p>Vaccination of pre-adolescent girls alone result in increase cancer reduction to 46.4% in SA and 51.5 in Uganda.</p> <p>HPV DNA three times per lifetime + Vaccination of pre-adolescence girls 59.7% in SA and 63.7% in Uganda.</p> <p>Absolute health gain from preadolescent vaccination against HPV 16/18 were quite high for the region overall, but large disparity exist across countries. Depending on estimated cancer incidence, population age structure and underlying competing mortality.</p> <p>Model predicted 670,000 total cases of cervical cancer would be averted in Africa by vaccinating 5 consecutive birth cohort at 70% coverage, out of this,125,000 averted cases would come from Nigeria. At I\$5 per vaccinated girl, HPV vaccine was cost saving in the vast majority of countries ,implying that the advance cost of vaccine would be totally recompensed sub sequential savings in cancer prevention.</p> <p>At a cost of I\$10 per vaccinated girl,(\$2 per dose),HPV vaccine remained cost savings in 14 sub-Saharan African countries and was associated with low ICER in the remaining countries.</p> <p>Using GDP per capital as the threshold below which interventions are considered cost effective, HPV was cost effective in nearly all sub-Saharan African countries when cost per vaccinated girl was \$25(\$5 per dose).However, the ICER becomes less favourable at higher vaccine cost.</p>
Sinanovic, E., eet al. (2009)	South Africa	This study seeks to answer the question of whether a cervical cancer prevention programme that incorporates an HPV vaccine is potentially more cost effective than the current strategy of screening alone.	Current strategy of screening within the National cervical cancer-screening programme compared to vaccination of 12-year old girls followed by screening.	Inflated to 2007 \$US.	100,000 hypothetical population of women ages 12 and 85 screened with no vaccination and vaccinated followed by screening respectively	CEA  Static Markov state transition model	Risk of HPV infection Low or high-grade squamous intraepithelial lesion or resolve, Those with low or high grade could have their disease persist,	Medical research council and actuarial society of South Africa.  Prices of screening tests were obtained from local manufacturers.	Time horizon: 0-85.  Health service(Payer's or provider) and societal perspectives.	All 100,000 women were disease –free at from the outset of the model.	<p>ICER, Quality adjusted Life Years (QALYs) YLS.</p> <p>Sensitive Analysis were performed on:</p> <ul style="list-style-type: none"> <li>-Screening coverage</li> <li>-Vaccine efficacy</li> <li>-Vaccine coverage</li> <li>-Delivery options</li> <li>-Death -rate from other causes</li> <li>-Discount rate for both cost and benefits</li> <li>-Health-related quality of life weights.</li> </ul>

							regress or progress .Cancer and death.				<p>Results were robust in sensitivity analysis with ICER most sensitive to: Discount rate, vaccine price and vaccine efficacy</p> <p><b>RESULT:</b> Provided, cost and benefits are not discounted, The vaccination followed by screening strategy is more cost-effective and the screening only strategy is dominated. Provided cost and benefits are discounted, the ICER s are US\$3320 and 4495 per life years saved.(YLS) from the health service perspective. In addition, US\$1078 AND 1460per QALY gained from the societal perspective.</p> <p>The key cost driver in the vaccine arm of the model is the vaccine price. The cost-effectiveness of adding vaccine to the existing screening program in south Africa is cost-effective. The ICER of adding</p> <p>HPV vaccination to the screening program ranged from US\$ 1078 per QALY gained to US\$ 4495 per life years saved. Mainly depending on weather, the study was viewed from a health services or societal perspective.</p> <p>Adding HPV vaccine would be considered very cost effective going by the suggestion of commission on microeconomics and health that an ICER per QALY gained below a country's GDP per capita is cost effective.</p> <p>South Africa's GDP per capital is US\$5724 and the ICER per QALY gained by adding the vaccine is between US\$1078 and US\$1460.</p> <p>However, Cost –effectiveness of decreases with increasing HIV-related mortality.</p> <p>When patient cost were included in the analysis, the ICER decreased by 26% on average which implies that, whilst the presence of vaccine has the potential to reduce the cost of cervical cancer to the health system, it also can potentially reduce the cost to patient, especially with the level of poverty in south Africa and the rest of developing countries.</p>
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Tracy, J. K., et al. 2014.	Mali, West Africa.	To predict the impact and cost-effectiveness of an HPV vaccination program in a single low resource country: Mali, West Africa	Impact of adolescent HPV vaccine in urban and rural areas of Mali.	2011US\$ discounted to 3% annually	A point simulation vaccination of a cohort of 333,146 urban and rural Malian Women age 10-14 .With no previous HPV vaccination.	Cost analysis Non compartmental Mathematical model	Susceptible stage, infection stage, recovered and immune, vaccinated, cervical intraepithelial neoplasm, invasive cervical cancer.	J.K Tracy et al.	50 year time horizon Societal perspective	<p>Full vaccination would confer lifelong immunity against HPV 16 and 18.</p> <p>HPV 16 was assumed twice as prevalent as HPV 18 due to unavailability of data on prevalence in this setting.</p> <p>HPV and the cumulative incidences of cervical cancer cases and death were all assumed nearly constant over time in the absence of vaccination.</p> <p>Infectivity of HPV 16 and 18 were assumed equivalent.</p>	<p>Life Year Saved (LYS).</p> <p>Sensitivity Analyses of the following were explored using different value for the sexual mixing parameters impact on cervical cancer outcome.</p> <p>-Variation in cervical cancer occurrence without vaccination and -----impact of vaccination on undiscounted life years lost from cervical cancer.</p> <p>-Different values of sexual mixing the projected life years gained –through vaccination.</p> <p><b>RESULT:</b></p> <p>The urban cost per discounted life year saved was I\$962(15% coverage) and I\$1538(905 coverage).</p> <p>HPV vaccine was more cost effective for all outcomes in the rural settings that in the urban setting.</p> <p>Cost per HPV cervical cancer death prevented in the urban setting was I\$7060 ((15% coverage) and I\$11500(90% coverage).</p> <p>Cost per HPV cervical death prevented I\$5180(15% coverage) to I\$7670( 90% coverage).</p> <p>In all coverage scenario(Urban and Rural),the projected cost per life year saved in Mali was below Mali's GDP per capita,Suggesting</p> <p>Vaccination would be cost effective.</p> <p>The model result t also indicated that assessing not only country specific HPV prevalence but also within country regional HPV prevalence is critical to effective HPV vaccination planning.</p>
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Footnotes and abbreviations :

\*YLS(Year Life saved), QALYs(Quality of Life Year Saved), DALYs(Disability Adjusted Life Years), MOHSW(Ministry of health and Social Welfare), ICER(Incremental Cost Effectiveness Ratio), CUA(Cost Utility

Analysis), CEA(Cost Effectiveness Analysis), HPV(Human Papillomavirus ), GAVI(Global Alliance for Vaccine and Immunization), GDP(Gross Domestic Product), LMIC(Low and Middle Income Country).



