



Research Paper

Human papillomavirus vaccination uptake in low- and middle-income countries: a meta-analysis

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ABSTRACT

Background: The proportion of incident cases of HPV-attributable cancers is highest in the low- and middle-income countries (LMICs) but many are yet to initiate HPV vaccination programs. This meta-analysis was performed to assess the uptake of HPV vaccination in LMICs at the beginning of the global strategy to eliminate cervical cancer and describes the gaps and challenges.

Methods: A systematic search was conducted in PubMed, EMBASE, Scopus, Web of Science, and CENTRAL databases for observational studies that reported the uptake of HPV vaccination until October 2020. The meta-analysis was done using a random-effects model to assess the pooled estimate of HPV uptake. CRD42021218429

Findings: During 2008–2020, an estimated 3.3 million females received at least one dose of HPV vaccine with 61.69% of the target population vaccinated. In countries with high uptake, the pooled estimate of uptake was higher in females than males (45.48% vs 8.45%) and showed significant decline in 2015–2020 compared to 2006–2014 (89.03% vs 41.48%). In countries with low uptake, the estimate of uptake was low in both males and females (5.31% vs 2.93%) and showed increase in uptake in 2015–2020 compared to 2006–2014 (0.76% vs 5.22%). In countries with high uptake, compared to routine programs, the estimate was higher when delivered through demonstration programs (89.94% vs 59.74%).

Interpretation: The major concern was a significant drop in the uptake in countries that started with high uptake, challenges in the maintenance of vaccine uptake, sustainability of funding and the lack of standard monitoring and reporting.

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1. Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection and is the second-leading cause of incident cases of infection-attributable cancers worldwide [1]. The high-risk types of HPV (types 16/18 and types 6/11/16/18/31/33/45/52/58) are

attributable to 73% and 90% respectively of global cervical, anogenital, and oropharyngeal cancer cases [2]. The global burden of incident cancers attributable to HPV has risen from 570,000 in 2012 to 690,000 in 2018 with the highest age-standardized incident rates reported in sub-Saharan Africa (19.3 cases per 100,000 person-years) followed by central and eastern Europe (10.9), south-eastern Asia (9.6), South America (9.6) and India (9.0) [1,2]. The age-standardized incident rates of these cancers show a clear association with national income as measured by the World Bank, increasing from 6.9 cases per 100,000 person-years in high-income and upper-middle-income countries to 9.2 in low-income countries [2]. The proportion of HPV-attributable cancer of cervix uteri is highest in the low-income countries while the burden of anogenital and head and neck cancer is higher in high-income countries [1].

There are four vaccines against the HPV: the quadrivalent (4vHPV) Gardasil approved in 2006, bivalent (2vHPV) Cervarix approved in

Abbreviations: 2vHPV, bivalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; 9vHPV, 9-valent HPV vaccine; CENTRAL, cochrane central register of controlled trials; CI, confidence interval; CIN2+, cervical intra-epithelial neoplasia grade II; EMBASE, excerpta medica dataBASE; GNI, gross national income; HPV, human papillomavirus; LMICs, Low- and middle-income countries; MSM, men having sex with men; RR, relative risk; STROBE, strengthening the reporting of observational studies in epidemiology; US, United States; WHO, World Health Organization

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Research in context

Evidence before this study

The burden of HPV-attributable cervical, anogenital, and oropharyngeal cancer is the highest in Low- and Middle-Income Countries, many of which lack a systematic cervical cancer screening program and capabilities for high-end treatment of cervical cancer. Population-level vaccination in high-income countries have demonstrated the decline in the prevalence of high-risk HPV, the decrease in the burden of HPV-attributable cancers, and cross-protection from other types of HPV. The implementation of an effective vaccination program in LMICs is projected to decrease the burden of disease by significant levels and possible elimination of cervical cancer by the turn of the century. However, many LMICs are yet to initiate an HPV vaccination program while many which had initiated are facing challenges in maintaining high uptake of vaccination.

Added value of this study

In November 2020, the World Health Organization (WHO) launched the Global Strategy to Accelerate the Elimination of Cervical Cancer, the first of its kind in the elimination of cancer. This targets 90–70–90 strategy where 90% of the girls are vaccinated by the age of 15 years, 70% of women have access to high-performance screening tests for cervical cancer and 90% of women with cervical cancer have adequate access to quality treatment by 2030. This meta-analysis was performed to estimate the present status of HPV vaccination uptake in LMICs at the start of this strategy.

Implications of all the available evidence

This study provides a timely assessment of uptake of HPV vaccine in demonstration and routine programs in LMICs based on peer-reviewed publications between 2008 and 2020. It contextualizes the present status of uptake in LMICs within the scope of global cervical cancer elimination targets and in efforts of reducing HPV-attributable cancers. The findings presented here identifies opportunities and challenges in achieving and maintaining high uptake of the vaccine, and in securing sustainable funds for the vaccine program.

with almost two-thirds of the cases occurring in countries with low-Human Development Indices [7]. In November 2020, the WHO launched the Global Strategy to Accelerate the Elimination of Cervical Cancer, the first of its kind in the elimination of cancer [8]. The WHO strategy recommends all countries to reach and maintain an incidence rate of cervical cancer below 4 per 100,000 women and eliminate cervical cancer as a public health problem in keeping with the 2030 agenda on Sustainable Development Goals. The elimination strategy aims to vaccinate 90% of girls by the age of 15 years [8]. The WHO recommends HPV vaccination to be included in national immunization programs for the primary target population of girls aged 9–14 years and secondary target population of females aged ≥ 15 years or adolescent males [9]. When the vaccination program is introduced, multiple cohorts of girls 9–14 years should be vaccinated [9,10] as this method of rollout has a greater and faster direct impact and herd effects of HPV vaccination [5].

As of 2021, there are considerable disparities between countries – while more than 85% of high-income countries had introduced HPV in the national immunization schedule, less than 25% of low-income, less than 30% of lower-middle-income, and less than 60% of upper-middle-income countries had done so [8]. This is coupled with a lack of a national cervical cancer screening program and limited facilities available for diagnosis and treatment of cervical cancer in the public sector in these countries [8]. In 2019, the LMICs were home to 27.4 million girls aged 9–14 years with 28.7 million girls aged 5–9 years who will graduate to the age group eligible for HPV vaccination in the next five years [11]. The current estimates of HPV vaccine coverage in many countries are based on proxy data or estimates are not available [12]. Therefore, this meta-analysis was conducted to report the uptake of HPV vaccination in terms of the proportion of girls, boys, and older females vaccinated and the serotype coverage of HPV vaccines (4vHPV, 2vHPV, and 9vHPV) in LMICs up till October 2020. In addition, the variations of HPV vaccine uptake studies in terms of gender and age groups, the operational definition of ‘uptake’, the nature of the HPV vaccination program (i.e. demonstration vs implementation), as well as the types of HPV vaccines and sponsorship, were qualitatively synthesized.

2. Methods

This meta-analysis was conducted following the recommendations of the Preferred Reporting Items of Systematic Reviews and Meta-analysis (PRISMA) statement [13,14]. We registered the study protocol with the PROSPERO International Prospective Register of Ongoing Systematic Reviews (CRD42021218429).

2.1. Gross national income (GNI) of economies

For the year 2020–2021, there were 135 economies classified as LMICs by the World Bank based on GNI per capita in 2019: there were 29 economies classified as low-income with GNI per capita of US dollar ≤ 1035 , 50 economies classified as lower-middle-income with GNI per capita between US dollar 1036 and 4045, and 56 economies as upper-middle-income with GNI per capita between US dollar 4046 and 12,536 [15].

2.2. Search strategy

PubMed, EMBASE, Scopus, Web of Science, and CENTRAL databases were searched for articles published in English up to 26 October 2020. The terms “Human papillomavirus”, “HPV” and “Papillomavirus infections” were used in combination with “vaccination”, “immunization”, “HPV Vaccine”, “Gardasil”, “Cervarix”, “Uptake” and “Coverage” as the keywords for literature search along with their synonyms. The search strategy is presented in detail in the supplementary material. We also searched Google Scholar for other relevant articles.

2010, 9-valent (9vHPV) Gardasil-9 approved in 2014 and the bivalent Cecolin approved in China in 2019 [3,4]. All vaccines are effective against the high-risk HPV 16/18 while Gardasil has additional coverage against HPV 6/11 and Gardasil-9 against HPV 6/11/31/33/45/52/58 [3]. A meta-analysis of the population-level impact of HPV vaccination for 5–8 years in fourteen high-income countries reported that the prevalence of HPV 16 and 18 decreased by 83% among girls aged 13–19 years and by 66% among women aged 20–24 years with significant cross-protection from HPV 31, 33 and 45 [5]. It also reported a decrease in the prevalence of anogenital wart by 67% among girls aged 15–19 years, by 54% among women aged 20–24 years and by 31% among women aged 25–29 years; by 48% among boys aged 15–19 years and by 48% among men aged 20–24 years [5]. This meta-analysis also demonstrated that after 5–9 years of vaccination, the prevalence of CIN2+, a pre-cancerous stage, decreased by 51% among screened girls aged 15–19 years and by 31% among women aged 20–24 years [5].

It is estimated that high HPV vaccination coverage in girls can lead to cervical cancer elimination in most low- and middle-income countries by the end of the century [6]. However, in the absence of further effort in improving vaccination coverage, there would be 44.4 million cervical cancer cases diagnosed globally over the period 2020–69,

2.3. Study selection

We worked with an information specialist to design an appropriate search strategy to identify original peer-reviewed cross-sectional or longitudinal studies that reported HPV vaccination uptake or coverage in low- and middle-income countries until October 2020. Studies that reported HPV vaccination in interventional studies, model or simulation studies, non-peer-reviewed publications, and those not in English were excluded. Article screenings for eligible studies were done by two independent reviewers (TD and TN). Discrepancies between the two reviewers were resolved by discussion and consensus. Covidence 2.0 (Veritas Health Innovation, Melbourne, Australia) was used for article screening.

2.4. Data extraction

Data extraction was done by two independent reviewers (TD and TN) into Microsoft Excel for published summary estimate data. The following data were extracted: study characteristics (authors, year of publication, study type, journal name, contact information, country, and funding); population characteristics (sample size, age at vaccination, percentage of vaccination uptake, special type of population (people living with HIV, male having sex with males, MSM), the number of dosage of HPV vaccines received (one, two or three), male/female uptake; HPV vaccine characteristics (4vHPV, 2vHPV, and 9vHPV; year of initiation of vaccination); vaccination program characteristics (whether vaccination was sponsored by the government, insurance or provided free of cost; whether vaccination was delivered through demonstration/pilot projects or via routine national programs; the percentage of vaccination uptake over time; the cost involved in vaccination); and income-level of the country based on the World Bank criteria. All relevant text, tables, and figures were examined for data extraction.

Data were imported to EpiData 3.1 (version 3.1 for entry, EpiData Association, Odense, Denmark) for validation and the discrepancies in the data points were resolved through discussion and consensus. The corresponding author of the study was contacted when there are incompletely reported data. If the authors did not respond within 14 days, we conducted the analyses using the available data.

2.5. Quality assessment

Two reviewers (TD and TN) worked independently to assess the risk of bias in the studies included for systematic review and meta-analysis using the eleven-item Hoy's risk of bias tool in prevalence studies [16]. We assessed the representativeness of the sample, sampling frame, sampling techniques, response rate, data collection method, case definition, measurement tools, study period, and data calculation. We assigned each domain as a low or high risk of bias while the overall risk of bias was reported as a low, moderate, or high risk of bias. The data for risk of bias assessment was extracted into Microsoft Excel and validated in EpiData 3.1 (version 3.1 for entry, EpiData Association, Odense, Denmark) and the discrepancies in the data points were resolved through discussion and consensus.

Additionally, we assessed the adequacy of reporting of the population at risk and sample selection; the uptake of vaccination, definition of vaccination status based on the type of vaccine and dosage (one, two, or three doses), and the reporting of the study using STROBE guideline. We assigned each domain as low risk of bias or high risk of bias. We contacted the corresponding author if there were inadequate information presented. If the authors did not respond within 14 days, we conducted the analyses using the available data.

2.6. Statistical analysis

The primary outcome assessed was the uptake of HPV vaccination, particularly for pre-pubertal girls and boys in low- and middle-

income countries. The uptake of HPV vaccination was measured with the percentage of pooled samples who had received at least one dose of the HPV vaccine in each country and total samples in each country with an associated 95% confidence interval (CI). The secondary outcomes were the types of vaccines used, vaccination uptake of the first, second, and third doses (until 2014); and the uptake in special sub-populations. The results of the studies included in the meta-analysis are presented using forest plots with statistical powers, confidence intervals, and heterogeneity.

We have defined uptake as the proportion of the eligible population who were reported to have received at least one dose of the HPV vaccine. While the studies used the terms 'uptake' and 'coverage' interchangeably, we have reserved the term 'coverage' for assessment of the size of population to whom vaccines were delivered from the deliverer point-of-view.

The methodological heterogeneity was assessed by examining sample characteristics, sampling method, mode of assessment of uptake, and the study design. The statistical heterogeneity was assessed using the I^2 statistics. The level of heterogeneity for I^2 statistic was interpreted as defined in chapter 9 of the cochrane handbook for systematic reviews of interventions: 0–40% may not be important; 30–60% may represent moderate heterogeneity; 50–90% may represent substantial heterogeneity; 75–100% considerable heterogeneity. The Freeman-Tukey double arcsine transformation was used to ensure admissible confidence intervals. The random-effects meta-analysis by DerSimonian and Laird method was used as clinical, methodological, and statistical heterogeneity encountered. The exact method was used for confidence interval computation. The meta-analysis was performed using STATA 13.1 (StataCorp, College Station, TX, USA) using *metaprop* command.

2.7. Role of funding source

There was no funding for this study.

3. Results

3.1. Study selection

The database search identified 11,073 potential records. After removing duplicates, 4267 were screened and 303 theme-related titles and abstracts were selected for full-text assessment (Fig. 1). A total of 256 were excluded: 136 wrong settings in now high-income economies, 65 not peer-reviewed, 20 wrong outcomes, 10 wrong study designs, 8 review articles, 6 duplicates, 4 wrong patient population, one book chapter, one case report, one editorial, one letter, one study protocol, one contained only errata information, and one full-text was not available. Forty-seven studies were eligible for qualitative synthesis and meta-analysis.

3.2. Study characteristics

The 47 studies included were published from 24 countries between 2008 and 2020: four low-income economies, fourteen lower-middle-income economies, and six upper-middle-income economies. There were 45 cross-sectional studies and two longitudinal studies. The number of study participants reported ranged from 73 to 18,44,062 with a total of 4,338,331 participants; 4,336,836 (99.97%) were females and 1395 (0.03%) were males. Eight studies had included the male population [17–23], one had reported uptake among people living with HIV [24] and one reported uptake among people with inflammatory bowel disease [18]. Eleven studies reported using nationally representative data while 36 reported using sub-national samples. Fourteen studies reported data from demonstration or pilot projects at introduction of the vaccination program [25–38], while eleven studies reported data from routine

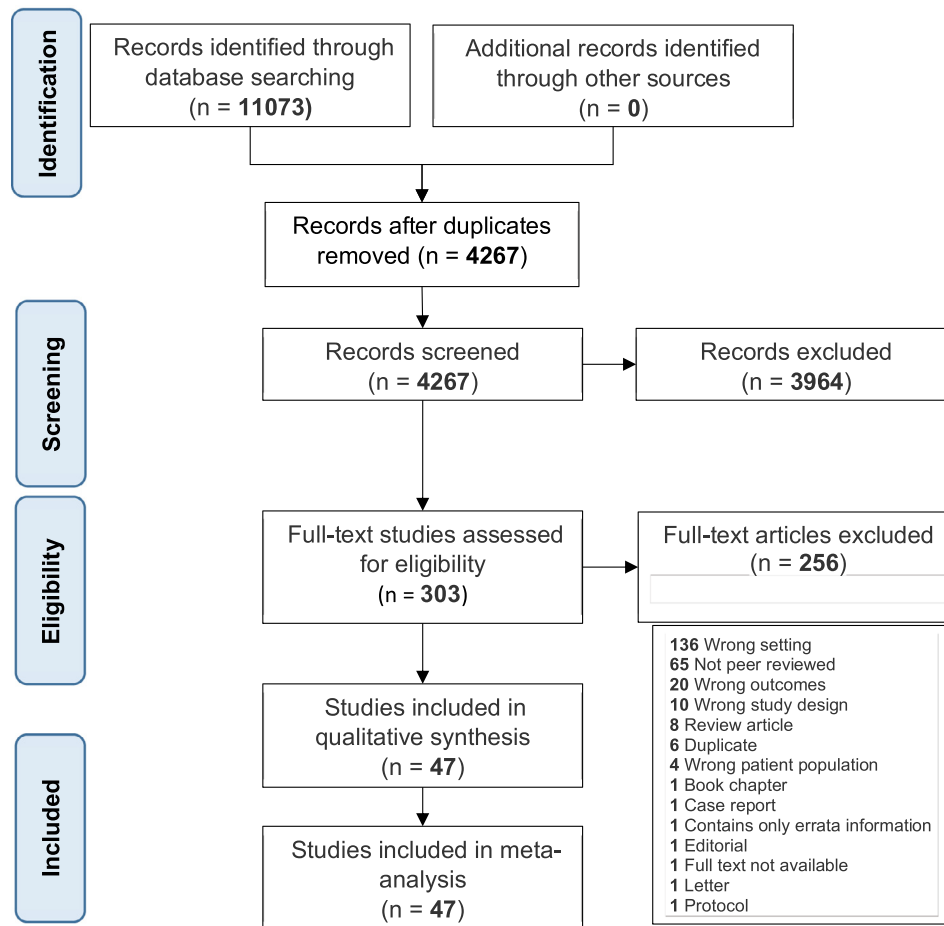


Fig. 1. Flowchart presenting the study selection with the preferred reporting Items for systematic reviews and meta-analyses (PRISMA) guidelines for the meta-analysis on human papillomavirus vaccine uptake in low- and middle-income countries, 2020.

immunization programs [23,39–48]. The types of studies, the country, total population, and year of reporting, types and sponsor of vaccine, representativeness of sample and the type of vaccination delivery (demonstration/pilot project or routine immunization program) are shown in Table 1.

3.3. Quality assessment

Five studies had an overall high risk of bias, 39 had a moderate risk of bias, and three had a low risk of bias. The domains with a high risk of bias were the representativeness of the sample (38, 80.9%), the reliability and the validity of the study tool (38, 80.9%) followed by the study period-length of the shortest prevalence period (31, 66.0%), and sampling technique (24, 51.1%). A summary of the percentages of studies with the risk of bias domain is shown in Fig. 2. The detailed risk of bias assessment is shown in Supplementary Table 3.

3.4. Qualitative synthesis

3.4.1. Variations of HPV vaccine uptake studies

Twenty-four studies reported the HPV vaccine uptake among girls, 17 reported among adult women, and six reported among both girls and adult women while only seven studies reported among adult men, and none reported among adolescent boys. The age range in which girls were vaccinated was from 8 to 19 years, with the lower limit reported in Argentina [49] and Malawi [35] and the upper limit reported in Nigeria [50].

The uptake of at least one dose of HPV vaccine was reported in 3,325,779 individuals (76.7%). In females, the first dose uptake was

reported in 3,325,707 (76.7%), the second dose uptake in 2,910,986 (67.1%) and the third dose uptake in 1,349,010 (31.1%). However, there were gross differences in the operational definition of vaccination uptake, and the uptake of only the ‘first-dose’ or ‘any dose’ was comparable across studies. The overall uptake of HPV vaccine, uptake of the first, second, and third doses, uptake in special population for countries is shown in Supplementary Table 2.

The vaccination programs were initiated as demonstration or pilot projects that covered selected regions of the country where vaccines were delivered through a mix of school-, community-, or facility based-programs between 2008 and 2017. Data on the uptake from demonstration projects were reported from Bhutan [27], Cambodia [29,32], Vietnam [33], Cameroon [25,32], Ghana [51], Kenya [34,38], Lesotho [32], Malawi [35], Bolivia [32], Haiti [32] and Peru [33]. The compliance to dosing schedules in demonstration projects in Bhutan, Bolivia, Cambodia, Cameroon, Haiti, Lesotho, and Nepal in 2009–2010 was 96.1% between the first and the second dose, 94.5% between the second and third dose, and 90.9% between the first and the third dose [32]. In Malaysia, the average compliance in completion of the third dose in the national school-based vaccination program between 2010 and 2016 was 99.0% [45]. However, even in a demonstration project in Kenya, higher percentages of non-compliance were reported with 63.8% receiving the second dose and only 39.1% completing the third dose [34].

These demonstration projects involved active communication strategy, the involvement of community leaders and parents, incentives such as t-shirts, bracelets, or even financial contributions to cover the cost of participation in the vaccination project and retain the vaccinated cohort until completion of the vaccine schedule [32].

Table 1
Characteristics of the studies included in the meta-analysis on human papillomavirus vaccine uptake by countries' income level, 2008–2020.

	Countries	No. of Studies	Year of Publication	Study Design	Total Sample	Female; n (%)	Female Age group	Year of Data Collection	Year of Vaccine Initiation	Type of HPV Vaccine	Sample Representation	Vaccine Sponsor	Vaccination Program
Upper-Middle-Income Countries													
1	Argentina	1	2012	Cross-sectional	1312	1312 (100.0)	Girls, Adult women	2009–2010	2011	Cervarix, Gardasil	Regional	Government	1 Other
2	Brazil	8	2013–2020	8 Cross-sectional	28,733	28,327 (98.6)	5 Girls, 3 Adult women	2014–2017	2010–2014	1 Cervarix, 7 Gardasil, 1 Not recorded	2 National, 6 Regional	8 Government	1 Demonstration, 5 Routine, 2 Others
3	China	3	2020	3 Cross-sectional	5831	5564 (95.4%)	1 Girls, 3 Adult women	2018–2019	2016–2017	3 Cervarix, 3 Gardasil, 2 Gardasil-9	1 National, 2 Regional	2 Self-sponsored, 1 Not recorded	3 Others
4	Malaysia	6	2011–2019	5 Cross-sectional, 1 Longitudinal	1,845,797	1,845,607 (99.9)	3 Girls, 3 Adult women	2010–2017	2006–2010	3 Cervarix, 2 Gardasil	1 National, 5 Regional	3 Government, 3 Not recorded	2 Routine, 4 Others
5	Peru	1	2011	Cross-sectional	8092	8092 (100.0)	Girls	2008	2008	Not recorded	Regional	INGO	1 Demonstration
6	South Africa	1	2018	Cross-sectional	408,273	408,273 (100.0)	Girls	2014	2014	Cervarix	National	Government	1 Demonstration
Lower-Middle-Income Countries													
7	Bangladesh	1	2020	Cross-sectional	600	600 (100.0)	Adult women	2019–2020	2016	Not recorded	Regional	INGO	1 Other
8	Bhutan	3	2012–2020	Cross-sectional	53,469	53,469 (100.0)	2 Girls, 1 Adult women	2009–2018	2009–2010	Gardasil	2 National, 1 Regional	2 Government, 1 INGO	2 Demonstration, 1 Routine
9	Bolivia	1	2017	Cross-sectional	34,380	34,280 (99.7)	Girls	2009	2009–2011	Gardasil	National	INGO	1 Demonstration
10	Cambodia	2	2017–2019	2 cross-sectional	2315	2315 (100.0)	2 girls	209–2017	2016–2019	1 Cervarix, 1 Gardasil	1 National, 1 Regional	1 INGO	2 Demonstration
11	Cameroon	2	2012–2017	2 cross-sectional	2153	2153	2 girls, 1 Adult women	2009–2011	2009–2010	2 Gardasil	1 National, 1 Regional	2 INGO	2 Demonstration
12	Ghana	1	2018	Cross-sectional	288	288 (100.0)	Adult women	2015	2013	Gardasil	Regional	INGO	1 Other
13	India	3	2011–2017	Cross-sectional	28,199	27,927 (99.0)	1 Girls, 2 Adult women	2009–2015	2009	3 Not recorded	Regional	1 INGO, 2 Not recorded	1 Demonstration, 2 Others
14	Kenya	2	2014–2018	1 cross-sectional, 1 longitudinal	3280	3280 (100.0)	2 Girls	2012–2014	2012	2 Gardasil	2 Regional	2 INGO	2 Demonstration
15	Lesotho	1	2017	Cross-sectional	40,100	40,100	Girls	2009–2011	2009	Gardasil	National	INGO	1 Demonstration
16	Nepal	1	2017	Cross-sectional	3000	3000	Girls	2009–2011	2010	Gardasil	National	INGO	1 Demonstration
17	Nigeria	5	2017–2020	5 Cross-sectional	1476	1476 (100.0)	3 Girls, 3 Adult women	2016–2018	2009*	1 Cervarix, 1 Gardasil, 4 Not recorded	5 Regional	1 Self-sponsored, 5 Not recorded	1 Demonstration, 4 Others
18	Pakistan	1	2017	Cross sectional	1038	1038 (100.0)	Girls and adult women	2011	Not recorded	Not recorded	Regional	Not recorded	1 Other
19	Ukraine	1	2020	Cross sectional	772	587 (76.0)	Adult women	2018	Not recorded	Not recorded	Regional	Self-sponsored	1 Other
20	Vietnam	2	2011–2018	2 cross sectional	7360	7285 (99.0)	1 Girl, 1 Adult women, 1 Not recorded	2008–2016	2006–2008	2 Not recorded	2 Regional	1 partial government-partial self funded, 1 INGO	1 Demonstration, 1 Other
Low Income Countries													
21	Haïti	1	2017	Cross sectional	3300	3300 (100.0)	Girls	2009–2011	2009	Gardasil	National	INGO	1 Demonstration
22	Malawi	1	2017	Cross sectional	11,240	11,240 (100.0)	Girls	2013–2016	2013	Gardasil	Regional	INGO	1 Demonstration
23	Rwanda	2	2018–2020	2 cross sectional	1,819,008	1,819,008 (100.0)	2 Girls	2011–2018	2011	2 Gardasil	2 national	2 Government	2 Routine
24	Uganda	6	2011–2020	6 cross sectional	28,315	28,315 (100.0)	6 Girls, 1 Adult women	2008–2016	2008–2012, 1 Not recorded	2 Cervarix, 4 Not recorded	2 National, 4 Regional	3 Government, 2 INGO, 1 Not recorded	4 Demonstration, 1 Routine, 1 Other
	Total	47	2011–2020	45 cross sectional, 2 longitudinal	4,338,331	4,336,836 (99.97)	39 Girls, 23 Adult women	2008–2020	2006–2017, 8 Not recorded, 4 Not yet initiated	13 Cervarix, 30 Gardasil, 2 Gardasil-9, 21 Not recorded	17 National, 39 Regional	19 Government, 19 INGO, 4 Self-sponsored, 1 Partial government-self sponsored, 13 Not recorded	14 Demonstration, 11 Routine, 22 Others

* Year when HPV vaccine was licenced in Nigeria, vaccination not yet initiated in pilot programs or national immunization schedules
INGO = international non-government organization.

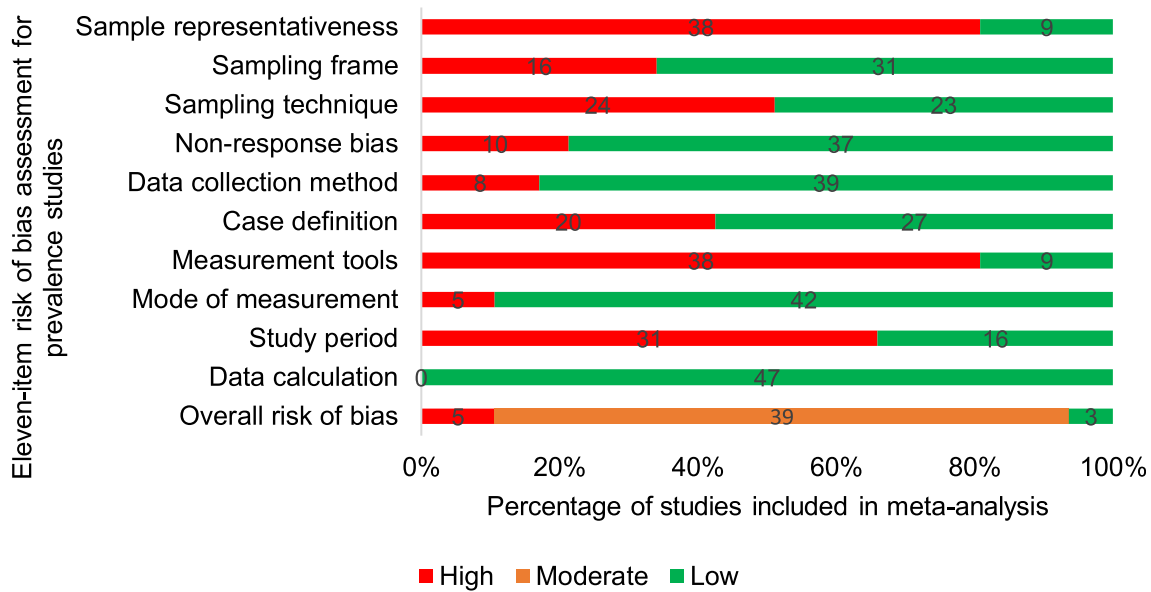


Fig. 2. Risk of bias assessment in prevalence studies based on Hoy's eleven-item criteria [16] for the studies included in the meta-analysis on human papillomavirus vaccine uptake in low- and middle-income countries, 2008–2020.

It also identified enablers and barriers to HPV vaccination uptake. Among parents or caregivers, the reported reasons for acceptance of vaccines were to protect their daughters from cervical cancer, that they were advised to get daughters vaccinated, and that the vaccines were given free [33,49]. The reasons for partial or no uptake were inconvenient location/time for vaccination, parent/caregiver beliefs that vaccines were not good for girls or that the vaccines were unsafe or unclear, concern for side-effects, lack of knowledge, and forgetfulness [29,35,38,41].

Overall, only 64 males (4.6%) had received at least one dose of vaccine, all of which were adult men. Only one study reported the uptake of at least one dose of HPV by 1.5% (95/5153) among persons living with HIV [24]. Among patients with inflammatory bowel disease, the uptake was 3.3% (8/239) [18]. None of the studies in the LMICs reported HPV uptake among MSM.

3.4.2. Types of vaccines and sponsors

Five studies reported the use of Cervarix between 2008 and 2017 in Cambodia, Malaysia, South Africa, and Uganda [26,29,36,42,52]. Five studies reported the use of Cervarix and Gardasil between 2009 and 2019 in Argentina, Brazil, China, Malaysia, and Nigeria [19,28,43,45,49,53]. Two studies reported the use of all three vaccines between 2018 and 2019 in China [54,55]. Sixteen studies reported the use of Gardasil alone in Bhutan, Bolivia, Brazil, Cambodia, Cameroon, Ghana, Haïti, Kenya, Lesotho, Malawi, Nepal [23,25,44,46–48,51,27,31,32,34,35,38–41]. There was no report on the use of Gardasil-9 alone. The type of vaccine administered was not reported in 19 studies.

At the time of publication, 19 studies reported that vaccines were sponsored by the governments in Bhutan, Brazil, Malaysia, Rwanda, South Africa, and Uganda [19,23,44–49,52,26,30,31,37,39–42]. Ten studies reported that the vaccines were sponsored by international non-governmental organizations in Bangladesh, Bhutan, Bolivia, Cambodia, Cameroon, Ghana, Haïti, India, Kenya, Lesotho, Malawi, Nepal, Peru, Uganda, and Vietnam [25,29,32–36,38,51,56]. Azougu et al. in Nigeria and You et al. in China reported self-sponsoring of vaccines and Tran et al. reported partial self-sponsoring and partial-government support for vaccines in Vietnam [17,53,57]. Thirteen studies did not report on the vaccine sponsors. The details of the types of vaccines and their sponsors are shown in Table 1.

3.5. Uptake of HPV vaccines

All 47 studies were included in the meta-analysis. The overall uptake of HPV vaccine any dose was 61.69% (95% CI 54.43–68.70), the highest in Haïti with 100% and lowest in Argentina with 0.46% (95% CI 0.17–0.99), $I^2 = 100\%$, $p < 0.001$ (Fig. 3). The overall uptake of the HPV vaccine showed a bimodal distribution, thus we decided to define a cut-off at 50%. There were 34 studies from 17 countries that reported overall high uptake of >50% with a pooled estimate of 86.52% (95% CI 80.32–91.70) and with no significant difference between countries in upper-middle-income (83.74, 95% CI 82.12–85.30), lower-middle-income (88.46, 95% CI 82.62–93.24) and low-income countries (84.67, 95% CI 67.96–95.94), $p = 0.298$ (Table 2, Supplementary Fig. 1). There were 13 studies from seven countries that reported overall low uptake of <50% with a pooled estimate of 3.50% (95% CI 1.16–7.00) with a significant difference between the upper-middle-income (6.93, 95% CI 6.36–7.54) and low income (3.48, 95% CI 1.81–5.66) economies, $p = 0.005$ (Table 2, Supplementary Fig. 2).

In countries with overall high uptakes, the pooled uptake of vaccination among females for the period 2008–2020 (45.48, 95% CI 23.36–68.58) was significantly higher than that among males for the period 2015–2020 after the gender-neutral vaccination policy was adopted (8.45, 95% CI 6.28–10.88), $p < 0.001$ (Supplementary Fig. 3). However, in studies that reported overall low uptake, the pooled uptake of vaccination was low among both females (5.31, 95% CI 2.91–8.36) and males (2.93, 95% CI 1.52–4.74), $p = 0.150$ (Supplementary Fig. 4).

In studies that reported high uptake, the pooled uptake of vaccination during the period 2008–2020 was higher among girls (87.98, 95% CI 82.01–92.86) than adult females (33.32, 95% CI 12.42–58.44), $p < 0.001$ (Supplementary Fig. 5). However, in studies with overall low uptake, the pooled uptake of vaccination was higher among adult women 5.26% (95% CI 3.76–6.99) than in girls 2.54% (95% CI 1.36–4.31), $p = 0.014$ (Supplementary Fig. 6).

In those countries with overall high uptake, there was a significant drop in the pooled uptake of vaccination from 89.03% (95% CI 83.25–93.70) in the period of female only vaccination policy from 2006 to 2014 to 41.48% (95% CI 21.50–63.04) in the period of gender-neutral vaccination policy after 2014, $p < 0.001$ (Supplementary Fig. 7). However, in countries with overall low uptake, the pooled

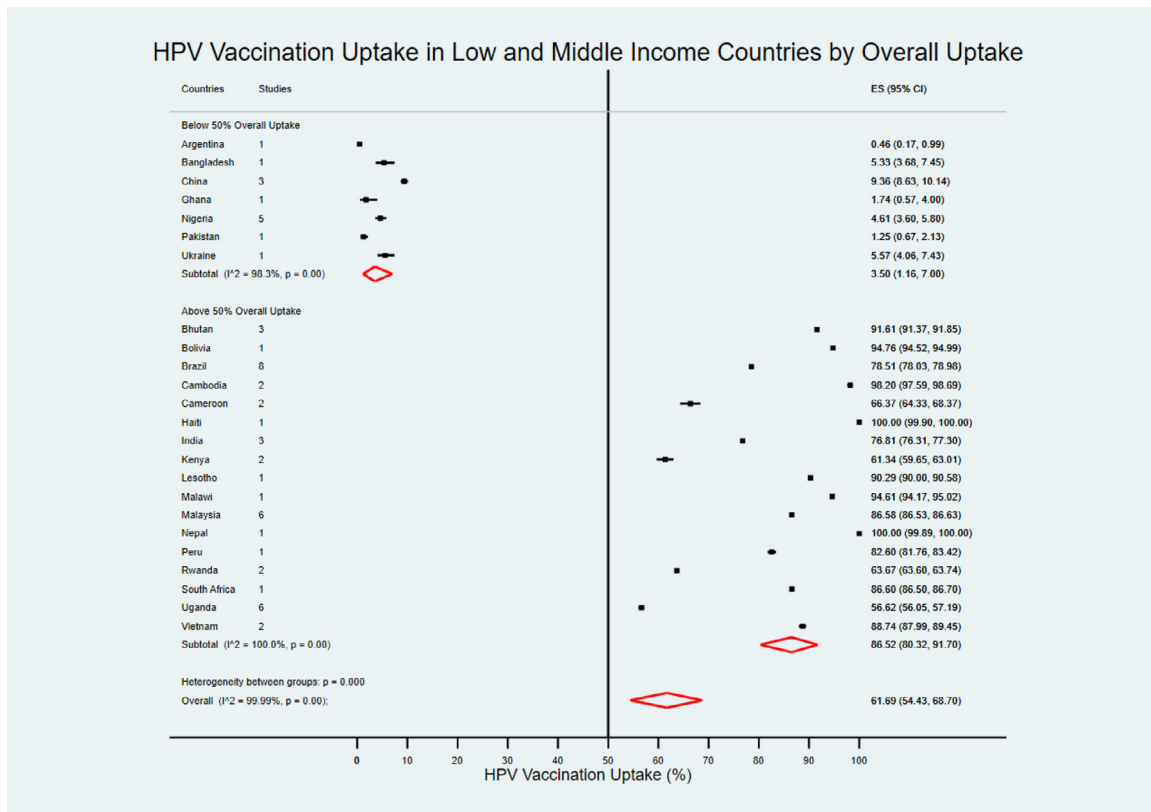


Fig. 3. The overall uptake of HPV vaccination in low- and middle-income countries, 2008–2020.

estimate of vaccination uptake increased from 0.76 (95% CI 0.44–1.16) in the period 2006–2014 to 5.22% (95% CI 2.98–8.04) in the period 2015–2020, $p < 0.001$ (Supplementary Fig. 8).

In countries with overall high uptake, the pooled uptake of vaccination was higher in settings where the vaccines were sponsored by international non-governmental organizations (90.82, 95% CI 86.11–94.64) compared to that sponsored by government alone (68.47, 95% CI 55.74–79.92), $p < 0.001$ (Supplementary Fig. 9). A similar trend was noted in countries with overall low overall uptake with higher pooled uptake in programs sponsored by international non-governmental organizations (3.96, 95% CI 2.76–5.37) compared to that sponsored by government alone (0.46, 95% CI 0.17–0.99), $p < 0.001$ (Supplementary Fig. 10).

The pooled uptake of vaccination was higher in studies that reported estimates from nationally representative data. In countries with overall high uptake, the pooled uptake of vaccination was 85.21% (95% CI 77.05–91.83) in assessments from nationally representative data and 75.39% (95% CI 68.83–81.41) in regionally representative samples, $p = 0.056$ (Supplementary Fig. 11). In countries with overall low uptake, the pooled uptake of vaccination was 10.97% (95% CI 10.04–11.95) in assessments from nationally representative data and 3.07% (95% CI 1.45–5.24) from regionally representative samples, $p < 0.001$ (Supplementary Fig. 12).

The pooled estimate of uptake of vaccine was higher when vaccines were delivered through demonstration programs where the vaccines were being introduced in countries. In countries with high overall uptake, the pooled estimate of uptake of vaccination in demonstration programs was 89.94% (95% CI 86.97–92.57) and the uptake was 59.74% (95% CI 42.75–75.61) in those delivered through routine programs, $p < 0.001$ (Supplementary Fig. 13). However, one demonstration project in Nigeria reported very low estimate of uptake (0.47, 95% CI 0.01–2.56). There were no studies that reported low estimate of uptake in routine vaccination programs (Supplementary Fig. 14).

In terms of the types of vaccines, in countries with overall high uptake, the single use of Gardasil alone had the highest uptake (90.18, 95% CI 79.74–97.13) followed by the combined use of Cervarix and Gardasil (86.67, 95% CI 86.62–86.72) and the use of Cervarix alone (61.44, 95% CI 40.14–80.67), $p = 0.020$ (Supplementary Fig. 15). In countries with overall low uptake, the highest uptake was reported with the combined use of Cervarix, Gardasil and Gardasil-9 (5.15, 95% CI 4.12–6.35) followed by the combined use of Cervarix and Gardasil (2.59%, 95% CI 0.00–13.23) and use of Gardasil alone (1.74, 95% CI 0.57–4.00); $p = 0.015$ (Supplementary Fig. 16).

The details of sub-group analysis by country levels of income, sex, population sub-type (girls or adult women), year of data collection, by vaccine sponsor (government or international non-government organizations), sample representativeness (national or regional), mode of delivery (demonstration project vs routine national programs), types of vaccine, year of publication of the studies is shown in Table 2 and the Forest plot is shown in Supplementary Figs. 1–18.

4. Discussion

This meta-analysis estimated the uptake of HPV vaccination in LMICs at the start of the “global strategy to accelerate the elimination of cervical cancer as a public health problem” in November 2020 [8]. During the period 2006–2020, the pooled estimate of vaccination uptake in 24 LMICs was 61.69% with a wide range of percentages of uptake reported from various countries. In countries that started with overall high uptake, the pooled uptake of the female target population was 77.93% with an uptake of 87.98% in the primary target population of girls and 33.32% in the secondary target population of adult women. In those countries that reported overall low uptake, the pooled uptake of female target population was 4.72%. In terms of the absolute numbers, an estimated 3.3 million females have been vaccinated until 2020, an increase from an estimated 1.4 million that were vaccinated between 2006 and 2014 [58]. The latter number however

Table 2
Random-effects meta-analysis on pooled human papillomavirus vaccine uptake estimates by study characteristics.

	Countries with Below 50% Overall Estimated Uptake						Countries with Above 50% Overall Estimated Uptake					
	No. of Studies	No. of Countries	Total Sample	Estimated Uptake, %	95% CI	Test of subgroup difference	No. of Studies	No. of Countries	Total Sample	Estimated Uptake, %	95% CI	Test of subgroup difference
Overall	13	7	11,317	3.50	1.16–7.00	NA	34	17	4,328,854	86.52	80.32–91.70	NA
Country Income	13	7	11,317	3.50	1.16–7.00	p=0.005	34	17	4,328,854	86.52	80.32–91.70	p=0.298
UMICs	4	2	7,143	6.93	6.36–7.54		16	4	2,290,895	83.74	82.12–85.30	
LMICs	9	5	4,174	3.48	1.81–5.66		11	9	1,74,589	88.46	82.62–93.24	
LICs	0	0	0	NA	NA		10	4	1,863,370	84.67	67.96–95.94	
Gender^a	10	5	8,671	4.69	2.62–7.30	p=0.150	14	7	21,755	32.97	16.34–52.15	p<0.001
Females	10	5	8,219	5.31	2.91–8.36		14	7	21,171	45.48	23.36–68.58	
Males	2	2	452	2.93	1.52–4.74		4	3	584	8.45	6.28–10.88	
Female Age Group	9	5	3,911	4.72	3.23–6.47	p=0.014	31	17	4,321,953	77.93	71.52–83.74	p<0.001
Girls	2	1	511	2.54	1.36–4.31		22	17	4,318,168	87.98	82.01–92.86	
Adult	7	5	3,400	5.26	3.76–6.99		9	5	3,785	33.32	12.42–58.44	
Year of Data Collection^b	12	7	11,021	3.52	1.14–7.10	p<0.001	33	17	4,328,447	77.88	71.52–83.64	p<0.001
2006–2014	2	2	2,350	0.76	0.44–1.16		18	17	4,306,453	89.03	83.25–93.70	
2015–2020	10	5	8,671	5.22	2.98–8.04		15	7	21,994	41.48	21.50–63.04	
Year of Publication	13	7	11,317	3.50	1.16–7.00	p<0.001	34	17	4,328,854	77.44	71.19–83.13	p<0.001
2011–2015	1	1	1,312	0.46	0.17–0.99		10	14	219,841	88.01	83.60–91.82	
2016–2020	12	6	10,005	4.30	1.92–7.54		24	11	4,109,013	60.96	50.15–71.25	
Sample Representativeness	13	7	11,317	3.82	1.51–7.12	p<0.001	34	17	4,328,854	80.74	74.55–86.26	p=0.056
National	1	1	4,220	10.97	10.04–11.95		10	12	4,225,376	85.21	77.05–91.83	
Regional	12	7	7,097	3.07	1.45–5.24		24	11	103,478	75.39	68.83–81.41	
Type of Vaccine	6	4	7,646	2.88	0.21–8.17	p=0.015	23	14	4,267,194	80.90	73.82–87.10	p=0.020
Cervarix only	0	0	0	NA	NA		5	4	421,742	61.44	40.14–80.67	
Gardasil only	1	1	288	1.74	0.57–4.00		15	11	2,000,966	90.18	79.74–97.13	
Cervarix and Gardasil	3	3	5,747	2.59	0.00–13.23		3	2	1,844,486	86.67	86.62–86.72	
Cervarix, Gardasil and Gardasil 9	2	1	1,611	5.15	4.12–6.35		0	0	0	NA	NA	
Vaccine Sponsor	3	3	2,200	2.06	0.07–6.34	p<0.001	27	17	4,321,162	84.21	78.14–89.46	p<0.001
Government	1	1	1,312	0.46	0.17–0.99		19	7	4,157,877	68.47	55.74–79.92	
INGO	2	2	888	3.96	2.76–5.37		8	13	163,285	90.82	86.11–94.64	
Vaccination Program	1	1	215	0.47	0.00–1.99	NA	24	17	4,320,183	83.83	77.68–89.16	p<0.001
Demonstration program	1	1	215	0.47	0.01–2.56		13	15	641,760	89.94	86.97–92.57	
Routine program	0	0	0	NA	NA		11	5	3,678,423	59.74	42.75–75.61	

^a Only studies collected data during 2015–2020 were included as HPV vaccine was approved for males in late 2014.

^b Included studies were classified into 2006–2014 group which was period of female only policy, and 2015–2020 group which was period of gender neutral policy.

UMIC = upper-middle income countries; LMIC = lower-middle income countries; LIC = low-income countries; INGO, international non-government organization; NA, not available; NA = not applicable. Cervarix = 2vHPV; Gardasil = 4vHPV; Gardasil-9 = 9vHPV.

represents that only 1% of 47 million women who received the full course of vaccine during this period were from LMICs [58]. Both the estimated uptake of the target population and the absolute number vaccinated represents the wide gap that needs to be bridged before achieving the WHO strategy of having 90% of girls fully vaccinated by 15 years of age by 2030 [8]. The current estimate suggests that a significant proportion of women, especially in countries that started with low uptake of vaccination, remain largely unprotected and in settings that lack a proper cervical cancer screening program [8].

As of 2021, 75% of low-income countries, 70% of lower-middle-income countries, and 40% of upper-middle-income countries are yet to include the HPV vaccine in their national immunization programs [8]. The WHO recommends vaccination of multiple cohorts of the primary population at the introduction of the program. Bhutan, Bolivia, Brazil, Cambodia, Cameroon, Haiti, India, Kenya, Lesotho, Malaysia, Nepal, Peru, Rwanda, Uganda, and Vietnam targeted school-based, hospital-facility, and community-based delivery models or mixed model that reported very low attrition from receiving the full three doses [27,34,40,45,47]. Our pooled estimates suggest that among countries that started with overall high uptake, the uptake of vaccination was significantly higher in demonstration projects. The demonstration projects in the initial phases of the vaccination program being introduced in the countries were sponsored by the international non-governmental organizations through the Gardasil Access Program (GAP), the Global Alliance (GAVI), the Program for Appropriate Technology in Health (PATH), and the Australian Cervical Cancer Foundation (ACCF) [59] achieving the high proportion of vaccination uptake of 89.94%. These projects helped identify and enumerate HPV target population based on birth cohort, student grades, or headcounts whichever available; developed training modules for vaccinators; and mobilized social support from parents, village, and religious leaders [59]. As these demonstration projects withdrew, there was a significant drop in the vaccination uptake in countries that started with overall high uptake, from 89.03% in the female-only vaccination period 2006–2014 to 41.48% in the gender-neutral vaccination period post-2014. However, there was a modest increase in uptake from 0.76% to 5.26% in the same time periods in countries that started with overall low uptake.

While the WHO recommendations included vaccination of adolescent boys in 2014 [9], only seven studies reported vaccination of boys and none had included it in the national immunization program at the time of publication of these studies [17–23,54]; a lower-middle income country, Bhutan, became the first in South East Asia to adopt gender-neutral vaccination policy in 2020. The overall vaccination of boys remained very low with virtually no reporting or monitoring of male vaccination. Male vaccination is an important public health intervention in reducing penile, anogenital and oropharyngeal cancers caused by high-risk HPV and cross-infection of females [60,61]. In settings where the coverage of female vaccination is less than 75%, gender neutral vaccination was found to be cost-effective with more rapid induction of herd protection for boys, indirect protection of unvaccinated women and direct protection of MSM population [62].

Until 2016, more than 40 LMICs had HPV vaccination demonstration projects where vaccines were partially or fully funded by international non-governmental organizations [59]. While a vaccination coverage of at least 70% was regarded as a threshold for optimum cost-effectiveness [63], in LMICs other factors such as costs of HPV vaccine delivery, strategies for catch-up booster vaccine administration, coverage of girls who are outside of schools and the cost of cervical cancer screening programs also determine the overall cost-effectiveness of the HPV vaccination program [64]. As the cost of vaccines is an important factor in government-funded immunization programs, the WHO endorsed the use of a two-dose HPV vaccination schedule to increase compliance and reduce costs [3,65]; the choice of vaccine should be based on locally relevant data such as the scale

of prevailing HPV strains and the population for which it is approved [9]. Among the studies, only two from China reported the use of Gardasil-9 which is relatively costlier given its protection against nine types of HPV while the rest reported using the bivalent or quadrivalent vaccines [54,55]. Beginning in 2020, the fourth HPV vaccine product Cocolin was approved by the Chinese Food and Drug Administration and was found cost-effective in cervical cancer prevention in China [4] where the Cocolin is priced at US dollar 47.7 per dose while the imported Cervarix is priced at US dollar 262 for three doses, Gardasil at US dollar 360 for three doses and Gardasil-9 at US dollar 586 for three doses [4].

As demonstrated by the drop in uptake of vaccination after the withdrawal of funding support for HPV vaccination, cost remains a major issue in the majority of the countries [26,28,52,53]. The WHO strategy for 2030 estimates that US dollar 10.5 billion is required in financing needs, of which 59% is for vaccination programs with the highest proportion required at the beginning of the initiation of the strategy in 2020 [8]. A review of vaccination costs in GAVI-eligible countries reported that 51% was driven by the actual cost of the vaccine that may be a limitation even in government-sponsored delivery models [66]. The other direct medical cost includes cold chain, education of staff, monitoring and evaluation, social mobilization and vaccination campaigns [67]. As demonstrated in Mozambique, the start-up cost for HPV vaccination program increased modestly with scale-up of vaccination coverage while the cost for training of personnel and social mobilization decreased over time [67]. The delivery cost was lower if HPV vaccination was integrated into existing health services [68] and if school-based delivery was adopted as the primary strategy [69].

An efficient vaccination program and high coverage not only protects those vaccinated but also has significant cross-protection and herd effects among boys and older women [5]. For vaccination strategies to meet disease reduction goals in the population, countries need to review their immunization program objectives, the factors associated with effective vaccination strategy and key aspects in field implementation of vaccines [70]. After the launch of the 2030 WHO strategy, several countries have already made policy level commitments to eliminate cervical cancer. Vaccination strategies require dedicated infrastructure for vaccine distribution and administration, funding of the services and monitoring and evaluation of vaccine coverage [70]. Interventions to improve field level HPV vaccine uptake among adolescents include providing adequate health education (relative effect, RR 1.43), financial incentives (RR 1.45), and policies promoting mandatory vaccination [71]. With regard to the delivery strategy, HPV uptake increased with class-based delivery in schools (RR 1.09) and multi-component provider interventions including an education session, repeated contacts, individualized feedback and incentives, and parent interventions such as providing information, sharing educational materials such as pamphlets and audio-visual materials (RR 1.41–2.3) [71].

The studies included in our meta-analysis demonstrate that there was a decline in vaccination uptake especially in those countries that started off with high uptake while those countries with low uptake have not made major improvements. This suggests the need for a proper framework for timely monitoring and reporting at a country level as per WHO standards. The WHO reporting of performance of vaccine programs requires monitoring of uptake by dose and by age or year of birth of the primary target population and ensuring that the coverage is maximized and maintained [12]. As a summary indicator, it is recommended to report the proportion of girls vaccinated with the complete series of HPV doses by 15 years of age [12].

The strategy to eliminate cervical cancer requires fully vaccinating 90% of girls by 15 years of age, screening 70% of women a high-performance test by 35 years of age and again at 45 years of age, and 90% of women identified with cervical disease receiving treatment [8]. If HPV vaccination and cervical screening are scaled up, the annual

cervical cancer incidence can be brought down by significant levels to target its elimination by the end of the 21st century [7] and combining it with effective screening methods will expedite reductions of cervical cancer in those countries with the highest burden [6]. Though HPV vaccination is the first step in the global elimination target, access to quality cervical screening tests and providing adequate care to those with cervical cancer are important components of this strategy.

This meta-analysis reports data only from observational studies from countries that published the vaccination uptake in peer-reviewed journals. Data from some countries with efficient and high coverage of HPV vaccines were not represented in those peer-reviewed articles selected for the meta-analysis.

However, the studies included in this meta-analysis report data from population-level assessments that give a representative picture of the scenario on HPV vaccination uptake. This may be compared to the program-level coverage reported by countries to the WHO.

The HPV vaccination uptake as of 2021 is low with wide variations between the countries across income levels. The current levels of vaccination in the primary target population of adolescent girls fall short of the 2030 targets and the levels of vaccination in the secondary target population are low among adult females and very low among males. In countries that started with high vaccination uptake, there is a significant drop in uptake over time while those that started with low uptake have not made a major increase. The countries in LMICs need major efforts in rolling out vaccination programs and monitoring its uptake.

Declaration of Competing Interest

All authors declare no competing interests.

Contributors

All authors were involved in the conception of this meta-analysis. KP, TD and TN performed the literature search. TD and TN screened the article abstracts. TD and TN performed data extraction and risk of bias assessment. All authors had access to the data. TD, TN, and KP performed the statistical analysis. TD drafted the manuscript. All Authors have critically reviewed and approved the manuscript.

Data statement

All authors had access to the validated dataset used for this meta-analysis. The dataset is available to from the corresponding author upon request.

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Supplementary materials

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