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Modeling Studies of Human Papilloma Virus (HPV) Vaccines Cost-Effectiveness and Cervical Cancer Elimination – A Systematic Review

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INTRODUCTION

- Human papillomavirus (HPV) affects more than 80% of sexually active population
- Globally ~625,000 cases/year are reported in women and ~69,000 cases/year in men, with cervical cancer contributing to the biggest HPV burden
- Currently four vaccines are available: bivalent HPV vaccine (2vHPV, Cervarix® and Cecolin®), quadrivalent (4vHPV, Gardasil®), nonavalent (9vHPV, Gardasil9®)
- Cost effectiveness models (CEMs) of HPV vaccination in a wider population (e.g., boys, men who have sex with men (MSM), and adults generally is widely debated
- We aimed to better understand modelling approaches toward the public health impact and cost-effectiveness CE of 4vHPV and 9vHPV vaccination across different countries

OBJECTIVES

- Summarize key inputs, assumptions, and approaches of CEMs of (pre-) adolescents and adults (including targeted vaccination of MSM, HIV+) HPV vaccination (Part I) and models on the WHO goal for cervical cancer (CC) elimination (Part II) that will allow for a critical evaluation and comparison of the published models

METHODS

- A systematic literature review was conducted to identify all relevant publications from Medline, Embase and Cochrane (2018 to October 2021) as per PICOTS criteria (**Table 1**)

Table 1. PICOTS Selection Criteria

	Inclusion Criteria	Exclusion Criteria
Population(s)	. Children aged 9 and above . Adults (including targeted vaccination of MSM, HIV+)	. Anyone under the age of 9 . Anyone ineligible for the HPV vaccine
Interventions	. Quadrivalent HPV vaccine . Nonavalent HPV vaccine	Interventions not specified under inclusion criteria
Comparisons	. Bivalent HPV vaccines . Cytology-based Pap test . HPV DNA testing . Cervical cancer screening program . No vaccination	Any comparisons not listed under the inclusion criteria
Outcomes	***Part I: Cost-effectiveness of HPV vaccination*** . Life-years gained (LYs) . Quality-adjusted life years gained . Cost/LY gained . Cost/QALY gained ***Part II: Cervical cancer elimination*** . Age-standardized cervical cancer incidence . Reduction in cervical cancer incidence . Number of cervical cancer cases averted . Number of deaths averted owing to prevention of cervical cancer incidence . Time to cervical cancer elimination	Any other outcome not specified under inclusion criteria
Time	. Publications from (including) 2008 onwards . Conference abstracts (IPVC and Eurogin) from mid-2019 onwards	Publications published prior to 2008
Study design	***Cost-effectiveness*** . Cost-effectiveness analyses . Cost-minimization analyses . Cost-utility analyses ***Cervical cancer elimination*** . Markov models . Other mathematical models	Study designs not specified under inclusion criteria
Other	. Countries: All countries . Language: English	. Not applicable . All other languages

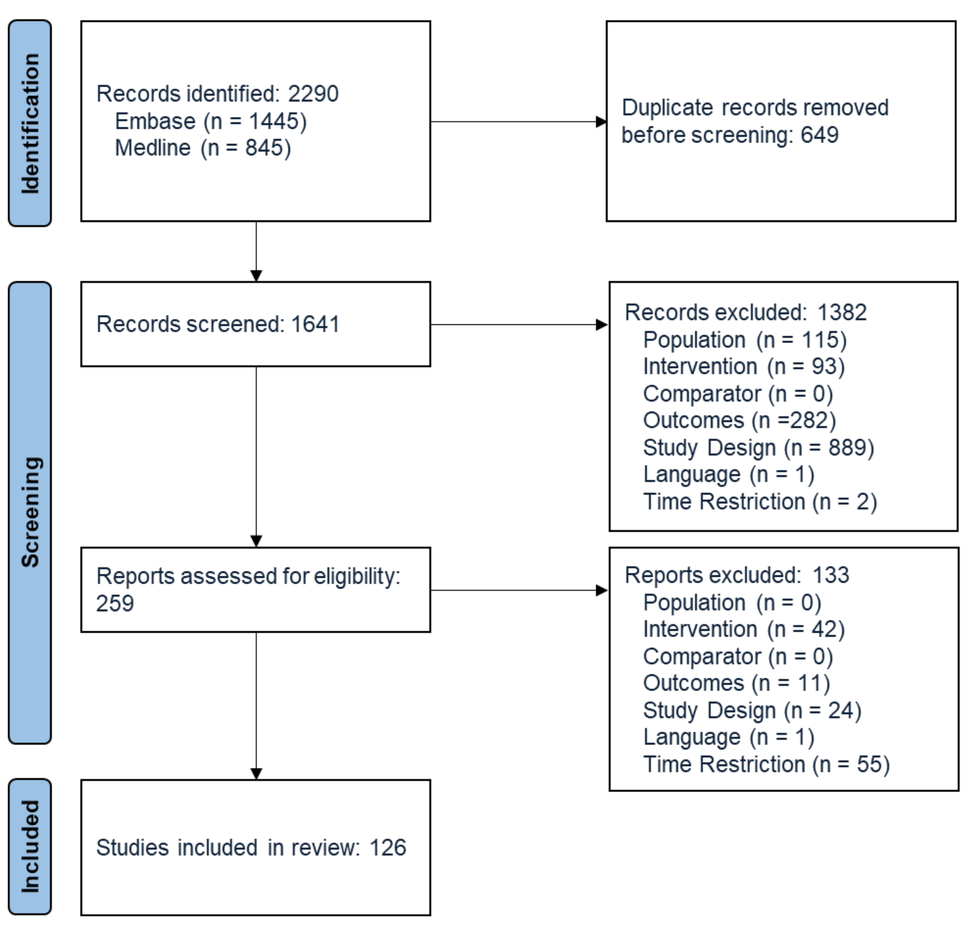
- Extracted information was summarized descriptively

RESULTS

Screening and Selection

- We retained 126 studies from an initial pool of 1641 unduplicated records. (**Figure 1**)
- 113 were cost-effectiveness models and 13 were elimination models

Figure 1. PRISMA Screening Diagram



Girls Only Vaccination (GOV)

- The cost-effectiveness of girls-only HPV vaccines was assessed in 68 studies.
- Eight studies included children (aged <11 years), 51 included pre-adolescents (11-13 years), 3 included adolescents (10-19 years), and 6 had a mixed population (12-26 years).
- Vaccine protection was assumed to be lifelong in most studies (n=51 of 68), and some studies tested multiple durability scenarios
- Herd immunity was considered in 27 studies.
- For 4vHPV, the efficacy considered in the model ranged from 50% to 100%
- Vaccination was considered a cost-effective strategy against the current scenario in all the studies except for two studies conducted in Iran (Khatibi 2014 and Yaghoubi 2018)
- The parameters that largely impacted the CE of vaccination in girls included discount rate (n=30), duration of protection (n=22), cost of vaccine (n=22), vaccine efficacy (n=10), utility values (n=7), burden of disease (n=7), time horizon (n=4), cross protection (n=5)

Gender Neutral Vaccination (GNV)

- Overall, 28 publications assessed the introduction of a GNV vaccination vs existing GOV
- Transmission dynamic model (n=21) was widely used to model the transmission of HPV which also accounts for herd effects, other models included Markov (n=4), deterministic SIRS (n=2) and Bayesian synthesis (n=1)
- CE of GNV at relevant threshold was most sensitive to assumptions of addition of all male-related HPV diseases line penile cancer, head & neck cancer, anal cancer etc. in the model (n=8), vaccine price (n=7) and discount rates of future benefits (n=7)
- GNV was often CE even when the assumed female coverage accounted for herd-protection (n=8) such that addition of male vaccination had substantial incremental benefits
- GNV by 9vHPV versus 4vHPV were sensitive to duration of protection (n=8), vaccine price (n=2) and cross-protection for 4vHPV, particularly in HPV-ADVISE models (n=4),
- In LMICs, GNV utilized, and models focused more on increasing uptake among girls

Adult Vaccination

- Overall, 10 publications assessing CE of adult (≥18 years of age) were identified
- Mixed population consisting of lower age limit for adolescent population and upper age limit for adult population for e.g., 12-26 years, 13-45 years, 12-24 years etc. were compared in 8 publications
- Most of the publications recommended against expansion of age for GNV population (n=7) whereas a female-catch up program in later ages (till 26 years of age) was preferred in some cases (n=3)
- CEM outcomes were largely driven by the upper bound of age cohorts and became less cost-effective as age limit increased, and assumptions around historical coverage rates impacted outcomes via potential herd effects to adult unvaccinated population

MSM Vaccination

- In total, six studies were identified that reported the cost effectiveness for targeted vaccination of MSM with or without HIV
- All studies included only adolescent and adult population (age 12 years to ≥27 years)
- Herd immunity was not included in the models across all the studies except for in Lin 2017
- Lifelong vaccine protection was assumed in all but one study, and a lifetime time horizon was assumed in all but one study
- Vaccine efficacy ranged between 63.7% to 90% across studies
- Vaccination among MSM was cost-effective in all the cases
- Factors primarily affecting CEM outcomes were vaccine cost, vaccine efficacy, duration of vaccine protection, disutility, cost of anal cancer, transition of HGAIN/HSIL to anal cancer

HPV Elimination (CCE)

- Thirteen studies assessed the impact of vaccination and screening strategies on CCE
- Key assumptions included compliance to HPV-related strategies, and most included screening techniques (n=12)
- The most common elimination threshold was ≤4 cases per 100,000 women per year(n=8)
- In a high-income countries (largely where national immunization programs were implemented after 2006 and HPV vaccination was introduced with high coverage rate along with established effective organized screening programs) CCE could be expected by 2028-2059
- Models in both HICs and LMICs demonstrated that high coverage of vaccination will have substantial effects on CCE but would be realized later in the century
- Sooner CCE depended upon effective scale-up of screening and treatment techniques especially in LMICs and efficacy of vaccination along with long-term vaccine protection

CONCLUSIONS

- Although the studies used slightly different baseline assumptions and modelling designs, their findings are consistent
- GOV was found to be cost-effective in all the scenarios while GNV was often CE when additional male-related HPV diseases were added to the model
- Vaccination in LMICs should be supported by GAVI alliance and UNICEF to eliminate CC

REFERENCES

Full reference list available upon request

DISCLOSURES

This study was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Wei Wang, Cody Palmer, and Ya-Ting Chen are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.Paridhi Jain, Nita Santpurkar, and Jelle Spoorendonk are employees of OPEN Health, which was paid consulting fees by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA to conduct and report this study.

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