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Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries

Marc Brisson, Jane J Kim*, Karen Canfell*, Mélanie Drolet, Guillaume Gingras, Emily A Burger, Dave Martin, Kate T Simms, Élodie Bénard, Marie-Claude Boily, Stephen Sy, Catherine Regan, Adam Keane, Michael Caruana, Diep T N Nguyen, Megan A Smith, Jean-François Laprise, Mark Jit, Michel Alary, Freddie Bray, Elena Fidarova, Fayad Elsheikh, Paul J N Bloem, Nathalie Broutet, Raymond Hutubessy*

Summary

Background The WHO Director-General has issued a call for action to eliminate cervical cancer as a public health problem. To help inform global efforts, we modelled potential human papillomavirus (HPV) vaccination and cervical screening scenarios in low-income and lower-middle-income countries (LMICs) to examine the feasibility and timing of elimination at different thresholds, and to estimate the number of cervical cancer cases averted on the path to elimination.

Methods The WHO Cervical Cancer Elimination Modelling Consortium (CCEMC), which consists of three independent transmission-dynamic models identified by WHO according to predefined criteria, projected reductions in cervical cancer incidence over time in 78 LMICs for three standardised base-case scenarios: girls-only vaccination; girls-only vaccination and once-lifetime screening; and girls-only vaccination and twice-lifetime screening. Girls were vaccinated at age 9 years (with a catch-up to age 14 years), assuming 90% coverage and 100% lifetime protection against HPV types 16, 18, 31, 33, 45, 52, and 58. Cervical screening involved HPV testing once or twice per lifetime at ages 35 years and 45 years, with uptake increasing from 45% (2023) to 90% (2045 onwards). The elimination thresholds examined were an average age-standardised cervical cancer incidence of four or fewer cases per 100 000 women-years and ten or fewer cases per 100 000 women-years, and an 85% or greater reduction in incidence. Sensitivity analyses were done, varying vaccination and screening strategies and assumptions. We summarised results using the median (range) of model predictions.

Findings Girls-only HPV vaccination was predicted to reduce the median age-standardised cervical cancer incidence in LMICs from 19·8 (range 19·4–19·8) to 2·1 (2·0–2·6) cases per 100 000 women-years over the next century (89·4% [86·2–90·1] reduction), and to avert 61·0 million (60·5–63·0) cases during this period. Adding twice-lifetime screening reduced the incidence to 0·7 (0·6–1·6) cases per 100 000 women-years (96·7% [91·3–96·7] reduction) and averted an extra 12·1 million (9·5–13·7) cases. Girls-only vaccination was predicted to result in elimination in 60% (58–65) of LMICs based on the threshold of four or fewer cases per 100 000 women-years, in 99% (89–100) of LMICs based on the threshold of ten or fewer cases per 100 000 women-years, and in 87% (37–99) of LMICs based on the 85% or greater reduction threshold. When adding twice-lifetime screening, 100% (71–100) of LMICs reached elimination for all three thresholds. In regions in which all countries can achieve cervical cancer elimination with girls-only vaccination, elimination could occur between 2059 and 2102, depending on the threshold and region. Introducing twice-lifetime screening accelerated elimination by 11–31 years. Long-term vaccine protection was required for elimination.

Interpretation Predictions were consistent across our three models and suggest that high HPV vaccination coverage of girls can lead to cervical cancer elimination in most LMICs by the end of the century. Screening with high uptake will expedite reductions and will be necessary to eliminate cervical cancer in countries with the highest burden.

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Introduction

Cervical cancer is the second most frequent cancer among women in low-income and lower-middle-income countries (LMICs).[1] In 2018, 290 000 (51%) of the 570 000 new cervical cancer cases worldwide occurred in women living in LMICs (500 000 [88%] when including upper-middle-income countries).[1] Without further intervention, these inequalities in the burden of cervical cancer are expected to grow, because recent increases in the uptake of human papillomavirus (HPV) vaccination and cervical

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*Joint first authors

Centre de recherche du CHU de Québec - Universite Laval, Québec, QC, Canada (Prof M Brisson PhD, M Drolet PhD, G Gingras PhD, D Martin PhD, É Bénard MSc, Prof M-C Boily PhD, J-F Laprise PhD, Prof M Alary MD); **Department of Social and Preventive Medicine, Universite Laval, Québec, QC, Canada** (Prof M Brisson, Prof M-C Boily, Prof M Alary); **MRC Centre for Global Infectious Disease Analysis, Department of Infectious Disease Epidemiology, Imperial College London, London, UK** (Prof M Brisson, Prof M-C Boily); **Center for Health Decision Science, Harvard T.H. Chan School of Public Health, Boston, MA, USA** (Prof J J Kim PhD, E A Burger PhD, S Sy MS, C Regan BA); **Cancer Research Division, Cancer Council NSW, Sydney, NSW, Australia** (K Canfell DPhil, K T Simms PhD, A Keane PhD, M Caruana DPhil, D T N Nguyen PhD, M A Smith PhD); **School of Public Health, Sydney Medical School, University of Sydney, Sydney, NSW, Australia** (K Canfell, K T Simms, A Keane, M Caruana, D T N Nguyen, M A Smith); **Prince of Wales Clinical School, University of New South Wales, Sydney, NSW, Australia** (K Canfell); **Department of Health Management and Health Economics, University of Oslo, Oslo, Norway** (E A Burger); **Centre for Mathematical Modelling of Infectious Disease, London School of**

Hygiene and Tropical Medicine, London, UK (Prof M Jit PhD); **Modelling and Economics Unit, Public Health England, London, UK** (Prof M Jit); **School of Public Health, University of Hong Kong, Hong Kong, China** (Prof M Jit); **Institut national de santé publique du Québec, Québec, QC, Canada** (Prof M Alary); **Section of Cancer Surveillance, International Agency for Research on Cancer, Lyon, France** (F Bray PhD); **and Department for the Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention** (E Fidarova MD), **Department of Immunization, Vaccines and Biologicals** (F Elsheikh MPH, P J N Bloem MBA, R Hutubessy PhD), **and Department of Reproductive Health and Research** (N Broutet MD), **World Health Organization, Geneva, Switzerland**

Correspondence to: Prof Marc Brisson, Centre de recherche du CHU de Québec, Universite Laval, Axe Santé des populations et pratiques optimales en santé, Québec, QC G1S 4L8, Canada
marc.brisson@crchudequebec.ulaval.ca

Research in context

Evidence before this study

In May, 2018, WHO issued a global call to eliminate cervical cancer as a public health problem. To inform its global strategy to accelerate cervical cancer elimination, WHO created the Cervical Cancer Elimination Modelling Consortium (CCEMC) to examine the following key questions: what elimination threshold should be used; what prevention strategies can lead to elimination; when could elimination be reached for different countries; and how many cancers could be averted. The current working definition of elimination is an age-standardised cervical cancer incidence of four or fewer cases per 100 000 women-years. Alternative definitions, such as an incidence of ten or fewer cases per 100 000 women-years and an 80–90% reduction in incidence, have also been suggested. The only previous multicountry modelling study of cervical cancer elimination suggests that global elimination is possible through girls-only human papillomavirus (HPV) vaccination at 80–100% coverage with a perfectly effective 9-valent vaccine and twice-lifetime HPV-based screening. Given that models necessarily include simplifying assumptions, the goal of the consortium is to use multiple models, taking into account their respective strengths and limitations, to illustrate the robustness of predictions. A systematic comparative modelling approach was used. To form the CCEMC, WHO selected three models that met the predefined eligibility criteria: HPV-ADVISE, Harvard, and Policy1-Cervix. The models projected reductions in cervical cancer incidence over time based on standardised HPV vaccination and cervical screening scenarios determined after consultations at various WHO technical expert, advisory group, and global stakeholder meetings. Three elimination thresholds were examined (cervical cancer incidence of four or fewer cases per 100 000 women-years, ten or fewer cases per 100 000 women-years, and ≥85% reduction in incidence).

Added value of this study

This comparative modelling analysis, which includes projections from three independent transmission-dynamic models, provides consistent results suggesting that 90% HPV vaccination coverage of girls can lead to cervical cancer elimination in most low-income and lower-middle-income countries (LMICs) within the next century. However, countries with the highest cervical cancer incidence (>25 cases per 100 000 women-years) might not reach elimination at the threshold of four or fewer cases per 100 000 women-years by vaccination alone, although these countries are predicted to have the greatest absolute reductions. More than 90% of these LMICs are in sub-Saharan Africa. Screening would accelerate elimination by 11–31 years and will be necessary to eliminate cervical cancer in countries with the highest incidence. Profound health benefits are predicted on the path to elimination. Intensive scale-up of girls-only vaccination with twice-lifetime screening is predicted to halve the age-standardised cervical cancer incidence by 2048 (and by 2061 with vaccination only), and to avert more than 74 million cervical cancer cases (61 million with vaccination only) in LMICs over the next century.

Implications of all the available evidence

The results of the CCEMC suggest that cervical cancer elimination as a public health problem is possible by the end of the century. However, to achieve elimination across all LMICs under the most ambitious threshold (four or fewer cases per 100 000 women-years), both high HPV vaccination coverage and screening uptake will be necessary, which will require considerable international commitment. These results have directly informed WHO's target of 90% HPV vaccination coverage, 70% screening coverage, and 90% of cervical lesions treated by 2030, as well as the WHO global strategy to accelerate cervical cancer elimination, which will be presented at the World Health Assembly in May, 2020.

cancer screening have mainly occurred in high-income countries. Less than 30% of LMICs have introduced HPV vaccination compared with more than 85% of high-income countries.[2,3] Additionally, only about 20% of women in LMICs have ever been screened for cervical cancer compared with more than 60% in high-income countries.[4,5]

Inequalities in HPV vaccination and screening uptake persist, despite the large body of evidence demonstrating that these interventions are highly effective and cost-effective. Large international randomised control clinical trials have shown that HPV vaccines are safe and highly effective against vaccine-type persistent infection and cervical precancerous lesions in women (with vaccine efficacy ≥93%).[6–8] These vaccines target high-risk HPV types that cause about 70% (bivalent and quadrivalent vaccines: HPV types 16 and 18) and 90% (9-valent vaccine: HPV types 16, 18, 31, 33, 45, 52, and 58) of cervical cancers.[9,10] Countries that have achieved high vaccination coverage have observed declines of 73–85% in vaccine-type HPV prevalence, and declines of 41–57% in high grade lesions (cervical intraepithelial neoplasia, grade 2 or worse) among young women, less than 10 years after implementation of HPV vaccination.[11] The effectiveness of population-based cervical cancer screening has also been shown, through the sharp declines in age-standardised cervical cancer incidence in high-income countries following the implementation of cytology-based screening.[12,13] Randomised controlled trials have shown that HPV-based tests are highly effective at detecting precancerous lesions and are likely to be more effective at preventing cervical cancer than visual inspection with acetic acid or

cytology.[14–16] Finally, mathematical modelling studies have consistently shown that girls-only HPV vaccination and cervical cancer screen-and-treat programmes are cost-effective in LMICs.[17–22]

Given the substantial global burden of cervical cancer, the increasing inequalities, and opportunities for effective and cost-effective primary and secondary prevention, the WHO Director-General made a global call in May, 2018, for action towards the elimination of cervical cancer as a public health problem.[23] To achieve this goal, WHO is developing, with its partners, a global strategy towards the elimination of cervical cancer.[24] Fundamental questions that must be addressed in the global strategy include: what elimination definition and threshold should be used, what prevention strategies can lead to elimination, when could elimination be reached, how many cervical cancers and deaths can be averted on the path to elimination, and what are the most efficient and cost-effective strategies to reach elimination? These important questions can only be addressed through mathematical modelling, which integrates our understanding of HPV transmission, cervical carcinogenesis, vaccine efficacy, and cervical screening and treatment performance to project the long-term health consequences of alternative cancer control policies. Hence, to inform its global strategy to accelerate cervical cancer elimination, WHO assembled the Cervical Cancer Elimination Modelling Consortium (CCEMC).[25,26]

In this Article, we describe the comparative modelling approach used by the CCEMC to inform WHO's global strategy towards the elimination of cervical cancer,[24] and present the CCEMC's predictions of the impact of various HPV vaccination and screening elimination strategies on cervical cancer incidence in 78 LMICs. The specific objectives of this analysis were to identify prevention strategies that lead to elimination, estimate the timing of elimination, and predict the number of cervical cancer cases averted on the path to elimination, for different elimination thresholds and country characteristics. In an accompanying Article,[27] we present the CCEMC's predictions of the impact of HPV vaccination, screening, and treatment scale-up on cervical cancer mortality.

Methods

Comparative modelling approach

This comparative modelling analysis adhered to recently published guidelines for multi-model comparisons[28] and for reporting model-based analyses of HPV vaccination and cervical screening[29] (appendix pp 26–28). A three-step systematic comparative modelling approach was used.

The aim of the first step was to identify and select the mathematical models. To minimise selection bias, WHO selected models that met the following predefined eligibility criteria: the models explicitly included the dynamic transmission of HPV infection, were capable of projecting the impact of HPV vaccination and cervical screening for all 78 LMICs, were independently developed and had been previously peer reviewed and published, and were able to provide predictions in a short timeframe to inform the WHO global strategy.[24] Four independent models were identified: HPV-ADVISE,[30,31] Harvard,[32,33] Policy1-Cervix,[34–36] and Spectrum.[37,38]

The aim of the second step was to identify HPV vaccination and screening strategies that can lead to cervical cancer elimination and examine between-model variability. The four models were used to predict the change in cervical cancer incidence over time for 40 standardised HPV vaccination and screening scenarios, with a subset of ten LMICs (appendix pp 14–15). Impact predictions were done without harmonising the basic structure of the models or parameters governing the setting and disease. The results were presented at various WHO technical expert, advisory group, and global stakeholder meetings, and ultimately three HPV vaccination and screening scenarios were identified to proceed in a larger number of countries (78 LMICs).[39] The three final scenarios that were selected for the global analysis (see scenario descriptions below and in the appendix p 16) were chosen as they showed potential for cervical cancer elimination in LMICs and follow WHO recommendations for HPV vaccination and cervical screening.[40,41]

Finally, the aim of the third step was to produce predictions of the population-level impact of the three HPV vaccination and cervical screening scenarios for all 78 LMICs. Three of the four models (HPV-ADVISE, Harvard, and Policy1-Cervix) were able to provide predictions for all 78 LMICs within the required timelines, and thus form the core models of the CCEMC. The structure of the models and the comparative modelling approach were presented and reviewed by the WHO Advisory Committee on Immunization and Vaccines related Research (IVIR).[39]

Model description

The three CCEMC models (HPV-ADVISE, Harvard, and Policy1-Cervix) have been used extensively to inform recommendations on cervical screening and HPV vaccination in Australia, Canada, the UK, the USA, and at a global level.[30–36] Although developed independently, the models have common features. First, they are transmission-dynamic models of HPV infection and the natural history of cervical cancer. Second, they include the following components: sexual behaviour and HPV transmission, natural history of cervical cancer, vaccination, and screening, diagnosis, management, and treatment of cervical lesions and cancer. HPV transmission and cervical carcinogenesis are modelled for the HPV types in the 9-valent vaccine (HPV types 16, 18, 31, 33, 45, 52, 58) and other high-risk types. The models simulate type-specific HPV transmission through sexual activity, based on different risk groups and sexual mixing. The models reproduce the type-specific natural history of cervical cancer, from persistent HPV infection to cervical

See Online for appendix

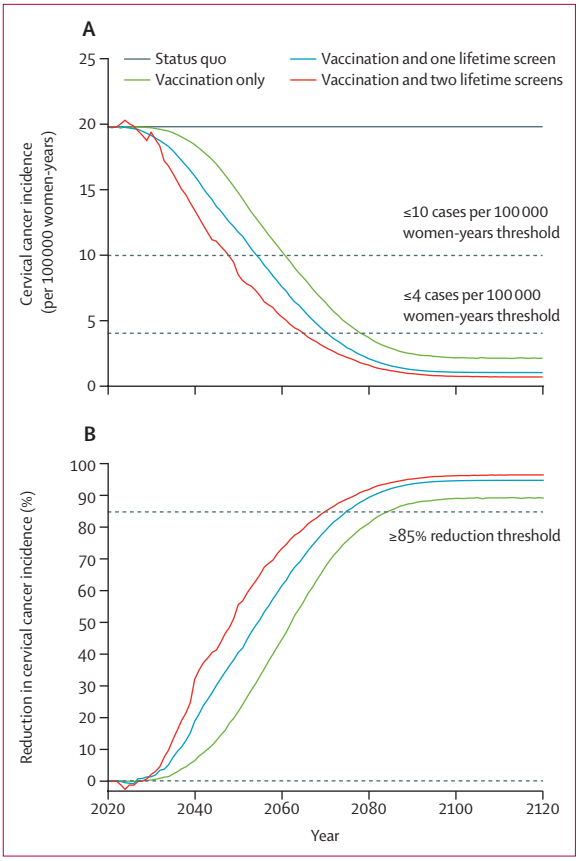

Figure 1: **Dynamics of cervical cancer incidence after HPV vaccination and cervical screening**
Average age-standardised cervical cancer incidence per 100 000 women-years (A) and relative reduction in incidence (B) after HPV vaccination and screening ramp-up in low-income and lower-middle-income countries. Median prediction from the three models. Vaccination coverage=90% at age 9 years (and at ages 10–14 years in 2020). Vaccine efficacy=100% against HPV16, 18, 31, 33, 45, 52, and 58. Vaccine duration=lifetime. Screening=HPV testing. Screening uptake=45% (2023–29), 70% (2030–44), and 90% (2045 onwards). Screen and treat efficacy=100%. Loss to follow-up=10%. Equilibrium occurs 90–100 years after the introduction of HPV vaccination only (and earlier for the screening scenarios). HPV=human papillomavirus.

cancer via precancerous cervical lesions (cervical intraepithelial neoplasia grade 1 to 3). All models assume that HPV vaccines are prophylactic and capture post-vaccination herd effects. They can also simulate complex cervical screening and treatment algorithms at the individual level, by tracking and simulating each woman's screening history. Finally, all models were calibrated to highly stratified sexual behaviour and epidemiological data, validated to clinical trials or post-vaccination data, or both, and reproduce the age-specific cervical cancer incidence estimates from the Global Cancer Observatory (GLOBOCAN) 2018 for all 78 LMICs[42] (see the appendix pp 18–23 for further details of the CCEMC models).

Vaccination and screening scenarios

Three standardised base-case HPV vaccination and cervical screening scenarios were examined. The first was vaccination only: routine vaccination of girls aged 9 years (with a 1-year multi-age cohort catch-up to age 14 years) reaching 90% coverage in the first year (2020). The second was vaccination and once-lifetime screening: scenario 1 plus one lifetime screen at age 35 years, assuming screening uptake ramp-up over time (45% in 2023, 70% in 2030, and 90% in 2045). The third was vaccination and twice-lifetime screening: scenario 1 plus two lifetime screens at ages 35 years and 45 years, assuming screening uptake ramp-up over time (45% in 2023, 70% in 2030, and 90% in 2045).

For the base-case scenarios, HPV vaccination was assumed to provide 100% efficacy against HPV types 16, 18, 31, 33, 45, 52, and 58, and lifelong duration of protection. Cervical screening was assumed to involve primary HPV screen-and-treat testing, with 100% pre-cancer treatment efficacy and 10% of individuals lost to follow-up (due to treatment non-compliance). To estimate the population-level impact of the base-case scenarios, we also modelled a status quo scenario, which assumes no further scale-up of preventive interventions (see appendix p 16 for more details). The 40 HPV vaccination and cervical screening scenarios from step 2 of the comparative modelling approach were used to understand the impact of model assumptions on predictions. The sensitivity analysis included varying HPV vaccination coverage, the targeted population (girls only *vs* girls and boys), ages at vaccination, screening frequency, the HPV types targeted by the vaccine, and the duration of vaccine protection. Results of the sensitivity analysis are shown for two example countries, representing one low-income country in sub-Saharan Africa (Uganda) and one lower-middle-income country in east Asia (Vietnam).

Outcomes

Population-level impact was measured with three main outcomes: age-standardised cervical cancer incidence, relative reductions in age-standardised cervical cancer incidence (*vs* status quo), and number of cases averted (*vs* status quo). The time horizon of the analysis was from 2020 to 2120. The age-standardised cervical cancer incidence and relative reductions in incidence over time were used to assess the feasibility and timing of cervical cancer elimination at different thresholds. We used the CCEMC models to independently estimate the outcomes for each of the 78 countries. Results were also aggregated by World Bank income level and region (see appendix p 17 for a description of country characteristics). Outcomes are presented with the median (range) of the predictions of the three models to represent between-model uncertainty.[28]

The age-standardised cervical cancer incidence over time was estimated for each CCEMC model, vaccination, and screening scenario, and for each country using the predictions of age-specific cervical cancer incidence over time and applying the age structure of the 2015 global female population aged 0–99 years.[43] Reductions (absolute

	Incidence per 100 000 women-years			Reduction in incidence (%)		Base-case elimination threshold: ≤4 cases per 100 000		Alternative elimination threshold: ≤10 cases per 100 000		Alternative elimination threshold: ≥85% reduction	
	2020	2045	Equilibrium	2045	Equilibrium	Countries (%)	Year of elimination	Countries (%)	Year of elimination	Countries (%)	Year of elimination
All low-income and lower-middle-income countries (n=78)											
Vaccination only	19·8 (19·4–19·8)	16·9 (16·2–17·5)	2·1 (2·0–2·6)	12·9 (11·6–14·4)	89·4 (86·2–90·1)	60·3 (57·7–65·4)	X (X–X)	98·7 (88·5–100·0)	X (2096–X)	87·2 (37·2–98·7)	X (X–X)
Vaccination and one lifetime screen	19·8 (19·4–19·8)	13·7 (13·3–13·8)	1·0 (0·9–2·0)	30·3 (28·6–30·8)	95·0 (89·0–95·3)	96·2 (60·3–97·4)	X (X–X)	100·0 (94·9–100·0)	2090 (2082–X)	100·0 (100·0–100·0)	2085 (2080–2100)
Vaccination and two lifetime screens	19·8 (19·3–19·9)	11·0 (10·7–11·6)	0·7 (0·6–1·6)	41·5 (40·6–46·1)	96·7 (91·3–96·7)	100·0 (70·5–100·0)	2098 (2097–X)	100·0 (98·7–100·0)	2085 (2078–X)	100·0 (100·0–100·0)	2081 (2077–2094)
World Bank income levels											
Low-income countries (n=34)											
Vaccination only	32·7 (32·7–33·6)	28·6 (28·0–31·1)	3·9 (3·4–5·7)	13·4 (12·7–14·3)	88·1 (84·1–89·5)	44·1 (41·2–50·0)	X (X–X)	100·0 (82·4–100·0)	2093 (2090–X)	82·4 (14·7–100·0)	X (2091–X)
Vaccination and one lifetime screen	32·7 (32·7–33·6)	22·6 (22·6–25·7)	1·8 (1·7–4·6)	31·1 (28·4–31·1)	94·7 (87·1–94·9)	97·1 (44·1–97·1)	X (X–X)	100·0 (94·1–100·0)	2082 (2079–X)	100·0 (100·0–100·0)	2083 (2079–2098)
Vaccination and two lifetime screens	32·8 (32·7–33·7)	19·0 (17·5–21·8)	1·2 (1·2–3·8)	41·9 (39·3–46·6)	96·4 (89·5–96·5)	100·0 (52·9–100·0)	2089 (2088–X)	100·0 (100·0–100·0)	2076 (2074–2099)	100·0 (100·0–100·0)	2079 (2073–2092)
Low-income and lower-middle-income countries (n=44)											
Vaccination only	17·8 (17·2–17·8)	15·3 (14·0–15·9)	1·8 (1·8–2·1)	12·3 (11·0–14·1)	89·7 (87·0–90·2)	72·7 (70·5–77·3)	X (X–X)	97·7 (93·2–100·0)	X (2096–X)	90·9 (54·5–97·7)	X (X–X)
Vaccination and one lifetime screen	17·8 (17·2–17·9)	12·4 (11·5–12·5)	0·9 (0·8–1·6)	29·8 (28·3–30·4)	95·1 (89·8–95·4)	95·5 (72·7–97·7)	X (X–X)	100·0 (95·5–100·0)	2090 (2082–X)	100·0 (100·0–100·0)	2085 (2080–2100)
Vaccination and two lifetime screens	17·8 (17·2–17·9)	9·7 (9·5–10·5)	0·6 (0·6–1·3)	41·1 (40·8–45·7)	96·8 (92·0–96·8)	100·0 (84·1–100·0)	2098 (2097–X)	100·0 (97·7–100·0)	2085 (2078–X)	100·0 (100·0–100·0)	2081 (2077–2094)
World Bank regions											
East Asia and Pacific (n=12)											
Vaccination only	19·9 (19·3–19·9)	17·0 (15·0–17·5)	2·2 (2·2–2·5)	13·7 (12·0–14·5)	87·3 (87·2–89·2)	100·0 (91·7–100·0)	2102 (2087–X)	100·0 (100·0–100·0)	2067 (2066–2069)	100·0 (91·7–100·0)	2091 (2087–X)
Vaccination and one lifetime screen	19·9 (19·2–19·9)	13·4 (12·0–13·7)	1·2 (0·9–1·7)	31·4 (30·8–32·5)	93·8 (90·3–95·3)	100·0 (100·0–100·0)	2079 (2075–2091)	100·0 (100·0–100·0)	2061 (2060–2061)	100·0 (100·0–100·0)	2078 (2078–2087)
Vaccination and two lifetime screens	19·9 (19·1–20·1)	10·3 (9·6–11·4)	0·8 (0·7–1·3)	44·7 (42·8–48·5)	96·0 (92·4–96·7)	100·0 (100·0–100·0)	2071 (2069–2085)	100·0 (100·0–100·0)	2052 (2050–2054)	100·0 (100·0–100·0)	2073 (2073–2081)
Europe and central Asia (n=6)											
Vaccination only	15·7 (15·6–15·7)	11·8 (11·6–12·3)	1·4 (1·2–1·7)	22·9 (21·7–25·0)	90·9 (88·5–92·7)	100·0 (100·0–100·0)	2080 (2078–2080)	100·0 (100·0–100·0)	2059 (2059–2060)	100·0 (100·0–100·0)	2085 (2081–2088)
Vaccination and one lifetime screen	15·7 (15·6–15·8)	8·9 (8·8–9·0)	0·7 (0·7–1·3)	43·2 (40·1–44·2)	95·6 (91·1–95·8)	100·0 (100·0–100·0)	2070 (2069–2075)	100·0 (100·0–100·0)	2052 (2052–2053)	100·0 (100·0–100·0)	2073 (2078–2079)
Vaccination and two lifetime screens	15·7 (15·5–15·7)	7·6 (6·8–7·7)	0·5 (0·5–1·1)	51·0 (49·6–56·7)	96·7 (92·5–96·8)	100·0 (100·0–100·0)	2065 (2063–2069)	100·0 (100·0–100·0)	2048 (2046–2049)	100·0 (100·0–100·0)	2068 (2066–2074)

(Table continues on next page)

	Incidence per 100 000 women-years			Reduction in incidence (%)		Base-case elimination threshold: ≤4 cases per 100 000		Alternative elimination threshold: ≤10 cases per 100 000		Alternative elimination threshold: ≥85% reduction	
	2020	2045	Equilibrium	2045	Equilibrium	Countries (%)	Year of elimination	Countries (%)	Year of elimination	Countries (%)	Year of elimination
(Continued from previous page)											
Latin America and Caribbean (n=5)											
Vaccination only	26·8 (25·6–27·0)	21·4 (18·9–21·9)	3·0 (2·7–3·7)	18·3 (18·2–20·3)	88·8 (84·1–90·1)	80·0 (80·0–80·0)	X (X–X)	100·0 (100·0–100·0)	2070 (2070–2071)	100·0 (X-100·0)	2091 (2086- X)
Vaccination and one lifetime screen	26·8 (25·8–27·0)	16·5 (15·3–16·7)	1·5 (1·3–3·0)	37·8 (33·7–38·5)	94·5 (87·0–95·2)	100·0 (80·0–100·0)	2079 (2074–X)	100·0 (100·0–100·0)	2065 (2061–2066)	100·0 (100·0–100·0)	2079 (2077–2099)
Vaccination and two lifetime screens	26·8 (25·7–26·8)	13·3 (13·2–14·3)	1·1 (1·0–2·6)	46·6 (43·1–50·3)	96·0 (88·9–96·4)	100·0 (100·0–100·0)	2073 (2069–2089)	100·0 (100·0–100·0)	2057 (2056–2058)	100·0 (100·0–100·0)	2076 (2072–2094)
North Africa and Middle East (n=7)											
Vaccination only	6·8 (6·5–6·8)	6·1 (5·2–6·4)	0·8 (0·5–0·9)	8·2 (6·9–10·5)	88·5 (84·9–92·9)	100·0 (100·0–100·0)	2081 (2076–2081)	100·0 (100·0–100·0)	2062 (2061–2066)	100·0 (71·4–100·0)	2090 (2085- X)
Vaccination and one lifetime screen	6·8 (6·5–6·9)	5·2 (4·5–5·2)	0·3 (0·3–0·7)	23·8 (21·3–23·9)	95·0 (87·5–95·9)	100·0 (100·0–100·0)	2073 (2073–2078)	100·0 (100·0–100·0)	2058 (2057–2058)	100·0 (100·0–100·0)	2081 (2080–2097)
Vaccination and two lifetime screens	6·8 (6·5–6·9)	4·1 (3·8–4·4)	0·2 (0·2–0·6)	35·7 (34·1–39·6)	96·6 (90·1–97·2)	100·0 (100·0–100·0)	2068 (2068–2074)	100·0 (100·0–100·0)	2050 (2048–2051)	100·0 (100·0–100·0)	2079 (2077–2094)
South Asia (n=7)											
Vaccination only	15·5 (14·6–15·5)	13·3 (11·3–13·8)	1·4 (1·1–1·5)	12·3 (10·9–14·6)	91·3 (88·3–92·8)	100·0 (100·0–100·0)	2074 (2072–2077)	100·0 (100·0–100·0)	2060 (2058–2061)	100·0 (100·0–100·0)	2087 (2082–2092)
Vaccination and one lifetime screen	15·5 (14·6–15·6)	10·8 (9·2–11·0)	0·7 (0·6–1·2)	28·9 (28·3–30·7)	95·8 (90·8–96·2)	100·0 (100·0–100·0)	2070 (2069–2071)	100·0 (100·0–100·0)	2053 (2053–2054)	100·0 (100·0–100·0)	2079 (2079–2087)
Vaccination and two lifetime screens	15·5 (14·6–15·6)	8·6 (7·6–9·3)	0·4 (0·4–0·9)	40·6 (40·4–44·6)	97·1 (92·9–97·3)	100·0 (100·0–100·0)	2063 (2063–2065)	100·0 (100·0–100·0)	2046 (2046–2049)	100·0 (100·0–100·0)	2074 (2074–2082)
Sub-Saharan Africa (n=41)											
Vaccination only	37·4 (37·4–38·7)	33·6 (33·0–37·5)	4·9 (4·5–6·7)	10·7 (10·0–11·7)	87·0 (84·1–87·9)	26·8 (24·4–36·6)	X (X–X)	97·6 (78·0–100·0)	X (2096–X)	75·6 (X-97·6)	X (X–X)
Vaccination and one lifetime screen	37·4 (37·4–38·6)	27·2 (27·1–31·5)	2·2 (2·0–5·5)	27·4 (25·0–27·5)	94·1 (87·0–94·7)	92·7 (26·8–95·1)	X (X–X)	100·0 (90·2–100·0)	2090 (2082–X)	100·0 (100·0–100·0)	2085 (2079–2100)
Vaccination and two lifetime screens	37·5 (37·4–38·8)	22·7 (21·0–26·7)	1·4 (1·4–4·4)	39·4 (36·5–43·9)	96·3 (89·6–96·4)	100·0 (43·9–100·0)	2098 (2097–X)	100·0 (97·6–100·0)	2085 (2078–X)	100·0 (100·0–100·0)	2081 (2073–2094)

Data are median (range) predictions from three dynamic models. Equilibrium occurs 90–100 years after the introduction of human papillomavirus (HPV) vaccination only (and earlier for the screening scenarios). X=elimination not reached in all countries in the income or regional group. Girls-only vaccination refers to vaccination coverage of 90% at age 9 years (and at ages 10–14 years in 2020). Vaccine efficacy=100% against HPV16, 18, 31, 33, 45, 52, and 58. Vaccine duration=lifetime cervical screening. Screening=HPV testing. Screening uptake=45% (2023–29), 70% (2030–44), and 90% (2045 onwards). Screen and treat efficacy=100%. Loss to follow-up=10%.

***Table*: Change in age-standardised cervical cancer incidence over time, percentage of countries reaching elimination for different thresholds, and year of elimination, by World Bank income level and region**

and relative) in age-standardised cervical cancer incidence over time were estimated compared to the status quo. Finally, the cumulative number of cases averted over time was estimated with a three-step process. First, for each CCEMC model, vaccination, and screening scenario, and country, we estimated the number of cervical cancers by year and age group by multiplying the predicted age-specific cervical cancer incidence and the age-specific UN population growth projections.[43] Second, we estimated the number of cervical cancers in each year by summing the cases predicted in each age group. Third, the number of cases averted in each year was estimated by subtracting the number of cases predicted under each vaccination and screening scenario from those predicted under the status quo. The number of cancer cases averted in each World Bank income level or region was estimated by aggregating the country-specific results. The model predictions were done independently by each group and collated by the study's coordinating centre (Laval University, Québec, QC, Canada). See the appendix (pp 18–25) for more methodological details.

Elimination thresholds

Our base-case definition of elimination is an age-standardised (2015 world standard) cervical cancer incidence of four or fewer cases per 100 000 women-years, which is the current working definition used by WHO and the proposed WHO global strategy towards elimination of cervical cancer.[24] The threshold was determined following multiple WHO technical expert meetings and global stakeholder consultations held between March and September, 2018.[24] Alternative definitions, such as a higher incidence threshold (ten cases per 100 000 women-years) and a percentage reduction in incidence (85–90%), were also discussed.[39] Thus, as a sensitivity analysis, two alternative definitions were explored: age-standardised cervical cancer incidence of ten or fewer cases per 100 000 women-years and a reduction in age-standardised cervical cancer incidence of ≥85% (*vs* status quo). Elimination was predicted to occur the first year in which a country reached the threshold definition. Elimination within a region or income level was predicted to occur the year in which all countries within the region or income level reached elimination.

Role of the funding source

This study was partly funded by WHO. WHO contributed to study design, data analysis, data interpretation, and writing of the report. The other funding sources had no role in this work. MB, JJK, and KC had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The CCEMC models predicted that girls-only HPV vaccination with 90% coverage will reduce the median age-standardised cervical cancer incidence in LMICs from 19·8 (range 19·4–19·8) to 2·1 (2·0–2·6) cases per 100 000 women-years over the next century, which represents an 89·4% (86·2–90·1) reduction in cervical cancer (*vs* the status quo; figure 1, table). The addition of screening was predicted to substantially accelerate declines in cervical cancer and to lead to lower cervical cancer incidence at equilibrium. HPV vaccination and once-lifetime screening was predicted to reduce the average age-standardised cervical cancer incidence in LMICs to 1·0 (0·9–2·0) cases per 100 000 women-years over the next century (95·0% [89·0–95·3] reduction), whereas HPV vaccination and twice-lifetime screening was predicted to reduce the average age-standardised cervical cancer incidence to 0·7 (0·6–1·6) cases per 100 000 women-years at equilibrium (96·7% [91·3–96·7] reduction). Additionally, the models predicted that cervical cancer incidence will be halved in LMICs by 2061 (2060–63) with HPV vaccination alone, by 2055 (2055–56) when adding once-lifetime screening, and by 2048 (2047–49) when adding twice-lifetime screening. Notably, the models predicted that HPV vaccination with or without screening will reduce age-standardised cervical cancer incidence in women of childbearing age (<45 years) by more than 85% before 2050 (appendix p 5).

The predicted dynamics of cervical cancer incidence following HPV vaccination only, and for HPV vaccination with once-lifetime or twice-lifetime screening, were very similar for the three models (figure 2). Additionally, although the age-standardised cervical cancer incidence in 2020 varied widely by country income level and region (figure 2; appendix p 5), the models predicted that the post-intervention dynamics and percentage reduction in cervical cancer incidence will be similar (figure 2, table). For example, the predicted percentage reduction in cervical cancer following HPV vaccination only varied from 87% (range 84–88) in sub-Saharan Africa to 91% (88–93) in South Asia, and percentage reductions following HPV vaccination with twice-lifetime screening varied from 96% (90–96) in sub-Saharan Africa to 97% (93–97) in South Asia. However, the models predicted that age-standardised cervical cancer incidence following HPV vaccination with or without screening will vary greatly between regions and countries because of the large heterogeneity in the starting incidence (figure 2, table), which contributed to variability between countries in the potential for and timing of elimination.

With the base-case elimination threshold (four or fewer cases per 100 000 women-years), the CCEMC models predicted that girls-only HPV vaccination could lead to cervical cancer elimination in 60% (range 58–65) of LMICs, HPV vaccination with once-lifetime screening could lead to elimination in 96% (60–97) of LMICs, and HPV vaccination with twice-lifetime screening could lead to elimination in 100% (71–100) of LMICs (figure 3, table). HPV vaccination alone was predicted to result in elimination in all regions in the world, except for sub-Saharan Africa, where 27% (range 24–37) of

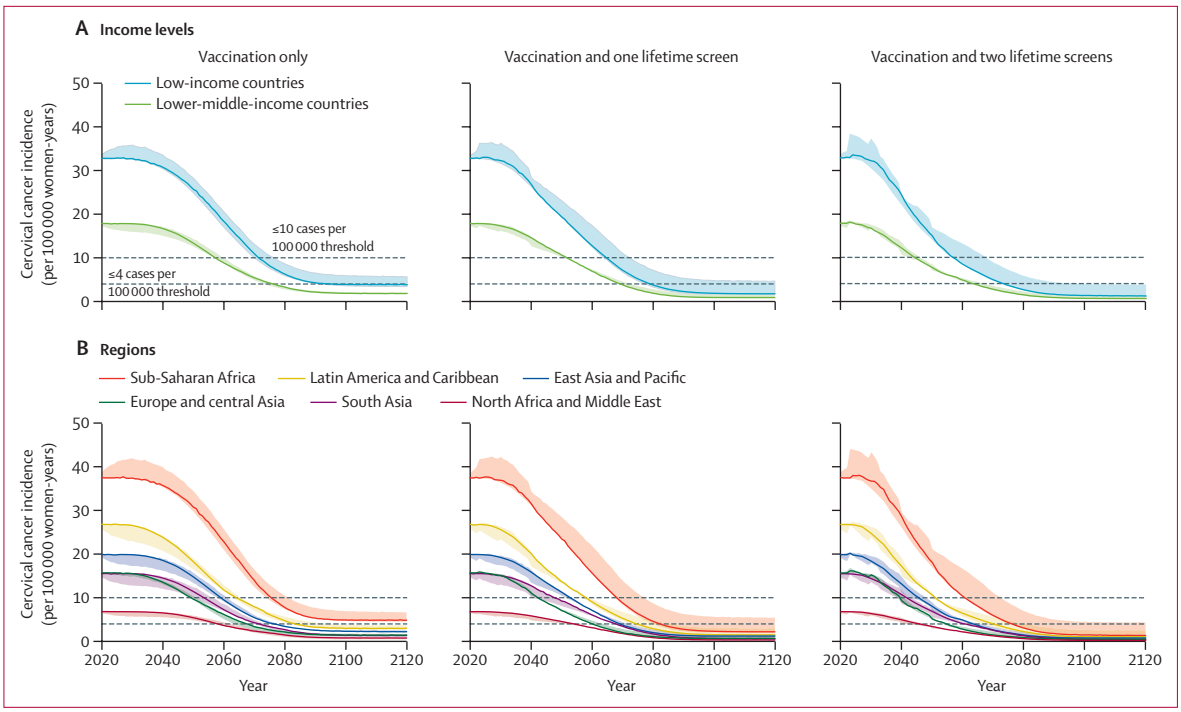

Figure 2: **Variability in model predictions of the impact of HPV vaccination and screening strategies**
The average age-standardised cervical cancer incidence per 100 000 women-years over time in low-income countries and lower-middle-income countries, by World Bank income level (A) and region (B). The solid line represents the median prediction and shaded area represents the minimum and maximum predictions of the three models. Vaccination coverage=90% at age 9 years (and at ages 10–14 years in 2020). Vaccine efficacy=100% against HPV types 16, 18, 31, 33, 45, 52, and 58. Vaccine duration=lifetime. Screening=HPV testing. Screening uptake=45% (2023–29), 70% (2030–44), and 90% (2045 onwards). Screen and treat efficacy=100%. Loss to follow-up=10%. Equilibrium occurs 90–100 years after the introduction of HPV vaccination only (and earlier for the screening scenarios). HPV=human papillomavirus.

countries would reach elimination, and Latin America and Caribbean, where 80% (80–80) of countries would reach elimination. The countries that were not predicted to reach elimination through HPV vaccination alone were those with an age-standardised cervical cancer incidence of more than 25 cases per 100 000 women-years in 2020 (figure 4, appendix p 7). These same countries were predicted to have the greatest absolute reductions in cervical cancer incidence following HPV vaccination (figure 4). Importantly, for these countries, mainly in sub-Saharan Africa, once-lifetime or twice-lifetime screening was required to achieve elimination. Country-specific and model-specific predictions of elimination and the age-specific cervical cancer incidence at equilibrium are shown in the appendix (p 7).

The models predicted that among the regions that can achieve elimination (four or fewer cases per 100 000 women-years) with girls-only HPV vaccination alone, elimination will occur between 2074 and 2102 (table). Adding twice-lifetime screening was predicted to accelerate elimination by 11–31 years. In sub-Saharan Africa, where both HPV vaccination and twice-lifetime screening are required to achieve elimination, elimination is predicted to occur slightly before 2100 (table). Country-specific and model-specific predictions of the year of elimination are provided in the appendix (p 8).

The CCEMC models predicted that girls-only HPV vaccination could lead to cervical cancer elimination in 99% (range 89–100) of LMICs based on a threshold of ten or fewer cases per 100 000 women-years, and in 87% (37–99) of LMICs based on a threshold of an 85% or greater reduction (table; figure 3; figure 4). Adding once or twice-lifetime screening was predicted to result in cervical cancer elimination for 100% of LMICs under both thresholds. Elimination was also predicted to occur faster with these thresholds (table).

The CCEMC models predicted that 21·3 million (range 20·7–21·3) cervical cancer cases will occur in LMICs between 2020 and 2060 without further interventions (status quo). During the same period, including girls-only HPV vaccination with 90% coverage was predicted to avert 3·2 million (3·0–3·6) cervical cancer cases; adding once-lifetime screening to vaccination was predicted to avert an extra 2·2 million (1·8–2·7) cases, and adding twice-lifetime screening was predicted to avert an extra 4·6 million (3·9–4·8) cancer cases (figure 5; appendix pp 2–4). Hence, in the short to medium term (<40 years), adding screening could more than double the number of cervical cancer cases averted in LMICs (*vs* HPV vaccination alone). In the longer term, the models predicted that 93·5 million (93·5–95·3) cervical cancer cases will occur in LMICs

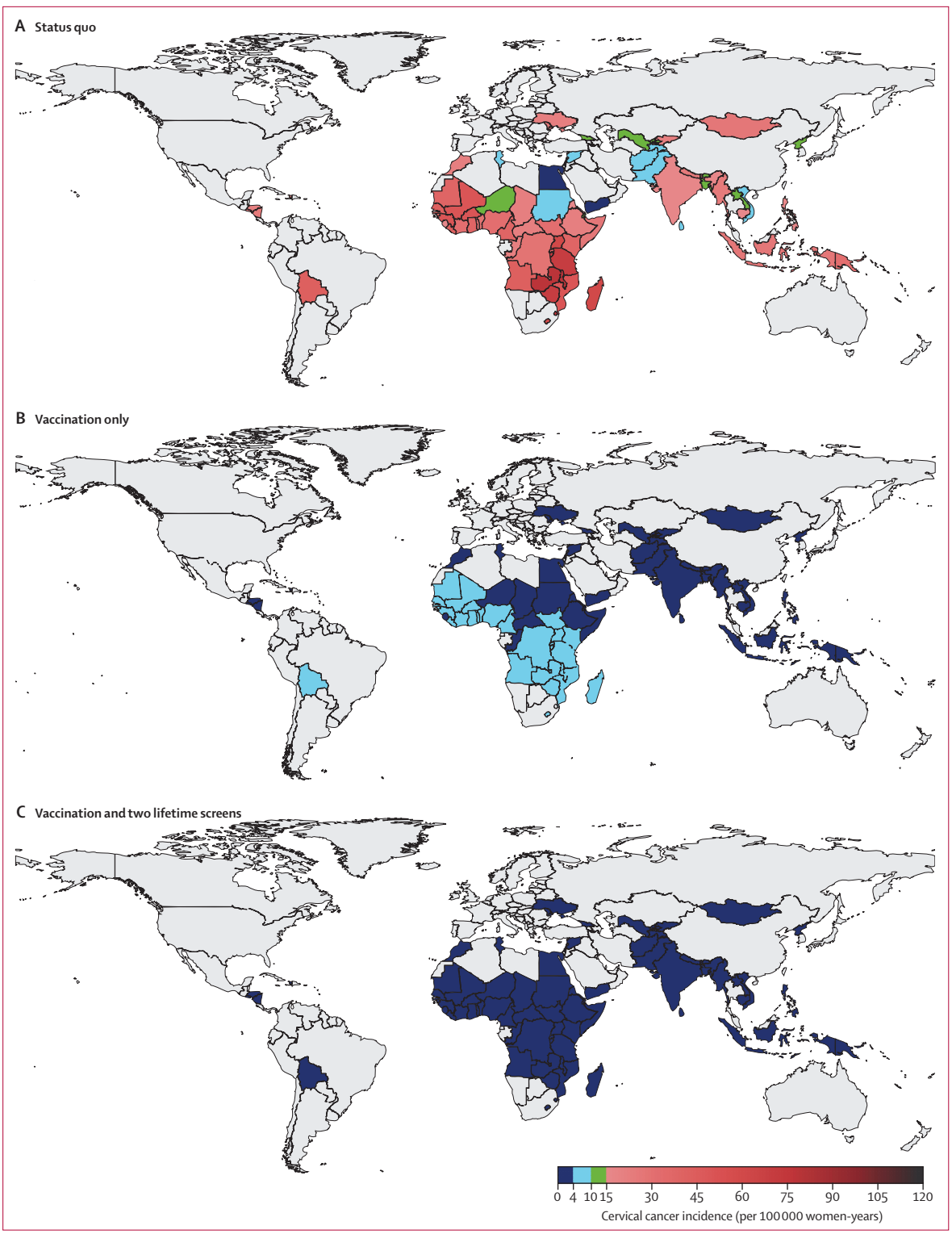

Figure 3: **Global map of cervical cancer elimination in 78 low-income and lower-middle-income countries**
Age-standardised incidence of cervical cancer at equilibrium (2100–20), assuming status quo (A), girls-only vaccination (B), and girls-only vaccination and two lifetime screens (C). Median prediction from the three models. Vaccination coverage=90% at age 9 years (and at ages 10–14 years in 2020). Vaccine efficacy=100% against HPV16, 18, 31, 33, 45, 52, and 58.Vaccine duration=lifetime. Screening=HPV testing. Screening uptake=45% (2023–29), 70% (2030–44), and 90% (2045 onwards). Screen and treat efficacy=100%. Loss to follow-up=10%. See videos 1–3 for the global maps of cervical cancer elimination over time and the appendix (p 6) for the change in the distribution of the country-specific age-standardised cervical cancer incidence over time. HPV=human papillomavirus.

See **Online** for videos 1, 2, and 3

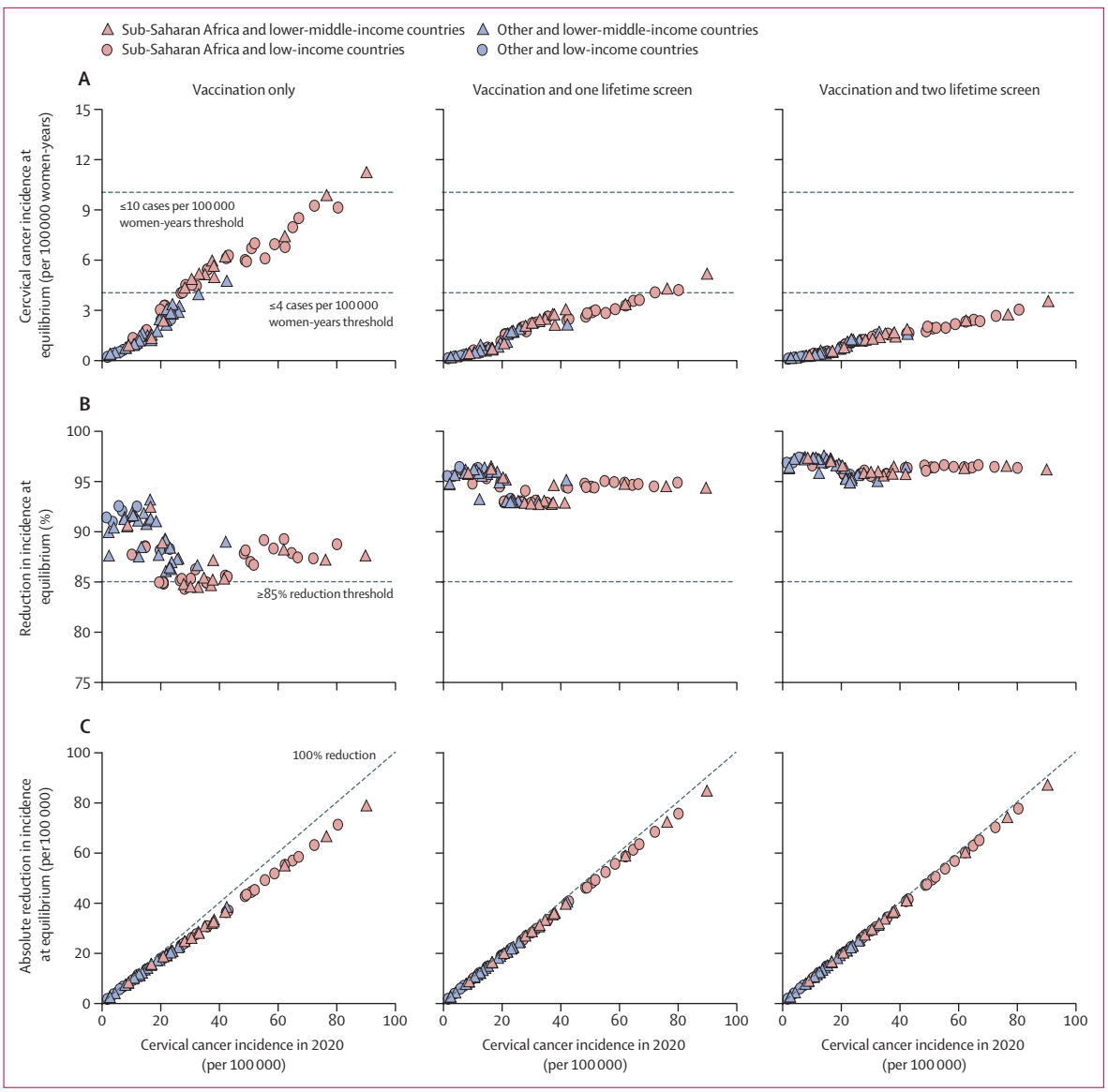

Figure 4: **Impact of current cervical cancer incidence on elimination predictions**
The age-standardised incidence of cervical cancer (A) and relative (B) and absolute (C) reduction in incidence at equilibrium (2100–20) following vaccination and screening, as a function of initial age-standardised incidence of cervical cancer for each low-income and lower-middle-income country. Median prediction from the three models. Vaccination coverage=90% at age 9 years (and at ages 10–14 years in 2020). Vaccine efficacy=100% against HPV16, 18, 31, 33, 45, 52, and 58. Vaccine duration=lifetime. Screening=HPV testing. Screening uptake=45% (2023–29), 70% (2030–44), and 90% (2045 onwards). Screen and treat efficacy=100%. Loss to follow-up=10%. HPV=human papillomavirus.

between 2020 and 2120 without further scale-up of HPV vaccination or cervical screening (ie, the status quo scenario). During this period, including girls-only HPV vaccination with 90% coverage was predicted to avert 61·0 million (60·5–63·0) cervical cancer cases; adding once-lifetime screening to vaccination was predicted to avert an extra 6·8 million (4·3–9·4) cases and adding twice-lifetime screening was predicted to avert an extra 12·1 million (9·5–13·7) cervical cancer cases (figure 5; appendix pp 2–4). Overall, an estimated 74·1 million (70·4–75·1) cases would be averted by 2120 through intensive scale-up of girls-only HPV vaccination with twice-lifetime screening. Predictions of the number of cervical cancer cases averted over time were similar for the three models, at the global and regional levels (appendix p 9).

Most cervical cancer cases averted through HPV vaccination and screening in LMICs were predicted to be among women living in sub-Saharan Africa (figure 5; appendix pp 2–4). For example, our models predicted that HPV vaccination and twice-lifetime screening will avert 49·9 million (range 49·5–50·9) cases in sub-Saharan

Africa over the next century, which represents about 70% of all cases averted in LMICs.

The sensitivity analysis suggests that a small reduction in HPV vaccination coverage from 90% to 80% would have little impact on the decline in cervical cancer incidence in the first 30 years following girls-only HPV vaccination (without screening), but would lead to slightly higher long-term incidence (appendix pp 10–11). Hence, some LMICs that can eliminate cervical cancer with 90% vaccination coverage (using the threshold of four or fewer cases per 100 000 women-years) might not with 80% coverage (eg, countries with current age-standardised cervical cancer incidence of 20–25 cases per 100 000 women-years). In general, if HPV vaccination coverage was high among girls, vaccinating boys was predicted to produce very small incremental gains in cervical cancer prevention (appendix pp 10–11). For example, the CCEMC models predicted that girls-only HPV vaccination with 90% coverage would produce the same reduction in cervical cancer incidence as vaccinating both girls and boys at 80% coverage. Hence, vaccinating boys in addition to girls would not be sufficient to help countries with the highest age-standardised cervical cancer incidence (eg, Uganda) reach the elimination threshold of four or fewer cases per 100 000 women-years. Finally, the models predicted that multi-age cohort vaccination up to age 25 years would substantially accelerate the declines in cervical cancer incidence, but would not change cervical cancer incidence at equilibrium (appendix pp 10–11). Thus, vaccinating older cohorts of girls or women would not ultimately change the potential for elimination.

A sensitivity analysis examining the impact of screening suggests that although twice-lifetime screening without HPV vaccination would substantially reduce cervical cancer incidence, the age-standardised cervical cancer incidence would remain higher than four cases per 100 000 women-years in the countries examined (appendix pp 10–11). Hence, HPV vaccination is required for most LMICs to reach cervical cancer elimination. In the context of high-coverage girls-only vaccination, adding a third lifetime screen (to HPV vaccination and twice-lifetime screening) was predicted to provide very small additional gains in cervical cancer prevention, and only slightly accelerated time to elimination.

Finally, our sensitivity analysis showed that the duration of protection and the number of types included in the HPV vaccine can affect whether girls-only HPV vaccination with twice-lifetime screening leads to cervical cancer elimination (appendix pp 10–11). When assuming 20 years of vaccine protection (instead of lifelong), the models predicted that the age-standardised cervical cancer incidence would be higher than four cases per 100 000 women-years in the countries examined. Thus, a long-term duration of vaccine protection (>20 years) is required to reach elimination in LMICs.

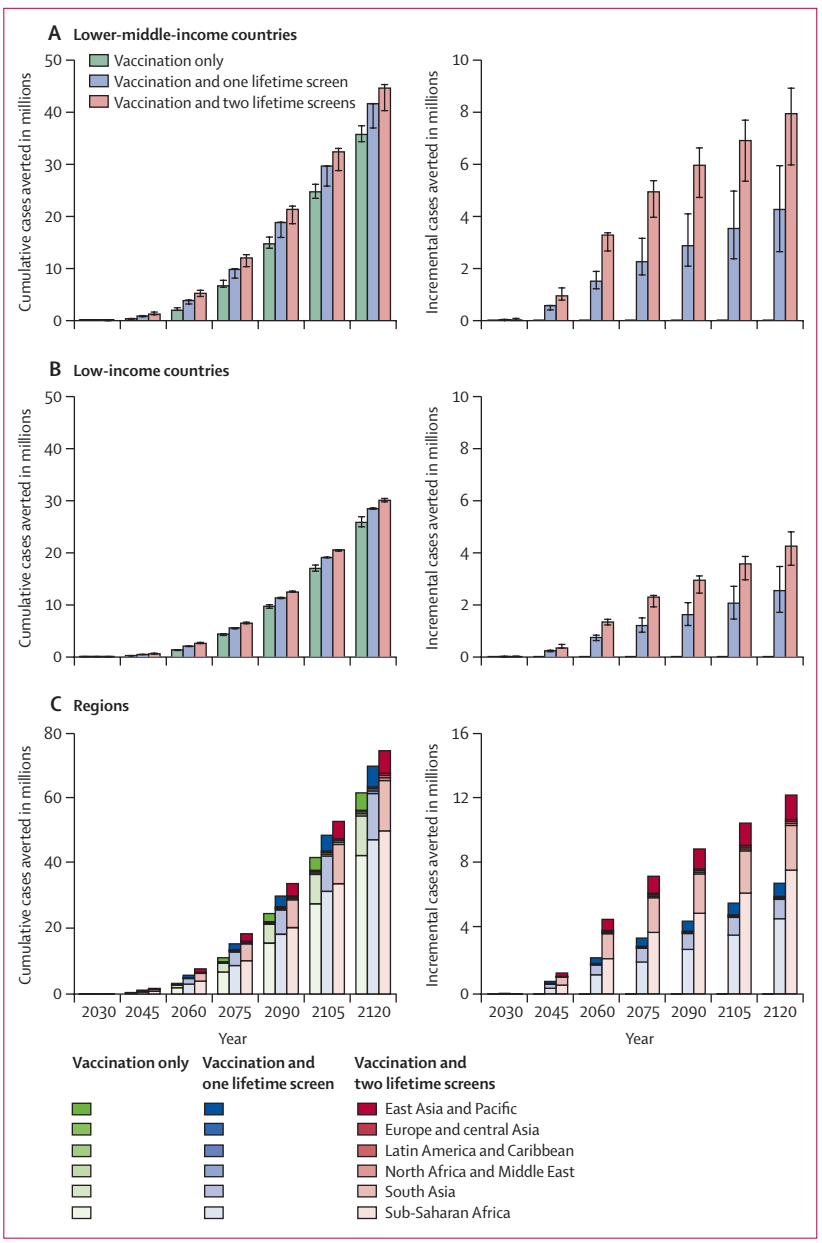

Figure 5: **Cervical cancer cases averted**
Cumulative cases averted by girls-only vaccination or girls-only vaccination plus screening, and incremental cases averted by screening in addition to vaccination over time, for lower-middle-income countries (A), low-income countries (B), and by region (C). Median prediction from the three models. Error bars represent the minimum and maximum estimates from the three models. Vaccination coverage=90% at age 9 years (and at ages 10–14 years in 2020). Vaccine efficacy=100% against HPV types 16, 18, 31, 33, 45, 52, and 58. Vaccine duration=lifetime. Screening=HPV testing. Screening uptake=45% (2023–29), 70% (2030–44), and 90% (2045 onwards). Screen and treat efficacy=100%. Loss to follow-up=10%. HPV=human papillomavirus.

The models predicted that cervical cancer elimination might be possible in LMICs with an age-standardised incidence of fewer than 25 cases per 100 000 women-years (eg, Vietnam) by use of a vaccine that includes only HPV types 16 and 18. However, for LMICs with the highest cervical cancer incidence (eg, Uganda), broad-spectrum protection against HPV types 16, 18, 31, 33, 45,

52, and 58 was predicted to be required for these countries to reach elimination.

Elimination was generally easier to achieve under the different scenarios examined in the sensitivity analysis with the thresholds of fewer than ten cases per 100 000 women-years and 85% or greater reduction. The models predicted that all vaccination strategies will achieve elimination, except for girls-only vaccination with 80% coverage. Twice-lifetime screening (without vaccination) could also potentially lead to elimination with these thresholds in LMICs that have an age-standardised cervical cancer incidence of less than 25 cases per 100 000 women-years (eg, Vietnam).

Discussion

Our comparative modelling analysis, which includes projections from three independent transmission-dynamic models, provides consistent results predicting that cervical cancer can be eliminated as a public health problem by the end of the century, based on WHO's proposed elimination threshold (ie, cervical cancer incidence of four or fewer cases per 100 000 women-years). Our modelling study shows that girls-only HPV vaccination would lead to cervical cancer elimination in most LMICs, if high coverage is reached (>90% coverage) and the vaccine provides long-term protection. However, countries with the highest cervical cancer incidence at present (>25 cases per 100 000 women-years), more than 90% of which are in sub-Saharan Africa, would not reach elimination by vaccination alone. To achieve cervical cancer elimination in all 78 LMICs, our models predict that scale-up of both girls-only HPV vaccination and twice-lifetime screening is necessary, with 90% HPV vaccination coverage, 90% screening uptake, and long-term protection against HPV types 16, 18, 31, 33, 45, 52, and 58. If this global elimination strategy of combined intensive scale-up of HPV vaccination and cervical screening can be achieved, our results suggest that cervical cancer elimination could be achieved in all countries by 2100. In doing so, cervical cancer incidence would be reduced by 97% and more than 74 million cases would be averted over the next century.

In January, 2019, the Executive Board of WHO requested the Director-General to lead the development of a draft global strategy to accelerate cervical cancer elimination, with clear targets for 2030.[24] The draft global strategy will be presented for consideration at the World Health Assembly in May, 2020. The results presented in this study were used to help inform the following key elements of the global strategy: the cervical cancer elimination threshold, the intervention strategies needed to achieve global elimination, and the 2030 targets towards global elimination.

Elimination of cervical cancer requires a clear and commonly agreed upon threshold, under which cervical cancer would no longer be considered a public health problem.[24] Establishment of this threshold thus requires a careful and informed process, as it is more complex than the definition of elimination (or eradication) of an infectious disease, which is simply reduction to zero incidence. The proposed threshold of four or fewer cases per 100 000 women-years was established on the basis of the definition of a rare cancer,[44] on the global distribution of cervical cancer incidence showing that this threshold is currently reached in only a few countries (compared with many countries reaching ten or fewer cases per 100 000),[42] as well as on our modelling results (and those of Simms and colleagues[34]) showing that cervical cancer elimination can be achieved in every country with this threshold. In this study, we examined the consequences of using alternative thresholds (ten or fewer cases per 100 000 women-years and ≥85% reduction), which were proposed during various WHO meetings and consultations,[24] on the achievability and timing of elimination in LMICs for different prevention strategies and country characteristics. Our results show that intensive scale-up of both HPV vaccination and twice-lifetime screening would eliminate cervical cancer in all LMICs for all thresholds investigated.

However, the choice of threshold can produce disparities in the effort required by countries to achieve elimination. For example, based on the threshold or ten or fewer cases per 100 000 women-years, only 1% of LMICs were unable to achieve elimination through HPV vaccination alone. By contrast, based on the proposed threshold of four or fewer cases per 100 000 women-years, 40% of LMICs were unable to achieve elimination through vaccination alone. These countries have the highest burden of cervical cancer (incidence >25 per 100 000 women-years) and are mostly in sub-Saharan Africa. For these countries, up to 90% uptake of twice-lifetime screening is required, in addition to vaccination, to reach the proposed elimination threshold. More generally, our results indicate that elimination will be hardest to achieve in countries with the highest burden of cervical cancer and lowest income level. Considerable financial and political international commitment is needed so that HPV vaccination and cervical screening resources can be prioritised for these countries, not only to achieve global elimination but also to reduce the enormous disparities in the worldwide cervical cancer burden. This is particularly important since current HPV vaccination and cervical screening uptake is very low in most low-income and sub-Saharan African countries.[2–5]

Partly based on the CCEMC projections presented here and the considerations described above, WHO has proposed the following triple-intervention global cervical cancer elimination strategy: intensive scale-up of girls-only HPV vaccination, twice-lifetime screening, and treatment of cancer and precancers.[24] The 2030 targets for this strategy are for 90% of girls to be fully vaccinated, for 70% of women to be screened at 35 years and 45 years of age, and for 90% of women diagnosed with cervical precancer or cancer to receive treatment or care. Our

findings suggest that to achieve global elimination by the end of the century, these targets need to be met in the countries with the highest burden of cervical cancer, and these countries also need to be supported to scale up twice-lifetime screening from 70% to 90% by 2045. Although we show that many LMICs could achieve elimination with HPV vaccination alone, the triple-intervention strategy was chosen as the global elimination strategy as it would accelerate elimination by 11–31 years and prevent an additional 12 million cervical cancer cases over the next century (compared with vaccination alone). Furthermore, combining cervical screening with HPV vaccination has been predicted to be cost-effective across several LMICs.[20–22] The CCEMC is currently examining the incremental cost-effectiveness of the triple-intervention cervical cancer elimination strategy at the global level. Importantly, the proposed global cervical cancer elimination strategy provides general direction about the country-specific strategies that should be used, which should be customised to country-specific epidemiological, economic, and social contexts. For example, countries might want to scale up vaccination and screening at different ages than those modelled, because of logistical issues or to maximise uptake.

The base-case vaccination-only strategy examined in the comparative-model analysis was routine girls-only HPV vaccination at age 9 years with a 1-year multi-age cohort catch-up for girls aged 10–14 years. This strategy was chosen as it is the recommended strategy by the WHO Strategic Advisory Group of Experts on Immunization (SAGE)[41] and a large body of evidence shows that it is highly cost-effective in LMICs and high-income countries.[17,19,31,32] However, given the recent worldwide shortage of vaccine supply, SAGE recommended in October, 2019, that multi-age cohort catch-up vaccination for girls aged 10–14 years should be postponed to alleviate the demand for vaccine doses in the coming years. The recommended WHO alternative strategies are variants of our base-case vaccination-only strategy: routine vaccination of girls aged 14 years, with a later switch to routine vaccination at an earlier age (eg, 9 years); and routine vaccination at age 9 years, with an extended interval of 3–5 years between doses.[45] The recommendations were partly based on results from HPV-ADVISE showing that these strategies would produce similar benefits to girls-only vaccination at age 9 years with a 1-year catch-up for girls aged 10–14 years.[46] Implementation of these alternative strategies would alleviate vaccine supply to allow sufficient doses for all LMICs to reach 90% coverage within the next few years.[45] Hence, assuming countries follow SAGE recommendations, the HPV vaccine shortage should have little long-term impact on our projections of time to elimination provided supply constraints are relieved over the next decade. In our sensitivity analysis, we examined the impact of gender-neutral and multi-age cohort vaccination up to 25 years of age on cervical cancer incidence over time. Because our models predict that 90% girls-only vaccination can almost eliminate HPV vaccine types, the incremental benefits of vaccinating boys on cervical cancer incidence were predicted to be small. Multi-age cohort vaccination up to 25 years of age was predicted to substantially accelerate elimination and avert additional cervical cancer cases but would have no effect on whether a country reaches elimination, which is only determined by long-term routine vaccination coverage. Given their low incremental impact in relation to the number of doses required, WHO recommended that countries should temporarily postpone the implementation of gender-neutral and multi-age cohort HPV vaccination strategies, to maximise the number of countries that can introduce vaccination.[45]

The two base-case screening strategies examined, primary HPV screen-and-treat testing with once-lifetime and twice-lifetime screening, were chosen as they are the recommended strategies by WHO.[40] These screening scenarios were meant to represent a wide range of validated HPV tests and future screening tests, given their high sensitivity and specificity (see Canfell, Kim, Brisson and colleagues[27] for an in-depth discussion of the screening strategies). Our results suggest that including screening in addition to HPV vaccination would substantially increase the number of cervical cancer cases averted and would accelerate elimination, mainly by preventing cases in older, unvaccinated women. Additionally, cervical cancer elimination can be achieved in all but three LMICs (in sub-Saharan Africa) with once-lifetime screening and in all LMICs with twice-lifetime screening. This is because even if HPV vaccination were to eradicate HPV types 16, 18, 31, 33, 45, 52, and 58, a proportion of LMICs (mainly in sub-Saharan Africa) would still have cervical cancer incidence greater than the threshold of four cases per 100 000 women-years; about 10% of cervical cancers are due to HPV types that are not in the currently available HPV vaccines[10] and many countries have cervical cancer incidence higher than 40 cases per 100 000 women-years.[1] For these countries, high cervical screening uptake will have to be sustained for elimination to be maintained (or additional types would have to be included in future HPV vaccines). Finally, in the sensitivity analysis, we predicted relatively small additional gains in cervical cancer prevention by including a third lifetime screen.

Our study has two major strengths. First, we used a comparative modelling approach including three models that have been extensively peer reviewed and validated with post-vaccination surveillance data.[30–36] Without harmonising the model structure or parameters, the three models produced very similar results in terms of absolute and relative reductions in cervical cancer incidence and cancer cases averted over time following HPV vaccination and cervical screening by country, income level, and region. Our results are consistent in part because the key drivers of our predictions (eg, achievability and timing of

elimination) are country-specific baseline cervical cancer incidence and percentage of cancers due to the HPV vaccine types, which were based on the same data sources.[1,10] However, the results were not sensitive to the main differences between our models, which were the sexual behaviour components. At high HPV vaccination coverage and vaccine efficacy, our models predicted similar dynamics and herd effects across the different LMICs, even though sexual behaviour varies substantially. Although we could not directly compare our results to other HPV transmission-dynamic models in LMICs because of the scarcity of such models and their incompatibility in intervention scenarios, a previous systematic comparison of 16 HPV models in high-income countries (including the three CCEMC models) showed consistent predictions of the population-level impact of HPV vaccination when coverage is high.[47] Second, key knowledge users from WHO were involved in all aspects of the study, from its design to interpretations of findings. Additionally, the modelling results were presented and discussed at multiple WHO advisory group and global stakeholder meetings.[24,39,48] This process has ensured that the study was responsive to the needs of global policy decisions and, importantly, that those using the findings are aware of both its strengths and limitations.

Our study has four main limitations. First, our projections are for more than 100 years, a period over which substantial demographic and behavioural changes and technological development are anticipated that can have an impact on cervical cancer incidence.[43,49] Population growth and changes in life expectancy can have an important impact on our predictions of cervical cancer cases averted. When producing projections with low population predictions from the UN,[43] we estimated that 62 million cervical cancer cases would be averted with the triple-intervention global elimination strategy, and that 88 million cases would be averted with the UN's high population predictions, versus 74 million cases with base-case projections (appendix p 12). However, given that the definition of elimination is based on age-standardised cervical cancer incidence, demographic changes are expected to have minimal impact on our predictions of the achievability and timing of elimination. Sexual behaviour has been changing in many LMICs, from a more traditional pattern of sexual behaviour, with a lower reported number of lifetime partners and wider age gaps between partners, to a more sex-similar pattern of behaviour, where both sexes have a similar and higher number of partners and narrow age gaps. In these countries (mainly in Asia), age-adjusted HPV infection and cervical cancer rates might be increasing,[49] and thus time to elimination might be slightly longer than predicted. Technological developments should not have major implications for our predictions, as we assumed 100% vaccine efficacy, high screening test sensitivity and specificity, and 100% treatment efficacy. Second, we assumed intensive scale-up and 90% uptake of HPV vaccination and cervical screening. These assumptions are based on data suggesting that worldwide coverage of measles, poliomyelitis, hepatitis B, and diphtheria-tetanus-pertussis vaccines have reached 84–90% (≥90% in many LMICs)[50] and that more than 90% of women in high-income countries are screened for cervical cancer at least once in their lifetime.[4] If scale-up is slower than modelled, this would delay the predicted timing of elimination and reduce the number of cancer cases averted, but it would not affect whether or not elimination can be achieved. Thirdly, our models do not include plausible biological interactions between HIV and HPV (eg, HPV acquisition and disease progression might be increased among people living with HIV).[51] By not capturing such interactions, our models might overestimate the impact of HPV vaccination in high HIV prevalence settings (five of 78 LMICs have HIV prevalence ≥10%[52]). Specific prevention strategies might be required for people living with HIV to accelerate cervical cancer elimination in high HIV prevalence settings. Modelling work is ongoing as part of the CCEMC to examine these issues. Finally, our country-specific cervical cancer incidence data are based on GLOBOCAN estimates,[42,53] which, where possible, are derived from extrapolation of recent trends in incidence obtained from national or subnational population-based cancer registries. If cervical cancer incidence is underestimated because of underreporting in these countries, elimination might take longer than predicted. There is an overwhelming need to strengthen population-based cancer surveillance in many LMICs to improve the accuracy of GLOBOCAN estimates, to inform local cancer control strategies, and to monitor whether elimination targets are being met.

In conclusion, our comparative modelling analysis suggests that cervical cancer elimination as a public health problem is possible by the end of the century, resulting in a 97% reduction in cervical cancer incidence in LMICs. To achieve elimination across all LMICs under the proposed threshold (four or fewer cases per 100 000 women-years), both high HPV vaccination coverage and screening uptake will be necessary, particularly in countries with the highest burden. Considerable international commitment will be required to achieve WHO's triple-intervention targets, particularly in countries with the highest burden of cervical cancer, where scale-up of vaccination and screening resources are most urgently needed. Our results are being used by WHO to inform its global strategy to accelerate cervical cancer elimination, which will be presented at the World Health Assembly in May, 2020.

Contributors

MB, JJK, and KC co-designed the study and co-led overall data interpretation. MB led the HPV-ADVISE analysis, JJK led the Harvard analysis, and KC led the Policy1-Cervix analysis. NB and RH also participated in study design. MD, EAB, EB, CR, KTS, and AK did the literature searches. MB, MD, GG, KTS, EB, CR, AK, M-CB, MA, FB, EF, PJNB, NB, RH, and DTNN participated in data collection and MB, JJK,

KC, GG, KTS, AK, EAB, EB, DM, SS, CR, J-FL, MC, RH, FB, and NB participated in data analysis. MB, GG, MD, and EB produced the tables and figures. MB, JJK, and KC drafted the Article and RH coordinated the CCEMC. All authors interpreted the results and critically revised the manuscript for scientific content. All authors approved the final version of the Article.

Declaration of interests

MB, MD, GG, DM, EB, J-FL, JJK, EAB, SS, CR, and DTNN report grants from WHO during the conduct of the study. KC, AK, KTS, MC, and MAS report grants from the National Health and Medical Research Council Australia during the conduct of the study. KC and MC are investigators of an investigator-initiated trial of cervical screening in Australia (Compass; ACTRN12613001207707 and NCT02328872), which is conducted and funded by the VCS Foundation, a government-funded health promotion charity; the VCS Foundation received equipment and a funding contribution from Roche Molecular Systems and Ventana USA but KC and MC (or their institution on their behalf) do not receive direct funding from industry for this trial or any other project. MAS also reports grants from Cancer Institute NSW during the conduct of the study. M-CB, MJ, MA, FB, EF, FE, PJNB, NB, and RH declare no competing interests.

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