Projected time to elimination of cervical cancer in the USA: a comparative modelling study

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Summary

Background In May, 2018, the Director-General of WHO issued a global call to eliminate cervical cancer as a public health problem, which will involve ambitious screening and vaccination coverage targets. We aimed to assess the potential for, and timing of, cervical cancer elimination in the USA and whether this could be expedited by adopting ambitious coverage targets, using two cervical cancer simulation models.

Methods In this modelling study, we used two independently-developed cervical cancer microsimulation models—Harvard and Policy1-Cervix—to estimate changes in the incidence of human papillomavirus (HPV)-induced cervical cancer over time in the USA, including herd effects from vaccination. We compared nine alternative scenarios for prophylactic HPV vaccination and cervical screening scale-up with a status quo scenario that involved no additional interventions in the context of a threshold for cervical cancer elimination of four or fewer cases per 100 000 women-years. We also estimated the number of cervical cancer cases that could be averted between 2019 and 2100 associated with the adoption of ambitious goals for cervical cancer screening and vaccination coverage, and other potential strategies.

Findings Under status quo assumptions, the Havard and Policy1-Cervix models projected that cervical cancer incidence would decrease to less than four or fewer new cases per 100 000 women-years by the 2038 and 2046, respectively. Scaling up screening coverage to 90% in 2020, was the most effective intervention to expedite time to elimination (10–13-year reduction), averting a mean of 1400–2088 additional cases annually between 2019 and 2100. Increasing HPV vaccination coverage to 90% or vaccinating adults aged 26–45 years had relatively little effect on cervical cancer incidence. Sensitivity analysis using different population structures resulted in differences in time to elimination (range –10 years to +27 years) compared with status quo predictions.

Interpretation The USA is on track to eliminate cervical cancer as a public health problem in the next two to three decades. Time to elimination could be expedited by 10–13 years by achieving higher screening coverage. Targeting of underscreened and under-vaccinated women remains key to achieving cervical cancer elimination for all women.

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Introduction

On May 19, 2018, the Director-General of WHO issued a global call for action towards the elimination of cervical cancer as a public health problem,[1] which will require ambitious targets for screening and vaccination coverage and scale-up of treatment for cancer and precancer. The draft WHO strategic plan for elimination proposes a cervical cancer incidence target of four or fewer cases per 100 000 women-years.[1] Similar to other high-income countries, the age-standardised incidence of cervical cancer in the USA is relatively low (approximately seven cases per 100 000 women-years[2]), but currently above the WHO elimination incidence target threshold. To achieve the target incidence, the WHO draft strategy proposes targets of 90% of girls vaccinated against human papillomavirus (HPV) by age 15 years, 70% of women screened twice in their lifetime (at 35 and 45 years of age), and 90% compliance with treatment recommendations for precancer and invasive cancer.[1]

Although the USA was one of the first countries to implement prophylactic HPV vaccination, the high coverage observed among adolescent girls and boys in other nations, such as the UK and Australia, has not been observed in the country.[3] Additionally, screening practice is suboptimal; many women are underscreened and an estimated 14% of women are never screened.[4] Although improvements are expected as a result of switching from Papanicolaou (Pap) or cytology-based screening to primary HPV-based testing,[5] the effectiveness of screening is dependent on high, routine coverage and compliance to follow-up and treatment recommendations. The combined effect of HPV vaccination and HPV-based screening will probably lead to substantial declines in cervical cancer incidence in the USA in the near future; however, adopting ambitious coverage goals could improve the effectiveness and efficiency of current cervical cancer control efforts.

Considering the long time period between acquiring an HPV infection and the development of cervical cancer, which can take decades, understanding the cervical

Research in context

Evidence before this study

We updated our previous literature search of PubMed for studies published in English between Jan 1, 2010, and Sept 24, 2018, to include studies published up to Oct 30, 2019, using the search terms "timing" or "timeline", "cervical cancer", and "elimination". Our search identified three studies that estimated the time to elimination of cervical cancer globally, in Australia, and in China; however, we found no studies that used a comparative modelling approach or that projected the timing of elimination in the USA using current screening and vaccination coverage rates and under a range of scenarios for scaling up human papillomavirus (HPV) vaccination, screening, and follow-up for surveillance.

Added value of this study

This study assessed the potential for, and timing of, cervical cancer elimination as a public health problem in the USA, and whether this could be expedited by adopting ambitious coverage targets. We simulated current screening and HPV vaccination as practised in the USA, including the introduction and scale-up of HPV vaccination from 2007. In this comparative model-based analysis, we found that scale-up of screening coverage could expedite the time to elimination of cervical cancer substantially, whereas scaling up vaccination coverage or expanding vaccination target populations (eg, to women or men in mid-adulthood) had little effect on the time to elimination of cervical cancer.

Implications of all the available evidence

The findings of this study offer two model-based projections of the achievability and timeliness of achieving WHO elimination threshold targets under current and improved coverage goals in the USA. Our findings suggest that the USA is on track to eliminate cervical cancer as a public health problem in the next two to three decades. Consistent with earlier studies, this goal can be expedited by improving screening coverage, even within countries with well-established screening programmes. These national estimates do not apply to all subgroups of women; therefore, reaching underscreened and under-vaccinated women remains key to achieving cervical cancer elimination for all women.

cancer burden in the USA in the future under current primary and secondary prevention efforts requires the use of mathematical simulation models, which have been used to support the planning of WHO's elimination goals.[1,6,7] The use of comparative modelling enhances model transparency and can help guide public health research and priorities. We aimed to assess the potential for, and timing of, cervical cancer elimination in the USA, and whether this could be expedited by adopting ambitious scaled-up screening and vaccination targets, using two cervical cancer models.

Methods

Analytical overview

We used two cervical cancer natural history models (Harvard and Policy1-Cervix [Cancer Council New South Wales, Sydney NSW, Australia]) that are part of the Cancer Intervention and Surveillance Modeling Network (CISNET) cervical consortium to project age-standardised cervical cancer incidence per 100 000 women-years and the number of cervical cancer cases averted between 2019 and 2100 associated with the adoption of ambitious goals for cervical cancer screening and vaccination coverage, and other potential strategies.

For more on **CISNET** see https://cisnet.cancer.gov/

See Online for appendix

We defined the elimination year as the year in which age-standardised incidence of cervical cancer consistently decreased to four or fewer new cases per 100 000 women-years, and additionally considered a lower, highly aspirational, hypothetical threshold of one new case per 100 000 women-years. Base-case results were age standardised to the 2000 US standard population, consistent with the methodology used in routinely published Surveillance, Epidemiology, and End Results Program statistics;[8] we also calculated results that were age standardised using the World Female Population 2015 (ages 0–99 years), which is now recommended for any comparisons between countries and for incidence calculations used to inform WHO strategic planning for cervical cancer elimination.[6,7,9] We calculated the number of newly diagnosed cervical cancer cases per year by applying the US female population projections for 2019–2100 (using linear interpolation for single years) from the UN Development Programme.[9]

Microsimulation models

The Harvard and Policy1-Cervix CISNET models, which have been described in detail previously,[5,10,11] differ with respect to the type and number of health states, HPV genotype categorisations, histological cancer types (squamous cell carcinoma in the Harvard model; all cervical cancer in the Policy1-Cervix model), and data sources used to parameterise the model before fitting to the US setting. Both models integrate empirical data from a range of sources by ensuring the resulting model predictions simultaneously correspond to observed data across multiple detailed US epidemiological targets (appendix pp 2–6).

The Harvard model is an individual-based (ie, micro-simulation) model of cervical carcinogenesis that tracks a birth cohort of individual women through a series of monthly transitions over their lifetimes, beginning at age 9 years.[12] Each month, a woman might acquire or clear an HPV infection, progress to, or regress from, cervical intraepithelial neoplasia grade 2 (CIN2) or CIN3, or progress to invasive cervical cancer. In contrast to the other CISNET-cervix models, CIN2 and CIN3 are

modelled as non-sequential precancerous health states with distinct probabilities of progression to cancer, whereas CIN1 is interpreted as a microscopic manifestation of acute HPV infection and is therefore incorporated into the HPV-infected state. Preclinical cancer might be identified through symptoms or might progress to a more advanced clinical stage. Each month, all women are at risk for all-cause mortality and hysterectomy; women with cervical cancer are at excess risk for mortality from cervical cancer. Transitions can be a function of age (ie, HPV incidence), time spent in a health state (ie, HPV clearance, precancer progression or regression), HPV genotype (HPV16, HPV18, HPV31, HPV33, HPV45, HPV52, HPV58, pooled other high-risk types, and pooled low-risk types), and history of HPV infection (natural immunity). Initial model parameterisation of HPV incidence and clearance, and progression to and regression from CIN2 or CIN3, involved a multidisciplinary approach requiring analysis of primary empirical data,[13,14] and was supplemented by data from published literature and expert opinion.[12] For parameters with high uncertainty, we relied on a multiparameter calibration process[12] to maximise correspondence between model-projected outcomes and empirical targets (appendix pp 2–6).

Policy1-Cervix is a comprehensive model of HPV transmission, HPV vaccination, cervical precancer, cancer survival, screening, diagnosis, and treatment.[10] The platform has been used to evaluate potential public health policies in Australia, England, New Zealand, the USA, and China (appendix p 2). The model simulates HPV infections that can persist or progress to CIN1, CIN2, or CIN3; CIN3 can then progress to invasive cervical cancer. Progression and regression depend on the type of HPV present (HPV16; HPV18; pooled HPV31, HPV33, HPV45, HPV52, and HPV58; and pooled other high-risk types), and can also vary by age, generally being more aggressive in older women than younger women. Unique to Policy1-Cervix, the model captures the observed increased risk of cervical precancer and cancer in women previously treated for precancer.[15] In addition to the model inputs (eg, background mortality) and calibration targets standardised across the CISNET models, Policy1-Cervix captures improved survival for women with screen-detected cancer on the basis of published studies (appendix p 12). Base-case results for Policy1-Cervix represent the aggregate results across each birth cohort for a simulation run of 100 million women per birth cohort, using a natural history parameter set that has been selected on the basis of consistency with a wide range of age-specific and type-specific targets across multiple settings (appendix p 2).

Both models applied common inputs for the US population, including age-specific hysterectomy rates on the basis of data from the National Hospital Discharge Survey;[16] all-cause mortality from the Berkeley Mortality Database;[17] and conditional 5-year stage-specific cervical cancer survival from the Surveillance, Epidemiology, and End Results Program.[18] The models generated estimates for age-standardised cervical cancer incidence per 100 000 women-years and the number of new cervical cancer cases between 2019 and 2100.

To standardise the models to the HPV and cervical disease burden in the USA, we selected sources for calibration target data on the basis of representativeness of the general population, sampling methods, and sample size. All data were collected from populations before HPV vaccination. Age-specific prevalence of HPV infections was based on data from the New Mexico HPV

	Screening		Vaccination*	
	Strategy	Coverage (from 2020 onwards)	Strategy	Coverage (from 2020 onwards)
Scenario 1	Cytology-based screening (age 21–65 years)	Status quo†	Females aged 12–26 years, males aged 12–21 years	Status quo‡
Scenario 2	Cytology-based screening (age 21–65 years)	90% coverage§	Females aged 12–26 years, males aged 12–21 years	Status quo‡
Scenario 3	Cytology-based screening (age 21–65 years)	Status quo†	Females aged 12–26 years, males aged 12–21 years	90% of females aged 12 years (status quo for males)¶
Scenario 4	Cytology-based screening (age 21–65 years)	90% coverage§	Females aged 12–26 years, males aged 12–21 years	90% of females aged 12 years (status quo for males)¶
Scenario 5	Cytology-based screening (age 21–65 years)	Status quo†	Females aged 12–26 years, males aged 12–21 years	90% of females and males aged 12 years¶
Scenario 6	Cytology-based screening (age 21–65 years)	90% coverage§	Females aged 12–26 years, males aged 12–21 years	90% of females and males aged 12 years¶
Scenario 7	Cytology-based screening (age 21–65 years)	Status quo†	Females aged 12–45 years, males aged 12–45 years	Status quo and extended MAC age 45 years‖
Scenario 8	Cytology-based screening (age 21–65 years)	90% coverage§	Females aged 12–45 years, males aged 12–45 years	Status quo and extended MAC age 45 years‖
Scenario 9	Cytology-based screening (age 21–65 years)	Status quo†	Females aged 12–26 years, males aged 12–21 years	Gradual scale-up 90% of females only by age 17 years**
Scenario 10	Cytology-based screening (age 21–65 years)	90% coverage§	Females aged 12–26 years, males aged 12–21 years	Gradual scale-up 90% of females only by age 17 years**

Scenario 1 represents the status quo screening and vaccination coverage in the USA; scenarios 2–4 represent high-coverage targets; and scenarios 5–10 represent alternative targets. HPV=human papillomavirus. MAC=multi-age cohort catch-up. NIS-Teen=National Immunization Survey-Teen. *Assumes nonavalent HPV9 vaccine starting in 2015 and historical vaccination coverage using the first-generation quadrivalent vaccine (HPV4) starting in 2007 for females and 2010 for males. †Assumes screening frequency, and compliance to diagnostic colposcopy and biopsy and precancer treatment referral on the basis of empirical data from the New Mexico HPV Pap Registry.[19] ‡Vaccination coverage was based on data from NIS-Teen (appendix pp 10–12). §Screening coverage assumes 90% compliance to primary screening tests, follow-up or surveillance, colposcopy, and treatment from 2020 onwards. Primary screening compliance assumes 90% of women comply with 3-year cytology and 10% of women never attend screening. ¶Assumes 90% coverage is achieved at age 12 years from 2020 onwards (individuals aged 13–26 years in 2020 continue to follow cumulative uptake reported in NIS-Teen). ‖Assumes status quo vaccine coverage on the basis of data from NIS-Teen and ongoing vaccine uptake of 2·6% per year in females aged 27–45 years and 1·9% per year in males age 22–45 years. **Gradual scale-up of vaccination involves 90% coverage achieved within 5 years (at age 17 years), with no change to uptake at age 12 years (29·5% uptake); 32·35% uptake annually until age 17 years; uptake at age 18 years and older in 2020 continues to follow cumulative uptake reported in NIS-Teen (appendix pp 10–12).

Table 1: **Alternative cervical cancer screening and HPV vaccination scenarios under current and scaled up US cervical cancer control strategies**

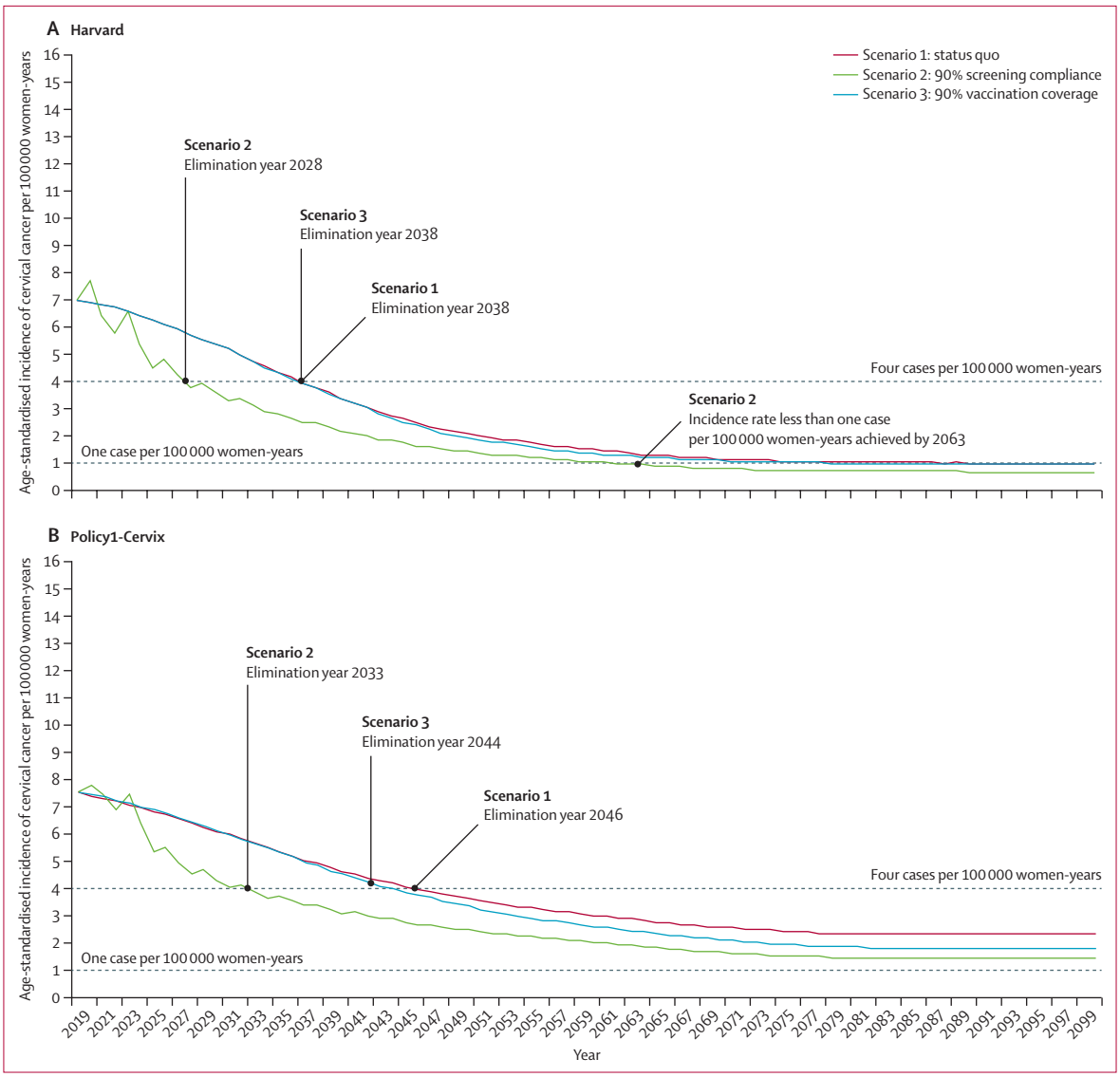

Figure 1: **Age-standardised* cervical cancer incidence per 100 000 women-years under status quo and two high-coverage screening and vaccination scenarios according to two cervical cancer simulation models**

(A) Harvard model. (B) Policy1-Cervix model. Status quo screening involved cytology screening every 3 years in women aged 21–65 years with management according to established guidelines. Screening practice was based on empirical laboratory-based data from the New Mexico HPV Pap Registry.[19] Age-specific and sex-specific HPV vaccination coverage was based on NIS-Teen interviews (appendix pp 10–12). The sawtooth pattern associated with the screening coverage scale-up scenarios reflects the detection of prevalent preclinical cancers among the underscreened and overscreened women converging to a 3-yearly interval in 2020. HPV=human papillomavirus. NIS-Teen=National Immunization Survey-Teen. *Standardised to the US 2000 population (age 0–99 years).[8]

Pap Registry (NMHPVPR), the only state-wide screening registry in the USA.[19,20] HPV type distribution in diagnosed cases of CIN and cancer were also included as calibration target data. For CIN2 and CIN3, HPV type distribution was based on data from the NMHPVPR.[21] HPV type distribution in cancer was based on a 2015 study by the US Centers for Disease Control and Prevention using tissue samples from US population-based cancer registries for cancers diagnosed between 1993 and 2005.[22]

Modelled scenarios

We compared a status quo scenario, reflecting current cervical cancer screening and HPV vaccination coverage (assuming these coverage rates remain unchanged indefinitely), with nine alternative screening and vaccination scale-up scenarios (table 1). Status quo screening assumed cytology screening every 3 years was recommended among women aged 21–65 years with management according to established guidelines.[23] Similar to previous analyses,[4] adherence to screening practice was based on

empirical laboratory-based data from the NMHPVPR and reflected a distribution of overscreening and underscreening (appendix p 8). For example, we assumed approximately 9%, 16%, 11%, 35%, and 14% of women attended screening every 1, 2, 3, 4, or 5 years, respectively, and 14% of women were assumed to never participate in screening. Among women who attend primary screening, we assumed compliance to recommended colposcopy or biopsy or precancer treatment varied from 47% to 76%, depending on preceding cytological or histological severity (appendix p 8). Status quo vaccination assumed age-specific and sex-specific HPV vaccination coverage based on National Immunization Survey-Teen (NIS-Teen) interviews (appendix pp 10–12), including historical vaccination coverage using the quadrivalent vaccine starting from 2007 for girls and 2010 for boys, and the nonavalent HPV vaccine from 2015 onwards, based on updated US guidelines (appendix pp 10–12). For example, based on status quo assumptions, the cumulative HPV vaccination coverage for adolescents who turn age 12 years in 2020 was assumed to reach around 65% by age 17 years for females and 55% by age 17 years for males, consistent with recent trends in NIS-Teen data (appendix pp 10–12). For ages 18 years and older, an annual rate of vaccination of 2·6% for females and 1·9% for males was assumed, which resulted in a cumulative vaccination coverage of 75% by age 26 years for females and 62% by age 21 years for males (appendix pp 11–12). Vaccination was assumed to provide 95% lifelong protection against incident HPV infections targeted by the vaccines.

Since screening coverage in the USA already exceeds the WHO 2030 target of 70% twice per lifetime, we considered a scaled-up screening target that was more ambitious than the WHO 2030 target. The scaled-up coverage strategies (starting in 2020) involved immediate 90% vaccination coverage of girls aged 12 years, or 90% screening coverage and 90% follow-up compliance to colposcopy or biopsy and precancer treatment, if indicated. We assumed no change in current access or delivery of treatment or palliation for invasive cervical cancer from that currently experienced in the USA. Screening coverage of 90% was applied, assuming that 10% of women were never screened and the remaining 90% complied with the recommended 3-year screening interval. Alternative strategies varied assumptions for vaccination by sex (including boys), age (including elective vaccination of men and women in mid-adulthood [up to age 45 years]), and allowing for delayed timing of vaccination coverage target (cumulative uptake of 90% achieved before age 18 years, rather than at age 12 years).

On the basis of a framework of recommended reporting standards for model-based analyses of HPV-related disease published in 2019,[24] we have included the HPV-FRAME checklist in the appendix (pp 14–16).

Sensitivity analysis

We did sensitivity analyses to assess the effect of alternative population structures on the elimination year, in particular the World Female Population 2015 (age 0–99 years), which is the benchmark population structure in use for global predictions by WHO (appendix p 12).[6,7,9] We also assessed the impact of scaled up 5-yearly primary HPV screening (rather than cytology) for women aged 30 years or older, and of birth-cohort-specific hysterectomy rates (appendix p 7). Birth-cohort-specific hysterectomy rates were derived using nationally representative data on hysterectomy incidence between 1965 and 2009 in the USA and result in lower future estimates of benign hysterectomy prevalence than base-case assumptions.

	Harvard	Policy1-Cervix
Scenario 1: status quo screening and vaccination	2038	2046
Scenario 2: 90% screening and status quo vaccination	2028	2033
Scenario 3: Status quo screening and vaccination of 90% of females only	2037	2044
Scenario 4: 90% screening and vaccination of 90% of females only	2028	2033
Scenario 5: status quo screening and vaccination of 90% of females and males	2037	2044
Scenario 6: 90% screening and vaccination of 90% of females and males	2028	2033
Scenario 7: status quo screening and low coverage MAC vaccination	2037	2044
Scenario 8: 90% screening and low coverage MAC vaccination	2028	2033
Scenario 9: status quo screening and 90% gradual vaccination of females only	2037	2045
Scenario 10: 90% screening and 90% gradual vaccination of females only	2028	2033

Scenario 1 represents the status quo; scenarios 2–4 represent high-coverage targets; and scenarios 5–10 represent alternative targets. Cervical cancer incidence was age standardised to the US 2000 standard population (age 0–99 years).[8] MAC=multi-age cohort catch-up.

Table 2: **Estimated elimination year for each screening and vaccination scenario assuming an elimination threshold of four or fewer new cases per 100 000 women-years**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Both models achieved good fit to common calibration targets and validation targets of historical (1950–59) and current (2008–12) cervical cancer incidence (appendix pp 3–6).

Under status quo screening and vaccination assumptions, cervical cancer incidence was projected to decrease to less than four new cases per 100 000 women-years by the year 2038 according to the Harvard model and by 2046 according to the Policy1-Cervix model, and did not decrease to less than one case per 100 000 women-years by 2100 in either model (figure 1). Scaling up of vaccination coverage to 90% in girls only had minimal impact on the elimination year (2038 in the Harvard model *vs* 2044 in Policy1-Cervix). By contrast, scaling up of screening coverage to 90% achieved an incidence of less than four new cases per 100 000 women-years 10–13 years earlier than that observed with the status quo scenario

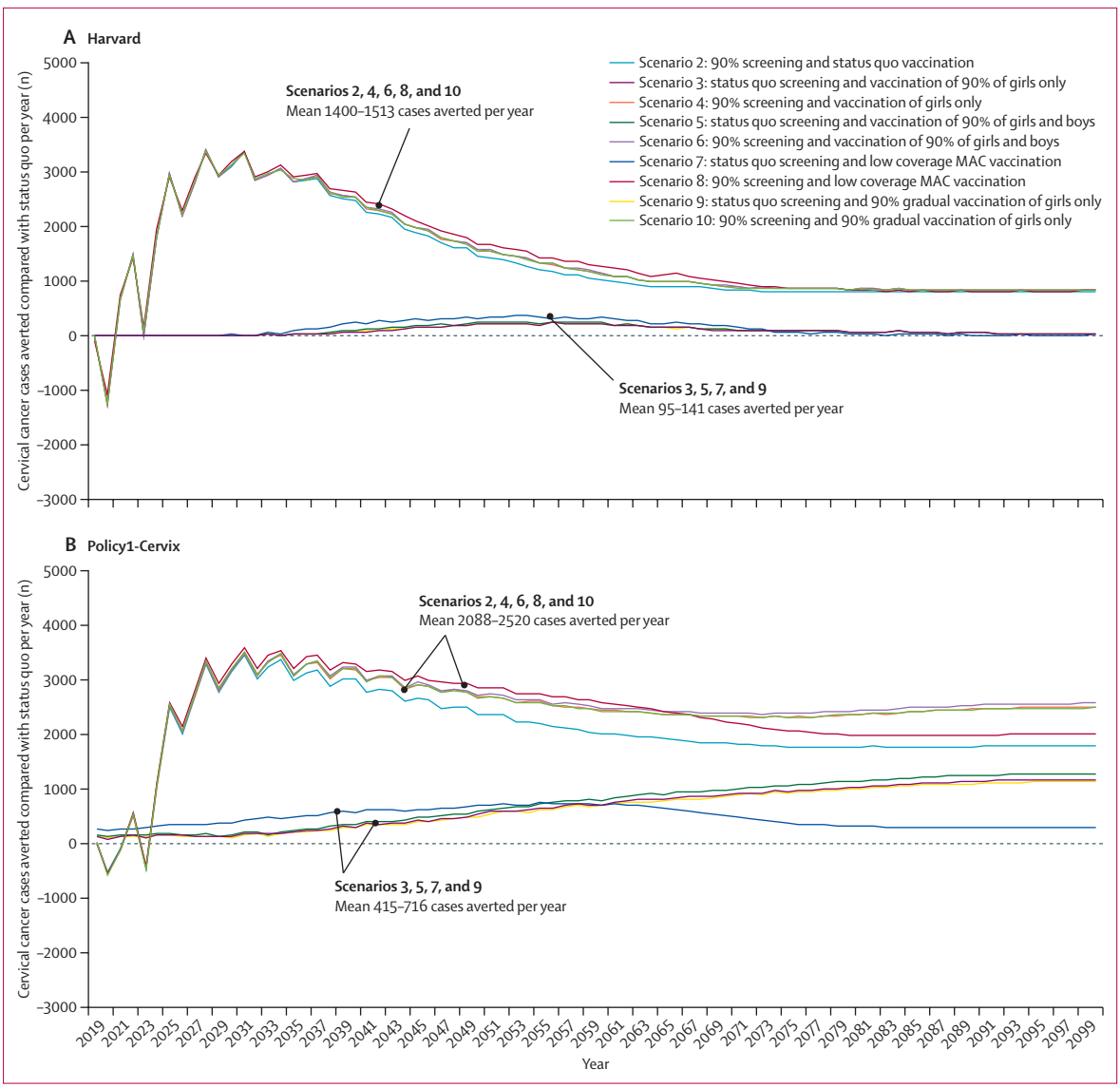

Figure 2: **Projections of number of cervical cancer cases averted annually according to alternative screening and HPV assumptions compared with status quo screening and vaccination assumptions for two cervical cancer simulation models**

Status quo screening involved 3-yearly cytology screening in women aged 21–65 years with management according to established guidelines. Screening practice was based on empirical laboratory-based data from the New Mexico HPV Pap Registry.[19] Age-specific and sex-specific HPV vaccination coverage was based on NIS-Teen interviews (appendix pp 10–12).The sawtooth pattern associated with the screening coverage scale-up scenarios reflects the detection of prevalent preclinical cancers among the underscreened and overscreened women converging to a 3-yearly interval in 2020. Negative averted cancer cases result from the earlier detection of preclinical cancers when screening coverage is scaled up. HPV=human papillomavirus. NIS-Teen=National Immunization Survey-Teen.

(elimination year 2028 for the Harvard model *vs* 2033 for Policy1-Cervix; figure 1). The alternative scenarios involving scaling up vaccination in additional groups (eg, boys, or women and men in mid-adulthood) also had only a marginal effect on the elimination year, and had no effect compared with scaling up coverage in girls only (table 2).

Depending on strategy and model, increasing only vaccination averted a mean of 95–716 additional cases per year compared with the status quo scenario, whereas increasing only screening coverage averted a mean of 1400–2088 additional cases per year compared with the status quo scenario (figure 2). Under status quo assumptions, the elimination year varied by up to 27 years when we used different populations and age ranges for age standardisation, and varied by up to 2 years when we assumed lower future rates of benign hysterectomies (table 3). Our projections for the US elimination year were 4–5 years earlier when we used the World Female Population 2015 (ages 0–99 years) structure, which is the benchmark population structure used for global predictions by WHO. Compared with improving cytology screening coverage (scenario 2),

	Harvard (projected elimination year 2038)†		Policy1-Cervix (projected elimination year 2046)†	
	Projected elimination year	Difference‡	Projected elimination year	Difference‡
Age 0–99 years				
Varying hysterectomy rates (US 2000 standard population)§	2038	0	2048	+2 years
World Female Population 2015¶	2034	–4 years	2041	–5 years
WHO Standard Million	2034	–4 years	2040	–6 years
Unweighted (average) population	2046	+8 years	2068	+22 years
Scaled up 5-yearly primary HPV screening‖	NA	NA	2028	–18 years
Age 9–99 years				
US 2000 standard population	2041	+3 years	2052	+6 years
World Female Population 2015	2038	0	2049	+3 years
WHO Standard Million	2037	–1 year	2046	0
Unweighted (average) population	2050	+12 years	2073	+27 years
Age 0–84 years				
US 2000 standard population	2037	–1 year	2045	–1 year
World Female Population 2015	2034	–4 years	2040	–6 years
WHO Standard Million	2034	–4 years	2039	–7 years
UNDP 2020 US population structure	2039	+1 years	2052	+6 years
Segi population structure	2032	–6 years	2036	–10 years
Unweighted (average) population	2042	+4 years	2058	+12 years

Differences in elimination years shown are relative to the base-case elimination year under status quo assumptions for each model, if an elimination threshold of four new cases per 100 000 women-years is reached. HPV=human papillomavirus. NA=not applicable. UNDP=UN Development Programme. *Different global population structures are cited in the appendix (p 12). †Base-case elimination year is based on incidences age standardised to the US 2000 population (aged 0–99 years), consistent with Surveillance, Epidemiology and End Results Program data.[8] ‡Compared with status quo elimination year. §Assuming birth-cohort-specific estimates for incidence of benign hysterectomy (appendix p 7). ¶Population structure used for global predictions by WHO (appendix pp 12–13). ‖Strategy involves the ambitious target of 90% coverage using primary HPV-based screening for women aged 30–65 years; analysis was not run using the Havard model.

Table 3: **Sensitivity analysis of the impact of population structure* used for age-standardisation and future hysterectomy rates on base-case elimination year under the status quo scenario**

improved screening coverage in the context of switching to primary HPV screening every 5 years for women aged 30 years and older decreased the time to elimination by an additional 5 years to 2028 in the Policy1-Cervix model.

Neither model predicted that cervical cancer incidence would decrease to less than the highly ambitious, hypothetical threshold of less than one case per 100 000 by 2100 under status quo screening and vaccination assumptions (figure 1). The Harvard model predicted that incidence could decrease to below this threshold by 2062 on the assumption that screening coverage was scaled up to 90% (assuming cytological assessments were done every 3 years), whereas in Policy1-Cervix incidence only decreased below this threshold in the context of scaled-up primary HPV screening coupled with scaled-up vaccination of adolescent females (either at age 12 years or by age 17 years; data not shown).

Discussion

The USA is on track to achieve cervical cancer elimination (incidence of four or fewer new cases per 100 000 women-years) between 2038 and 2046, but improving cervical screening coverage could substantially expedite the timing of cervical cancer elimination in the USA by 10–13 years, especially in the context of primary HPV screening. To our knowledge, this is the first study to use comparative modelling analysis to project the timeframe to cervical cancer elimination in the USA.

The variation in timing of elimination between the two models reflects the underlying uncertainty in the HPV transmission and cervical cancer disease process. Despite the 8-year difference in elimination year between the status quo projections for the two models, we identified greater convergence between the models for scenarios in which screening was scaled up than scenarios in which only vaccination was scaled up. Both models demonstrated that increasing screening coverage has a greater effect on elimination year and on cervical cancer cases prevented between 2020 and 2100 than increasing vaccination coverage alone.

The models projected cervical cancer elimination in the USA will occur 10–18 years later than that previously projected for Australia, where high-coverage vaccination was introduced early and screening has been transitioned to HPV-based methods.[10] Our US projections for elimination timing are, however, slightly earlier than that projected in a global analysis;[25] the difference is probably due to more conservative assumptions being made for status quo vaccination and screening coverage in the earlier global study compared to those applied in this

analysis. Similar to projections from Australia,[10] the elimination year was relatively sensitive to the population used for age standardisation (more so than to vaccination coverage). The standard population age range and structure used for age standardisation might be considered a relatively unimportant or technical detail, but does affect the year of elimination (by up to 27 years in our analysis), and is likely to differentially affect the relative importance of screening compared with vaccination. For example, population structures that place a greater weight on cancer incidence in younger women are likely to produce lower age-standardised rates and also reflect vaccine impact more quickly, and thereby predict an earlier elimination year. In contrast, older age population structures that place a greater emphasis on cancer incidence among older women are likely to yield higher age-standardised rates and therefore a later elimination year, and are likely to imply more policy emphasis on the importance of screening. However, it is crucial to note that a standard population for cervical cancer elimination calculations has been proposed[6,7,25] and it is important to use this population when comparing time to elimination between countries. Country-specific analyses should ensure cervical cancer incidence is assessed in the context of both local and global population structures (ie, using World Female Population 2015 [ages 0–99 years], the standard for comparing elimination timing across countries).

By contrast, further increases in vaccination coverage had relatively little effect on the predicted year of elimination in the USA. Current HPV vaccination rates in the USA were projected to achieve cumulative coverage of around 75% by age 26 years in females and around 62% by age 21 years in males on the basis of both empirical data and assumed projections; thus improving vaccination coverage to 90% did not yield substantial gains beyond those already observed, taking into account existing herd effects. The additional benefits of scaling up vaccination coverage were greater in Policy1-Cervix than Harvard, which is likely to be a result of differential estimates of herd effects, stemming from differences in our dynamic model assumptions, such as our sexual behaviour networks. Consequently, the effect of herd immunity in the Harvard model under status quo assumptions (ie, cumulative coverage of around 75% among females and around 62% among males) was large enough that extending direct protection to many of the unvaccinated women who were already receiving some level of indirect protection did not yield substantial gains. Our findings do not suggest that efforts to increase vaccination coverage are unnecessary, but rather that this approach is not the most expeditious method of reducing cervical cancer incidence in the USA because of the long time between acquiring an HPV infection and being diagnosed with cervical cancer (or other HPV-related cancers). Eventually, vaccination should reduce reliance on screening.[26–29] Additionally, high HPV vaccination coverage remains important in reducing HPV-related non-cervical cancers and genital warts, in both men and women.

Our analysis had several limitations. We did not consider the cost-effectiveness of the various strategies, or the health benefits beyond cervical cancer. In particular, the cost-effectiveness of the increasingly incremental gains for vaccination and screening participation interventions required to reach the highly aspirational incidence threshold of less than one case per 100 000 women-years was not established. Additionally, we did not consider the changes to screening performance and practices when cohorts of HPV-vaccinated girls and adolescents reach cervical cancer screening age, including the likelihood that vaccinated women could be screened less frequently or the possibility that cytology sensitivity could potentially be affected as a result of laboratory staff becoming less practised at recognising cervical abnormalities in the context of lower disease prevalence.[30] Each of these limitations might have led to differences in long-term projections, but are less likely to have affected our estimates for the elimination year. A previous analysis for Australia found no difference in the estimated year of elimination (at the incidence threshold of four or fewer new cases per 100 000 women-years) even when cohorts who were age-eligible for nonavalent vaccine were not screened at all since elimination was already on track to be achieved through the combination of primary HPV screening and quadrivalent vaccination with high coverage.[10] A further limitation is that all models reflect the quality of the data used to inform them. To some extent this limitation is mitigated in this analysis by ensuring that the models fit to a range of detailed empirical targets. For example, we relied on high-quality data from the NMHPVPR to inform population-level estimates of HPV prevalence, and screening coverage and compliance. Screening practice in the state of New Mexico might not be generalisable nationally;[4] however, cancer burden and demographics are broadly consistent. Additionally, these national-level estimates do not consider different subgroups of women. Cervical cancer risk varies substantially within the USA and is elevated among underscreened women and women who have never been screened;[31] therefore, it is understandable that scaled-up screening led to immediate high effectiveness. New screening modalities such as HPV testing on self-collected samples could help reduce the proportion of women who are never screened and those who are underscreened, and the longer screening interval of 5 years for HPV-based screening might make higher coverage rates more attainable.[32] Reaching underscreened women and achieving timely vaccination of groups who are less likely to be screened remain key to realising cervical cancer elimination equitably.

We assumed immediate changes to cervical cancer screening and vaccination beginning in year 2020. Any delay in achieving the coverage targets would delay the timing of elimination. Therefore, our projections can be

considered to represent the earliest estimates of when these interventions could enable cervical cancer incidence rates in the USA to decrease below the WHO threshold of elimination.

In conclusion, under status quo assumptions, using two independent models, we found that cervical cancer rates will decrease to less than four new cases per 100 000 women in the next two to three decades in the USA. Elimination of cervical cancer might be expedited if screening coverage is improved.

Contributors

EAB, MAS, KC, and JJK designed the study. Data analysis was done by EAB, MAS, JK, KTS, SS, KC, and JJK. EAB and MAS drafted the manuscript with input from all authors. All authors approved the final version of the report. EAB and MAS contributed equally to the study.

Declaration of interests

EAB reports grants from the Norwegian Cancer Society during the conduct of the study. MAS reports grants from the National Health and Medical Research Council (Australia) and the Cancer Institute NSW, during the conduct of the study. KC reports grants from the National Health and Medical Research Council (Australia) and is co-principal investigator of an unrelated 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 neither KC (nor her institution on her behalf) have received direct funding from industry for this trial or any other project. All other authors declare no competing interests.

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