# Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020–99: a modelling study

*Kate T Simms, Julia Steinberg, Michael Caruana, Megan A Smith, Jie-Bin Lew, Isabelle Soerjomataram, Philip E Castle, Freddie Bray, Karen Canfell*

## Summary

**Background** Cervical screening and human papillomavirus (HPV) vaccination have been implemented in most high-income countries; however, coverage is low in low-income and middle-income countries (LMICs). In 2018, the Director-General of WHO announced a call to action for the elimination of cervical cancer as a public health problem. WHO has called for global action to scale-up vaccination, screening, and treatment of precancer, early detection and prompt treatment of early invasive cancers, and palliative care. An elimination threshold in terms of cervical cancer incidence has not yet been defined, but an absolute rate of cervical cancer incidence could be chosen for such a threshold. In this study, we aimed to quantify the potential cumulative effect of scaled up global vaccination and screening coverage on the number of cervical cancer cases averted over the 50 years from 2020 to 2069, and to predict outcomes beyond 2070 to identify the earliest years by which cervical cancer rates could drop below two absolute levels that could be considered as possible elimination thresholds—the rare cancer threshold (six new cases per 100 000 women per year, which has been observed in only a few countries), and a lower threshold of four new cases per 100 000 women per year.

**Methods** In this statistical trends analysis and modelling study, we did a statistical analysis of existing trends in cervical cancer worldwide using high-quality cancer registry data included in the Cancer Incidence in Five Continents series published by the International Agency for Research on Cancer. We then used a comprehensive and extensively validated simulation platform, Policy1-Cervix, to do a dynamic multicohort modelled analysis of the impact of potential scale-up scenarios for cervical cancer prevention, in order to predict the future incidence rates and burden of cervical cancer. Data are presented globally, by Human Development Index (HDI) category, and at the individual country level.

**Findings** In the absence of further intervention, there would be 44·4 million cervical cancer cases diagnosed globally over the period 2020–69, with almost two-thirds of cases occurring in low-HDI or medium-HDI countries. Rapid vaccination scale-up to 80–100% coverage globally by 2020 with a broad-spectrum HPV vaccine could avert 6·7–7·7 million cases in this period, but more than half of these cases will be averted after 2060. Implementation of HPV-based screening twice per lifetime at age 35 years and 45 years in all LMICs with 70% coverage globally will bring forward the effects of prevention and avert a total of 12·5–13·4 million cases in the next 50 years. Rapid scale-up of combined high-coverage screening and vaccination from 2020 onwards would result in average annual cervical cancer incidence declining to less than six new cases per 100 000 individuals by 2045–49 for very-high-HDI countries, 2055–59 for high-HDI countries, 2065–69 for medium-HDI countries, and 2085–89 for low-HDI countries, and to less than four cases per 100 000 by 2055–59 for very-high-HDI countries, 2065–69 for high-HDI countries, 2070–79 for medium-HDI countries, and 2090–2100 or beyond for low-HDI countries. However, rates of less than four new cases per 100 000 would not be achieved in all individual low-HDI countries by the end of the century. If delivery of vaccination and screening is more gradually scaled up over the period 2020–50 (eg, 20–45% vaccination coverage and 25–70% once-per-lifetime screening coverage by 2030, increasing to 40–90% vaccination coverage and 90% once-per-lifetime screening coverage by 2050, when considered as average coverage rates across HDI categories), end of the century incidence rates will be reduced by a lesser amount. In this scenario, average cervical cancer incidence rates will decline to 0·8 cases per 100 000 for very-high-HDI countries, 1·3 per 100 000 for high-HDI countries, 4·4 per 100 000 for medium-HDI countries, and 14 per 100 000 for low-HDI countries, by the end of the century.

**Interpretation** More than 44 million women will be diagnosed with cervical cancer in the next 50 years if primary and secondary prevention programmes are not implemented in LMICs. If high coverage vaccination can be implemented quickly, a substantial effect on the burden of disease will be seen after three to four decades, but nearer-term impact will require delivery of cervical screening to older cohorts who will not benefit from HPV vaccination. Widespread coverage of both HPV vaccination and cervical screening from 2020 onwards has the potential to avert up to 12·5–13·4 million cervical cancer cases by 2069, and could achieve average cervical cancer incidence of around four per 100 000 women per year or less, for all country HDI categories, by the end of the century. A draft global strategy to accelerate cervical cancer elimination, with goals and targets for the period 2020–30, will be considered at

*Lancet Oncol* 2019

Published Online
February 19, 2019
http://dx.doi.org/10.1016/S1470-2045(18)30836-2

See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(19)30072-5

**Cancer Research Division, Cancer Council New South Wales, Woolloomooloo, Sydney, NSW, Australia** (K T Simms PhD, J Steinberg DPhil, M Caruana DPhil, M A Smith PhD, J-B Lew PhD, Prof K Canfell DPhil); **Prince of Wales Clinical School, University of New South Wales, Sydney, NSW, Australia** (Prof K Canfell); **School of Public Health, University of Sydney, Sydney, NSW, Australia** (Prof K Canfell); **Section of Cancer Surveillance, International Agency for Research on Cancer, Lyon, France** (I Soerjomataram PhD, F Bray PhD); **Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA** (P E Castle MD); **and Global Coalition against Cervical Cancer, New York, NY, USA** (P E Castle)

Correspondence to:
Prof Karen Canfell, Cancer Research Division, Cancer Council New South Wales, Woolloomooloo, Sydney, NSW 2011, Australia
**karen.canfell@nswcc.org.au**

**the World Health Assembly in 2020. The findings presented here have helped inform initial discussions of elimination targets, and ongoing comparative modelling with other groups is supporting the development of the final goals and targets for cervical cancer elimination.**

**Funding** National Health and Medical Research Council (NHMRC) Australia, part-funded via the NHMRC Centre of Excellence for Cervical Cancer Control (C4; APP1135172).



## Introduction

An estimated 530 000 cervical cancer cases were diagnosed globally in 2012, with 85% of these occurring in less developed regions.[1] The average worldwide age-standardised incidence rate of cervical cancer in 2012 was 14 cases per 100 000 women.[1] First-generation human papillomavirus (HPV) vaccines, including the quadrivalent vaccine, Gardasil (Merck, Kenilworth, NJ, USA), and the bivalent vaccine, Cervarix (GlaxoSmithKline, London, UK), can prevent about 70% and 84% of cervical cancers, respectively (if the potential for cross-protection against certain non-vaccine-included types is confirmed for the bivalent vaccine). A next-generation nonavalent HPV vaccine, Gardasil 9 (Merck), can prevent approximately 90% of cervical cancers. However, these vaccines do not treat pre-existing infections and related cervical abnormalities. Thus, several generations of women need effective cervical screening. In 2016, the American Society of Clinical Oncology (ASCO) released cervical screening guidelines[2] recommending screening for women aged 30–49 years one to three times per lifetime in lower-resource settings with primary HPV testing, on the basis of very strong evidence that HPV testing is a more effective, reliable, and adaptable method of screening (via the use of self-collected specimens) than traditional cytological methods.

### Research in context

#### Evidence before this study

Although more than 30% of females aged 10–20 years in developed countries have received the human papillomavirus (HPV) vaccine, less than 3% had been vaccinated in less developed regions by 2014. More than 280 million vaccine doses have already been delivered worldwide, and Gavi, The Vaccine Alliance has articulated an aim to deliver another 30–40 million doses per year from 2020 onwards. Resource-stratified guidelines for cervical screening recommend HPV testing at least once per lifetime, even in low-income countries. WHO has called for global action towards scale-up of these proven approaches to cervical cancer prevention, towards the elimination of cervical cancer. However, the effect and timing on cervical cancer incidence of current vaccination coverage rates, the added benefit of Gavi achieving its targets, and the potential global effect of achieving uniform high-coverage HPV vaccination and screening is not well understood. We searched PubMed for studies published from Jan 1, 2010, to Sept 24, 2018, with the search terms "timing" or "timeline", "cervical cancer", and "elimination". English-only publications were included. Only one previous study that estimated the timeline to elimination of cervical cancer in any country was identified; this study, co-authored by some of us, estimated that Australia, a very-high-Human Development Index (HDI) country with early and high coverage implementation of both HPV vaccination and cervical screening, will achieve a cervical cancer incidence of less than four cases in 100 000 women by 2035.

#### Added value of this study

Given current trends in cervical cancer incidence, and existing screening and vaccination coverage, the number of cervical cancer cases per annum will increase from about 600 000 in 2020, to 1·3 million in 2069, resulting in 44·4 million new cases of cervical cancer during this period, with almost two-thirds of the burden being in countries with low or medium HDI. Widespread coverage of both HPV vaccination and cervical screening from 2020 onwards has the potential to avert up to 12·5–13·4 million further cases by 2070 and could achieve an average cervical cancer incidence of less than four cases per 100 000 in all country HDI categories, by the end of the century. This study highlights that, as we previously found in Australia, elimination of cervical cancer is possible in most countries, provided high-coverage screening and vaccination can be achieved.

#### Implications of all the available evidence

The Director-General of WHO has announced a call to action for the elimination of cervical cancer as a public health problem, with intent to submit a resolution on a global cervical cancer elimination strategy at the World Health Assembly in 2020. The findings of this study reinforce that high priority should be given to the effective implementation of high-coverage cervical screening and HPV vaccination in low-income and middle-income countries. The study also suggests that if an annual elimination threshold of four cases per 100 000 were to be set, this threshold would be achievable as an average rate in each HDI category by the end of the century, but would not necessarily apply to all individual low-HDI countries. Our findings also imply that extremely rapid and effective scale-up of prevention interventions would be required to reach global average incidence rates approaching four per 100 000 women across all HDI categories by the end of the century.

Globally, considerable disparities exist between countries and within countries in terms of HPV vaccination and cervical cancer screening coverage rates. In 2008, overall screening uptake was reported to be 19% in low-income and middle-income countries (LMICs), compared with 63% in high-income regions.[3] HPV vaccination coverage is much lower in LMICs than in high-income countries; by 2014, an estimated 33·6% of girls and women aged 10–20 years in high-income countries had received the full course of the HPV vaccine, compared with 2·7% of such females in LMICs.[4] Gavi, The Vaccine Alliance, has announced intent to provide support for the bivalent vaccine and quadrivalent vaccine pilot programmes in selected countries, with an aim to support delivery of 30–40 million doses of vaccine annually from 2022.[5] Assuming a two-dose schedule, this programme could result in up to an additional 15–20 million girls and women vaccinated per annum in these countries (equivalent to 25–35% of the world's 10-year-old population); however, vaccine supply challenges could affect the achievability of these targets.[6]

Offsetting the effects of vaccination are population growth and ageing, which are likely to result in an increase in the number of cervical cancer diagnoses over the remainder of the century, particularly in LMICs, even in regions where cervical cancer incidence rates have been declining.[7] Cervical cancer incidence has been in constant flux in the past half century, with the risk of cervical cancer in successive generations decreasing in some settings, due to effective cytology screening,[7,8] and increasing in other settings, potentially because of sexual behavioural differences or HPV co-factor exposures in successive cohorts in the absence of screening intervention.[9,10] These existing trends in cervical cancer incidence must be taken into account when considering the impact of future interventions. The long-term interplay of these factors with the time-delayed effects of vaccination, and the potential benefit of screening or adult HPV vaccination in hastening preventive effects, are not well understood.

In May, 2018, the Director-General of WHO called for "coordinated action globally to eliminate cervical cancer". This call has been supported by several key agencies, with intent to submit a resolution on a global cervical cancer elimination strategy at the World Health Assembly to be held in May, 2020. An elimination threshold in terms of cervical cancer incidence has not yet been defined as part of this process, but an absolute cervical cancer incidence could be chosen for such a threshold. Findings from our recent analysis showed that in view of current prevention efforts, rates of cervical cancer could fall below four cases per 100 000 women by 2021–35 in Australia;[11] however, to date, quantitative estimates of the effect of the global implementation of massively scaled up vaccination and screening initiatives on cervical cancer rates and burden of disease (case numbers) are not available. Such estimates provide crucial background to future discussions of an appropriate threshold.

In this context, the current study aimed to predict the global burden of cervical cancer over the remainder of this century under a range of scenarios, including current country-specific uptake of HPV vaccination and screening, as well as the possibility of very rapid (or gradual) scale-up of HPV vaccination and cervical screening worldwide. We aimed to quantify the cumulative potential effects of increased global vaccination and screening coverage on cervical cancer cases averted during the 50 years from 2020–69 and to extend predictions of cervical cancer incidence rates to 2099 to capture the full effect of HPV vaccination, which takes many decades to be observed. Using these predictions, we aimed to identify the earliest years by which cervical cancer rates could drop below two absolute levels, which could be considered as potential elimination thresholds—the rare cancer threshold (six cases per 100 000 women per year as defined in Europe and Australia)[12,13] and a lower threshold (four cases per 100 000 women per year).

## Methods

### Study design and data sources

In this statistical trends analysis and modelling study, we used an extensively validated dynamic model of HPV transmission, HPV vaccination, cervical precancer, cancer survival, screening, diagnosis, and treatment (Policy1-Cervix).[14–18] The platform has been used to do evaluations to inform current and future vaccination and screening policy decisions for a range of countries including Australia, England, New Zealand, the USA, and China. Details of model structure and function are provided in the appendix (pp 1–4).

See Online for appendix

We projected the global burden of cervical cancer using country-specific and age-specific incidence rates of cervical cancer for countries included in GLOBOCAN estimates for 2012 from the International Agency for Research on Cancer (IARC),[1] with corresponding population estimates and projections obtained from the UN Population Division[19] (data were available for 181 countries from GLOBOCAN and UN population projections, and of these, 177 were described in the Human Development Index [HDI] report). To capture and project trends in cervical cancer incidence caused by effects other than future screening or vaccination (given that vaccination and screening is being explicitly captured by Policy1-Cervix), we analysed high-quality cancer registry data from IARC's Cancer Incidence in Five Continents series using data from volumes 8–11 covering the 20-year period between 1993 and 2012. The analysis included 37 registries across 20 high-density countries in eight geographical regions representing countries across the four HDI categories (low, medium, high, and very high), which are based on the 2015 Human Development Report.[20] Details on how Policy1-Cervix and the trends

| | 2023 | 2030 | 2045 | 2050 |
|---|---|---|---|---|
| **Screening** | | | | |
| Very-high-HDI countries | 66% | 70% | 80% | 90% |
| High-HDI countries | 50% | 70% | 80% | 90% |
| Middle-HDI countries | 20% | 40% | 70% | 90% |
| Low-HDI countries | 10% | 25% | 60% | 90% |
| **Vaccination** | | | | |
| Very-high-HDI countries | 33% | 45% | 72% | 90% |
| High-HDI countries | 14% | 45% | 72% | 90% |
| Middle-HDI countries | 9% | 30% | 48% | 60% |
| Low-HDI countries | 6% | 20% | 32% | 40% |

Assumed percentage of females within each HDI category who are vaccinated or screened. When simulating scale-up, we assumed a linear increase in vaccination and screening coverage rates between the coverage rates reported here for 2023, 2030, 2045, and 2050. We assumed screening would occur once per lifetime between the ages of 30 and 49 years, with a uniform probability of attending at any age in this range. HDI=Human Development Index.

***Table 1:*** **Assumed percentage of females vaccinated and screened by 2023, 2030, 2045, and 2050 in the example gradual scale-up scenario**

analysis are used to project the future rates and burden of cervical cancer estimates are in the appendix (pp 6–15).

### Screening and vaccination scenario description

Estimates of current screening and vaccination coverage are based on country-specific coverage rates from published sources[4] and from the Catalan Institute of Oncology HPV Information Centre.[21] We used country-specific data on the proportion of cancers attributable to vaccine-included types (appendix p 16),[21] and took into account global observations that a higher proportion of cervical cancers are caused by HPV types 16 and 18 in women younger than age 40 years than in women older than 70 years.[22] We assumed 100% efficacy of HPV vaccination against new infections with vaccine-included types in females and males aged up to 26 years (in relevant scenarios) and also assumed 90% efficacy in females and males aged 16–49 years, and considered cross-protection against non-vaccine-included types for the bivalent vaccine. Detailed assumptions are described in the appendix (pp 16–19).

When projecting cervical cancer incidence rates forward in time, we assumed that the population structure remains unchanged from the 2015 world population (so-called population year standardisation, as has been done in other evaluations for projected incidence rates),[23] and we age standardised our rates to the 2015 world female population. The effects of year standardisation and age standardisation are discussed in the appendix (pp 35–40).

Results are presented at the global level and are stratified by the four HDI tiers (low, medium, high, and very high) for the 177 of 181 countries who had an HDI category. Results are also presented for all 181 individually.

When estimating the future incidence of cervical cancer, we assumed that current annual screening and vaccination coverage rates would be maintained, and we also considered six scenarios for further scale-up. First, Gavi commitments for HPV vaccine support are achieved in targeted countries by 2020 (appendix p 18). We assume that 50–80% coverage is achieved in girls aged 10 years in these countries, resulting in 27–39 million HPV vaccine doses required from 2020, similar to that predicted in the 2017 supply and procurement roadmap.[5] Second, 80–100% vaccination coverage is achieved globally from 2020 onwards in girls aged 12 years across all countries. Third, HPV testing (or other screening technology with equivalent high sensitivity and performance) twice per lifetime, at ages 35 years and 45 years, with 70% of the total population of age-eligible women attending each test, is implemented in all countries without existing cervical screening (and countries in which screening is done but coverage is <30%) from 2020 onwards, in line with the resource-stratified ASCO guidelines;[2] we assumed that 85% of women with screen-positive results would comply with follow-up recommendations. Fourth, 80–100% vaccination coverage is achieved globally in girls aged 12 years from 2020 onwards across all countries (using a nonavalent vaccine or another vaccine with equivalent broad-spectrum protection), and HPV testing twice per lifetime at ages 35 years and 45 years with 70% coverage is achieved from 2020 onwards (with screening assumptions as previously described). Fifth, 80–100% vaccination coverage is achieved with a broad-spectrum vaccine with nonavalent vaccine-equivalent protection for both girls and boys aged 12–15 years and 70% vaccination coverage is achieved as a one-off catch-up in the year 2020 for females and males aged 16–49 years (an exploratory strategy known as HPV-FASTER, for which cost-effectiveness has not been shown; also note that licensing of vaccines in various jurisdictions is only to age 45 years); we assumed that the vaccine was 90% effective at preventing new infections in women and men older than 26 years who are currently uninfected (regardless of whether they were previously exposed) and 100% effective for younger ages. Sixth, a more gradual scale-up, in which increasing screening coverage once per lifetime between ages 30–49 years (with a uniform probability of attending between these ranges) and vaccination with the nonavalent vaccine in girls aged 12 years is achieved gradually from 2023–50, with slower scale-up for less developed regions (table 1; appendix p 18).

When modelling screening, we assumed that HPV DNA testing (or a test with equivalent performance characteristics) was used. Test accuracy, compliance, and downstream management of women who are HPV positive were based on a model of screening in rural China.[24] We assumed that 85% of women who were HPV positive at screening were appropriately managed and treated. More detailed screening-related assumptions are described in the appendix (pp 16–20).

### Sensitivity analysis

We did a sensitivity analysis by varying key parameters in the model, including UN population projection estimates

(low variant and high variant estimates as lower and upper ranges), future trends assumptions (using lower and upper CI estimates), herd effects from vaccination (baseline and no herd effects as upper and lower ranges), and screening coverage (40–80% as lower and upper ranges), as described in the appendix (pp 33–40). We also did an extensive sensitivity analysis around the effect of population year and standardisation (appendix pp 32–39).

### 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 the data in the study and had final responsibility for the decision to submit for publication.

## Results

In the absence of further change in cervical screening coverage or vaccination coverage, we found that the annual global number of cervical cancer cases is predicted to increase from about 600 000 in 2020 to 1·3 million in 2069 because of population growth and ageing, as well as changes in underlying risk factor exposures in populations (including changes in HPV exposure in successive cohorts and changes in distribution of exposure to HPV lifestyle co-factors in populations, including HIV, smoking, use of oral contraceptives, parity, and age of first full-term pregnancy), which are captured in the analysis of cervical cancer incidence trends. The combined effect of these factors is predicted to result in a total 44·4 million new cases over the 50 year period (figure 1A; table 2). In the absence of current vaccination coverage (approximately 7·5% globally), an additional 1·3 million cancer cases would have occurred from 2020 to 2069 (figure 1A). If Gavi vaccination targets are met with the quadrivalent vaccine, bivalent vaccine, or the nonavalent vaccine, then 1·5–2·5 million cases of cervical cancer could be averted by 2069 for the quadrivalent vaccine, 1·8–2·9 million cases for the bivalent vaccine (if cross-protection against some non-vaccine-included-types is sustained), or 2·0–3·1 million cases for the nonavalent vaccine. At 80–100% coverage with the nonavalent vaccine, 6·7–7·7 million cases of cervical cancer will be averted (15–17% reduction), but more than half of these averted cases will occur in the last decade of this period (2060–69). If women are offered two screenings during their lifetime in addition to high-coverage nonavalent vaccination, an earlier impact will be achieved, with an additional 5·7–5·8 million cases averted, resulting in a total of 12·5–13·4 million cases averted over this period (28–30% reduction). If high coverage vaccination is achieved for female and male individuals aged 12–49 years (HPV-FASTER; exploratory analysis), 14·0–14·3 million cancer cases could be averted.

Figure 2A and table 3 show the projected burden of cervical cancer by HDI category. Given current screening and vaccination annual coverage rates,

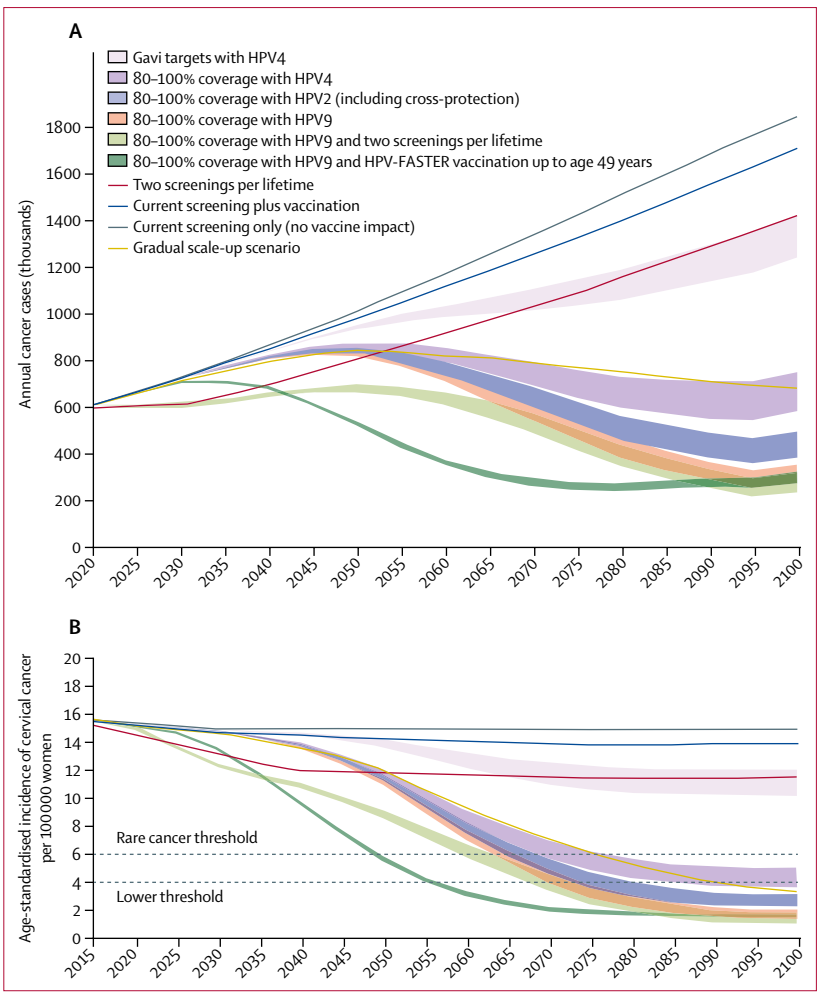



***Figure 1:*** **Projected global number of cervical cancer cases in 2020–99 (A) and projected age-standardised incidence rate of cervical cancer (B), given alternate vaccination and screening scenarios**

Shaded regions represent the range of outcomes from lowest to highest vaccination coverage considered in each scenario. Age-standardised incidence rate calculated using the 2015 world female population for ages 0–84 years.[19] HPV4=tetravalent vaccine. HPV2=bivalent vaccine. HPV9=nonavalent vaccine.

around two-thirds of the world's 44·4 million incident cervical cancer cases predicted over the period 2020–69 will occur in countries indexed as having a low or medium HDI. If rapid scale-up to 80–100% coverage with a broad-spectrum vaccine (eg, the nonavalent vaccine) is achieved together with two screenings per lifetime, three-quarters of the global 12·5–13·4 million cases would be averted in countries indexed as low HDI and medium HDI.

Combined implementation of high-coverage nonavalent vaccination and two screenings per lifetime (ie, rapid scale-up scenario) will result in cervical cancer incidence decreasing to six cases per 100 000 women per year from 2045–49 in very-high HDI countries, 2055–59 in high-HDI countries, 2065–69 in medium-HDI countries, and 2085–89 in low-HDI countries, and below four cases per 100 000 from 2055–59 in very-high HDI countries, 2065–69 in high-HDI countries, 2070–79 in medium-

| | Current screening and vaccination | Gavi targets* with HPV4 | Gavi targets* with HPV2 | Gavi targets* with HPV9 | 80–100% female-only vaccine coverage with HPV4 | 80–100% female-only vaccine coverage with HPV2 | 80–100% female-only vaccine coverage with HPV9 | Screening twice per lifetime at 70% coverage and no vaccination | Screening twice per lifetime and 80–100% female-only vaccine coverage with HPV4 | Screening twice per lifetime and 80–100% female-only vaccine coverage with HPV2 | Screening twice per lifetime and 80–100% female-only vaccine coverage with HPV9 | 80–100% vaccine coverage with HPV9 for females and males for ages 12–15 years and 70% vaccination coverage in ages 16–49 years (HPV-FASTER) | Gradual scale-up scenario |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total cases over 2020–69 | 44·4 | 42·0–42·9 | 41·5–42·6 | 41·3–42·5 | 38·4–39·5 | 37·3–38·4 | 36·7–37·7 | 37·2 | 32·5–33·5 | 31·6–32·5 | 31·1–31·9 | 30·2–30·5 | 38·4 |
| Total cases averted (percentage decrease compared with current screening and vaccination) | NA | 1·5–2·5 (3–6%) | 1·8–2·9 (4–7%) | 2·0–3·1 (4–7%) | 4·9–6·0 (11–14%) | 6·1–7·1 (14–16%) | 6·7–7·7 (15–17%) | 7·2 (16%) | 11·0–11·9 (25–27%) | 11·9–12·8 (27–29%) | 12·5–13·4 (28–30%) | 14·0–14·3 (31–32%) | 6·1 (14%) |
| Total cases averted over 2020–29 | .. | 0 | 0 | 0 | 0 | 0 | 0 | 0·4 | 0·4–0·4 | 0·4–0·4 | 0·4–0·4 | 0 | 0 |
| Total cases averted over 2030–39 | .. | 0 | 0 | 0 | 0·1–0·1 | 0·1–0·1 | 0·1–0·1 | 1·3 | 1·4–1·4 | 1·4–1·5 | 1·5–1·5 | 0·3–0·3 | 0·2 |
| Total cases averted over 2040–49 | .. | 0·1–0·2 | 0·1–0·2 | 0·2–0·3 | 0·4–0·5 | 0·5–0·6 | 0·6–0·7 | 1·6 | 2·1–2·1 | 2·1–2·2 | 2·2–2·3 | 1·8–1·9 | 0·7 |
| Total cases averted over 2050–59 | .. | 0·4–0·7 | 0·5–0·8 | 0·5–0·9 | 1·3–1·7 | 1·7–2·0 | 1·8–2·2 | 1·9 | 2·9–3·2 | 3·2–3·4 | 3·3–3·6 | 4·5–4·6 | 1·8 |
| Total cases averted over 2060–69 | .. | 1·0–1·6 | 1·1–1·8 | 1·2–2·0 | 3·1–3·8 | 3·8–4·4 | 4·2–4·8 | 2·1 | 4·2–4·8 | 4·8–5·3 | 5·2–5·7 | 7·3–7·4 | 3·3 |
| Total cases over 2020–99, extended impact | 87·7 | 74·6–79·6 | 72·5–78·2 | 71·3–77·4 | 56·4–61·7 | 51·1–55·2 | 48·1–51·5 | 72·9 | 48·6–53·2 | 43·9–47·5 | 41·2–44·2 | 38·4–39·0 | 60·7 |
| Total cases averted over 2020–99 (percentage decrease compared with current screening and vaccination), extended impact | NA | 8·1–13·1 (9–15%) | 9·5–15·2 (11–17%) | 10·3–16·4 (12–19%) | 26·0–31·3 (30–36%) | 32·5–36·6 (37–42%) | 36·2–39·7 (41–45%) | 14·8 (17%) | 34·6–39·1 (39–45%) | 40·3–43·9 (46–50%) | 43·5–46·5 (50–53%) | 48·7–49·3 (55–56%) | 27·0 (31%) |

Results are categorised in 10 year intervals and extended periods as noted (2020–59 and 2020–99); note that the sum of case numbers over shorter periods might not be exactly equivalent to those reported over extended periods because of rounding. Ranges represent variation in outcomes from vaccination coverage range examined in each scenario. HPV4=tetravalent vaccine. HPV2=bivalent vaccine. HPV9=nonavalent vaccine. NA=not applicable. *We assumed 50–80% coverage could be achieved across Gavi-supported countries.

***Table 2:*** **Projected total worldwide cervical cancer cases and cases averted, given different vaccination and screening scenarios (millions)**



www.thelancet.com/oncology **Published online February 19, 2019 http://dx.doi.org/10.1016/S1470-2045(18)30836-2**

HDI countries, and 2090–2100 and beyond in low-HDI countries (figure 1B, table 4). If delivery of vaccination and screening is more gradually scaled-up over the period 2020–50 (eg, 20–45% vaccination coverage and 25–70% once-per-lifetime screening coverage by 2030, increasing to 40–90% vaccination coverage and 90% once-per-lifetime screening coverage by 2050, when considered as average coverage rates across HDI categories), end of the century

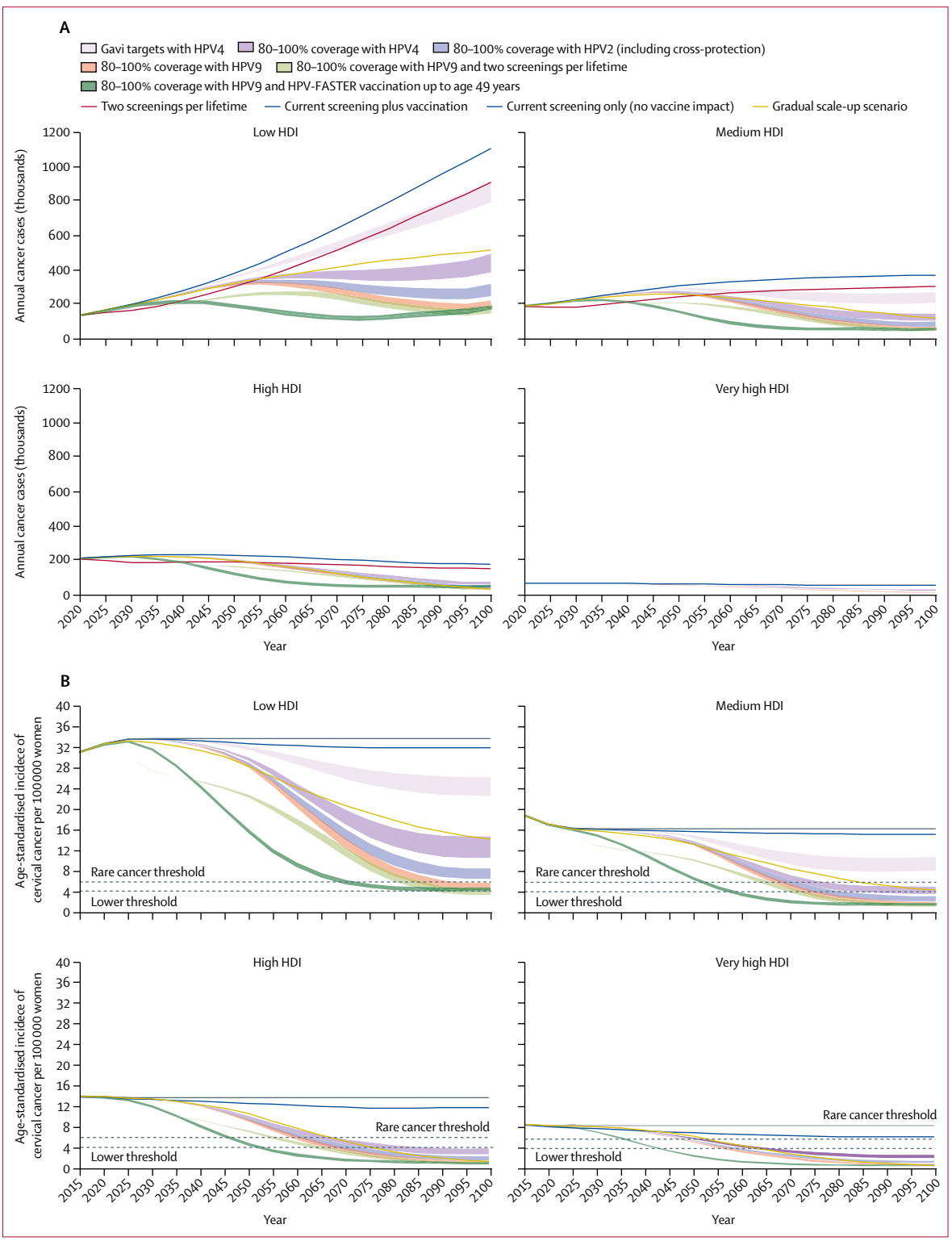



***Figure 2:*** **Predicted number of cervical cancer cases worldwide by country HDI category (A) and predicted age-standardised incidence rate of cervical cancer by country HDI category (B), under a range of interventions**
The width of the coloured regions represents the upper and lower bound of vaccination coverage. Age-standardised incidence rate calculated using the 2015 world female population for ages 0–84 years.[19] For very-high-HDI countries, the estimates take into account the ongoing benefits of the implementation of high-coverage screening programmes for long periods of time (>10 years) in many of these countries. However, we did not explicitly model future improvements to these programmes via increased coverage or implementation of routine primary HPV testing. HDI estimates for North Korea, Somalia, Puerto Rico, and Réunion (France) were not available from the Human Development Report, and they are therefore not included in this subgroup analysis (although country-level predictions for these countries are presented in the appendix pp 21–31). ASR=age-standardised rate. HPV4=tetravalent vaccine. HPV2=bivalent vaccine. HPV9=nonavalent vaccine.

| | Current screening and vaccination (percentage of world total) | Gavi targets with HPV9* | 80–100% female-only vaccine coverage with HPV4 | 80–100% female-only vaccine coverage with HPV2 | 80–100% female-only vaccine coverage with HPV9 | Screening twice per lifetime at 70% coverage and no vaccination | Screening twice per lifetime and 80–100% female-only vaccine coverage with HPV4 | Screening twice per lifetime and 80–100% female-only vaccine coverage with HPV2 | Screening twice per lifetime and 80–100% female-only vaccine coverage with HPV9 | 80–100% vaccine coverage with HPV9 for both sexes for ages 12–15 years and 70% vaccination coverage in ages 16–49 years (HPV-FASTER) | Gradual scale-up scenario |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Low HDI** | | | | | | | | | | | |
| Total cases over 2020–69 | 16·3 (37%) | 14·7–15·3 | 13·4–15·0 | 12·8–13·3 | 12·5–13·0 | 13·2 | 11·0–12·4 | 10·5–11·3 | 10·3–10·6 | 9·7–9·9 | 13·6 |
| Total cases averted (percentage decrease compared with current screening and vaccination) | NA | 1·0–1·6 (10%) | 1·3–2·9 (18%) | 3·0–3·5 (21%) | 3·3–3·8 (23%) | 3·1 (19%) | 3·9–5·3 (32%) | 5·0–5·7 (35%) | 5·6–6·0 (37%) | 6·4–6·6 (40%) | 2·7 (16%) |
| **Medium HDI** | | | | | | | | | | | |
| Total cases over 2020–69 | 13·7 (31%) | 12·2–12·7 | 11·8–12·5 | 11·5–11·9 | 11·4–11·7 | 11·1 | 9·8–10·3 | 9·5–9·9 | 9·4–9·7 | 9·1–9·2 | 11·7 |
| Total cases averted (percentage decrease compared with current screening and vaccination) | NA | 1·0–1·5 (11%) | 1·2–1·9 (14%) | 1·8–2·1 (16%) | 2·0–2·3 (17%) | 2·5 (19%) | 3·4–3·9 (29%) | 3·8–4·2 (30%) | 4·0–4·3 (31%) | 4·5–4·6 (34%) | 2·0 (15%) |
| **High HDI** | | | | | | | | | | | |
| Total cases over 2020–69 | 11·3 (25%) | 11·3–11·3 | 10·2–10·5 | 10·1–10·3 | 10·0–10·2 | 9·6 | 8·8–9·0 | 8·6–8·8 | 8·5–8·7 | 8·4–8·5 | 10·1 |
| Total cases averted (percentage decrease compared with current screening and vaccination) | NA | 0 | 0·9–1·1 (9%) | 1·0–1·3 (11%) | 1·2–1·4 (12%) | 1·7 (15%) | 2·3–2·5 (22%) | 2·5–2·7 (24%) | 2·6–2·8 (24%) | 2·8–2·9 (25%) | 1·2 (10%) |
| **Very high HDI** | | | | | | | | | | | |
| Total cases over 2020–69 | 3·2 (7%) | 3·2 –3·2 | 3·0 –3·0 | 2·9–3·0 | 2·8–2·9 | 3·2 | 3·0 –3·0 | 2·9–3·0 | 2·8–2·9 | 2·8 | 2·9 |
| Total cases averted (percentage decrease compared with current screening and vaccination) | NA | 0 | 0·1–0·2 (6%) | 0·2–0·3 (8%) | 0·2–0·3 (10%) | 0 | 0·1–0·2 (6%) | 0·2–0·3 (8%) | 0·2–0·3 (10%) | 0·2–0·3 (10%) | 0·2 (7%) |

Results are reported over the period 2020–69. Note that the sum of case numbers from different HDI categories might not be exactly equivalent to those reported previously for global totals due to rounding. Ranges represent variation in outcomes from vaccination coverage range examined in each scenario. HDI estimates for North Korea, Somalia, Puerto Rico, and Réunion (France) were not available from the Human Development Report, and they are therefore not included in this subgroup analysis (although country-level predictions for these countries are presented in the appendix pp 21-31). For very-high-HDI countries, the estimates take into account the ongoing benefits of the implementation of high-coverage screening programmes for long periods of time (>10 years) in many of these countries. However, we did not explicitly model future improvements to these programmes via increased coverage or implementation of routine primary HPV testing. HPV4=tetravalent vaccine. HPV2=bivalent vaccine. HPV9=nonavalent vaccine. NA=not applicable. HDI=Human Development Index. *We assumed 50–80% coverage could be achieved across Gavi-supported countries.

***Table 3:*** **Projected total cancer cases (millions) and total cancer cases averted (millions) worldwide by country HDI category, 2020–69**

www.thelancet.com/oncology **Published online February 19, 2019 http://dx.doi.org/10.1016/S1470-2045(18)30836-2**

| | Very high HDI | High HDI | Medium HDI | Low HDI | Worldwide mean |
|---|---|---|---|---|---|
| Rare cancer threshold (six cases per 100 000) | 2045–49 | 2055–59 | 2065–69 | 2085–89 | 2060–69 |
| Lower threshold (four cases per 100 000) | 2055–59 | 2065–69 | 2070–79 | 2090–2100 onwards | 2070–79 |

HDI=Human Development Index.

*Table 4:* **Timeline by mean annual cervical cancer incidence decrease to less than the rare cancer threshold (six cases per 100 000 women) or a threshold of four cases per 100 000, by country HDI category, for rapid scale-up scenarios**

incidence rates will be reduced by a lesser amount. In this gradual scale-up scenario, average cervical cancer incidence rates will decline to 0·8 cases per 100 000 for very-high-HDI countries, 1·3 per 100 000 for high-HDI countries, 4·4 per 100 000 for medium-HDI countries, and 14 per 100 000 for low-HDI countries by the end of the century (figure 2b). Under the gradual scale-up scenario, average cervical cancer rates will decline to 0·8 cases per 100 000 for very-high-HDI countries and 1·3 per 100 000 for high-HDI countries by the end of the century; however, cervical cancer incidence will remain higher than 4.4 per 100 000 in medium-HDI countries and 14 per 100 000 in low-HDI countries at the end of the century (figure 1b).

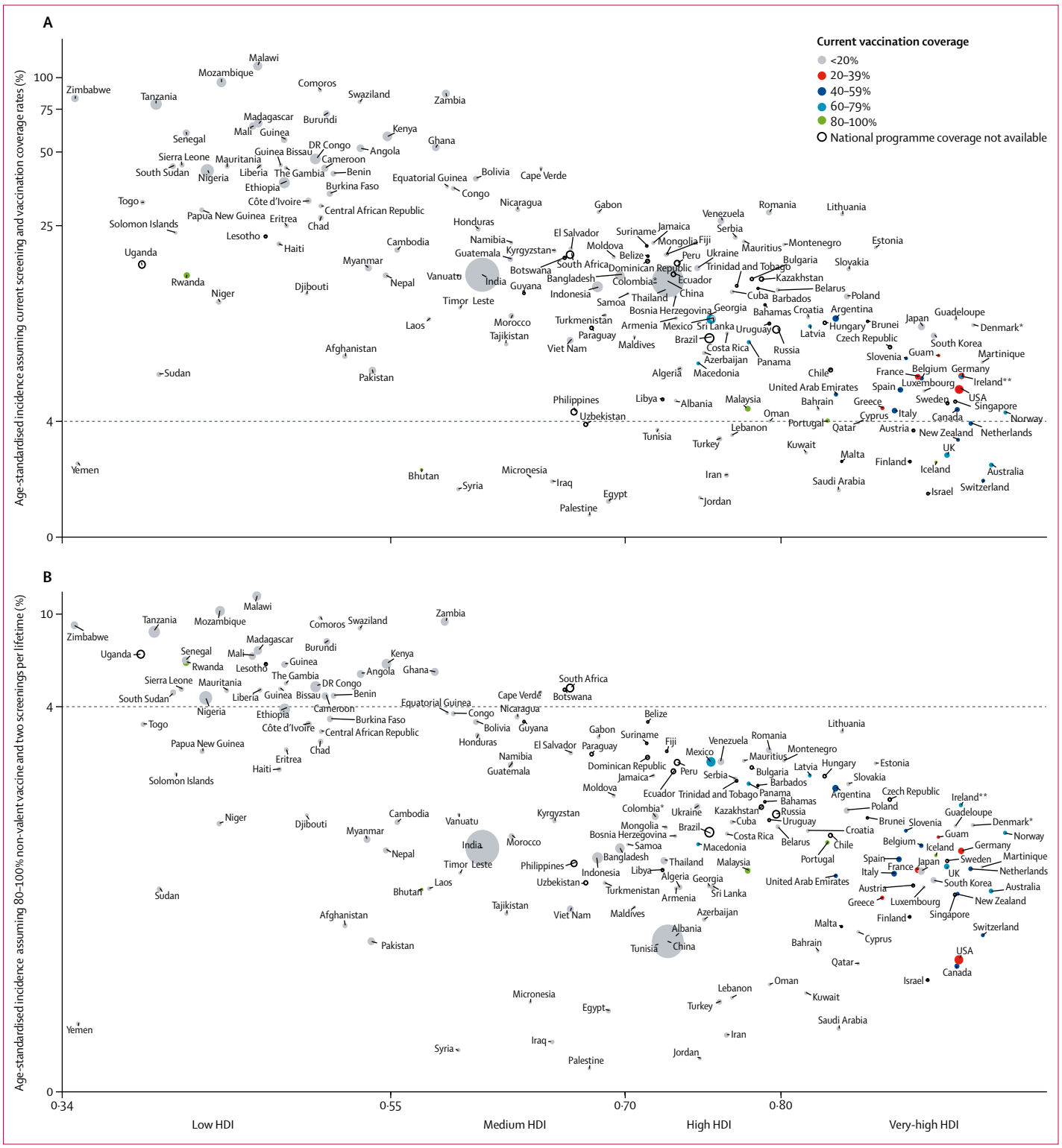
Our aggregate findings at the HDI level and global level are based on predicted incidence rates at the individual country level. We present the rates predicted at the end of the century for each country if no further action is taken (current screening and vaccination coverage; figure 3A). Generally, countries with high or very high HDI are predicted to have lower cancer incidence than medium-HDI or low-HDI countries due in large part to higher vaccination and screening coverage. If rapid scale-up of high HPV vaccination coverage and cervical screening coverage is achieved by 2020, many countries will achieve an incidence of cervical cancer below four cases per 100 000; however, several countries (mainly in Africa) will still have an incidence of cervical cancer higher than four cases per 100 000 by the end of the century (figure 3B). The effects of varying key parameters as part of the one-way sensitivity analysis are shown in the tornado diagrams in the appendix (pp 33–35). Assumptions about future trends have the largest effect on the number of cervical cases averted over the 50 year period 2020–69 if high-coverage screening and vaccination is achieved globally from 2020 onwards (variation in the number of cases averted over the period 2020–69 of about 11–15 million; appendix pp 33–35).

## Discussion

In this analysis, we have estimated that given the current levels of HPV vaccination and cervical screening, which are substantially higher in high-HDI and very-high-HDI countries than in medium-HDI and low-HDI countries, the annual global cervical cancer burden will increase from 600 000 new cases in 2020, to 1·3 million new cases by 2069. This increase would result in 44·4 million cervical cancer cases being diagnosed during the period 2020–69; two-thirds of these cases would occur in countries currently categorised as low HDI or medium HDI. High coverage vaccination, if it could be scaled up quickly, will have a substantial effect on the burden of disease, but this effect will be mainly realised later in the century; nearer-term effects require effective scale-up of cervical screening. One of the highest-impact scenarios that we examined was the combined intervention of the nonavalent HPV vaccination of young girls and HPV screening twice per lifetime at age 35 years and 45 years, with high coverage achieved from 2020 onwards, which could prevent up to 12·5–13·4 million cases of cervical cancer in the next half century. In this scenario, the estimated year at which rates of less than six new cervical cancer cases per 100 000 women will be achieved is 2045–49 for very-high-HDI countries, 2055–59 for high-HDI countries, 2065–69 for medium-HDI countries, and 2085–89 for low-HDI countries, and the year at which rates decrease below four new cases per 100 000 is estimated to be 2055–59 for very-high-HDI countries, 2065–69 for high-HDI countries, 2070–79 for medium-HDI countries, and 2090–2100 onwards for low-HDI countries. If this level of scale-up is achieved, more than three-quarters of the averted cases would occur in low-HDI or medium-HDI countries; many of these countries have no existing national screening or HPV vaccination initiatives, but many are eligible for Gavi funding. An exploratory HPV-FASTER scenario was also predicted to have an important effect within the first few decades; however, this scenario would need to be carefully evaluated for cost-effectiveness, and we made the assumption here that the vaccine would be effective even in adults who had previously been exposed to a particular HPV type if they were not currently infected with that type at the time of vaccination; in practice, there are uncertainties about the long-term population-level effectiveness of vaccination of adults in this group. Notably, the overall population effectiveness of this strategy depends on the risk of subsequent exposure to HPV after vaccination.

If both screening and vaccination coverage is more gradually scaled up in 2020–50 (eg, 20–45% vaccination and 25–70% once-per-lifetime screening coverage by 2030, increasing to 40–90% vaccination and 90% once-per-lifetime screening coverage by 2050, when considered as

average coverage over HDI categories), we found that average annual cervical cancer incidence rates will remain higher than 4·4 per 100 000 in medium-HDI countries and 14 per 100 000 in low-HDI countries. Therefore, in the absence of rapid scale-up, a reduction in cervical cancer incidence to four per 100 000 will be delayed in countries



with low and medium HDI, and, unfortunately, disparities in cervical cancer rates will still persist at the end of the century. Furthermore, we found that some countries in eastern Africa are not likely to achieve rates of less than four cases per 100 000 by the end of the century, even if high-coverage HPV vaccination and cervical screening coverage twice per lifetime could be achieved by 2020. Therefore, for these countries, other interventions will probably be required, such as HIV control (since the risk of HPV progression to cervical cancer is increased in women with HIV) and more frequent screening. It should also be noted that considerable disparities also exist within countries, even in very-high-HDI or high-HDI countries, and our findings for the average rates of cervical cancer in a country or HDI category do not imply that elimination will be achieved in all high-risk subgroups within countries. Therefore, achieving equity of outcomes should continue to be a priority.

Our study has several strengths. The model used for this evaluation is a comprehensive dynamic model of HPV transmission, vaccination, and cervical screening, capturing the effects of herd protection and detailed screening management. The model has been validated across diverse populations,[17,18,26] and was also validated against independent model predictions of the longer-term effect of Gavi targets on cancer cases averted[27] (appendix p 20). The model incorporated a detailed trends analysis incorporating data from 37 cancer registries from 20 high-density countries in eight regions that represented populations from low-HDI, medium-HDI, high-HDI, and very-high-HDI categories.

***Figure 3:*** **Age-standardised incidence rate of cervical cancer predicted for the year 2099 given current screening and vaccination (A) or with 80–100% HPV9 coverage and two screenings per lifetime achieved with rapid scale-up in all countries from 2020 onwards (B)**

Age-standardised incidence rate was calculated using the 2015 world female population for ages 0–84 years.[19] (A) The y-axis represents the ASR of cervical cancer (using the 2015 world female population) on a log scale in the year 2099, once the full impact of any existing programmes have been considered and taking into account in statistical trends (rates not comparable to GLOBOCAN 2012 directly for this reason); the size of the circles represent the cumulative case numbers of cervical cancer over 2020–69 given current screening and vaccination coverage. (B) The y-axis represents the burden with 80–100% nonavalent vaccine coverage and two screenings per lifetime is achieved rapidly in all countries from 2020 onwards. The x-axis shows the HDI as reported in the 2016 Human Development Report. Countries with either no current national HPV vaccination programme, or with a current programme but less than 20% coverage are shaded grey; countries with 20–39% coverage are shaded red; countries with 40–59% coverage are shaded blue; countries with 60–79% coverage are shaded light blue; countries with 80–100% coverage are shaded green; and countries with a national programme but no reported coverage are unshaded. HDI estimates for North Korea, Somalia, Puerto Rico, and Réunion (France) were not available from the Human Development Report, and they are therefore not included in this subgroup analysis (although country-level predictions for these countries are presented in the appendix pp 21–31). Denmark and Columbia showed a substantial decrease in coverage rates which is captured here. Ireland also showed a decrease in coverage rates,[25] however, this was not explicitly captured in this analysis.Declines reported in these countries are all reflected in the figure. ASR=age-standardised incidence rate. HDI=Human Development Index. HPV=human papillomavirus.

This study also had several limitations and simplified assumptions were made in the analysis. We assumed high vaccine effectiveness at two doses for vaccination of those aged 15 years or younger, and lifetime duration of protection, which is supported by evidence showing more than 95% effectiveness in HPV-naive individuals, and evidence suggesting that vaccine duration of protection will be very long or lifelong.[28] We also considered cross-protection for the bivalent vaccine on the basis of strong evidence of at least 7 years of cross-protection,[29] but assumed that the quadrivalent vaccine and the nonavalent vaccine provided no cross-protection, on the basis of evidence suggesting that quadrivalent cross-protection is likely to be limited to moderate protection against HPV type 31 and modelled analysis suggesting that realistic cross-protective efficacy for the quadrivalent vaccine has minimal effects on health outcomes in vaccinated cohorts.[30–33] There is also no evidence to suggest nonavalent vaccine cross-protective efficacy for the remaining non-vaccine-included types. We also did not fully account for geographical differences in sexual behaviour across settings, which will influence the magnitude of herd protection in cohorts offered vaccination and adjacent cohorts. However, we found that herd effects had a relatively small effect on projected averted cancer cases (difference of fewer than 0·5 million in averted cases during 2020–69 when disregarding herd effects) and no observable change in the timeline for rates reaching four cases per 100 000 when considering the global mean. By contrast, uncertainties in trends analysis, which accounts for potential changes in sexual behaviour over time, cofactors in HPV progression, and other factors (appendix pp 33–35) had a more substantial effect on the timeline to elimination and the burden of cervical cancer during 2020–69 (>3 million variation in averted cases in upper *vs* lower trend assumptions).

We also found that the timing for achieving elimination threshold rates was sensitive to the population structure used to estimate the age-standardised rate. For this analysis, we chose to use the 2015 world female population for both year and age standardisation, although we considered how our predictions would vary if we used the Segi world population, or the 2030 world female population for age standardisation (appendix pp 36–41). This emphasises the importance of clarity in the expected population standardisation process in establishing elimination thresholds for cervical cancer incidence. We also made a simplifying assumption that very-high-HDI and high-HDI countries that have already implemented an HPV vaccination programme did so in the year 2010, and we did not consider the effect of catch-up programmes, the change to nonavalent vaccination (which has occurred in some countries), or changes to more effective primary HPV-based screening, which means we might have underestimated the timeline to elimination for some very-high-HDI and high-HDI countries (appendix pp 16–18).

For more on **The Global Initiative for Cancer Registry** see http://gicr.iarc.fr

In the HPV-FASTER scenario, we made the assumption that a vaccination coverage of 70% for both female and male individuals aged 16–49 years would be achieved globally by 2020; three doses are required to achieve effective vaccination in this age group. However, even in developed settings, vaccination of the adult population does not reach the level of coverage achieved in childhood and adolescent programmes. For instance, in the USA, although pregnant women are recommended to receive vaccines for influenza and diphtheria, tetanus, and pertussis, both of which require only one dose for full efficacy, uptake of such vaccines in pregnant women is only about 50% in the USA,[34,35] despite their frequent attendance for various prenatal screening visits, with similarly low coverage in Australia.[36] Successfully providing three doses of the HPV vaccine with appropriate spacing of doses to women or men is likely to be even more challenging, particularly in less developed regions. One important consideration with regard to HPV-FASTER is the number of doses required to vaccinate females and males aged 16–45 years, particularly given that vaccine supply is in shortfall to demand.[6] Achieving 70% coverage in these age groups in the year 2020 would require over 6 billion HPV doses (assuming a three-dose schedule is required in adults).

We did not explicitly account for country-specific HIV prevalence in our analysis, although country-specific estimates accounted for current burden of cervical cancer. The worldwide prevalence of HIV in adults (aged 15–49 years) is 0·8%; however, in some countries in sub-Saharan Africa, HIV prevalence is as high as 18–27%.[37,38] A study in South Africa in a population with high HIV prevalence found that see-and-treat screening with HPV testing was effective in reducing cervical intraepithelial neoplasia grade 2+ within 12 months after effective treatment.[39] The present study assumes that women with HIV would have the same incidence of high-grade dysplasia lesions and respond equally well to treatment as their HIV-negative counterparts. Evidence to support these assumptions is mixed[39–43] and importantly does not account for the impact of effective antiretroviral therapy for HIV treatment initiated early in the disease course with sustained HIV suppression over decades. WHO has recommended more frequent screening in women who are HIV positive, which we have not explicitly considered here;[44] in this sense, our predictions for the effect of screening could be considered conservative. Taking all these factors together, the effectiveness of screening in populations with high HIV prevalence might differ from what we have presented. More clinical data from LMICs on the effectiveness of HPV-based screening will be essential to better inform future analyses.

We used GLOBOCAN estimates for cervical cancer rates in 2012. Owing to the continued paucity of high-quality, population-based cancer registries in LMICs, incidence data in many countries remain either non-existent or have problems of incompleteness or validity, and when there is no local information, GLOBOCAN estimates rely on extrapolations from neighbouring settings. The Global Initiative for Cancer Registry is a partnership that attempts to redress this situation by supporting the development of robust data from population-based cancer registries to inform local cancer control planning. We also assumed in our most optimistic scenarios that rapid scale-up to high global vaccination coverage rates (≥80%) is achievable. Some LMICs have introduced national HPV vaccination programmes with high coverage, including Bhutan and Rwanda, with Rwanda achieving more than 95% three-dose coverage since 2010.[4] A one-dose vaccination trial is ongoing,[45] and if non-inferiority is shown, this strategy is likely to greatly facilitate an increase in coverage. Additionally, delivery of vaccines either as part of childhood immunisation schedules or in the antenatal setting[46] could increase the potential for high global coverage, given that other antenatal vaccines have achieved more than 80% coverage in many low-income settings.[47] However, evidence for the safety and effectiveness for delivery of vaccines in early childhood or in the antenatal setting would be required.

We also made some assumptions about future adherence to cervical screening. There are cultural, logistical, and financial barriers to scaling up cervical screening coverage in many settings, and providing access to screening tests and quality colposcopy, pathology, and precancer treatment procedures can present a substantial challenge. Cervical screening guidelines released by ASCO in 2016[2] recommend HPV testing at least one to three times per lifetime across all settings, with more frequent screening in settings with more access to resources. Self-collection for HPV testing has also been shown to be acceptable for women across many settings, and the sensitivity and specificity of PCR-tested self-collected samples compared with clinician-collected samples is favourable.[48,49] The HPV test has also been listed as an essential diagnostic test by WHO,[50] and if organisations can help to provide this key diagnostic at an affordable price, it could help to facilitate the roll-out of screening in these settings.

Although we did not explicitly estimate mortality in this study, cervical cancer incidence reductions will have an eventual impact on cause-specific mortality; in addition, cervical screening is likely to have some benefits in terms of survival improvements because of downstaging of detected cancer. Screening is required for a substantial effect on cervical cancer mortality to be observed before 2040, because our predictions imply that vaccine effect on cervical cancer will not be substantial until after 2040.

We did not explicitly estimate the impact of HPV vaccination on other HPV-related cancers over the course of the century, and it should be noted that the burden of disease for other HPV-related anogenital and oropharyngeal cancers in both males and females will be

favourably affected if massive high-coverage global scale-up of high-coverage HPV vaccination can be achieved.

In conclusion, our findings show that a failure to expand current programmes to reach the women who would most benefit from cervical cancer prevention strategies will have devastating consequences. Almost 45 million women will be diagnosed with cervical cancer over the next half century, with two-thirds (30 million) of those cases occurring in low-HDI and medium-HDI countries. On the basis of an estimated mortality-to-incidence ratio in unscreened populations of around 50%,[1] more than half of these cases in countries with medium or low development would be expected to be fatal in the absence of improvements in treatment services, and thus our findings imply that up to 15 million deaths from cervical cancer could occur in low-HDI and medium-HDI countries. WHO has called for urgent action to scale up implementation of proven measures towards achieving the elimination of cervical cancer as a global public health problem, including vaccination against HPV, screening and treatment of pre-cancer, early detection and prompt treatment of early invasive cancers, and palliative care. A draft global strategy to accelerate cervical cancer elimination, with goals and targets for the period 2020–30, will be considered at the World Health Assembly in 2020. The findings presented here have helped inform initial discussions of elimination targets, and ongoing comparative modelling with other groups is supporting the development of the final goals and targets for cervical cancer elimination.

#### Contributors

KTS contributed to the study design, model evaluation, data analysis, and data interpretation, created the figures, and led the write-up. JS contributed to the study design, led the statistical trends analysis, and contributed to data analysis, data interpretation, and the write-up. MC contributed to the study design, Policy1-Cervix model development, figure development, data analysis, data interpretation, and the write-up. MAS contributed to the study design, figure development, data analysis, data interpretation, and the write-up. J-BL contributed to the study design, figure development, and data interpretation. IS contributed to the study design, statistical trends analysis, data interpretation, and the write-up. PEC contributed to the study design and data interpretation, provided overall advice on policy-relevant scenarios, and contributed to the write-up. FB contributed to the study design, conceived the statistical trends component, contributed to data interpretation, provided overall advice on policy-relevant scenarios, and contributed to the write-up. KC conceived the study and oversaw all aspects of study design, model evaluation, data analysis, data interpretation, figure design, and the write-up.

#### Declaration of interests

KTS, PEC, MC, MAS, J-BL, and KC report grants from the National Health and Medical Research Council during the conduct of the study. MC is an investigator and KC is co-Principal Investigator on an investigator-initiated trial of cytology and primary HPV 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 has received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana, USA. However, neither KC, MC, nor their institution on their behalf (Cancer Council New South Wales) receive direct or indirect funding from industry for Compass Australia or any other project. PEC has received at reduced or no cost HPV tests and assays for research from Roche, Becton Dickinson, Cepheid, and Arbor Vita Corporation. FB and IS declare no competing interests.

#### Acknowledgments

We thank Prof Valerie Beral, Adam Keane, and Eleonora Feletto, who provided helpful comments. Partial funding for this work was obtained from the National Health and Medical Research Council (NHMRC) Australia, including an NHMRC Career Development Fellowship for KC (APP1007994) and an NHMRC Centre of Excellence for Cervical Cancer Control (APP1135172).

#### References

1 Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136:** E359–86.

2 Jeronimo J, Castle PE, Temin S, et al. Secondary prevention of cervical cancer: ASCO resource-stratified clinical practice guideline. *J Glob Oncol* 2016; **0:** JGO006577.

3 Gakidou E, Nordhagen S, Obermeyer Z. Coverage of cervical cancer screening in 57 countries: low average levels and large inequalities. *PLoS Med* 2008; **5:** e132.

4 Bruni L, Diaz M, Barrionuevo-Rosas L, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. *Lancet Glob Health* 2016; **4:** e453–63.

5 Gavi, The Vaccine Alliance. Supply and procurement roadmap: human papilloma virus vaccine, 2017. https://www.gavi.org/library/gavi-documents/supply-procurement/hpv-supply-and-procurement--roadmap/ (accessed Aug 12, 2018).

6 UNICEF Supply Division. Human papillomavirus vaccine supply and demand update. 2018. https://www.unicef.org/supply/files/HPV_2_Status_Update.pdf (accessed Oct 16, 2018).

7 Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. *Lancet Oncol* 2012; **13:** 790–801.

8 Dhillon PK, Yeole BB, Dikshit R, Kurkure AP, Bray F. Trends in breast, ovarian and cervical cancer incidence in Mumbai, India over a 30-year period, 1976-2005: an age-period-cohort analysis. *Br J Cancer* 2011; **105:** 723–30.

9 Bray F, Lortet-Tieulent J, Znaor A, Brotons M, Poljak M, Arbyn M. Patterns and trends in human papillomavirus-related diseases in central and eastern Europe and central Asia. *Vaccine* 2013; **31:** H32–45.

10 Wabinga HR, Nambooze S, Amulen PM, Okello C, Mbus L, Parkin DM. Trends in the incidence of cancer in Kampala, Uganda 1991–2010. *Int J Cancer* 2014; **135:** 432–39.

11 Hall MT, Simms KT, Lew J-B, et al. The projected timeframe until cervical cancer elimination in Australia: a modelling study. *Lancet Public Health* 2018; published online Oct 2. http://dx.doi.org/10.1016/S2468-2667(18)30183-X.

12 Gatta G, van der Zwan JM, Casali PG, et al. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer* 2011; **47:** 2493–511.

13 Australian Government. Rare and less common cancers. 2014. https://canceraustralia.gov.au/about-us/news/rare-and-less-common-cancers (accessed Sept 24, 2018).

14 Lew J-B, Simms KT, Smith MA, et al. Primary HPV testing versus cytology-based cervical screening in women in Australia vaccinated for HPV and unvaccinated: effectiveness and economic assessment for the National Cervical Screening Program. *Lancet Public Health* 2017; **2:** e96–107.

15 Canfell K, Lew JB, Smith M, Walker R. Cost-effectiveness modelling beyond MAVARIC study end-points. In: Kitchener HC, Blanks R, Cubie H, et al, eds. MAVARIC: a comparison of automation-assisted and manual cervical screening: a randomised controlled trial. Health Technology Assessment. *Health Technol Assess* 2011; **15:** 1–170.

16 Kitchener HC, Canfell K, Gilham C, et al. The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. *Health Technol Assess* 2014; **18:** 1–196.

17 Lew J-B, Simms K, Smith M, Lewis H, Neal H, Canfell K. Effectiveness modelling and economic evaluation of primary HPV screening for cervical cancer prevention in New Zealand. *PLoS One* 2016; **11:** e0151619.

18 Simms KT, Smith MA, Lew JB, Kitchener HC, Castle PE, Canfell K. Will cervical screening remain cost-effective in women offered the next generation nonavalent HPV vaccine? Results for four developed countries. *Int J Cancer* 2016; **139:** 2771–80.

19 UN, Department of Economic and Social Affairs, Population division. World population prospects. 2015 revision. 2016. http://www.un.org/en/development/desa/publications/world-population-prospects-2015-revision.html (accessed Feb 2, 2016).

20 UN. Human development report, 2015. http://hdr.undp.org/sites/default/files/2015_human_development_report.pdf (accessed March 13, 2016).

21 Catalan Institute of Oncology HPV Information Centre. Data query. 2014. http://www.hpvcentre.net/dataquery.php (accessed Aug 4, 2016).

22 Hammer A, Rositch A, Qeadan F, Gravitt PE, Blaakaer J. Age-specific prevalence of HPV16/18 genotypes in cervical cancer: a systematic review and meta-analysis. *Int J Cancer* 2016; **138:** 2795–803.

23 Norheim OF, Jha P, Admasu K, et al. Avoiding 40% of the premature deaths in each country, 2010–30: review of national mortality trends to help quantify the UN sustainable development goal for health. *Lancet* 2015; **385:** 239–52.

24 Canfell K, Shi JF, Lew JB, et al. Prevention of cervical cancer in rural China: evaluation of HPV vaccination and primary HPV screening strategies. *Vaccine* 2011; **29:** 2487–94.

25 Health Protection Surveillance Centre. HPV vaccine uptake in Ireland: 2015/2016. Dublin: Health Protection Surveillance Centre, 2017.

26 Canfell K, Clements M, Harris J. Cost-effectiveness of proposed changes to the National Cervical Screening Programme. Report to the NZ National Screening Unit, 2009.

27 Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. *Lancet Glob Health* 2014; **2:** e406–14.

28 Stanley M. HPV—immune response to infection and vaccination. *Infect Agent Cancer* 2010; **5:** 19.

29 Kavanagh K, Pollock KG, Cuschieri K, et al. Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. *Lancet Infect Dis* 2017; **17:** 1293–302.

30 Simms KT, Laprise JF, Smith MA, et al. Cost-effectiveness of the next generation nonavalent human papillomavirus vaccine in the context of primary human papillomavirus screening in Australia: a comparative modelling analysis. *Lancet Public Health* 2017; **1:** e66–75.

31 Mesher D, Soldan K, Lehtinen M, et al. Population-level effects of human papillomavirus vaccination programs on infections with nonvaccine genotypes. *Emerg Infect Dis* 2016; **22:** 1732–40.

32 Tabrizi SN, Brotherton JM, Kaldor JM, et al. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. *Lancet Infect Dis* 2014; **14:** 958–66.

33 Malagón T, Drolet M, Boily M-C, et al. Cross-protective efficacy of two human papillomavirus vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2012; **12:** 781–89.

34 Ahluwalia IB, Ding H, D'Angelo D, et al. Tetanus, diphtheria, pertussis vaccination coverage before, during, and after pregnancy—16 states and New York City, 2011. *MMWR Morb Mortal Wkly Rep* 2015; **64:** 522–26.

35 Ding H. Influenza vaccination coverage among pregnant women—United States, 2016–17 influenza season. *MMWR Morb Mortal Wkly Rep* 2017; **66:** 1016–22.

36 Macartney K, Regan A, Marshall H. Vaccines to expect when you're expecting, and why 2016. http://theconversation.com/vaccines-to-expect-when-youre-expecting-and-why-50587 (accessed Jan 5, 2018).

37 WHO. Global Health Observatory data: prevalence of HIV among adults aged 15 to 49 by WHO region. 2018. http://apps.who.int/gho/data/view.main.22500WHOREG?lang=en (accessed Feb 11, 2019).

38 WHO. Global Health Observatory data: prevalence of HIV among adults aged 15 to 49 by country. 2018. http://apps.who.int/gho/data/node.main.622?lang=en (accessed Feb 11, 2019).

39 Denny L, Kuhn L, Hu CC, Tsai WY, Wright TC Jr. Human papillomavirus-based cervical cancer prevention: long-term results of a randomized screening trial. *J Natl Cancer Inst* 2010; **102:** 1557–67.

40 Keller MJ, Burk RD, Xie X, et al. Risk of cervical precancer and cancer among HIV-infected women with normal cervical cytology and no evidence of oncogenic HPV infection. *JAMA* 2012; **308:** 362–69.

41 Debeaudrap P, Sobngwi J, Tebeu P-M, Clifford GM. Residual or recurrent precancerous lesions after treatment of cervical lesions in HIV-infected women: a systematic review and meta-analysis of treatment failure. *Clin Infect Dis* 2019; published online Jan 2. DOI:10.1093/cid/ciy1123.

42 Harris TG, Burk RD, Palefsky JM, et al. Incidence of cervical squamous intraepithelial lesions associated with HIV serostatus, CD4 cell counts, and human papillomavirus test results. *JAMA* 2005; **293:** 1471–76.

43 Blitz S, Baxter J, Raboud J, et al. Evaluation of HIV and highly active antiretroviral therapy on the natural history of human papillomavirus infection and cervical cytopathologic findings in HIV-positive and high-risk HIV-negative women. *J Infect Dis* 2013; **208:** 454–62.

44 WHO. WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva: World Health Organization, 2013.

45 US National Library of Medicine. Scientific Evaluation of one or two doses of the bivalent or nonavalent prophylactic HPV vaccines 2018. https://clinicaltrials.gov/ct2/show/NCT03180034 (accessed Oct 9, 2018).

46 Canfell K. HPV vaccination and pregnancy. *BMJ* 2015; **351:** h4705.

47 Wallace AS, Ryman TK, Dietz V. Overview of global, regional, and national routine vaccination coverage trends and growth patterns from 1980 to 2009: implications for vaccine-preventable disease eradication and elimination initiatives. *J Infect Dis* 2014; **210** (suppl 1)**:** S514–22.

48 Arbyn M, Verdoodt F, Snijders PJF, et al. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol* **15:** 172–83.

49 Polman NJ, Ebisch RMF, Heideman DAM, et al. Performance of human papillomavirus testing on self-collected versus clinician-collected samples for the detection of cervical intraepithelial neoplasia of grade 2 or worse: a randomised, paired screen-positive, non-inferiority trial. *Lancet Oncol* 2019; **20:** 229–38.

50 WHO. First-ever WHO list of essential diagnostic tests to improve diagnosis and treatment outcomes. Geneva: World Health Organization, 2018.