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Benefits, harms and cost-effectiveness of cervical screening and treatment in 78 low-income and lower-middle income countries for women in the general population: modelling to support updated WHO cervical screening and treatment guidelines to prevent cervical cancer

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Abstract

A strategy for the elimination of cervical cancer as a public health problem, through the scale-up of human papillomavirus (HPV) vaccination, cervical screening and precancer/cancer treatment, was launched by the World Health Organisation (WHO) in November 2020. To support the strategy, WHO published updated cervical screening and treatment guidelines in 2021. A modelled assessment of the benefits, harms and cost-effectiveness of screening approaches for the general population across 78 low- and lower-middle income countries (LMICs) informed the updated guidelines. With the support of the WHO Guidelines Development Group for Screening and Treatment to Prevent Cervical Cancer, we used an established modelling platform, *Policy1-Cervix*, to evaluate the impact of seven screening algorithms based on primary visual inspection with acetic acid ('VIA'), primary cytology, and primary HPV DNA ('primary HPV') with no triage, or triage using HPV16/18 genotyping, colposcopy, cytology, or VIA. Screening intervals of 3 and 5 years were considered for primary VIA and cytology, and intervals of 5 and 10 years were considered for primary HPV. Screening and triage test performance was informed by updated systematic review evidence. For this normative analysis informing guidelines in screened populations, we assumed 70% of women attended each routine screen, and 90% complied with follow-up or treatment. Outcomes included reduction in cancer incidence and mortality, number of precancer treatments needed to prevent a death (NNT) and preterm delivery events directly due to precancer treatment and cost-effectiveness (US$/Health-Adjusted Life Year Saved [HALYS]). A range of assumptions were considered in sensitivity and supplementary analyses. We found that primary HPV DNA testing approaches, regardless of triaging method, were the most effective and cost-effective screening approaches and they appear on, or near to, the cost-effectiveness frontier. Primary HPV DNA testing without triage every 5 years for ages 30–50 years could result in a 64% reduction in cervical cancer mortality rates, compared to no screening. This strategy was associated with an NNT of 54 to prevent one death and was associated with an incremental cost-effectiveness ratio (ICER) of US$530/HALY saved (69/78[88%] of LMICs have a GDP-per-capita of > = US$518). Strategies involving primary HPV with triage of HPV positive women before treatment were almost as effective, reducing overall cervical cancer mortality rates by 60–63%, had a similar position on the cost-effectiveness frontier, but had an improved benefits-to-harms profile compared to HPV screening without triage, with an NNT of 26–37 to prevent a death. Compared to VIA screening, primary HPV screening, even without triaging, generated at least 60% fewer precancer treatment events and had 47% fewer additional preterm delivery events. In conclusion, primary HPV testing approaches were the most effective, optimised benefits-to-harms, and were cost-effective compared to primary VIA or cytology. If loss-to-follow-up after triage is limited, triaging HPV positive women before treatment reduces precancer treatments and preterm delivery events with minimal loss in effectiveness, and thus further improves the benefits-to-harms. Based on these findings, WHO now recommends primary HPV screening with or without triage for women in the general population. Going forward, country-specific analyses will continue to have an important role because they will be able to consider local factors that influence follow-up options and feasible triage testing approaches.

Introduction

In 2020, an estimated 604,000 women were diagnosed with cervical cancer, and 342,000 women died from the disease, with 47% of these deaths occurring in low and lower-middle income countries (LMICs) and a further 40% in upper-middle income countries. Longstanding issues with limited access to cervical cancer prevention and cancer treatment services in LMICs means that, on average, age-standardised cervical cancer incidence rates are more than two-fold higher, and age-standardised cervical cancer mortality rates are more than four times higher, than in high-income countries.[1]

In May 2018, the Director-General of WHO issued a call to action to eliminate cervical cancer as a public health problem.[2] A global strategy was requested and then endorsed by member states, and in November 2020 the strategy was launched.[3] The strategy recommends that countries implement the '90-70-90' intervention targets by 2030 which are: 1) 90% of girls fully vaccinated with the human papillomavirus (HPV) vaccine by 15 years of age; 2) 70% of women screened using a high-performance test (currently, primary HPV screening) by 35 years of age and again by 45 years of age; and 3) 90% of women identified with cervical precancer or invasive cervical cancer are provided with access to adequate treatment and care.[3] Countries will subsequently be considered to have eliminated cervical cancer as a public health problem when rates of new cases fall below 4 per 100,000 women-years.

Modelling performed by the WHO Cervical Cancer Elimination Modelling Consortium (CCEMC) found that if the 2030 triple-intervention targets are achieved in 78 LMICs, cervical cancer would be eliminated in all LMICs and a total of 74.1 million cancer cases and 62.6 million deaths would be averted over the course of the century.[4,5] The analysis performed by the CCEMC assumed the use of primary HPV testing at ages 35 and 45 years with immediate treatment for HPV positive women; however, the analysis did not consider alternate triaging technologies, screening ages or intervals, or detailed downstream management options that could be appropriate for LMICs.

In 2013, WHO had published a Comprehensive Cervical Cancer Control manual for women with or without human immunodeficiency virus (HIV).[6] For women aged 30–49 years with negative or unknown HIV status, primary HPV screening was recommended at least every 5 years in settings with adequate resources to implement the tests, followed with triage with either Visual Inspection with Acetic Acid (VIA) or treatment after evaluation of eligibility for ablative treatment. In settings without adequate resources for HPV screening, primary VIA at 3–5 yearly intervals was recommended. For all settings, either cryotherapy or Large Loop Excision of the Transformation Zone (LLETZ) was recommended for women requiring precancer treatment. For women with HIV + status or unknown status in areas with high endemic HIV infection, WHO recommended that screening intervals should be no longer than 3 years.

Since this 2013 publication, updated evidence on test performance and on treatment methods – particularly the emergence of increased evidence supporting HPV screening and evidence to support using ablative treatment as a modality - has become available.[7] Primary testing with cytology has been in place in many high-income settings for some decades, reducing rates of cervical cancer incidence and

mortality. However, many high-income countries are transitioning from primary cytology to primary HPV testing based on evidence that primary HPV is a more effective and cost-effective primary screening approach.[8,9] A large community-based randomized-control trial in India following a total of 70,000 women after VIA screening over 12 years, indicated that there was no significant reduction in cervical cancer incidence in women who were screened with VIA compared to unscreened women (RR = 0.97; [95% CI:0.80–1.19]), but a mortality reduction of 31% (RR = 0.69; [95% CI:0.54–0.88]) was observed,[10] implying low sensitivity for detecting high-grade lesions that could progress to cancer. This was consistent with an earlier study that found no significant reduction in incidence and mortality after one round of VIA screening in 30,000 women.[11] The American Society of Clinical Oncology (ASCO) released guidelines for cervical screening in 2016, recommending primary HPV testing be used for all settings. Recently, the release of a new Handbook of Cervical Screening by the International Agency on Research on Cancer (IARC) synthesised the updated evidence on primary screening technologies, emphasising that HPV testing is a more effective screening modality compared to cytology and VIA.[12]

In response to these developments, WHO initiated the development of updated cervical screening and treatment guidelines in 2020, and the first iteration of these were disseminated in July 2021.[13] To inform the guidelines update, a Guidelines Development Group for Screening and Treatment to Prevent Cervical Cancer (GDG) was formed, and WHO consulted with methodologists and technical expert to determine the relevant research questions, timelines and methodology. Modelling was commissioned to support the work of the GDG and to quantify the benefits, harms, and cost-effectiveness of potential screening strategies in the general population and in women living with HIV. Here, we present the modelled assessment for the general population of women across 78 LMIC, and in a companion paper we present results for women living with HIV.

We used the *Policy1-Cervix* platform, a well-established and extensively validated dynamic model of HPV transmission, vaccination, HPV type-specific natural history, cancer survival, screening, diagnosis and treatment,[4,5,8,14–23] to predict outcomes over the lifetime of females aged 10–84 years who turn 30 in 2030 (born 2000) across all 78 LMIC (model schematically shown in Appendix pp 25–26). We assessed the impact of seven screening algorithms including primary visual inspection with acetic acid ('VIA'), primary cytology, and primary HPV DNA ('primary HPV') with no triage, or triage using HPV16/18 genotyping, colposcopy, cytology, or VIA. In the base case, we made the following assumptions: screening intervals of 3 and 5 years were considered for primary VIA and cytology, and intervals of 5 and 10 years were considered for primary HPV. Screening and triage test performance for the base case and the ranges considered for sensitivity analysis were informed by updated systematic review evidence. In this normative analysis we assumed 70% of women attended each routine screen, and 90% complied with follow-up or treatment. We report on the cost and cost-effectiveness of each strategy as a cost per HALY saved, assuming 0% discounting for effects and 3% discounting for costs. [24] Outcomes included reduction in cancer incidence and mortality, number of precancer treatments needed to prevent a death (NNT), preterm delivery events directly due to precancer treatment, and the incremental cost-effectiveness ratio (ICER, expressed as US$/Health-Adjusted Life Year Saved [HALYS]).

Results

Reductions in cervical cancer incidence and mortality

In the absence of further intervention (no screening), over the lifetime of a cohort of 100,000 unscreened women in 78 LMICs, 1,950 cervical cancer cases and 1,456 deaths are predicted to occur (Table 1) and the average age-standardised cervical cancer incidence rate (ASIR) and mortality rate (ASMR) would be 19.8 and 14.1 per 100,000 women, respectively.

In the base case analysis, primary HPV testing without triage every 5 years for ages 30–50 years was the most effective strategy, with a 56% reduction in cervical cancer incidence and a 64% reduction in cervical cancer mortality rates compared to no screening (Fig. 1, Table 2 and Table 1). Strategies involving triage of HPV positive women before treatment reduced cervical cancer mortality rates by 60–63% (range dependent on triage test). Primary cytology with HPV triage, when offered every 3 years, could reduce cervical cancer cases by 43% and deaths by 52%. Primary VIA testing when offered every 3 years for ages 30–50 could reduce cervical cancer cases by 39% and deaths by 47%. Even if VIA could achieve sustained, population-level sensitivity to CIN2 + of 60% (which was discussed as a favourable assumption), primary VIA testing every 3 years for ages 30–50 years would reduce cervical cancer cases by 46% and deaths by 56% and thus still be less effective than primary HPV testing every 5 years.

Table 2
Screening ages and frequencies considered for each screening algorithm.

Screening algorithms	Screening frequency and age-range (number of lifetime routine screening tests)
Primary VIA*	• 3 yearly, 30–50 years (7X)
Cytology, HPV triage**	• 5 yearly, 30–50 years (5X)
Primary HPV*	• 5 yearly, 30–50 years (5X)
Primary HPV, HPV16/18 triage^	• 10 yearly, 30–50 years (3X)
Primary HPV, VIA triage^^	• 10 yearly, 35–45 years (2X) 'Elimination strategy'
Primary HPV, colposcopy triage	
Primary HPV, cytology triage**	

*All positive women treated after assessment of eligibility for ablative treatment. **Triage positive referred to colposcopy. ^^VIA triage positive women treated after assessment of eligibility for ablative treatment. ^HPV 16/18 positive women treated after assessment of eligibility for ablative treatment. Women positive for HPV types other than HPV 16/18 ('OHR') are triaged with VIA.

Table 3

Aggregate costs across 78 LMICs for each screening-related event.[+]

Event	Cost (US$ 2019)	
	Base-case	Range in sensitivity analysis
Primary VIA^	7.12	+/-20% (5.70–8.54)
Primary HPV DNA (+/-16/18)*	15.09	+/-30% (10.56–19.62)
Primary cytology^	18.02	+/-20% (14.42–21.62)
VIA triage[O]	2.95	+/-20% (2.36–3.54)
Cytology triage[O]	15.62	+/-20% (12.5-18.74)
HPV triage[O]	8.15	Upper end informed by current high-end values; lower end represents potential cost at higher volumes (5-10.06)
Colposcopy[O,#]	9.96	-
Ablative treatment	11.76	+/-30% (8.23–15.29)
Excisional treatment	41.67	+/-30% (29.17–54.17)
Histology[@]	17.96	-
Punch biopsy/Biopsy	11.61	-
ECC	6.4	-
Cancer diagnosis and treatment– FIGO 1[a]	261.43	one-way: +40%, no lower bound (366.00) For PSA:+/-20% (209.14-313.72)
Cancer diagnosis and treatment– FIGO 2[a]	540.23	one-way: +40%, no lower bound (756.32) For PSA:+/-20% (432.18-648.28)
Cancer diagnosis and treatment– FIGO 3[a]	673.93	one-way: +40%, no lower bound (943.50) For PSA:+/-20% (539.14-808.72)
Cancer diagnosis and treatment– FIGO 4[a]	307.95	one-way: +40%, no lower bound (431.13) For PSA:+/-20% (246.36-369.54)
Palliative care[a]	115.13	-
Yearly surveillance after treatment[a]	57.66	-

Event	Cost (US$ 2019)	
	Base-case	Range in sensitivity analysis
+Aggregate costs represent the average across 78 LMIC, i.e. the sum of the country-level costs weighted by the proportion of the 78 LMIC population of 30–49 year-old females in each country.		
^ Includes consumables, administering provider/workforce, and programmatic utilisation costs.		
* Includes cost of test, sample drop-off and transport, laboratory staff time, lab supplies, general administration and overhead costs using WHO-CHOICE methodology and database.		
[O] Same as primary, but includes a proportion of the labour, programmatic and utilisation costs from primary visits due to not requiring another visit. When VIA is used during colposcopy, we assume no cost.		
# Includes consumables/equipment, workforce.		
@Includes consumables/equipment, workforce including pathologist and biomedical scientist.		
[a]Cancer costs are only applied to the proportion of cancers that are treated and assumed to apply to 90% of screen-detected cases. Surveillance costs are applied from 1 year after diagnosis until death, or a maximum of 5 years if the woman survives for this amount of time.		

When considering a lower-end assumption for primary HPV test sensitivity (88% for detection of CIN2+), primary HPV testing every 5 years, regardless of triaging decision, could still reduce cervical cancer cases by at least 50% and deaths by 59%. Therefore, even when assuming a lower-end performance for primary HPV testing and simultaneously assuming an upper-end performance assumption for primary VIA testing, primary HPV testing every 5 years still reduced cervical cancer incidence and mortality rates by more than primary VIA testing every 3 years (Appendix pp7).

Primary HPV screening every 10 years (either at ages 30, 40 and 50, or at ages 35 and 45 which were the ages considered for the CCEMC elimination modelling) could reduce cervical cancer incidence rates by at least 32% and mortality by at least 39%, regardless of whether women were triaged before treatment.

Primary HPV testing also remained the most effective screening approach when considering lower screening adherence assumptions, although absolute reductions in cervical cancer incidence and mortality rates were correspondingly lower across all scenarios. The absolute difference in reductions in incidence and mortality (versus no screening) were predicted to be 10–24% lower than equivalent strategies under base case adherence assumptions (Appendix pp 6). When considering a scenario of favourable assumptions for VIA as a triage after HPV positive test, the reduction in mortality rates were higher than base-case, but not as large as reductions when assuming higher HPV test performance (Appendix pp 2–3).

Balance of benefits and harms

Over the lifetime of a cohort of 100,000 women, primary HPV screening without triage every 5 years for ages 30–50 years was predicted to result in 50,214 precancer treatments and 88 additional preterm delivery events, and the number of women needed to undergo cervical precancer treatment to avert a cancer death (NNT) was predicted to be 54 (Table 1). Primary HPV screening with triaging with VIA, HPV16/18 genotyping, cytology or colposcopy would generate 29–55% fewer precancer treatments and 24–46% fewer additional preterm deliveries when comparing to primary HPV testing without triage, given a set screening interval. Primary HPV testing every 5 years for ages 30–50 with any of the triaging options also generated NNTs of 26–37, which is lower than Primary HPV testing without triage.

When assuming base case assumptions around VIA test performance, primary VIA screening resulted in the highest number of precancer treatments overall, with more than 110,000 precancer treatments predicted over the lifetime of the cohort of 100,000 women – more than double the lifetime number of precancer treatments compared with any of the primary HPV or primary cytology strategies (Table 1, Fig. 2). Primary VIA screening also generated at least 127 additional preterm deliveries over the lifetime of the cohort. The number needed to treat (NNT) to avert a cervical cancer death was > 190 for primary VIA strategies, nearly four times more than that predicted for any of the primary HPV testing strategies. The number of precancer treatments increased again when VIA performance was assumed to have high sensitivity, resulting in more than 120,000 precancer treatments over the lifetime of the cohort. The NNT when assuming high sensitivity VIA screening was over 160 – more than triple that predicted for any of the primary HPV screening strategies.

In sensitivity analysis, we also explored the assumption that only excisional treatment can cause additional preterm delivery events (i.e. that ablation does not result in additional preterm deliveries). With this assumption, the number of additional preterm deliveries is predicted to be 58–79% lower than equivalent scenarios under base-case assumptions around the rate of preterm deliveries after precancer treatment (Table 1).

Cost-effectiveness:

As a reference point for a potential Willingness-to-Pay (WTP) threshold across 78 LMICs, the population-weighted average GDP per capita (pc) for 2019 across the 78 LMIC is US$2,093, and 71 of 78 [91%] of LMICs had a GDP pc equal to or above US$518. In the base case analysis, primary HPV testing approaches, regardless of whether triage was used, were on, or near to, the cost-effectiveness frontier. Primary HPV screening without triage was on the cost-effectiveness frontier, and had an ICER of US$530/HALY saved when screening every 5 years from ages 30–50 years, an ICER of US$413/HALY saved when screening every 10 years from ages 30–50 years and an ICER of US$135/HALY saved when screening every 10 years from ages 35–45 years (Fig. 3). Primary HPV screening with triage was generally near the cost-effectiveness frontier. Under base case assumptions, primary VIA and primary cytology screening strategies were furthest from the cost-effectiveness frontier and were the least cost-effective strategies.

When considering in sensitivity analysis a discount rate of 3% for both costs and effects, lower adherence assumptions, or using life-years instead of HALYs, primary HPV without triage remained the most cost-effective strategy but the ICERs varied from the base-case (Appendix pp 15–21). Acceptability curves depicting the percentage of the probabilistic sensitivity analysis (PSA) samples that yielded each scenario as most cost-effective as a function of the WTP threshold are shown in Fig. 4. For WTP under US$140, the status quo (i.e. no screening) was found to have the highest probability of being the most cost-effective strategy. For WTP between US$140 and US$420, primary HPV without triage every 10 years from ages 35–45 had the highest probability of being the most cost-effective; for WTP between US$425 and US$520, primary HPV without triage every 10 years from ages 30–50 had the highest probability of being the most cost-effective; and for WTP greater than US$525, primary HPV without triage every 5-years from ages 30–50 (5X per lifetime) had the highest probability of being the most cost-effective.

Supplementary analyses

Management of HPV-positive and triage-negative women

When assuming women who are primary HPV test positive and triage negative are followed-up in 24 months instead of 12 months but that loss-to-follow-up remained at 10%, there was less than 1% difference in ASIR, but a 5–22% decrease in pre-cancer treatments and 5–23% reduction in NNT versus the base case (ranges represent variations across different screening frequencies and triage strategies). However, a 30% loss-to-follow-up at the 24 month visit was assumed, there was a 1–9% increase in ASIR versus the base case, with the greatest increase observed when VIA was used as the triage test. When assuming women received an HPV test at both 12 and 24 months before discharge from follow-up, there was only a 1–4% decrease in ASIR incidence, and a 2–6% increase in pre-cancer treatments and 2–3% increase in NNT versus the base-case assumption of one visit at 12 months only (Appendix pp 2–3).

Management of women after treatment for precancer (without known CIN3 detected by histology)

For all primary screening approaches, when considering a single visit at 24 months (with 30% loss-to-follow-up) instead of 12 months for this group, there was a 1–2% increase in ASIR, a 1–2% decrease in pre-cancer treatments and 0–3% reduction in NNT versus base-case. When considering a single visit at 12 months with co-testing instead of HPV testing alone, a 1–2% decrease in ASIR i, a 1–9% increase in pre-cancer treatments and a 2–5% increase in NNT (Appendix pp 3–4).

Discussion

We have performed a modelled assessment of the benefits, harms and cost-effectiveness of seven priority screening algorithms across all 78 LMICs, in order to inform updated WHO guidelines for cervical screening and treatment. Our main conclusion was that primary HPV screening would engender the greatest reductions in cervical cancer incidence, would optimise the balance of benefits-to-harms and would be cost-effective compared to other primary testing approaches.

As expected, increasing the number of lifetime screens experienced by women in the population results in greater program-level effectiveness. In settings that support 5-yearly HPV screening for ages 30–50 years, we found that this would result in the largest reductions in the lifetime number of cervical cases and deaths, with a 50% or larger reduction in cervical cancer cases and 60% or larger reduction in cervical cancer deaths. Primary HPV testing every 5 years was more effective than primary VIA every 3 years and generated substantially fewer precancer treatments and fewer additional preterm delivery events, even when highly favourable assumptions were made around the performance of primary VIA testing. Primary HPV testing every 5-years for ages 30–50 was more effective than primary HPV screening every 10 years, which was the screening interval considered in the CCEMC; therefore, adopting 5-yearly primary HPV testing could further accelerate elimination timing when compared to the timing presented in our earlier evaluations.[4,5]

Primary HPV testing without triage was the most effective approach; however, triaging HPV positive women had close-to-equivalent effectiveness and had the capacity to reduce precancer treatment rates and additional adverse pregnancy events compared to not triaging. Our findings therefore support the use of primary HPV testing for the 78 LMICs; the choice of triaging strategy and the start age (30 or 35 years) and the screening interval (whether 5 or 10 years) can be contextualised to a country or setting and will depend in part on resourcing, the availability of specific tests and local considerations for the benefits versus harms profile for screening. These findings have directly informed updated 2021 cervical screening guidelines from WHO.[7] Evidence informing optimal screening and modelling for women living with HIV was separately performed, and is presented in a companion manuscript [ref companion manuscript Hall].

Successful experiences are emerging with the use of primary HPV testing with self-collection and same-day ablative treatment in LMIC; for example this has been found to be acceptable, effective and cost-effective in Papua New Guinea.[25,26] Countries will likely observe high rates of detection of prevalent precancer and invasive cancer in the first round of screening with HPV (since it is a highly sensitive test). However, in the second and subsequent rounds of screening, the detected disease will be more likely to be incident, and thus the balance of benefits-to-harms may change and may be less favourable to HPV screen without triaging. Emerging technologies such as Automated Visual Evaluation (AVE) could play a role in reducing the harms associated with precancer treatment of HPV positive women in subsequent rounds, and will be an important consideration in future.[27] In the current analysis, we found that primary HPV with any triage option, including with VIA triage, was effective. VIA was assumed to have low sensitivity, however in the algorithms modelled here, women who are negative for VIA triage were recommended to return in 12 months for a repeat HPV test (90% follow-up rate) with immediate ablation for eligible women if persistently HPV positive, therefore resulting in minimal loss of effectiveness for this specific algorithm. Conversely, primary VIA testing was found to be ineffective and not cost-effective, as when it is used as a primary screen, VIA-negative women are not followed-up unless they are invited for a routine test at the next screening interval.

The WHO guidelines for cervical screening and treatment recommend that women who test HPV positive but triage-negative return in 24 months, whereas for our base case we assumed a 12 month return. We explored this extended return interval in supplementary analysis and found that if 90% adherence with follow-up was maintained at 24 months, then there was less than 1% difference in effectiveness, but more than 5% reduction in precancer treatments compared with 12 month return; however, if loss-to-follow-up increases with the extended return time so that only 70% of women return by 24 months, the effectiveness of the program was substantially reduced. It will thus be critical to establish screen-triage-and-treat programs in the context of an investment in integrated systems for maintaining high follow-up rates for women referred for surveillance. It has previously been found, for example, that establishing a digital registry system to support an HPV screening program in Malaysia, at a cost of US$8.50 per woman, would be cost-effective if it increased adherence with follow-up from 50–75–90%, and this investment would substantially improve the effectiveness of the screening program. [28]

Throughout this evaluation, we assumed that 90% of screen-detected cervical cancers would be offered adequate treatment and care, but that there were no additional survival benefits for symptomatically detected cervical cancers. However, we also explored a range of cancer treatment assumptions in sensitivity analysis, including a scenario in which cancer treatment access remained unchanged for both symptomatically-detected and screen-detected cases, and a scenario in which 90% of both symptomatically-detected and screen-detected cancers received access to adequate cancer treatment and care, and found that 5-yearly primary HPV testing still resulted in the largest reductions in incidence and mortality compared to other primary testing approaches. Scaling-up of cervical screening is likely to result in a large number of prevalent cancers being detected for the first few years of implementation, and it is important that effective referral pathways are implemented so that women with detected cancer can receive adequate treatment and care.

A strength of our study is we used the *Policy1-Cervix* model platform which has been extensively calibrated and validated to a range of settings, has explicitly supported HPV transition in a range of high-income countries,[8,16,17] and was one of three models used by the CCEMC to assess the impacts of cervical cancer elimination strategies on cervical cancer incidence and mortality.[4,5] This involved a detailed calibration to six regions encompassing the 78 LMICs including calibration to HPV prevalence, HPV type distribution, cervical cancer incidence and mortality and cancer treatment access rates for each of the six regions. Another strength is that throughout the evaluation, the modelling team regularly met with GDG members and relevant technical teams to agree on key parameters and assumptions and discuss the interpretation of results. For this analysis, the model incorporated detailed screening management algorithms including testing, triage, follow-up, colposcopy management and post-treatment follow-up. Screening test and treatment performance assumptions were informed by updated systematic reviews or literature reviews and cost inputs used country level data from screening experiences.[13,29]

There are some limitations to this analysis. This analysis was designed to assess the outcomes of different screening approaches at a population-weighted average across 78 LMICs (‘normative results’). This review will therefore provide guidance to countries, however given the substantial variation in

disease burden, resourcing and logistics between countries and even within countries, detailed country-level analyses will continue to have a role in helping tailor these guidelines to a specific setting. For example, we have previously performed detailed country-level evaluations of primary HPV testing in Malaysia and Papua New Guinea, and found that primary HPV testing was cost-effective in both settings.[26,28] Data on test performance comes predominantly from high-income settings, but for standardised quality-assured testing methodologies (such as HPV testing) we assumed the performance would be unchanged in LMICs. Another limitation of the analysis is that data on adverse obstetric outcomes comes predominantly from high-income countries, and there are considerable uncertainties in the application to LMIC and potential differences by ablation or depth of excision.[30] We also made the favourable assumption that 70% of women would attend each screening visit and that 90% of women referred for follow-up would attend. Finally, the cost of assays and clinical procedures and care are highly variable between countries and future market forces and other factors could have a substantial impact on cost estimates. In probabilistic sensitivity analysis, however, we found that primary HPV testing was still the most cost-effective screening approach after considering uncertainties in cost estimates. In general, to address these limitations, we performed extensive sensitivity analysis to assess the impact of uncertainties in costs, test performance, adherence assumptions and rates of preterm delivery after ablation. In all cases, primary HPV testing remained the most effective and cost-effective primary screening approach, and the approach which optimised the balance of benefits-to-harms.

We did not consider the impact of screening in women who had been offered HPV vaccination as adolescents. Even if vaccination could be rapidly scaled-up for 9–14 year-olds across 78 LMICs in line with WHO targets and recommendations, it will be at least 15–20 years before these females reach ages eligible for screening, and a total of 35–40 years for all screen-age eligible women (ages 30–50) to have been offered HPV vaccination. Therefore, for the next few decades, most women of screening age in LMIC will be unvaccinated. We have previously assessed optimal screening management for cohorts offered HPV vaccination in high-income countries in which vaccinated cohorts have already entered screening programs, and found that primary HPV testing remained the optimal approach, but that the number of screens required in a lifetime could be reduced.[8,16,18.31]

We considered screening and triage technologies for which there was a sufficient evidence base to support modelling, and relied on updated systematic reviews that built on a recent major review of the evidence.[32] It is important to note that more recently the WHO guidelines have been updated to include guidance on use of primary HPV mRNA testing[33,34] and dual-stain cytology triage.[50] Emerging triage approaches, such as AVE and extended partial genotyping[27] will be evaluated in subsequent iterations of the Guidelines.

There will be many challenges associated with scaling-up HPV testing in LMICs, including supply and delivery challenges for validated screening tests,[35] as well as health system and infrastructure challenges associated with setting up referral pathways for diagnosis and treatment of more advanced lesions. However, the COVID-19 pandemic has led to widespread dissemination of testing platforms compatible

with HPV testing, which could help facilitate scale-up of HPV screening. Our results for primary HPV screening can be taken to apply to a wide range of clinically validated HPV tests, including technologies allowing point-of-care testing and also self-collection, which has been shown to achieve similar test performance to clinician-collected samples if PCR-based testing is used.[36 37] Point-of-care HPV testing combined with thermal ablation treatment could be used, for example, in rural or inaccessible areas, so that HPV-positive women can be offered treatment in the same visit, thereby reducing loss-to-follow-up. Using this options to overcome social and cultural barriers to screening has potential to greatly increase the acceptability of screening and may help achieve high coverage.[38] Integrating screening programs with existing primary care services, for example by offering HPV testing at sexual health clinics, ante-natal care consultations or family planning consultations, will also facilitate access to screening. Integration of HPV testing into existing community outreach centres for HIV control has been shown, for example to result in high screening uptake in Zimbabwe.[39]

To support the implementation of screening in countries, WHO has released a guide to strengthening cervical cancer prevention[40] and guidelines for precancer treatment.[41] Cervical screening and treatment have also been identified by WHO as 'best buys' in cancer control for Member States.[42] The elimination strategy is a component of the United Nations Global Strategy for Women's, Children's and Adolescent's Health and investment in cervical cancer elimination will support several sustainable development goals (SDGs) and targets, including SDG 3 (good health and well-being), SDG 5 (gender equity) and SDG 10 (reducing inequalities). Ultimately, the successful implementation of the WHO elimination strategy has been shown to be cost-effective[3] and will prevent over 62 million deaths in LMIC over the next century.[5] The development of updated cervical WHO screening and treatment guidelines is a critical enabler of the global strategy to accelerate the elimination of cervical cancer as a public health problem.

Declarations

Ethics Declaration

Conflicts of interest

KS received salary support from the Cancer Institute NSW (Australia, grant number CDF1004). MA was supported by the Horizon 2020 Framework Programme for Research and Innovation of the European Commission, through the RISCC [risk-based screening for cervical cancer] Network (Grant No. 847845). KC receives salary support from the National Health and Medical Research Council (Australia, grant no. APP1135172) is co-principal investigator and MC is an 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 Australian Centre for the Prevention of Cervical Cancer, a government-funded health promotion charity. Australian Centre for the Prevention of Cervical Cancer has received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and operational support from the Australian Government. The salary funders declared here had

no role in the study design, in the collection, analysis, and interpretation of data in the writing of the report nor and in the decision to submit the article for publication.

Inclusion and Ethics in Global Research

This paper is one of a pair of papers to inform the updated WHO 2021 guidelines for screening and precancer treatment for cervical cancer prevention, one for the general population and the current paper for women living with HIV. This research was conducted in close collaboration with the World Health Organisation Guidelines Development Group for Screening and Treatment to Prevent Cervical Cancer (GDG), which is comprised of a range of scientists, health care providers, implementers, ministries of health representatives, systematic reviewers, program implementation experts and civil society. The GDG contained members from all five WHO regions (AFRO, SEARO, WPRO, EURO and EMRO), and, using the GRADE framework and the WHO Handbook for Guideline Development, assessed cervical screening options with a focus on low- and middle-income countries, including countries with high HIV prevalence. The use of Tanzania-specific modelling for women living with HIV was conducted in collaboration with local co-authors and cites local published research, including current epidemiologic metrics for both HPV and HIV disease, and cervical cancer prevention including HPV vaccination and cervical screening and treatment.

Data availability

All data inputs required to perform this specific evaluation are described in the methods section and supplementary material accompanying this manuscript.

Code availability

The model used for this evaluation, *Policy1-Cervix*, is a well-established model platform spanning multiple software programs and related tools which has been developed over a period of 20 years. Each of these software programs, modules and tools consist of multiple versions for use in different contexts and their accurate and appropriate use requires substantial supervised training. *Policy1-Cervix* models HPV transmission, type-specific natural history, cervical screening, diagnosis and treatment, and has been extensively validated against data from a range of countries (Appendix pp 28-31). We assume that natural history parameters describing the rates of progression and regression between HPV-CIN1/2/3 and cancer by age and HPV type remain unchanged across settings; however, the incidence rates of HPV are dependent on the underlying sexual behaviour which varies by setting. Other variations by setting include cervical cancer survival rates, other cause mortality rates, national screening program recommendations and screening compliance rates and HPV vaccination coverage rates. In the case of *Policy1-Cervix-HIV* (the development of which was, in part, informed by *Policy1-Cervix*) additional key national data targets also include HIV epidemic data such as HIV incidence, prevalence and mortality. A process of model calibration and validation is therefore undertaken for each setting to ensure the model replicates all

available observed data. For settings in which a substantial amount of data is available (typically well-developed settings with adequate monitoring systems in place), calibration is undertaken to ensure that outcomes from the model fit across all available data sources by age, including type-specific HPV prevalence, rates of abnormal tests, rates of histologically detected high-grade disease, type-specific cervical cancer incidence and cervical cancer mortality. Detailed calibration across these targets is described in previous publications for Australia,[8] New Zealand,[16] USA,[43] and England[17] and for *Policy1-Cervix-HIV*, targets include calibration to historical HIV and cervical cancer rates for Tanzania[23] [Hall, plosone, 2020]. This thorough process involves collecting nationally representative data on screening test performance, screening compliance rates at each stage of the screening pathway (for instance rates of screening initiation by age, rates of return for routine testing, rates of follow-up and referral for diagnosis), colposcopy performance rates, precancer treatment efficacy rates and cancer survival rates by stage of disease; additionally, capturing historical HPV vaccination coverage by age and vaccine type is critical. For *Policy1-Cervix-HIV*, HIV rates and uptake of ART are also critical. Therefore, the validity of a model depends not just on the underlying model structure, but also on the detailed process of identifying the relevant nationally-representative data to inform the model, and modelling the setting-specific screening behaviour, ART uptake and HPV vaccination rates, which all play a critical role in producing an accurate model. We have also published validation of our model platform, in the form of validated predictions of reduction in HPV prevalence rates after HPV vaccination in Australia,[44] predictions of cervical cancer incidence rates after overlaying imperfect screening compliance in the USA[45], cervical cancer mortality rates across 78-LMICs separately for 6 regions after applying survival input values based on treatment access rates[5]. We have performed comparative modelling exercises with other independently developed models in the space and have generally found concordance with model outcomes against other well-established modelling platforms[43] and similar predictions with the other modelling groups across 78-LMICs.[4,5] Nationally representative data for less-developed settings is generally scarce; however, wherever possible, we sought the best available estimates on cervical cancer incidence and mortality and cervical cancer survival rates, as described in our earlier publications.[4,5] Furthermore, the calibration of *Policy1-Cervix* to a range of data sources across different developed countries indicates the model's ability to capture the underlying natural history for cervical disease, making it an ideal candidate for use in data-scarce settings. The *Policy1-Cervix* platform was reviewed and endorsed by the WHO Advisory Committee on Immunization and Vaccines related Implementation Research (IVIR-AC) for the use in modelling elimination targets across the 78-LMICs for WHO. Reporting on key model outputs was done according to a consensus-based framework for modelled evaluations of HPV prevention and cervical cancer control: HPV-FRAME, and is shown in the appendices for both manuscripts.

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feedback on our results. Their names are listed in the annex of the WHO guidelines, see https://www.who.int/publications/i/item/9789240030824.

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer /World Health Organization. This work was funded by UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP/World Health Organization).

Online Methods

We used the *Policy1-Cervix* platform, an extensively validated dynamic model of HPV transmission, vaccination, HPV type-specific natural history, cancer survival, screening, diagnosis and treatment,[5,8,14–23] to predict outcomes for each strategy across the lifetime of females aged 10–84 who turn 30 in 2030 (born 2000) across all 78 LMIC (Appendix pp 25–26). The Policy1-Cervix model was one of three models used by the CCEMC to evaluate the impact of cervical cancer elimination targets in 78 LMIC and was reviewed and endorsed by the WHO Advisory Committee on Immunization and Vaccines related Implementation Research (IVIR-AC) for the use in modelling elimination targets for WHO. Details of the modelled approach on the calibration to 78 LMICs is described in detail in the earlier CCEMC publications.[4,5] A list of each of the 78 countries included along with their GDP per-capita is described in the Appendix pp 45–48. Reporting is performed according to HPV-FRAME standards for models evaluating HPV vaccination and cervical screening[46] (Appendix pp 49–51).

To ensure adequate communication between the different expert groups involved in informing the update of cervical screening and treatment guidelines, weekly meetings were held between the modelling team, representatives from the WHO Secretariat and representatives from the systematic review and costing teams. Regular meetings were also held between GDG members and the systematic review, modelling and costing teams to present and discuss the priority management algorithms and evaluation results. The modelled evaluation was performed over a three-stage process, which is described in detail in Appendix pp 25–27.

Screening strategies

We considered the benefits, harms and cost-effectiveness of seven priority screening algorithms as identified by the GDG, compared to no-screening: Primary VIA, Primary cytology with HPV DNA triage (ASC-US referral), Primary HPV DNA without triage (assessment of eligibility for ablative treatment), Primary HPV DNA with HPV16/18 triage, VIA triage, cytology triage, and colposcopy triage. Detailed management for each of these screening scenarios, including downstream management for women in follow-up, at colposcopy and after precancer treatment are described Appendix pp 41–45. Screening ages

and frequencies considered for this analysis are shown in Table 2. Variations in age-ranges and frequencies considered generate a total of 19 scenarios.

Test performance

Based on updated systematic review evidence on cross-sectional sensitivity and specificity (Appendix pp 33–39), as well as test performance rates from the literature these reviews, we assumed a CIN2 + sensitivity of 94% for primary HPV DNA testing and 70% for primary cytology testing (we focussed on CIN2 + rather than CIN3 + because women with histological CIN2 + are treated in the algorithms modelled). These studies include a range of validated HPV DNA testing assays, which may target slightly different groups of HPV types, though they overlap on the most oncogenic ones.[37] For VIA, test performance was based on a combination of evidence from cross-sectional studies and larger scale population-level longitudinal studies (Appendix pp 33–36). Based on this combined evidence, the GDG agreed that for VIA we would assume 40% sensitivity to CIN2 + for the base-case analysis but also consider 60% sensitivity to CIN2 + as a favourable upper bound ('high sens').

Screening adherence

In this normative analysis across countries, we made relatively favourable assumptions about screening and follow-up attendance, in order to predict the relative impact and cost-effectiveness of screen-and-treat strategies in LMIC in the 'realistic best case scenario', understanding that especially at the inception of new programs, participation is unlikely to be this high in all settings. For the base-case analysis, we assumed that 70% of women attend each routine screening visit, but that 10% would be never screeners (so the 70% are selected from the 90% of ever-screeners). We made the favourable assumption that women referred for follow-up or treatment would attend at 90% adherence if the follow-up was to occur on a later day. If same-day treatment could be offered after an HPV positive result – for instance, primary HPV with VIA triage or primary HPV without triage – we assume that a point-of-care HPV test is used 50% of the time and that 100% compliance with follow-up is achieved when the point-of-care-test is used. This results in an average of 95% of women complying with same-day treatment after primary HPV with VIA triage or primary HPV without triage. We assumed that same-day test and treatment would be available for all primary VIA scenarios and therefore made the favourable assumption that 100% adherence would be achieved in women eligible for same-day treatment after primary VIA. We assumed 90% of screen-detected cervical cancer cases would receive adequate treatment, however access to cancer treatment for symptomatically detected cancers would remain unchanged from the status-quo (rates vary by country, averaging up to 33% across all 78 LMICs). In sensitivity analysis we considered a favourable scenario in which 90% of both screen-detected and symptomatically detected cervical cancers receive adequate treatment.

Outcomes assessed

For each strategy we report on outcomes over the lifetime of unvaccinated women who would turn 30 in 2030, the first cohort to be fully impacted by scale-up of cervical screening to 70% coverage by 2030.

Outcomes assessed include the lifetime number of cervical cancer cases and deaths and age-standardised incidence and mortality rates as a measure of the benefits. We assessed the number of precancer treatments needed to avert a cervical cancer death ('NNT') and preterm delivery events due directly to precancer treatment ('additional preterm delivery events') as a measure of the harms associated with screening. We also report on resource utilisation events including the lifetime number of VIA, cytology and HPV tests, ablation and excisional treatment events, and colposcopy and biopsy events. We report on the cost and cost-effectiveness of each strategy as a cost per HALY saved, assuming 0% discounting for effects and 3% discounting for costs as recommended by WHO for health economic evaluation of vaccination programs [47] , and assuming discounting starts from age 30. We presented results at a population-weighted average across 78 LMICs which we refer to as a 'normative approach', using 2015 population structure for population-weighted contribution of each country. There is no defined willingness-to-pay (WTP) when presenting cost-effectiveness at this multi-country average level; however, as a reference point for a potential WTP threshold in this population, the population-weighted average GDP-per-capita (pc) for 2019 across the 78 LMICs is US$2,093, and 71 of 78 [91%] LMICs had a GDP-per-capita equal to or above US$518, considering countries GDP per-capita being related to the countries willingness-to-pay. [48] We identified strategies that appear on, or near, the cost-effectiveness frontier as being the strategies with the best balance of costs and effects.

Model of obstetric complications

To evaluate adverse obstetric outcomes due to precancer treatment, we developed a Monte Carlo individual-based simulation model which incorporates country-specific and age-specific fertility rates, as well as precancer treatment outcomes by mode of treatment, and explicitly model additional preterm delivery events as a result of ablation and excisional treatments for 78-LMICs. This was adapted from a previous component of *Policy1-Cervix* which has been used to simulate adverse obstetric outcomes after screening in high-income countries.[49] Combining systematic review evidence on the risk of preterm delivery after excision (excision versus no treatment: 11.2% versus 5.5%, RR 1.87, 95% CI 1.64 to 2.12)[30] with a detailed model of cervical cancer screening and precancer treatment for Australia,[50] estimated preterm delivery events for Australia[49] and Australian fertility data, we estimated that women with a history of excisional treatment have an excess probability of preterm delivery of 4.8% for each subsequent pregnancy. Systematic reviews indicate that the risk of preterm delivery after ablation is lower than that after excision (ablation versus no treatment: 7.7% versus 4.6%, RR 1.35, 95% CI 1.20 to 1.52).[30] We therefore estimated that the additional probability of preterm delivery per pregnancy in women with a history of ablation without excision is (1.35-1)/(1.87-1)*4.8%=1.9%. We obtained national age-specific fertility rates for each of the 78 LMICs from the United Nations (2019),[51] and performed a population-weighted average to generate fertility rates for all 78 LMIC. We conservatively assumed that multiple treatments of the same type do not generate any additional risk of adverse pregnancy outcomes. In sensitivity analysis, we also considered a scenario in which ablative treatments did not increase the probability of preterm deliveries for subsequent pregnancies.

Costs and HALYs

Costs for each screening event were provided separately for each of the 78 LMICs by WHO.[52,53] We present the population-weighted aggregate cost (weightings for ages 30–49) of each event across the 78 LMICs, shown in Table 3. Ranges considered in sensitivity analysis are also shown.

Disability weights for cancer states were estimated by the Global Burden of Disease study 2010,[54] and were applied to cancer based on stage and time since diagnosis. The disability weights used to evaluate HALYs are shown in Appendix Table 4 (pp 46–51).

Supplementary analysis – alternative follow-up management

Management of HPV-positive and triage-negative

For the base case we assumed women who tested HPV positive and triage-negative would return in 12 months for an HPV test; if negative at this visit, women are then referred for their next routine screening visit or discharged from screening. As a supplementary analysis, we considered two alternative management options for this group based on discussions with the GDG: one was a less-aggressive management option in which triage-negative women return in 24 months for the follow-up HPV test (assuming 10% loss-to-follow-up for the return visit at 24 months, but also considering an supplementary analysis of 30% loss-to-follow-up), and another more aggressive management option in which women return at both 12 and 24 months, with 10% loss-to-follow-up assumed for each visit; in this more aggressive scenario, women are returned to routine screening or discharged from screening after testing negative at both visits.

Management of women after treatment for precancer (and did not have CIN3 detected by histology)

For the base case, we assumed that women who have been treated for cervical precancer and did not have a histological diagnosis of CIN3 would return in 12 months for an HPV test and are returned to routine screening (or discharged if outside of the age range) if negative at this visit. In the supplementary analysis, we considered alternative management scenarios as informed by discussion with the GDG. One was the option in which these women would return in 24 months for an HPV test and assumed a 30% loss-to-follow-up at this extended timeframe. The other was an option in which these women return at 12 months for an HPV and cytology co-test, with a 10% loss-to-follow-up assumed at this visit; women are returned to routine screening (or discharged if outside of the age-range) after testing negative with both tests.

Sensitivity analysis

A range of sensitivity analyses were considered. These are summarised in Appendix Table 4 (Appendix pp 46–51). A lower screening adherence scenario, in which we assumed 50% adherence with routine attendance (30% of women never attend, 50% selected from the pool of ever-screeners) and 75% for adherence with treatment or follow-up visits (100% for same-day eligibility) was explored for all screening

approaches. We also perform sensitivity analysis on primary test performance assumptions, including a lower bound CIN2 + sensitivity assumption of 30% for VIA, 46.8% for cytology and 88% for HPV testing and an upper bound CIN2 + sensitivity assumption of 60% for VIA, 80% for cytology and 95.7% for HPV. We considered a scenario in which 90% of symptomatically-detected cancers received adequate treatment in addition to the screen-detected cases, and a scenario in which both symptomatic and screen-detected cancers received treatment at current access rates (33% across all 78 LMICs). We also performed one-way sensitivity analysis assuming a 3% discount rate for both costs and effects, and considering life-years instead of HALYs.

PSA was also performed to explore uncertainties in costs. We generated 10,000 cost parameter sets based on the upper and lower ranges for each parameter as described in Table 3 (these ranges were discussed with the WHO GDG). To generate the sets, we divided cost values into five independent groups of variables, namely (1) cancer diagnosis, staging and treatment costs; (2) pre-cancer treatment costs; (3) HPV test costs; (4) VIA test costs; and (5) cytology test costs, and generated 10,000 samples with Latin hypercube sampling. Acceptability curves were generated for a range of WTP values from US$100-$2,000/HALY saved.

References

1. Ferlay J EM, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F. Global Cancer Observatory: Cancer Today. 2020; https://gco.iarc.fr/today/home. Accessed 1/4/22.
2. World Health Organisation. WHO Director-General calls for all countries to take action to help end the suffering caused by cervical cancer. 2019; https://www.who.int/reproductivehealth/call-to-action-elimination-cervical-cancer/en/. Accessed 13/10/2020.
3. World Health Organisation. Global strategy to accelerate the elimination of cervical cancer as a public health problem. 2020; https://www.who.int/publications/i/item/9789240014107. Accessed 12/01/2021.
4. Brisson M, Kim JJ, Canfell K, et al. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet (London, England). 2020;395(10224):575–590.
5. Canfell K, Kim JJ, Brisson M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet (London, England). 2020;395(10224):591–603.
6. World Health Orgaization. WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. 2013; https://apps.who.int/iris/bitstream/handle/10665/94830/9789241548694_eng.pdf?sequence=1. Accessed 12/01/2020.
7. World Health Organisation. *WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition* 2021.

8. Lew JB, 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(2):e96-e107.
9. Lew JB, Simms KT, Smith MA, Saville M, Hammond I, Canfell K. Cost-effectiveness estimates: the need for complete reporting - Authors' reply. Lancet Public Health. 2017;2(5):e212.
10. Shastri SS, Mittra I, Mishra GA, et al. Effect of VIA screening by primary health workers: randomized controlled study in Mumbai, India. J Natl Cancer Inst. 2014;106(3):dju009.
11. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. N Engl J Med. 2009;360(14):1385–1394.
12. Lauby-Secretan B, Mackie A, Wentzensen N. The IARC Perspective on Cervical Cancer Screening. New England Journal of Medicine. 2022:607–608.
13. World Health Orgaization (WHO). WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention. 2021; Second edition:https://apps.who.int/iris/rest/bitstreams/1354685/retrieve. Accessed 15/06/2021.
14. Hall MT, Simms KT, Lew JB, et al. The projected timeframe until cervical cancer elimination in Australia: a modelling study. Lancet Public Health. 2019;4(1):e19-e27.
15. 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. 2016;1(2):e66-e75.
16. 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(5):e0151619.
17. 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(23):1–196.
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(12):2771–2780.
19. Smith MA, Hall MT, Saville M, et al. Could HPV testing on self-collected samples be routinely used in an organised cervical screening program? A modelled analysis. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research*, cosponsored by the American Society of Preventive Oncology. 2021;30(2):268–277.
20. Simms KT, Hanley SJB, Smith MA, Keane A, Canfell K. Impact of HPV vaccine hesitancy on cervical cancer in Japan: a modelling study. Lancet Public Health. 2020;5(4):e223-e234.
21. Burger EA, Smith MA, Killen J, et al. Projected time to elimination of cervical cancer in the USA: a comparative modelling study. The Lancet Public Health. 2020.
22. Simms KT, Steinberg J, Caruana M, et al. 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. Lancet Oncol. 2019;20(3):394–407.

23. Hall MT, Smith MA, Simms KT, Barnabas R, Canfell K, Murray JM. The past, present and future impact of HIV prevention and control on HPV and cervical disease in Tanzania: a modelling study. *PLoS One* 2019 (submitted).
24. Feachem RG. Commission on macroeconomics and health. In. Vol 80: SciELO Public Health; 2002:87–87.
25. Vallely AJ, Saville M, Badman SG, et al. Point-of-care HPV DNA testing of self-collected specimens and same-day thermal ablation for the early detection and treatment of cervical pre-cancer in women in Papua New Guinea: a prospective, single-arm intervention trial (HPV-STAT). The Lancet Global Health. 2022;10(9):e1336-e1346.
26. Nguyen DTN, Simms KT, Keane A, et al. Towards the elimination of cervical cancer in low-income and lower-middle-income countries: modelled evaluation of the effectiveness and cost-effectiveness of point-of-care HPV self-collected screening and treatment in Papua New Guinea. BMJ global health. 2022;7(3):e007380.
27. Xue Z, Novetsky AP, Einstein MH, et al. A demonstration of automated visual evaluation of cervical images taken with a smartphone camera. International Journal of Cancer. 2020;147(9):2416–2423.
28. Keane A, Ng CW, Simms KT, et al. The road to cervical cancer elimination in Malaysia: Evaluation of the impact and cost-effectiveness of human papillomavirus screening with self-collection and digital registry support. International journal of cancer. 2021;149(12):1997–2009.
29. Unitaid. Unitaid and Cervical Cancer. 2022; https://www.clintonhealthaccess.org/news/unitaid-and-global-health-partners-reach-90-percent-treatment-target-for-women-screened-with-cervical-cancer-in-multi-country-pilots/. Accessed 18/12/2022.
30. Kyrgiou M, Athanasiou A, Kalliala IEJ, et al. Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease. Cochrane Database of Systematic Reviews. 2017(11).
31. Simms K, Steinberg J, Caruana M, et al. Timeline to eliminating of cervical cancer: projections of the impact of HPV vaccination and cervical screening in 181 countries:2020–2099. Lancet Oncology. 2019;20(3):394–407.
32. Bouvard V, Wentzensen N, Mackie A, et al. The IARC Perspective on Cervical Cancer Screening. New England Journal of Medicine. 2021;385(20):1908–1918.
33. Arbyn M, Simon M, de Sanjosé S, et al. Accuracy and effectiveness of HPV mRNA testing in cervical cancer screening: a systematic review and meta-analysis. Lancet Oncol. 2022;23(7):950–960.
34. World Health Organisation. WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention: use of mRNA tests for human papillomavirus (HPV). 2021, Licence: CC BY-NC-SA 3.0 IGO; https://www.who.int/publications/i/item/9789240040434.
35. Arbyn M, Simon M, Peeters E, et al. 2020 list of human papillomavirus assays suitable for primary cervical cancer screening. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2021;27(8):1083–1095.

36. Arbyn M, Smith SB, Temin S, Sultana F, Castle P. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. BMJ. 2018;363:k4823.
37. Arbyn M SM, Peeters E, Xu L, Meijer CJLM, Berkhof J, Cuschieri K, Bonde J, Ostrbenk Vanlencak A, Zhao FH, Rezhake R, Gultekin M, Dillner J, de Sanjosé S, Canfell K, Hillemanns P, Almonte M, Wentzensen N, Poljak M. 2020 list of human papillomavirus assays suitable for primary cervical cancer screening. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2021;27(8):1083–1095.
38. Nelson EJ, Maynard BR, Loux T, Fatla J, Gordon R, Arnold LD. The acceptability of self-sampled screening for HPV DNA: a systematic review and meta-analysis. Sexually transmitted infections. 2017;93(1):56–61.
39. Fitzpatrick MB, El-Khatib Z, Katzenstein D, Pinsky BA, Chirenje ZM, McCarty K. Community-based self-collected human papillomavirus screening in rural Zimbabwe. BMC Public Health. 2019;19(1):603.
40. World Health Organization. Global Health Observatory (GHO) data. https://www.who.int/gho/immunization/en/. Accessed December 19 2019.
41. World Health Organization. *Assessment and harmonization of laboratory diagnostic procedures related to human papillomavirus vaccine research and development. Report of a technical meeting Heidelberg, 6–7 March 2001*. Geneva: World Health Organization, Department of Vaccines and Biologicals; 2001.
42. World Health Orgaization. 'Best Buys' and other recommended Interventions for the Prevention and Control of Noncommunicable Diseases. 2017; https://www.who.int/ncds/management/WHO_Appendix_BestBuys.pdf. Accessed 29/01/2021.
43. Burger EA, de Kok I, Groene E, et al. Estimating the Natural History of Cervical Carcinogenesis Using Simulation Models: A CISNET Comparative Analysis. J Natl Cancer Inst. 2020;112(9):955–963.
44. Smith MA, Canfell K. Testing previous model predictions against new data on human papillomavirus vaccination program outcomes. BMC research notes. 2014;7(1):1–5.
45. Kim JJ, Simms KT, Killen J, et al. Human papillomavirus vaccination for adults aged 30 to 45 years in the United States: A cost-effectiveness analysis. PLOS Medicine. 2021;18(3):e1003534.
46. Canfell K, Kim JJ, Kulasingam S, et al. HPV-FRAME: A consensus statement and quality framework for modelled evaluations of HPV-related cancer control. Papillomavirus Res. 2019;8:100184.
47. World Health Orgaization. WHO guide for standardization of economic evaluations of immunization programmes, 2nd edition. 2019. Licence: CC BY-NC-SA 3.0 IGO; https://apps.who.int/iris/rest/bitstreams/1257211/retrieve. Accessed 20/01/2021.
48. WHO-CHOICE. Cost effectiveness and strategic planning 2014; http://www.who.int/choice/costs/CER_thresholds/en/.
49. Velentzis LS, Caruana M, Simms KT, et al. How will transitioning from cytology to HPV testing change the balance between the benefits and harms of cervical cancer screening? Estimates of the

impact on cervical cancer, treatment rates and adverse obstetric outcomes in Australia, a high vaccination coverage country. Int J Cancer. 2017;141(12):2410–2422.

50. Velentzis LS, Caruana M, Simms KT, et al. How will transitioning from cytology to HPV testing change the balance between the benefits and harms of cervical cancer screening? Estimates of the impact on cervical cancer, treatment rates and adverse obstetric outcomes in Australia, a high vaccination coverage country. International Journal of Cancer. 2017;141(12):2410–2422.
51. Nations U. Department of Economic and Social Affairs Population: Fertility. 2019; Age-specific fertility. Available at: https://population.un.org/wpp/Download/Standard/Fertility/. Accessed 13/10/2020.
52. WHO. Updated Appendix 3 of the WHO Global NCD action plan 2013–2030. 2021; https://cdn.who.int/media/docs/default-source/ncds/mnd/2022_discussion_paper_final.pdf?sfvrsn=78343686_7. Accessed 8 June 2021.
53. Organization WH. WHO report on cancer: setting priorities, investing wisely and providing care for all. 2020.
54. Salomon JA, Vos T, Hogan DR, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet (London, England). 2012;380(9859):2129–2143.

Table 1

Table 1 is available in the Supplementary Files section.

Figures

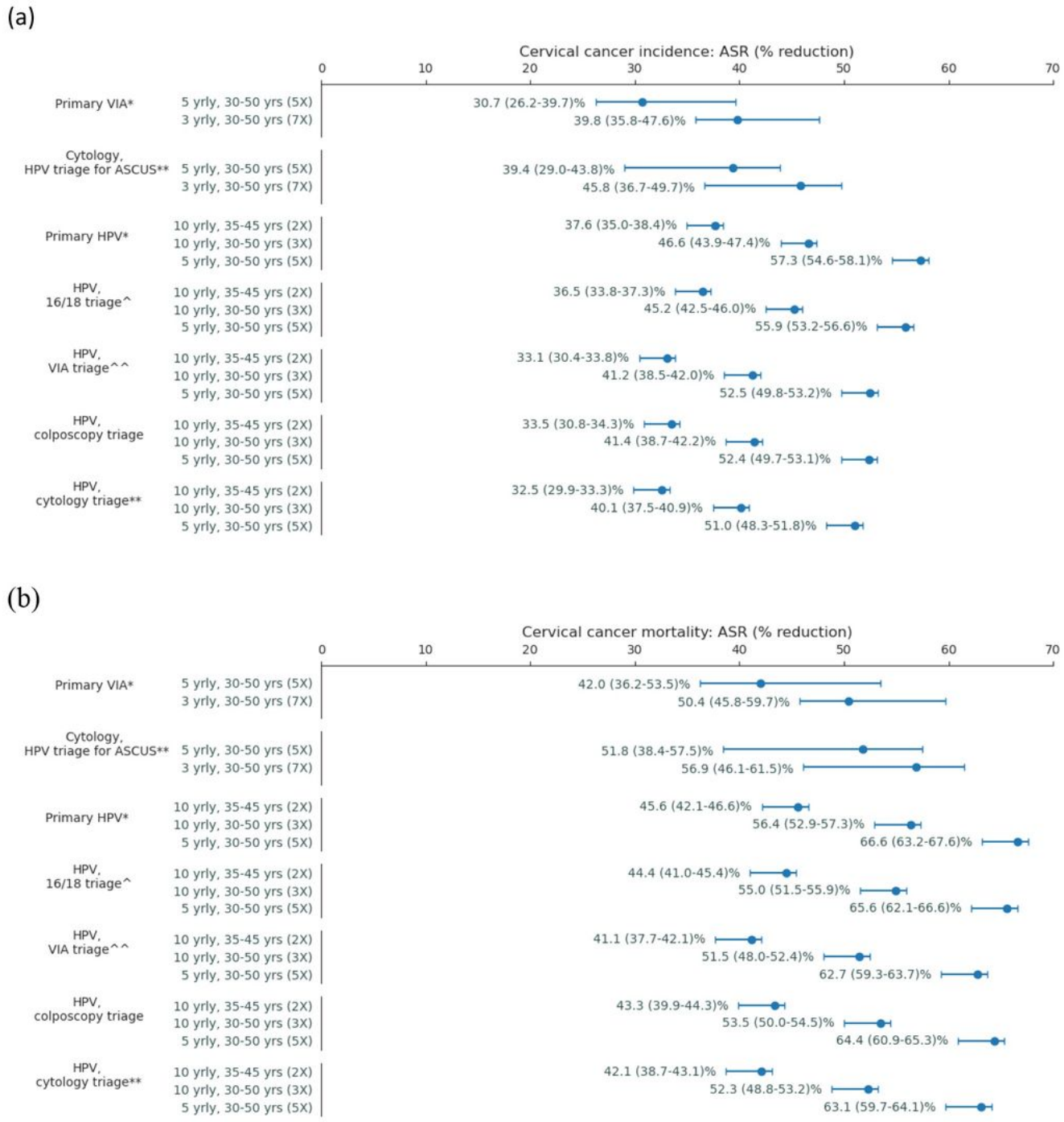

Figure 1

Reductions in cervical cancer incidence and mortality. (A) Age-standardised cervical cancer incidence (ASIR) reductions, and (b) Age-standardized cervical cancer mortality (ASMR) reduction given base case assumptions with upper and lower ranges representing higher and lower range of primary test performance assumptions.

* All positive women treated after assessment of eligibility for ablative treatment. **Triage positive referred to colposcopy. ^^VIA triage positive women treated after assessment of eligibility for ablative treatment. ^HPV 16/18 positive women treated after assessment of eligibility for ablative treatment. Women positive for HPV types other than HPV 16/18 ('OHR') are triaged with VIA.

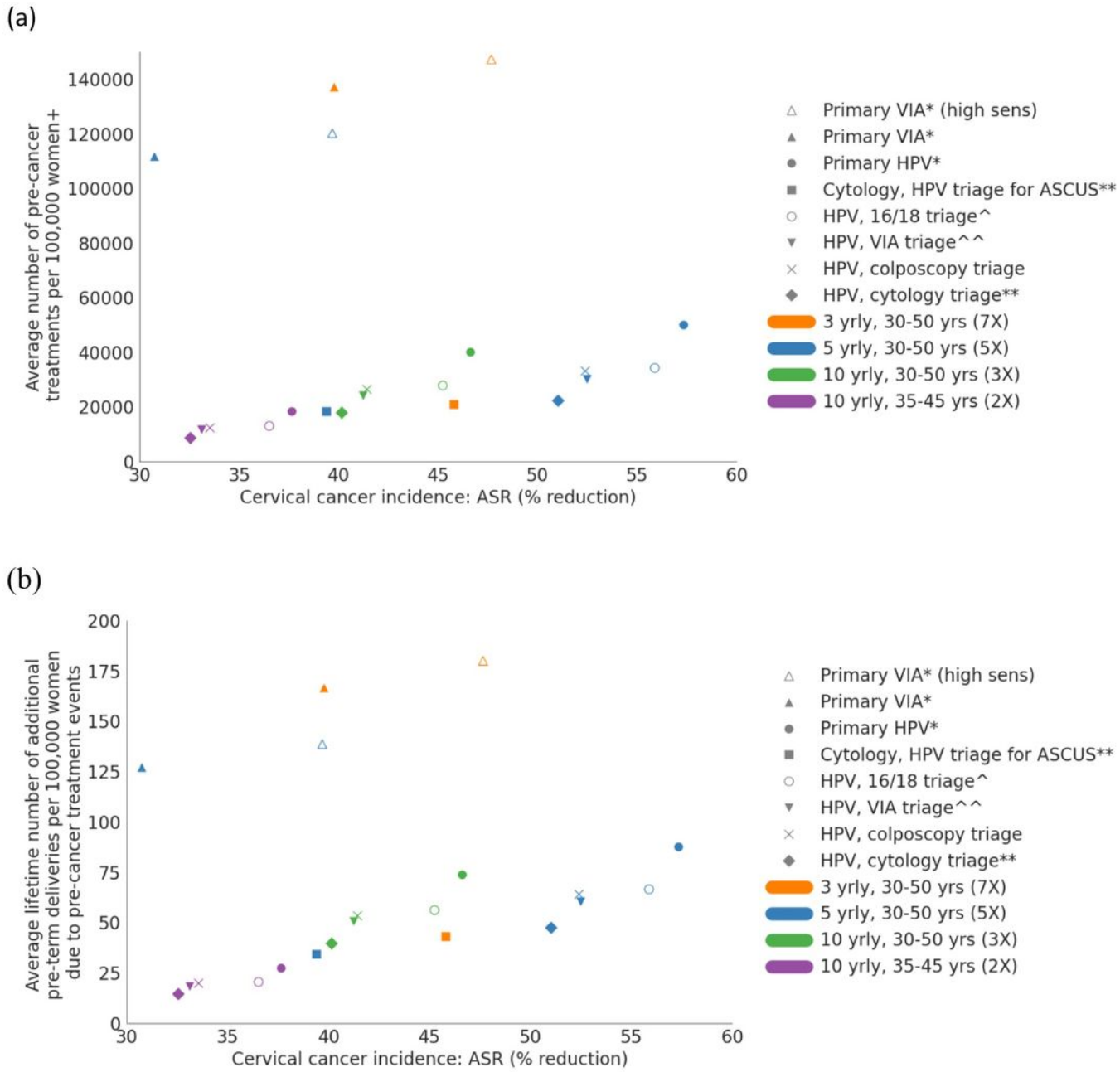

Figure 2

Benefits-to-harms of alternate screening strategies. Comparison of cervical cancer incidence (ASIR) reduction with (a) lifetime number of precancer treatments and (b) lifetime number of additional preterm deliveries due to precancer treatments.

*All positive women treated after assessment of eligibility for ablative treatment. **Triage positive referred to colposcopy. ^^VIA triage positive women treated after assessment of eligibility for ablative treatment. ^HPV 16/18 positive women treated after assessment of eligibility for ablative treatment. Women positive for HPV types other than HPV 16/18 ('OHR') are triaged with VIA. + Note there could be multiple treatments in women who require follow-up.

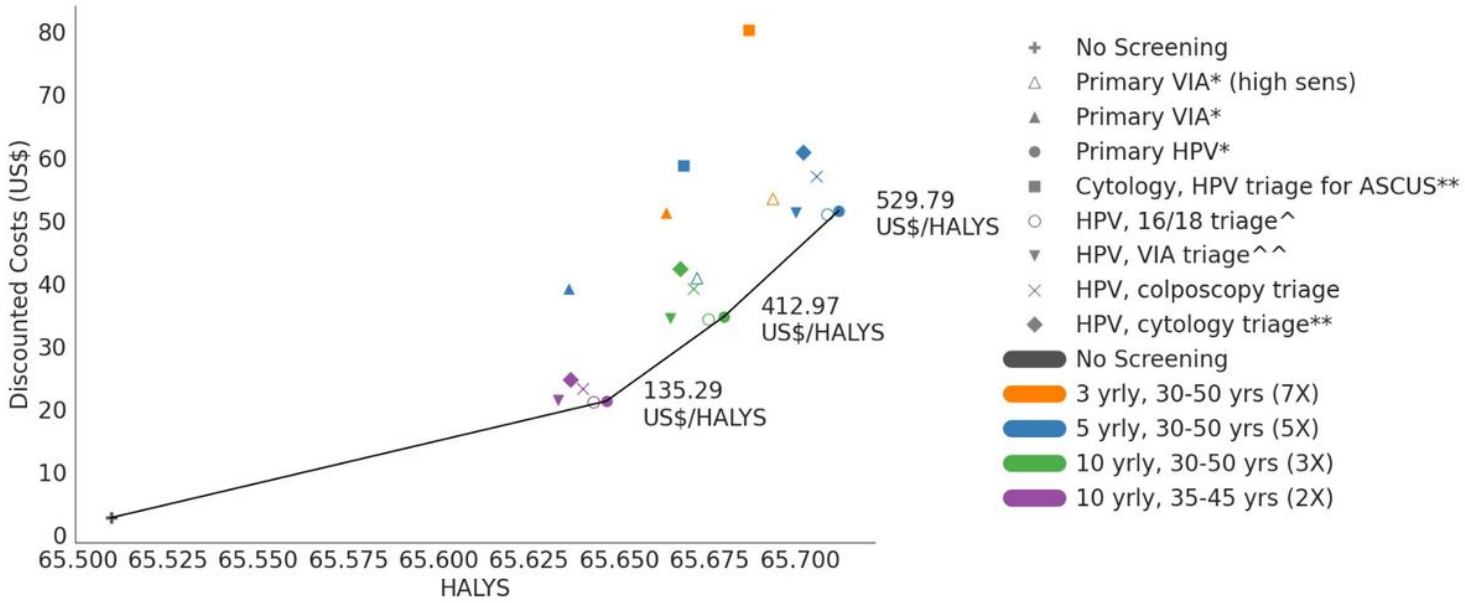

Figure 3

Cost-effectiveness plane (Cost/HALY)+

+ 0% discount rate for effect, 3% discount rate for cost. HALY: health-adjusted life-years
* All positive women treated after assessment of eligibility for ablative treatment. **Triage positive referred to colposcopy. ^^VIA triage positive women treated after assessment of eligibility for ablative treatment. ^HPV 16/18 positive women treated after assessment of eligibility for ablative treatment. Women positive for HPV types other than HPV 16/18 ('OHR') are triaged with VIA.

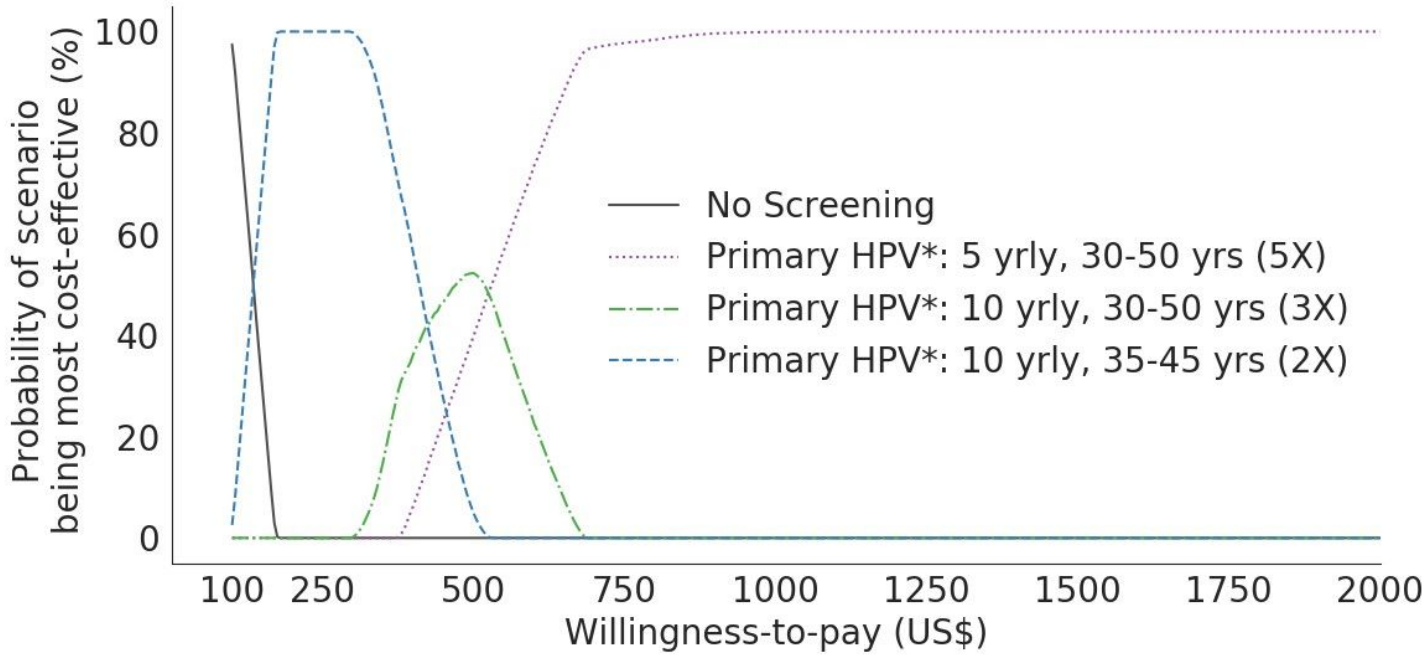

Figure 4

Acceptability curves showing the probability of a strategy being the most cost-effective strategy for a range of WTP^

^Some strategies had a small probability of being cost-effective but are not visible on the graph and are as follows: Primary VIA screening (high sensitivity) every 5-years for ages 30-50 had <3% probability of being the most cost-effective approach for WTP US$285-$555/HALY saved. Primary VIA screening (high sensitivity) every 3 years for ages 30-50 had <5% chance of being the most cost-effective approach for WTP US$465-$1055/HALY saved. Primary HPV with HPV16/18 triage every 5 years for ages 30-50 had <0.1% chance of being the most cost-effective approach for WTP US$390-405/HALY saved. *All HPV positive women assumed to be treated after assessment of eligibility for ablative treatment.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- Appendix.docx
- nreditorialpolicychecklistgeneral.pdf
- nrreportingsummarygeneral.pdf