Appendix: The road to cervical cancer elimination in Malaysia: Evaluation of the impact and cost-effectiveness of HPV screening with self-collection and digital registry support

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Section A. Description of Policy1-Cervix

‘Policy1-Cervix’ is a multi-compartmental model of HPV transmission, HPV vaccination, cervical precancer, cancer survival, screening, diagnosis and treatment (Fig. A1). The natural history component of the model simulates HPV infection which can persist, progress to, or regress from, cervical intraepithelial neoplasia grades I, II and III (CIN1, CIN2, CIN3). Distinct transition rates between states are modeled for types HPV 16, HPV 18, other high-risk nonavalent-included types (31/33/45/52/58), and other non-nonavalent included high risk types. CIN 3 state can progress to the cervical cancer natural history, detection and treatment module. Women who progress to undiagnosed cervical cancer can then either progress to the next stage or be detected at that stage, with different rates of progression and detection for each stage. Diagnosed invasive cervical cancer is then calculated according to a stage-based yearly-survival table.

The model can incorporate a screening overlay, where women may be managed according to test outcomes and screening history as outlined by the algorithms in Methods, main manuscript (Fig. 2). Screening and diagnostic tests are captured through the use of a test probability matrix, which has a probability of yielding an outcome, such as ‘HPV positive’ for the self-collected HPV test or ‘ASC-US’ for an LBC triage, that depends on the true underlying health state of a woman. Pre-cancer treatments such as LEEP and thermocoagulation have a probability of improving a woman’s underlying health state. Both screening, diagnostic and treatment performance are informed by data on test accuracy and treatment efficacy. The model platform captures the increased risk of CIN2+ recurrence in successfully treated women (compared to the baseline risk of CIN2+ in the population), as previously described. Women who survive more than 10 years are assumed to have been cured of cervical cancer.

To capture the impact of HPV vaccination, we used a general dynamic transmission model, which accounts for the additional effects of herd immunity through vaccination. This model has been described in greater detail in the supplementary material of our previous studies. ‘Policy1-Cervix’ has been used to perform evaluations across a range of settings (see Policy1.org for details). It has also been extensively validated: for example, predictions of HPV prevalence changing after quadrivalent HPV vaccination have been validated against observed declines. Predictions of age-specific cervical cancer incidence and mortality, and the rate of histologically confirmed high-grade lesions and screening participation rates as validated
against national data from multiple HICs\textsuperscript{4-6}. As part of a comparative modeling exercise of 78 low- and lower-middle income countries for the WHO targets for elimination of cervical cancer as a public health problem, it has been validated against two other models.\textsuperscript{2,3}

Figure A1. Schematic of Policy-1 Cervix.
Section B. HPV-FRAME reporting standard

| a) Inputs                                      | Reported? (Y/N) | Reported by age? (Y/N) | Reported by sex (F/M/both) | Comments                                                                                                                                 |
|------------------------------------------------|-----------------|------------------------|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Core reporting standard                        |                 |                        |                             | Vaccination (current): females aged 13 years.                                                                                           |
| Target population for intervention             | Y               | Y                      | F-only                      | Screening at ages 35 and 45.                                                                                                           |
|                                                |                 |                        |                             | Cancer treatment (current): all ages.                                                                                                   |
| Sexual behaviour                               | Y (for dynamic models) | Y (for dynamic models) | Y                           | The transmission model/sexual behaviour parameters were used to inform the expected reduction in the HPV incidence rates due to HPV vaccination; as reported in Section A, these data come from a global model. |
| Cohort examined for evaluation/time horizon    | Y               | N                      | F-only                      | Simulations run over 2020-2100.                                                                                                        |
|                                                |                 |                        |                             | Age-standardized rates and resource utilization reported over 2020-2100.                                                                 |
|                                                |                 |                        |                             | Cumulative cases and deaths averted reported at 2020-2069 and 2020-2099.                                                              |
|                                                |                 |                        |                             | Overall budget impact and cost-effectiveness reported over 2020-2029.                                                                |
|                                                |                 |                        |                             | Cost-effectiveness reported over 2023-2100 (from first HPV scale-up year).                                                           |
| Quality of life assumptions                    | N/A             | N/A                    | N/A                         | Cost-effectiveness reported in terms of life-years saved only                                                                             |
| Calibration                                   | Y               | Y                      | F-only                      | Age-specific cancer incidence separately matched against data for Peninsular and East Malaysia.                                          |
|                                                |                 |                        |                             | Cancer stage distribution matched against data for Malaysia nationally.                                                                |
|                                                |                 |                        |                             | HPV type distribution matched against data for study in Peninsula nationally.                                                          |


| Validation (where possible) | Y | Y | F-only | Age-specific mortality matched against data for Peninsular Malaysia (but not matched nationally). HPV prevalence matched against data for Peninsula. Cervical cancer 5-year survival matched against data for Malaysia nationally. |
|-----------------------------|---|---|--------|-------------------------------------------------------------------------------------------------------------------------------------|
| Costs                       | Y | N | F-only | Costs sourced from local data except for thermal ablation and visual assessment for treatment (based on data for Papua New Guinea). |

**Reporting standard for HPV vaccination in adolescent individuals**

| Vaccine uptake       | Y | Y | Y | Based on state-based data, aggregated by population to Peninsula and East Malaysia separately. |
|----------------------|---|---|---|-------------------------------------------------------------------------------------------------------------------------------------|
| Vaccine efficacy     | Y | Y | F-only | 100% vaccine efficacy was assumed, independent of age. |
| Vaccine cross-protection | Y | N | F-only | 71.9% cross-protection against HPV types 31, 52 and 52 for 20 years based on a recent study in Japan. |

**Reporting standard for model of cervical screening**

| Routine screening behaviour (routine and follow-up and test of cure) | Y | Y | F-only | Screening coverage reported as going to 45% in 2023, 70% in 2030 and 90% in 2045. Compliance to follow-ups assumed to be 90% with a digital registry. |
|--------------------------------------------------------------------|---|---|--------|-------------------------------------------------------------------------------------------------------------------------------------|
| Screening test(s) and colposcopy accuracies                        | Y | Y (implicitly) | F-only | Sources for sensitivities and specificities of each test reported in the main text. Assumed to be independent of age. |
| Abnormal test management (primary and triage)                      | Y | Y (implicitly) | F-only | As depicted in Fig. 2 in the manuscript. Assumed to be independent of age. |
| Diagnostic follow-up of abnormal tests                             | Y | Y (implicitly) | F-only | As depicted in Fig. 2 in the manuscript. Assumed to be independent of age. |
| Management by disease grade (confirmed disease)                    | Y | Y (implicitly) | F-only | As depicted in Fig. 2 in the manuscript. Assumed to be independent of age. |
| Sources of information for screening structure and parameterization | Y | Y | F-only | The screening pathways were informed by pilot trials conducted by the Ministry of Health and Project ROSE |

**Reporting standards for integrated models of HPV vaccination and cervical screening**

| HPV type incidence, clearance and progression rates | Y (implicitly) | Y (implicitly) | F-only | Type-specific HPV incidence, clearance and progression were modeled separately for HPV16, 18, other oncogenic nonavalent- |
Included types (31/33/45/52/58) and other oncogenic nonavalent-non-included types. (Detailed model descriptions and references to other sources included in Section, page 1).

| Herd effects                  | Y (implicitly) | Y (implicitly) | Y (implicitly) | Herd effects were assumed to be captured by the dynamic transmission component of the model (see Section, page 1) |
|-------------------------------|----------------|----------------|----------------|----------------------------------------------------------------------------------------------------------------------------------|
| Association between vaccination and screening uptake | Y (implicitly) | Y (implicitly) | F-only | Vaccine and screening uptake were assumed to be independent of one another. |

**Reporting standard for models of HPV prevention in LMICs**

| HPV prevalence rates, if endemic in country | Partially | Partially | F-only | Data available only in Peninsular Malaysia; calibration to age-specific HPV prevalence-only reported there. |
|---------------------------------------------|-----------|-----------|--------|----------------------------------------------------------------------------------------------------------------------------------|
| Description of any opportunistic or pilot/demonstration screening project ongoing | Y | Y | F-only | Both currently offered cytology-based screening HPV self-sampling-based Project ROSE are described. |

**b) Outputs**

| Reported? (Y/N) | Reported by age? (Y/N) | Reported by sex (F/M/both) | Comments |
|----------------|------------------------|--------------------------|----------|

**Core reporting standard**

| Cancer incidence, mortality, life years, QALYs/DALYs (as appropriate) | Y | Y | F-only | Age-standardized and age-specific incidence and mortality rates were reported. |
|---------------------------------------------------------------------|---|---|--------|----------------------------------------------------------------------------------------------------------------------------------|
| HPV prevalence, pre-intervention | Partially | Partially | F-only | Age-specific prevalence reported for Peninsular Malaysia only due to lack of data. |
| CIN2 detected | N | N | N | This level of detail is not reported. |
| Sensitivity analysis on key inputs | N | N | N | |
| Incremental cost-effectiveness ratios and costs saved | Y | N | F-only | 3% discounting on both costs and life-years saved. |

**Reporting standard for HPV vaccination in adolescent individuals**
| Event                                           | Y  | N  | F-only | Description                                                                 |
|------------------------------------------------|-----|-----|--------|----------------------------------------------------------------------------|
| Absolute reductions in HPV infections, cervical, and other HPV-related cancers and/or warts post-vaccination | N   | N   |        | This paper focuses primarily on the additional benefits of HPV-based screening for cervical cancer in the context of an already-established vaccination program. |
| Absolute reduction in CIN2+ post-vaccination    | N   | N   | N      | This paper focuses primarily on the additional benefits of HPV-based screening for cervical cancer in the context of an already-established vaccination program. |
| Absolute reduction in invasive cancer post-vaccination | Y   | N   | F-only | This paper focuses primarily on the additional benefits of HPV-based screening for cervical cancer in the context of an already-established vaccination program. |

**Table B1. HPV-FRAME.** Includes core reporting standard, reporting standard for a model of HPV vaccination, model of integrated HPV vaccination and cervical screening, and model for LMICs, according to Canfell et al, 2019.7
Section C. Model calibration and validation

The model was calibrated separately to Peninsular and East Malaysia by using data on age-specific cervical cancer incidence from the National Cancer Registry Report for 2007-2011 and the latest IARC-based registry data in Penang and Sarawak (Fig. 1a,b). For both regions, National Cancer Registry Report for 2007-2011 was also used to calibrate to cervical cancer stage distributions (Fig. 1c), and a cross-sectional study was used to calibrate to the proportion of high-risk HPV types in the population (Fig. 1d). Symptomatic stage-dependent overall survival rates were based on a multi-country review and scaled to match CONCORD data on overall 5-year relative survival rates in Malaysia (Fig. 1e). 10-year survival was extrapolated by assuming it linearly tapers from the fifth year value to a value of 100% for women who survive after 10 years or more. To obtain screen-detected survival rates, we applied a scaling function based on stage-specific survival ratios between symptomatically-detected cancer and screen-detected cancer in Australia and New Zealand.

The model outputs were validated against data on age-specific HPV prevalence (Fig. 1f); age-specific cervical cancer incidence (Fig. 1g) based on national GLOBOCAN estimates and National Cancer Registry Report for 2007-2011; and age-specific cervical cancer mortality (Fig. 1h) based on national GLOBOCAN estimates and aggregated datasets on mortality in Peninsular Malaysia. These datasets were purchased from the Department of Statistics and are not publicly available; poorly coded death certifications were redistributed based on those that were appropriately coded. The cervical cancer mortality did not match GLOBOCAN estimates but there was good match to cervical cancer mortality in Peninsular Malaysia, cervical cancer survival and stage distribution. The mortality-to-incidence ratio (MIR) from GLOBOCAN is very high and not in alignment with the other data; it is estimated from national incidence using statistical models, with the fitted MIR derived from recorded data from cancer registries, and MIR between countries scaled according to levels of HDI.
Section D. Detailed test and treatment parameters

Detailed test and treatment parameters are listed in Table D1. The sensitivity and specificity of self-collected HPV DNA testing and HPV 16/18 genotyping was based on a review and extension of previous meta-analysis of the performance of HPV-testing\textsuperscript{16} and on an analysis of the relative sensitivity and specificity of self-collection versus clinician-collected samples.\textsuperscript{17} The accuracy of colposcopy performance was based on the data from the Chinese SPOCCS-1 study\textsuperscript{18} whilst the parameters for test accuracy of LBC were based on international meta-analyses.\textsuperscript{19,20} The test accuracy of VAT was based on the findings of a screening demonstration project in India and a population-based study in China.\textsuperscript{21,22} The success rate for outpatient LEEP was based on a review of medical records of patients who had undergone LEEP at the Obstetrics and Gynaecology Hospital of Fudan University\textsuperscript{23} and the success rate for inpatient LEEP was based on systematic review of cold knife conization.\textsuperscript{24} In both instances, the recurrence of HPV was determined using data from a study on HPV testing to predict residual/recurrent disease after LEEP.\textsuperscript{25} The success rate of thermoablation was based on a global meta-analysis\textsuperscript{26} and pooled data from Bangladesh, Brazil and India.\textsuperscript{27}

| Item                          | Value      | Reference | Notes          |
|-------------------------------|------------|-----------|----------------|
| **Test characteristics (CIN2+)** |            |           |                |
| HPV DNA self-sampling         | Se: 97.6%  | \textsuperscript{16,17,19} |                |
|                               | Sp: 94.4%* |           |                |
| Liquid-based cytology         | Se: 76.7%  | \textsuperscript{19,20} | Threshold is LSIL+ |
| Procedure          | Sp (percent) | Range          | Notes                                                                 |
|--------------------|-------------|----------------|------------------------------------------------------------------------|
| Colposcopy         | 97.5%*      |                |                                                                        |
|                    | 81.0%       |                |                                                                        |
|                    | 77.0%       |                |                                                                        |
| **Pre-cancer treatment success rate (CIN2+)** |             | 78.14-83.68% | Range indicates different rates for CIN2 and CIN3                       |
| Thermoablation     | 78.14-83.68%| 26,27          |                                                                        |
| Outpatient LEEP    | 93.60%      | 23,25          | Assumed same as cold knife conization (CKC)                              |
| Inpatient LEEP     | 98.57%      | 24,25          |                                                                        |

**Table D1. Screening and pre-cancer treatment characteristics.**

* These test accuracy numbers used [e.g for baseline HPV testing we assume ~93-98% positivity for women with CIN2+ and ~44-84% positivity for women with HPV or CIN1] result in a higher specificity when applied to the modeled health state used for Malaysia, when compared to reported specificity rates. However, when we use a health state from a HIC setting, the estimated specificity is lower and more comparable with reported rates.
Section E. Detailed cost parameters

Detailed cost parameters are listed in Table E1. Costs for outpatient consultation fees, colposcopies and LEEP were obtained from the Government of Malaysia Fee Schedule. LBC costs, HPV DNA test costs and registration costs were based on in-country expert advice. As local data on use of thermal ablation and VAT in point-of-care (which we are modeled for rural East Malaysia) were not available, these values were assumed. Costs of cancer treatment were calculated using a population-weighted average of the costs of treatment therapies received by cancer patients, depending on the treatments used at each stage and the proportion of women diagnosed at that stage. The underlying costs were based on the Government of Malaysia Fee Schedule and data on the sub-stage distributions were based on a combination of expert opinion and published data. This includes work-up costs, ongoing costs, follow-up costs and palliative care costs. The cost of vaccination was based on the in-country label price for Cervarix, with additional administrative and wastage costs based on a review of international papers for rotavirus dose costs, which has a similar overhead to HPV vaccines. All costs were inflated to 2019 USD and use 2019 average exchange rate, according to World Bank data.

| Item                     | Unit cost | Reference               | Notes                                                                 |
|--------------------------|-----------|-------------------------|----------------------------------------------------------------------|
|                          | USD (2019) | RM (2019) #             |                                                                    |
| **Screening and triage** |           |                         |                                                                    |
| Digital registration     | 8.45      | 35.00                   | VCS Foundation, Personal Communication Applied once in a lifetime with first primary screen. |
| Service                                      | Cost   | Fee   | Notes                                                                 |
|----------------------------------------------|--------|-------|----------------------------------------------------------------------|
| HPV DNA test                                 | 55.56  | 230.00| Costs include outpatient consultation fees and estimated costs of HPV DNA test |
| Liquid-based cytology                        | 41.06  | 150.00| Costs include outpatient consultation fees and estimated costs of LBC test |
| Visual assessment for treatment              | 1.14   | 4.29  | Assumed                                                               |
| Pre-cancer treatment and diagnostics         |        |       |                                                                      |
| Thermoablation                               | 15.70  | 58.90 | Assumed                                                               |
| Outpatient LEEP and histology                | 253.09 | 1,047.79 | Includes cost of services using fee schedule and testing. Includes histology |
| Inpatient LEEP and histology                 | 445.76 | 1,845.46| Includes cost of services using fee schedule and testing. Includes colposcopy. |
| Liquid-based cytology                        | 21.74  | 90.00 | Only as part of diagnostic work-up (no consultation fees included)   |
A weighted average cost of procedures received by cancer patients to confirm diagnosis. Assumed to apply at diagnosis year. Includes histology and LEEP.

### Cancer work-up

| Stage   | Cost 1   | Cost 2   | Year |
|---------|----------|----------|------|
| Stage 1 | 1,139.99^ | 4,719.56 | 28   |
| Stage 2 | 1,695.97^ | 7,021.31 | 28   |
| Stage 3 | 1,695.97^ | 7,021.31 | 28   |
| Stage 4 | 1,695.97^ | 7,021.31 | 28   |

### Cancer treatment

A weighted average cost of procedures received by cancer patients to confirm diagnosis. Assumed to apply at diagnosis year.

| Stage   | Cost 1   | Cost 2   | Year |
|---------|----------|----------|------|
| Stage 1 | 6,078.85^ | 25,166.43 | 28   |
| Stage 2 | 10,000.80^ | 41,403.33 | 28   |
| Stage 3 | 11,635.51^ | 48,171.03 | 28   |
| Stage 4 | 11,950.22^ | 49,473.89 | 28   |
Cancer follow-up

Tests or procedures to check for disease progress and outpatient consultation fees, years after diagnosis. A value is applied for each diagnosed stage based on survival length.

| Year   | Unit cost | Year-end cost |
|--------|-----------|---------------|
| Year 1 | 481.69^   | 1,994.18      |
| Year 2 | 138.79^   | 574.59        |
| Year 3+| 92.53^    | 383.06        |

Palliative care

Assumed to apply in year of cancer mortality.

| Year   | Unit cost | Year-end cost |
|--------|-----------|---------------|
|        | 4,601.38^ | 19,049.71     |

Vaccination cost per dose

| Cost type        | Label price | Overhead cost | Wastage cost | Total cost |
|------------------|-------------|---------------|--------------|------------|
| Label price      | 9.70        | 5.36          | 0.48         | 15.54      |
| Overhead cost    | 40.15       | 22.18         | 2.01         | 64.34      |

Table E1. Unit costs for health economic evaluation.

^ Costs inflated from 2014 to 2019 (~12.7%).

# Average conversion rate from 2019 (4.14 RM per USD).
Section F. Supplementary Results: Unvaccinated cohorts

The main results looked at screening when added to the current vaccination program in Malaysia. However, it is of interest to assess the potential effects of screening alone, independent of vaccination. Therefore, we also modeled the screening scenarios in the absence of vaccination, including for some of the supplementary results in Section G and H.

Figure F1 shows the yearly colposcopies and pre-cancer treatments as a function of time in the unvaccinated cohorts. By contrasting it with Figure 4, it can be seen that the decrease in pre-cancer treatments from 2031-2045 in vaccinated cohorts is mostly due to the effects of vaccination as the female population becomes immune to HPV16/18 across all ages; the rise in 2045 is due to the final scale-up to 90% coverage.

Table F1 shows that for unvaccinated cohorts over 2020-2069, the number-needed-to-colposcope to avoid one case of cervical cancer (or death) for HPV self-sampling would be 21 (34); for pre-cancer treatment (i.e. number-needed-to-treat), it would be 22 (36). HPV self-sampling with triage had greater efficiencies, with a number-needed-to-colposcope to avoid one case (death) being 12 (20) and the number-needed-to-treat to avoid one case (death) being 13 (22).

Table F2 shows that for unvaccinated cohorts over 2020-2100, twice-lifetime screening was very cost-effective (CER=$3,460-$3,713<0.5xGDP per-capita), depending on if triage is used for HPV positive women. Furthermore, for these unvaccinated cohorts, 5-yearly screening is also cost-effective (ICER=$9,412-$9,944<1xGDP per-capita), depending on if triage is used for HPV positive women; this is in contrast to the case in which current vaccination coverage continues (see Section G).
Figure F1. Resource utilization over time in unvaccinated cohorts as screening is rolled out. (a) Colposcopies. (b) Pre-cancer treatments (inpatient and outpatient LEEP, and thermoablation).
Note that Vax + HPV self-sampling and Vax + HPV self-sampling + triage uses twice-lifetime screening at ages 35 and 45 in Peninsular Malaysia and in urban East Malaysia. However, for rural East Malaysia, once-lifetime at age 35 point-of-care testing is used. See Methods, main manuscript, for details.
Table F1. Efficiency of precancer treatments (inpatient and outpatient LEEP, and thermoablation) and number averted for unvaccinated cohorts over 2020-2069.

Note that 2x-lifetime HPV self-sampling and 2x-lifetime + HPV self-sampling + triage uses twice-lifetime screening at ages 35 and 45 in Peninsular Malaysia and in urban East Malaysia; for rural East Malaysia, once-lifetime at age 35 point-of-care testing is used (see Methods, main manuscript, for details). Note also that 5-yearly HPV self-sampling and 5-yearly HPV self-sampling + triage uses five-yearly screening for ages 30-65 in Peninsular Malaysia and in urban East Malaysia; for rural East Malaysia, thrice-lifetime at age 30, 40 and 50 point-of-care testing is used (see Section H for details).

^ Ranges for “no registry” scenarios indicate the upper (75%) and lower bound compliance assumptions (50%); compliance with a registry is assumed to be 90%.
| Scenarios                                                                 | Discounted costs per woman (USD) | Discounted life-years per woman | Cost-effectiveness ratio (USD/LYS) |
|--------------------------------------------------------------------------|----------------------------------|---------------------------------|-----------------------------------|
| No vaccination or screening                                              | $93.02                           | 30.5418                         | -                                 |
| 2x-lifetime HPV self-sampling                                           | $126.98                          | 30.5509                         | $3,712.74                         |
| 2x-lifetime HPV self-sampling + triage                                  | $124.00                          | 30.5507                         | $3,460.04                         |
| 5-yearly HPV self-sampling                                              | $221.10                          | 30.5609                         | $9,412.00*                        |
| 5-yearly HPV self-sampling + triage                                     | $213.50                          | 30.5597                         | $9,944.44*                        |
| 2x-lifetime HPV self-sampling (no registry)                             | $126.45-126.78                   | 30.5471-30.5495^                | $4,311.77-6,351.62^               |
| 2x lifetime HPV self-sampling + triage (no registry)                    | $124.46-125.29                   | 30.5462-30.5488^                | $4,476.51-7,303.16^               |

Table F2. Cost-effectiveness of screening unvaccinated cohorts across Malaysia for 2023-2100. All values are a yearly average.

Note that 2x-lifetime HPV self-sampling and 2x-lifetime + HPV self-sampling + triage uses twice-lifetime screening at ages 35 and 45 in Peninsular Malaysia and in urban East Malaysia; for rural East Malaysia, once-lifetime at age 35 point-of-care testing is used (see Methods, main manuscript, for details). Note also that 5-yearly HPV self-sampling and 5-yearly HPV self-sampling + triage uses five-yearly screening for ages 30-65 in Peninsular Malaysia and in urban East Malaysia; for rural East Malaysia, thrice-lifetime at age 30, 40 and 50 point-of-care testing is used (see Section H for details).

* ICER versus equivalent 2x-lifetime strategy.

^ Ranges for “no registry” scenarios indicate the upper (75%) and lower bound compliance assumptions (50%); compliance with a registry is assumed to be 90%.
Section G. Supplementary Results: twice-lifetime screening without a digital registry

The main analysis assumes a digital registry will be used for call and recall in a screening program and allow it to reach a compliance to follow-ups of 90% with a cost of $US 8.45 per woman initially screened. This reflects the compliance assumptions of 90% assumed for modeling performed to support the new WHO guidelines; this is unlikely to be achieved without that strong data support and monitoring systems that comes with a registry. To look at the individual importance of such a registry we model here the range of compliance that might be expected without a registry, namely 50-75%, with no associated costs of registration. The ranges in the following results therefore encapsulate both bivalent and quadrivalent options as well as the upper and lower bounds of compliance without a registry. The upper bound of compliance of 75% reflects a study in three Central American countries of cervical screening, which found an average compliance for triage and treatment of 73.7% and 72.0%, respectively.\(^3\)\(^5\) It also matched alternative assumptions of 75% explored in sensitivity analysis in modeling performed to support the 2021 WHO cervical cancer screening guidelines. Although this compliance was considered as a lower bound of compliance in the context of registry support, it could also be construed as an upper bound without registry support. The lower bound of 50% reflects the lowest compliance observed in the Central American countries, namely a compliance of 50.1% for triage follow-up in Honduras.\(^3\)\(^5\)

By the year 2070, twice-lifetime HPV testing with self-collection, no digital registry and current vaccination could avert 36,400-45,100 cases of cervical cancer and 17,500-21,900 deaths (Table G1). The addition of a digital registry therefore averts 3,000-8,400 (6-23%) more cases and 1,800-4,900 (8-28%) more deaths (Table 1). Without a digital registry, elimination would not be achieved until 2058-2066 (Fig. G1), which is 3-7 years slower than if a digital registry were available (Fig. 3). If primary HPV with a triage for HPV positive women were instead used but did not include a digital registry, 33,900-43,300 cases of cervical cancer and 16,100-20,900 deaths could be averted (Table G1). In this scenario, a digital registry averts 3,700-9,500 (9-28%) more cases and 2,200-5,700 (11-35%) more deaths (Table 1). National elimination would occur in 2060-2071 (Fig. G1), which is 4-9 years slower than if a digital registry were available (Fig. 3).
Table G2 shows that, regardless of whether triage is used, the implementation of HPV self-sampling without a digital registry would have a slightly lower budget impact, i.e. $US 2.2-3.3 million less per year (Table 1, Table G2). It would also be less cost-effective, i.e. the CER is $US/LYS 382-6,166 higher than if there were a digital registry, regardless of whether or not HPV positive women receive triage. If HPV positive women are triaged without a digital registry, the strategy may not even be cost effective (CER=$US/LYS 8,055-13,774, which the GDP of Malaysia $US 11,373 falls within the range of).

If HPV self-sampling without a digital registry were implemented, the number of precancer treatments would follow a similar pattern over time to if there were a registry (Fig. G2) but with a lower volume. For example, the peak in 2031 with no registry consists of 12,900-19,700 precancer treatments, which is 18-45% less than if there were a digital registry. A similar effect occurs for when HPV positive women are triaged, with a peak in 2031 of 5,000-8,800 if there were no registry, which is 37-63% less than if there were a digital registry. The number of colposcopies follow a similar pattern. However, these reductions are due to high-risk women scheduled for colposcopies and precancer treatments being lost to follow-up due to the lack of a registry for call and recall. This reduces the effectiveness of the program, and this is reflected by no or only slightly improved efficiency in terms of NNT to avoid a case or death, especially relative to the effect of adding triage for HPV positive women (see Section E).
## Table G1. Model predictions of cumulative cervical cancer cases and deaths and how they differ between scenarios.

Note that Vax + HPV self-sampling and Vax + HPV self-sampling + triage uses twice-lifetime screening at ages 35 and 45 in Peninsular Malaysia and in urban East Malaysia. However, for rural East Malaysia, once-lifetime at age 35 point-of-care testing is used. See Methods, main manuscript, for details.
Figure G1. National age standardized rates over time for the different scenarios; registry scenarios not shown here for clarity (but see Fig. 3). (a) Cervical cancer incidence. (b) Cervical cancer mortality.

Note that Vax + HPV self-sampling and Vax + HPV self-sampling + triage uses twice-lifetime screening at ages 35 and 45 in Peninsular Malaysia and in urban East Malaysia. However, for rural East Malaysia, once-lifetime at age 35 point-of-care testing is used. See Methods, main manuscript, for details.
Figure G2. Resource utilization over time as screening programs are scaled up. (a) Colposcopies. (b) Precancer treatments (inpatient and outpatient LEEP, and thermoablation).

Note that $Vax + HPV$ self-sampling and $Vax + HPV$ self-sampling + triage uses twice-lifetime screening at ages 35 and 45 in Peninsular Malaysia and in urban East Malaysia. However, for rural East Malaysia, once-lifetime at age 35 point-of-care testing is used. See Methods, main manuscript, for details.
| Scenarios                                           | Discounted costs per woman (USD) | Discounted life-years per woman | Cost-effectiveness ratio (USD/LYS) | Annual budget impact (USD millions) over 2020-2029 | Annual cost difference versus ‘Vax only’ (USD millions) |
|----------------------------------------------------|----------------------------------|--------------------------------|-----------------------------------|-----------------------------------------------------|---------------------------------------------------------|
| Vax only                                           | $74.57-77.38                     | 30.5490-30.5504                 | -                                 | $30.8-30.9M                                         | -                                                      |
| Vax + HPV self-sampling (no registry)              | $107.87-110.43                   | 30.5521-30.5546                 | $7,334.53-11,852.09               | $41.9-43.2M                                         | $11.1-12.3M (+36.0-39.8%)                              |
| Vax + HPV self-sampling + triage (no registry)     | $106.04-108.71                   | 30.5514-30.5540                 | $8,054.55-13,773.69               | $41.0-42.1M                                         | $10.2-11.3M (+33.3-36.4%)                              |

Table G2. Cost-effectiveness across Malaysia for 2023-2100 and budget impact over 2020-2029. All values are a yearly average.

Note that Vax + HPV self-sampling and Vax + HPV self-sampling + triage uses twice-lifetime screening at ages 35 and 45 in Peninsular Malaysia and in urban East Malaysia. However, for rural East Malaysia, once-lifetime at age 35 point-of-care testing is used. See Methods, main manuscript, for details

*ICER versus equivalent 2x-lifetime strategy.
Section H. Supplementary Results: 5-yearly screening with a digital registry

Recent Malaysian screening guidelines recommend screening every 5 years starting at age 30.36 Therefore, we also performed modeling analysis for Malaysia at ages 30-65 every 5 years, all else being equal. Given the remoteness of rural East Malaysia, we modeled thrice-lifetime screening at ages 30, 40, 50 with all else being equal.

By the year 2070, 5-yearly primary HPV testing with self-collection, a digital registry and current vaccination could avert 81,100-82,500 cases of cervical cancer and 41,000-41,400 deaths (Table H1). The addition of 5-yearly screening therefore represents a 156-200% increase in cases averted and 196-250% increase in deaths averted versus vaccination alone. It is also a 72-81% increase in cases averted and 75-83% increase in deaths averted versus twice-lifetime HPV screening with vaccination (Table 1). By the year 2100, 5-yearly HPV self-sampling with vaccination could avert 167,200-170,400 cervical cancer cases and 85,300-86,200 deaths. The combination of current vaccination and 5-yearly HPV self-sampling could achieve elimination by 2038 (Fig. H1). This is 18-24 years faster than twice-lifetime screening with vaccination and 28-41 years faster than current vaccination alone. Mortality rates could level out at 0.2 per 100,000. If we instead scale-up using 5-yearly primary HPV with a triage for HPV positive women, there would be 2,500-2,800 more cervical cancer cases and 900-1,000 more deaths (Table H1) by 2070 than the strategy in which all HPV positive women are referred to colposcopy. The ASR of incidence and mortality would level out at similar values, with national elimination also occurring in 2038.

Table H2 shows that the implementation of 5-yearly HPV self-sampling is not cost-effective, with an ICER of $US/LYS 12,468-13,448, which is >1xGDP pc of Malaysia, i.e. $US 11,373; this is also true for HPV self-sampling with triage of HPV positive women ($US/LYS 12,062-12,882). This could partly be due to the unit costs for HPV DNA (Section E), which are based on current trials, and are likely to be considerably lower when scaled up to a national program with bulk purchasing. Furthermore, the time horizon of this analysis extends out to 2100 when all of the population would be vaccinated. In contrast, for unvaccinated cohorts, 5-yearly screening would indeed be cost-effective (Section F). The average budget impact of vaccination and HPV self-sampling with triage would be $US 72.1 million per year, >60%
more than twice-lifetime screening (Table 2) and >130% more than that of current vaccination only. Not using triage would further increase this by $US 2.3 million per year.

If 5-yearly HPV self-sampling were implemented in addition to current vaccination, the number of precancer treatments (Fig. H2) would increase from 36,000-36,300 in the year 2023 (the first screening program year) to a peak of 61,500-70,600 in 2046 (after screening coverage is scaled up in 2030), and decrease to 46,500-56,500 by 2100. The peak occurs in line with the final screening coverage scale-up to 90% in 2045; this is in contrast to twice-lifetime screening where the peak occurs in 2031, in line with scale-up to 70% coverage in 2030. This is because the competing effect of increasingly vaccinated populations has a greater impact when screening frequency is less. The 5-yearly HPV-based screening also has a higher peak compared to twice-lifetime screening, being >2.5x more per annum. The number of colposcopies follow a similar pattern. If vaccination and 5-yearly HPV self-sampling with triage for HPV positive women were instead implemented, the number of precancer treatments is greatly reduced, with the peak yearly number of precancer treatments being 28,100-33,600, with a similar reduction in colposcopies. This effect is even greater than with twice-lifetime screening, and results in similar resource use to twice-lifetime HPV screening with no triage.
| Scenarios                                      | Cumulative number | Reduction versus no vaccination or screening | Reduction versus current vaccination |
|-----------------------------------------------|-------------------|---------------------------------------------|-------------------------------------|
|                                               | Year 2070         |                                             |                                     |
|                                               | Cases  | Deaths | Cases       | Deaths       | Cases  | Deaths       |
| No vax or screening                           | 124,900 | 60,100 | 27,000-32,200 | 11,700-14,000 |
| Vax only                                      | 92,700-97,800 | 46,100-48,400 | 81,100-82,500 | 41,000-41,400 | 50,400-54,100 | 27,400-29,300 |
| Vax + 5-yearly HPV self-sampling              | 42,300-43,800 | 18,700-19,100 | 41,000-41,400 | 47,900-51,300 | 26,500-28,300 |
| Vax + 5-yearly HPV self-sampling + triage     | 44,800-46,600 | 19,600-20,100 | 78,300-80,100 | 40,000-40,500 | 47,900-51,300 | 26,500-28,300 |
|                                               | Year 2100         |                                             |                                     |
|                                               | Cases  | Deaths | Cases       | Deaths       | Cases  | Deaths       |
| No vax or screening                           | 218,800 | 106,800 | 82,500-97,000 | 39,000-46,200 |
| Vax only                                      | 121,800-136,300 | 60,600-67,700 | 167,200-170,400 | 85,300-86,200 | 73,300-84,600 | 40,000-46,300 |
| Vax + 5-yearly HPV self-sampling              | 48,500-51,600 | 20,600-21,500 | 167,200-170,400 | 85,300-86,200 | 69,300-79,700 | 38,400-44,400 |
| Vax + 5-yearly HPV self-sampling + triage     | 52,500-56,600 | 22,100-23,300 | 162,200-166,300 | 83,400-84,600 | 69,300-79,700 | 38,400-44,400 |

Table H1. Model predictions of cumulative cervical cancer cases and deaths and how they differ between scenarios.

Note that 5-yearly HPV self-sampling and 5-yearly HPV self-sampling + triage uses five-yearly screening for ages 30-65 in Peninsular Malaysia and in urban East Malaysia; for rural East Malaysia, thrice-lifetime at age 30, 40 and 50 point-of-care testing is used (see Section H for details).
Figure H1. National age standardized rates over time for the different scenarios. (a) Cervical cancer incidence. (b) Cervical cancer mortality.

Note that 2x-lifetime HPV self-sampling and 2x-lifetime + HPV self-sampling + triage uses twice-lifetime screening at ages 35 and 45 in Peninsular Malaysia and in urban East Malaysia; for rural East Malaysia, once-lifetime at age 35 point-of-care testing is used (see Methods, main manuscript, for details). Note also that 5-yearly HPV self-sampling and 5-yearly HPV self-sampling + triage uses five-yearly screening for ages 30-65 in Peninsular Malaysia and in urban East Malaysia; for rural East Malaysia, thrice-lifetime at age 30, 40 and 50 point-of-care testing is used.
Figure H2. Resource utilization over time as screening programs are scaled up. (a) Colposcopies. (b) Precancer treatments (inpatient and outpatient LEEP, and thermoablation).

Note that 2x-lifetime HPV self-sampling and 2x-lifetime + HPV self-sampling + triage uses twice-lifetime screening at ages 35 and 45 in Peninsular Malaysia and in urban East Malaysia; for rural East Malaysia, once-lifetime at age 35 point-of-care testing is used (see Methods, main manuscript, for details). Note also that 5-yearly HPV self-sampling and 5-yearly HPV self-sampling + triage uses five-yearly screening for ages 30-65 in Peninsular Malaysia and in urban East Malaysia; for rural East Malaysia, thrice-lifetime at age 30, 40 and 50 point-of-care testing is used (see Section H for details).
| Scenarios                                      | Discounted costs per woman (USD) | Discounted life-years per woman | Cost-effectiveness ratio (USD/LYS) | Annual budget impact (USD millions) over 2020-2029 | Annual cost difference versus ‘Vax only’ (USD millions) |
|-----------------------------------------------|----------------------------------|---------------------------------|-----------------------------------|-----------------------------------------------------|-------------------------------------------------------|
| Vax only                                      | $74.57-77.38                     | 30.5490-30.5504                 | -                                 | $30.8-30.9                                          | -                                                     |
| Vax + 5-yearly HPV self-sampling              | $209.94-213.88                   | 30.5624-30.5626                 | $12,468.35-13,447.95*             | $74.3-74.5M                                         | $43.5-43.6M (+141.3-141.3%)                           |
| Vax + 5-yearly HPV self-sampling + triage     | $202.44-205.94                   | 30.5619-30.5622                 | $12,062.34-12,881.95*             | $72.1-72.1M                                         | $41.2-41.3M (+133.6-134.2%)                           |

Table H2. Cost-effectiveness across Malaysia for 2023-2100 and budget impact over 2020-2029. All values are a yearly average.

Note that 5-yearly HPV self-sampling and 5-yearly HPV self-sampling + triage uses five-yearly screening for ages 30-65 in Peninsular Malaysia and in urban East Malaysia; for rural East Malaysia, thrice-lifetime at age 30, 40 and 50 point-of-care testing is used.

*ICER versus equivalent 2x-lifetime strategy.
Section I. Supplementary Results: Sensitivity analysis

We used one-way sensitivity to assess the uncertainty in the CER and the number of deaths averted for both screening algorithms. They include varying the costs of HPV DNA test kits by +/-35%, varying registry costs by +/-30%, and varying vaccine costs by +/-20%. We also looked at situations in which compliance for any follow-ups improved to 95%. Finally, we modeled an alternative screening scenario for Vax + HPV self-sampling in which cytology was performed to inform management of women with no visible transformation zone at colposcopy.

Varying the registry costs, HPV DNA test costs and vaccine costs all resulted in HPV-based screening with self-collection remaining cost-effective and having a similar CER (Table I1). Assuming a higher follow-up compliance of 95% resulted in an additional 600-700 lives saved over the next 50 years and was slightly more cost-effective than baseline. Using the alternative post-colposcopy management in which women without a visible transformation zone receive cytology, was still cost-effective.

| Parameter variations | Deaths averted by 2070 versus Vax only | Cost-effectiveness ratio (USD/LYS) over 2023-2100 |
|----------------------|---------------------------------------|-----------------------------------------------|
|                      | Vax + HPV self-sampling                | Vax + HPV self-sampling + triage              |
| None (baseline)      | 9,900-10,900                          | 6,953.32-7,549.10                             |
|                      | 9,300-10,300                          | 6,935.36-7,607.96                             |
| -35% HPV DNA test kit costs | 9,900-10,900                          | 5,531.61-5,984.36                             |
|                      | 9,300-10,300                          | 5,409.50-5,924.87                             |
| +35% HPV DNA test kit costs | 9,900-10,900                          | 8,375.02-9,113.85                             |
|                      | 9,300-10,300                          | 8,461.22-9,291.05                             |
| -30% Registry costs | 9,900-10,900                          | 6,778.31-7,355.06                             |
|                      | 9,300-10,300                          | 6,749.45-7,400.80                             |
| +30% Registry costs | 9,900-10,900                          | 7,129.05-7,743.96                             |
|                      | 9,300-10,300                          | 7,122.03-7,815.98                             |
| -20% vaccine costs  | 9,900-10,900                          | 6,953.32-7,549.10                             |
|                      | 9,300-10,300                          | 6,935.36-7,607.96                             |
| +20% vaccine costs  | 9,900-10,900                          | 6,953.32-7,549.10                             |
|                      | 9,300-10,300                          | 6,935.36-7,607.96                             |
| 95% compliance       | 10,500-11,600                         | 6,617.66-7,197.58                             |
|                      | 10,100-11,200                         | 6,448.83-7,096.25                             |
| Alternative Vax + HPV self-sampling flowchart* | 9,700-10,800                          | 7,110.75-7,710.12                             |
|                      | 9,300-10,300                          | 6,935.36-7,607.96                             |
| Gradual screening scale-up^ | 9,900-10,900                          | 7,407.26-8,131.40                             |
|                      | 9,300-10,300                          | 7,466.79-8,249.52                             |
Table I. Outcomes of sensitivity analysis. See Methods, main manuscript, for further details on the parameter variations.

*Cytology was taken for any women with a transformation zone that wasn’t visible at colposcopy.

^Coverage increases annually by 10% from 2024, reaching 70% in 2030, and then increases to 90% in 2045. Note that Vax + HPV self-sampling and Vax + HPV self-sampling + triage uses twice-lifetime screening at ages 35 and 45 in Peninsular Malaysia and in urban East Malaysia. However, for rural East Malaysia, once-lifetime at age 35 point-of-care testing is used. See Methods, main manuscript, for details.
Section J. Comparison with previously published work

We recently obtained health impact estimates for Malaysia as part of a global modeling exercise of 181 countries. Our global study modeled both the status quo and an intervention that used twice-lifetime HPV screening and nonavalent vaccination. For the status quo, the global modeling predicted elimination would not occur (whereas this study found that current vaccination could achieve elimination in 2066-2079), higher cumulative case numbers over 2020-2069 (136,150 versus 92,700-97,800 here), and higher ASR of incidence by 2100 (4.5 per 100,000 women versus 2.7-3.7 per 100,000 here). This likely due to the fact that (1) the global study assumed vaccination started in 2020, ten years later than this study; and (2) the global study was calibrated to Globocan 2012 data, which estimated a significantly higher burden-of-disease than the Globocan 2018 data used as part of the calibration here. For the intervention, the global modeling predicted a later timeline to elimination (2065-2070 versus 2055-2059 here) and lower cumulative cases averted due to screening over 2020-2069 (12,752 versus 15,900-17,800 here), yet lower ASR incidence by 2100 (0.8 per 100,000 women versus 1.7-2.4 per 100,000 here). The lower case numbers averted and longer timeframe to elimination in the global study may be due to less favourable screening assumptions at play in the short term, along with delayed initiation of vaccination, ten years earlier than our study, and higher starting values of ASR resulting from Globocan 2018 calibration. The lower ASR is likely due to the long-term added benefit 100% coverage of nonavalent vaccination.
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