Harvard School of Public Health
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Harvard Cervical: Model Profile

Harvard T.H. Chan School of Public Health

Contact

Jane Kim (jkim@hsph.harvard.edu)

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Version Table

Version	Date	Notes
1.0.00	2025-09-30	Major update
HI.001.03202020.9999	2020-03-20	Historical release

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Readers Guide

Reader's Guide

Core Profile Documentation

These topics will provide an overview of the model without the burden of detail. Each can be read in about 5-10 minutes. Each contains links to more detailed information if required.

Model Purpose
This document describes the primary purpose of the model.

Model Overview
This document describes the primary aims and general purposes of this modeling effort.

Component Overview
A description of the basic computational building blocks (components) of the model.

Parameter Overview
Describes the basic parameter set used to inform the model, more detailed information is available for each specific parameter.

Assumption Overview
An overview of the basic assumptions inherent in this model.

Output Overview
Definitions and methodologies for the basic model outputs.

Results Overview
A guide to the results obtained from the model.
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Model Purpose

Summary

The Harvard HPV and cervical cancer models simulate human papillomavirus (HPV) infection and possible progression to cervical cancer. The models have been used to inform optimal strategies to reduce cervical cancer morbidity and mortality worldwide.

Purpose

Simulation modeling is a useful (and perhaps even necessary) tool for informing cervical cancer policy. Consider the following:

- The pathway to a case of cervical cancer begins with a sexually-transmitted HPV infection.
- There are several subtypes of HPV, some more carcinogenic (e.g. HPV types 16 and 18) than others.
- An HPV infection can clear on its own, and thus trigger an immune response that reduces future infection of the same HPV type.
- Infections that don't clear on their own can progress to pre-cancerous lesions, which if not screen-detected and treated can progress to cervical cancer. This progression could take decades to occur.
- High-risk HPV infections (i.e. the most carcinogenic subtypes) can be prevented via a prophylactic vaccine, usually administered before sexual debut. However, the efficacy of the vaccine wanes over time.

All of these aspects can be incorporated into a simulation model. The model can then be used to determine and evaluate current and potential interventions to reduce cervical cancer morbidity and mortality.

The Harvard team utilizes two distinct models which can be run independently or can be linked.

1. **HARVARD-CC** is our workhorse model. It is initially run as a comprehensive cervical cancer natural history model for a specific population of interest. Interventions can then be overlaid, namely HPV vaccination and/or cervical cancer screening programs. These interventions are evaluated on their health benefits to the population, balanced by the costs to implement them.
2. **HARVARD-HPV** is a dynamic agent-based model of HPV transmission. It simulates heterosexual partnership acquisition and dissolution in a population of interest, and then the subsequent spread of HPV in that population. HPV vaccination can then be introduced. Importantly, indirect benefits of vaccination (i.e. herd immunity) are able to be captured in this model, alongside direct benefits.

The models are equipped to be able to adapt to new scientific developments and the research questions they pose, such as improvements in vaccine efficacy or in screening technologies.

The Harvard models have been used to answer policy questions such as:

- Optimal age to begin a vaccination program.
- Cost-effectiveness of including boys in a vaccination program.
- Impact of switching to a one-dose vaccine.
- Evaluation of current and proposed screening algorithms (screening frequency, screening start age, which procedures to use and when to use them, how often to follow up positive results, screening stop age) in various contexts (e.g. vaccinated vs. unvaccinated populations, low cervical cancer burden countries vs. high burden, etc.). This includes informing the U.S. Preventive Services Task Force in determining national cervical cancer screening guidelines.
- Examination of racial disparities in cervical cancer in the United States.

- Timing of potential cervical cancer elimination, given ongoing vaccination and screening.

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Model Overview

Model Overview

Summary

This document provides an overview of the two Harvard models (HARVARD-CC and HARVARD-HPV), focusing on their origin stories and their current usage.

Purpose

Using an iterative approach combining empirical data with decision analytic modeling, the Harvard models serve as tools to provide policy-makers with evidence on the effectiveness of different prevention methods and screening for HPV-induced cervical cancer. See Model Purpose for more details.

Background

HARVARD-CC is a comprehensive natural history model that guides the development and evaluation of HPV vaccines and cervical cancer screening programs in order to accelerate the implementation of sustainable, cost-effective strategies to reduce morbidity and mortality from cervical cancer. The model simulates a setting-specific cohort of women one at a time over their lifetime, subject to different screening and vaccination strategies.

HARVARD-CC was originally developed to examine U.S.-specific policy questions surrounding cervical cancer screening. Over the years, the model has expanded to address key scientific developments in this field (including the HPV vaccine and new screening technologies), as well as to evaluate population-level effects for multiple birth cohorts. It has also expanded to address global HPV prevention and reduction strategies in numerous international settings. Currently, HARVARD-CC is continuously being adapted as research emerges regarding the natural history of HPV infections and progression to cervical cancer.

The advent and evolution of the HPV vaccine facilitated the need for the HARVARD-HPV model. The model simulates an entire population of women and men at once, allowing heterosexual partnerships to form and dissolve based on the overall sexual behavior of the population. HPV infection is then seeded and allowed to spread. Once HPV prevalence reaches a steady state, vaccine programs can be introduced, and the direct and indirect effects of vaccination over time can be monitored. Direct benefits are tied to the characteristics of the vaccine (e.g. coverage, efficacy, and waning), while indirect benefits (i.e. herd immunity, or benefits gained by unvaccinated individuals through the presence of vaccinated individuals) are more complex. Indirect benefits are additionally a function of the population's sexual behavior.

Linking the two Harvard models involves taking the calculated benefits of vaccination from HARVARD-HPV (represented as reductions in HPV incidence by cohort) and applying them to HPV incidence rates in HARVARD-CC. HARVARD-CC then carries forward the HPV incidence reductions and translates them into cervical cancer reductions under various screening scenarios.

Both models are evaluated as first-order Monte Carlo simulations, in which events are simulated for a sequence of individuals using random numbers based on event probabilities (e.g., the probability of a woman with persistent HPV-16 and cervical lesions progressing to invasive cancer), thus producing individual "case histories". This method permits the risk of any event to depend on an individual's history, an important attribute when comparing screening, vaccination, and combined screening and vaccination. The models maintain a tally of all clinical events and accrued costs, as well as composite month-by-month totals. By running large numbers of simulated cases, stable estimates of long-term outcomes are produced in the form of a distribution of survival values and lifetime costs.

See Component Overview for more details on the structure of each model; see Parameter Overview for more details on the inputs for each model; see Output Overview for more details on model outputs.

Assumption Overview

Summary

Both HARVARD-CC and HARVARD-HPV make several (but necessary) assumptions in each of their components.

Background

A number of assumptions are necessary for our models. HARVARD-CC has been adapted to numerous countries, each representing a specific epidemiologic background. Across these country-specific models, however, we hold a common "base" assumption regarding the underlying mechanism of the natural history of HPV infections and cervical cancer, allowing for variations in the level or magnitude of these probabilities through setting-specific multipliers. Because of this assumption, a set of common inputs (baseline probabilities) is used across all country-specific models (e.g. HPV infection incidence and clearance, development of precancer and cancer, and mortality from cancer as well as non-cancer causes), with setting-specific multipliers applied to generate outcomes similar to primary epidemiologic data.

In addition to country-specific models the HARVARD-CC model has been adapted to reflect data specific to Black women in the United States. This version of the model uses the US common inputs related to HPV natural history, but also incorporates Black-race-specific data for various demographic and health-care specific inputs.

Assumption Listing

HARVARD-CC

Below is a list of some of the assumptions made by HARVARD-CC.

- The model starts as a first-order microsimulation of each individual starting at age 9 prior to acquisition of HPV infections.
- Death is stratified to reflect mortality due to country-specific, age- and sex-specific deaths from all-causes and invasive cervical cancer; women may die of cancer or of any other cause at any time in life.
- When the model is run as a single birth cohort, the time horizon of the analysis incorporates each woman's entire lifetime and is divided into equal one-month increments during which women "transition" from one health state to another.
- When HARVARD-CC is run for population-level analyses, we simulate multiple birth cohorts (current and future) over their lifetimes and post-process age- and cohort-effects to the calendar year.
- Consistent with the latest scientific evidence that HPV is responsible for all cervical cancer, we assume that invasive cancer will not occur in the absence of infection with an oncogenic HPV type.
- The model simulates the natural history of cervical carcinogenesis, and does not include other outcomes of HPV infection (i.e., anal cancer, head and neck cancer, etc.).
- We assume that our probabilities of age-related HPV incidence serve as a proxy for both age and sexual risk in the base case as well as the HPV type distributions among a woman's sexual partner(s).
- CIN1 is not an explicit health state in the model, as CIN1 is interpreted as a microscopic manifestation of acute HPV infection and is incorporated into the HPV-infected state.
- Among women with CIN regression, we assume a proportion will continue to have a detectable HPV infection.
- Individuals can acquire independent infections with multiple HPV genotypes, with each type able to progress and regress independently. However, if a woman develops a type-specific cancer, other

concurrent HPV infections and associated precancers are no longer at risk of progressing/regressing.

- The model does not currently simulate HIV separately; any deaths attributed to HIV/AIDS are included in non-cancer mortality.
- If a woman with undetected cancer undergoes a hysterectomy, the procedure detects the cancer.
- Monthly transition probabilities are a function of baseline probabilities (often duration-based or age- and/or type-specific, calculated from primary data and published literature) and the application of multipliers (sometimes type-specific and calibrated through a parameter search strategy that draws sets randomly from a uniform distribution).
- Screening tests are always adequate (e.g., does a woman's sample need to be re-collected because the original sample was inadequate for evaluation), meaning sufficient for analysis.
- If a diagnostic colposcopy detects a lesion, a biopsy is automatically performed; if no lesions are found in colposcopy, the woman will not receive a biopsy.
- Successful treatment returns women to normal or HPV, i.e. not all women lose their infections.
- Women with detected cancer are not screened. Women with detected cancer are referred to secondary or tertiary hospitals and follow their stage-specific prognosis.
- All vaccine doses are administered at the same time.
- There is no correlation between natural immunity and vaccine immunity.
- Vaccination does not require a first infection for activation, as in natural immunity.
- As HARVARD-CC is static, herd Immunity is not captured directly through sexual mixing, but may be applied ad-hoc to the proportion of unvaccinated women.
- Cost per vaccinated women includes three doses, wastage, delivery, and programmatic costs. We assume the cost of the vaccine increases linearly with the number of doses. We assume this cost includes health provider time delivering the vaccine, vaccine wastage, disposable supplies, equipment, and facilities as well as patient time and transport.
- Screening costs are categorized costs into direct medical costs (e.g., staff, disposable supplies, equipment, and specimen transport), women's time costs (time spent traveling, waiting, and receiving care), transportation costs, and programmatic costs.
- Costs for diagnosis and treatment, including costs associated with false-positive results, referral of women ineligible for cryosurgery, and treatment complications are included.
- Cancer treatment costs are applied at the time of cancer diagnosis. Additional monthly surveillance costs (among those remaining alive) and a 1-time cost of dying can be applied.
- Both costs and benefits (life expectancy) are discounted and can be set to begin at a specified age (or analysis year for population-level analyses).

HARVARD-HPV

Below are some selected assumptions made by HARVARD-HPV:

- The simulation begins with a fixed-size, HPV-free population of males and females of all ages, based on a setting's population pyramid.
- HPV infection of each type is seeded by infecting a small amount of individuals, then allowing 100 years of HPV transmission to reach a steady state of HPV in the population.
- No immigration inflow or outflow of the population is considered.

- Individuals can acquire independent infections with multiple HPV genotypes.
- Natural immunity is acquired after clearing an HPV infection. Subsequent acquisition and clearance of the same genotype can lead to increased natural immunity for that type.
- SAC (i.e. representing an individual's risk of acquiring HPV) is a static attribute for individuals. An individual's SAC is assigned at birth and does not change with age. The entire population is categorized into four SAC groups, ranging from low to very high sexual activity.
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- Partnership formation driven by males, i.e. the model simulates males looking for female partners.
- HPV type-specific transmission probabilities (per-partnership, per-month) can be increased by a multiplier at younger ages, but is otherwise constant over the population.
- Vaccine protection may wane assuming a normal distribution (mean and standard deviation) for when waning begins.

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Parameter Overview

Summary

This document provides an overview of the parameters (inputs) of HARVARD-CC and HARVARD-HPV. HARVARD-CC will be described in its entirety first, followed by HARVARD-HPV.

Background

To parameterize HARVARD-CC and the HARVARD-HPV, we determine initial plausible point estimates for each model input parameter based on data from the published literature. To the extent possible, primary data from the specified country are used.

Some parameters are not observable (e.g. monthly probability of CIN progression); and hence, point estimates do not exist for these parameters. A calibration process is necessary to assign values to these parameters. See Results for a summary of calibration results.

Parameter Listing Overview

HARVARD-CC

The data-driven parameters of HARVARD-CC can be divided into four categories: natural history, cost-effectiveness, vaccination, and screening.

Natural history parameters include:

- Mortality rate: monthly, by age.
- Hysterectomy rate: monthly, by age.
- Cancer mortality rate: monthly, by duration of disease and further adjusted by age; separate for undetected, symptom detected, and screen detected.
- HPV incidence: monthly, by age and HPV type; calibrated for each setting.
- Disease progression: monthly, by duration, for all disease states (CIN2, CIN3, CA1, CA2, CA3, CA4); calibrated for each setting.
- Disease regression: monthly, by duration, for all disease states; can be calibrated for each setting, but currently not.
- Cancer symptom detection: monthly, by age and cancer stage.
- Natural immunity: both in terms of whether immunity is conferred (immune factor) and the amount of immunity (immune degree), by HPV type; calibrated for each setting.

Cost-effectiveness parameters include:

- Screening costs: procedures, office visits, and patient time.
- Vaccine costs: per dose.
- Health state costs: cancer costs either by stage of detection (one-time lifetime cost), or on a per-year basis (initial year, ongoing years, and final year).
- Age-based quality of life utilities.
- Cancer disutilities: by stage and by year (initial year, ongoing years, and final year).
- Screening procedure disutilities.

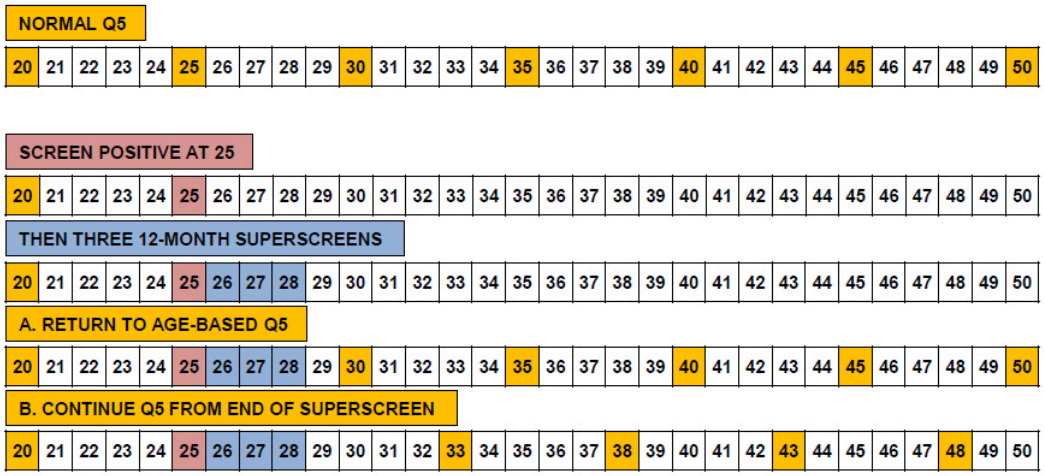
Vaccination parameters include:

- Age of vaccination.
- Probability of receiving vaccine (i.e. coverage), by dose.
- Efficacy of vaccine: both in terms of whether protection is conferred (vaccine factor) and the amount of protection (vaccine degree), by dose.
- Wane start: time after receiving the vaccine at which protection begins to wane.
- Wane time: time after wane start until protection reaches zero.

Screening parameters include:

- The specific screening algorithm to follow; there are currently 100 screening algorithms programmed into HARVARD-CC. Algorithms define a primary screening modality and then define subsequent procedures for each screening result.
- Screening start, end, and switch ages (some screening strategies switch their modality at a certain age).
- Screening compliance: for primary screens, follow-up screens, colposcopy, and treatment.
- Screening interval between primary screens.
- Screening interval for surveillance screens following an abnormal result (i.e. superscreening), as well as the number of consecutive negative surveillance screens required before returning to routine screening, and whether to return to age-based screening or continue screening from the end of superscreening. See below more details.
- Screening interval for reduced screening due to persistent normal results (i.e. subscreening).
- Screening procedure test performance (sensitivity and specificity): for cytology, HPV DNA testing, co-testing, VIA, and colposcopy and biopsy.

The following graphic describes superscreening in more detail.



The first bar shows routine Q5 (e.g. five-yearly interval) screening beginning at age 20, with the golden boxes indicating a screen. The next bar shows a scenario with a positive screen test at age 20 (red box), then three surveillance screens (e.g. superscreening) 12-months apart (blue boxes). The third bar shows return to age-based screening, so screening continues at ages 30, 35, 40, 45, and 50; in other words, the ages that screening would have occurred without the positive screen. The final bar, in contrast, shows resetting the screening interval at the end of superscreening; in other words, resuming Q5 at age 28, resulting in screens at 33, 38, 43, and 48.

HARVARD-HPV

The data-driven parameters of HARVARD-HPV can be categorized into three main types: natural history, sexual mixing, and vaccination.

Natural history parameters include:

- Mortality rate: annual by age; separate for women and men.
- Fertility rate: annual by age, although model can also be run with a constant population size (e.g. birth rate = death rate).
- HPV transmission: monthly probability by type from infected individual to non-infected partner (“per partnership per month”); separate for women-to-men and men-to-women; calibrated for each setting.
- HPV regression: probability by duration of infection and by type; separate for women and men.
- Degree of natural immunity: protection an individual receives from being reinfected with an HPV type after having previously cleared it; separate for women and men; calibrated for each setting.

- Natural immunity boost: option to boost natural immunity exponentially after each subsequent infection and clearance.

Sexual mixing parameters include:

- SAC distribution: population-level distribution of SAC (sexual activity class) by age; separate for women and men.
- Sexual debut: probability of sexual debut, by age and SAC; separate for women and men.
- Number of partners: number of partners for the next 12 months by age and SAC, will be further adjusted by partnership probability; separate for women and men.
- Partnership probability: the probability that a partnership actually forms, by age and SAC.
- Partnership durations: Weibull parameters governing the length of a partnership, by age and SAC.
- Partnership dissolution: alternative to partnership durations, monthly probability of a partnership dissolving, by age and SAC.
- Assortativity by age: preference for finding partner in same age bucket, one age bucket below, or one age bucket above.
- Assortativity by SAC: preference for finding partner in same SAC, one SAC below, or one SAC above.

Vaccination parameters include:

- Start year: simulation year to being vaccination program.
- Mode: Routine birthday, routine timepoint, or campaign.
- Coverage table: vaccine coverage level for every age at every year; separate for women and men; separate for each dose.
- Efficacy: vaccine efficacy degree (partial protection per individual), by HPV type and number of doses; separate for women and men.
- Waning start: number of years until vaccine waning begins, by dose; separate for women and men.
- Waning total: number of years for vaccine to lose all effectiveness, by dose; separate for women and men.

Component Overview

Summary

This document provides specifics on the structure and components of HARVARD-CC and HARVARD-HPV. HARVARD-CC will be described in its entirety first, followed by HARVARD-HPV.

Overview

Both the HARVARD-CC and HARVARD-HPV models simulate individuals becoming infected with HPV, albeit very differently. HARVARD-CC is a stochastic model that creates individual women one at a time, then simulates their HPV-related natural history. Potential progression to cervical cancer, as well as interventions to prevent progression to cervical cancer through screening and vaccination, are the critical components of HARVARD-CC. HARVARD-HPV creates an entire population of women and men at once. Their interactions to transmit HPV to each other, as well as vaccination to prevent transmission are the critical components of HARVARD-HPV.

Component Listing

HARVARD-CC

HARVARD-CC is an empirically-calibrated stochastic first-order Monte Carlo simulation model of cervical cancer. The individual-based state-transition model reflects multiple HPV types, can explore interactions between screening and vaccination, and is able to be linked to the companion HARVARD-HPV transmission model allowing incorporation of herd immunity effects.

There are two main components of HARVARD-CC:

1. Natural History
2. Cervical Cancer Prevention

HARVARD-CC: Natural History

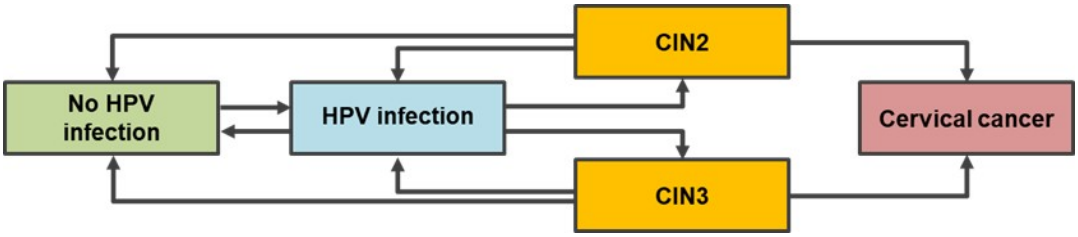
The natural history component includes: risk factors for cervical cancer (e.g., age of sexual debut), acquisition of type-specific HPV infections, probability of HPV persistence, risk of progression to (and regression from) precancerous lesions cervical intraepithelial neoplasia grades 2 and 3 (CIN2; CIN3), and progression to invasive cancer. Cervical cancer may be detected symptomatically or may progress to a more severe cancer stage.

Disease progression in the model is characterized as a sequence of monthly transitions between health states. HPV types are categorized as: high-risk type 16; high-risk type 18; high-risk type 31; high-risk type 33; high-risk type 45; high-risk type 52; high-risk type 58; other high-risk types, including 35, 39, 51, 56, 59, 66, 68, 73, and 82; and low-risk types, consisting of non-oncogenic types of HPV, including 6, 11, 26, 32, 34, 40, 42, 44, 53, 54, 55, 57, 61, 62, 64, 67, 69, 70, 71, 72, 81, 83, and 84. Health states reflecting invasive cancer include both detected and undetected cancer; a cancer is considered detected when either symptoms lead to a correct diagnosis or a previously undiagnosed malignancy is detected by screening.

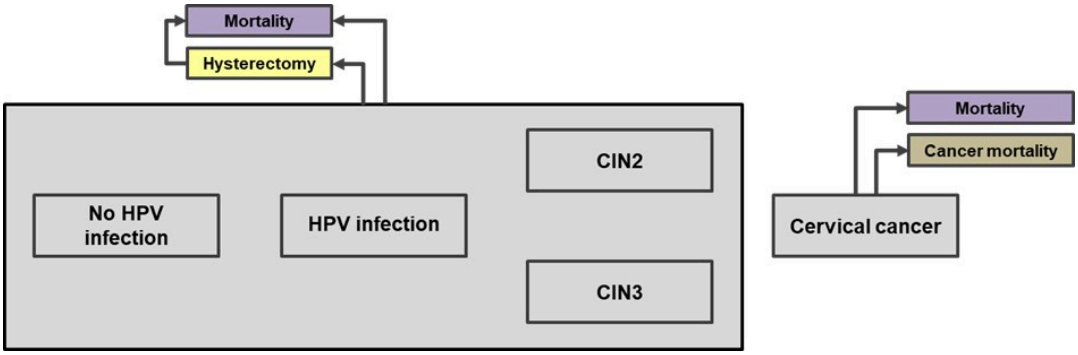
The probabilities governing these monthly transitions depend on age; HPV type; duration of HPV infection; type-specific natural immunity; as well as a woman's history of prior infection, previously treated CIN, and patterns of screening. Each month, simulated women can become infected with HPV and those with HPV infection may progress to (or regress from) cervical histopathologic changes that can be detected by screening or diagnostic procedures. Women with cervical intraepithelial lesions can progress, regress, or persist. Women who progress to invasive cancer can become symptomatic or can progress to more advanced stages of cervical cancer. All women are at risk of death from other causes. Women without cancer or with undetected cancer are additionally subjected to age-based hysterectomy rates. If a woman undergoes a hysterectomy, all HPV-related disease progression stops and they are only subject to the risk of death from other causes.

The natural history component is adapted to different epidemiologic settings by fitting (or calibrating) the model using the best available country-specific data, e.g., HPV prevalence, HPV type distribution in CIN2, CIN3 and cervical cancer.

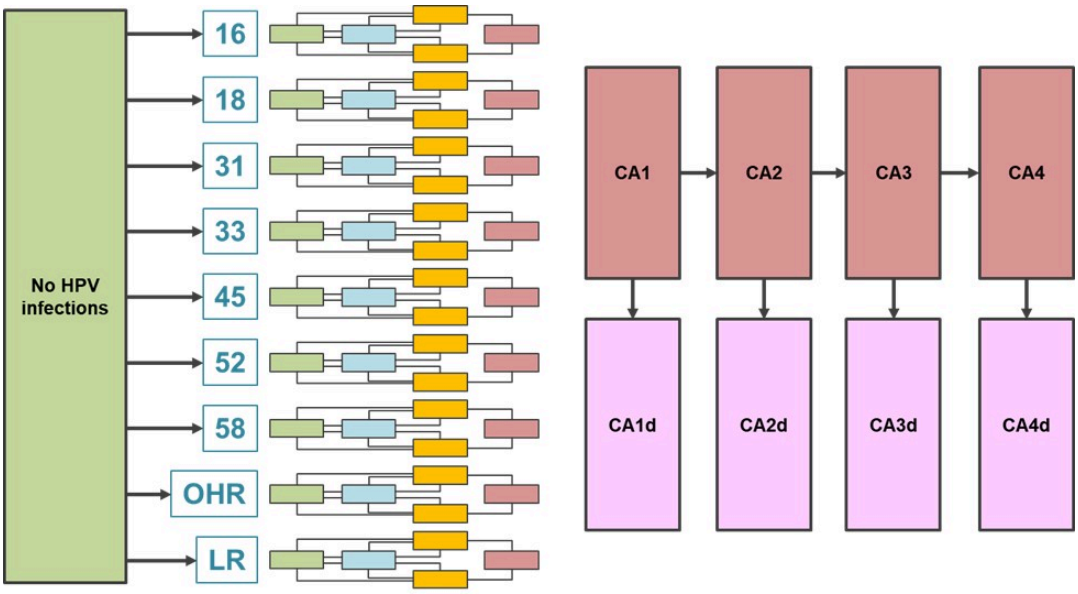
Below is a general schematic of transition states in the model.



The schematic can be modified to show the mortality and hysterectomy transitions.



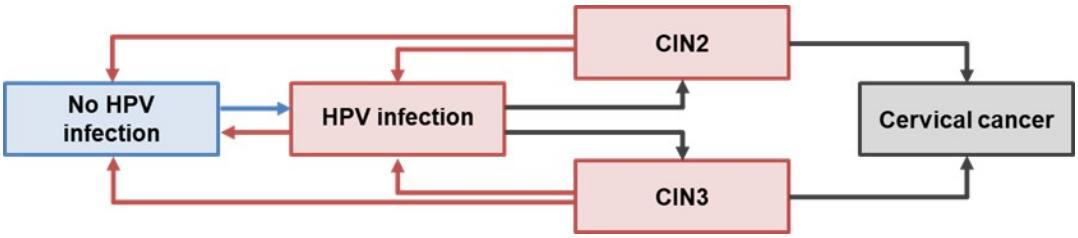
The schematic can again be modified to show the different HPV types HARVARD-CC simulates -- high-risk type 16; high-risk type 18; high-risk type 31; high-risk type 33; high-risk type 45; high-risk type 52; high-risk type 58; other high-risk types (OHR); and low-risk types (LR). Each HPV type can be acquired independently (i.e. individuals can be infected with multiple HPV types concurrently) and progress/regress at its own rate. If an HPV type reaches the Stage I Cervical Cancer state (CA1), the model enters into a cancer natural history component that no longer tracks HPV infection. In this component, cancers can progress (up to Stage IV) or can be symptomatically detected (CAd) and remain in that stage. Note that low-risk types cannot progress to cancer.



HARVARD-CC: Cervical Cancer Prevention

The cervical cancer prevention component includes: 1.) primary prevention (vaccination), and 2.) secondary prevention (screening to detect pre-cancerous cervical lesions with the possibility of treatment for lesions and cancer).

Returning to the general model schematic, vaccination affects the transition from no disease to a diseased state (blue boxes and arrows), and screening affects the transitions from diseased states to less serious or no disease states (red boxes and arrows).



HARVARD-CC can simulate an HPV vaccination program of the nonavalent vaccine, providing protection against high-risk types 16, 18, 31, 33, 45, 52, and 58, as well as low-risk types 6 and 11. Vaccination strategies vary according to: age of vaccination, vaccine coverage, vaccine efficacy and duration of immunity, number of doses, and magnitude of protection. Using these vaccine parameters, the direct protection from vaccination can be calculated on an individual-level and then aggregated among all simulated individuals. However, since there is no interaction between individuals, herd immunity (indirect protection is not able to be captured.

Screening, diagnosis, and treatment of precancerous disease in HARAVRD-CC occurs as a series of steps: starting with primary screening, moving to additional diagnostic workup which may vary based on the screening result, and finally to any necessary treatment of precancerous disease or ongoing surveillance of disease. Numerous aspects of both the ideal and realized clinical pathway can be altered in the model to address policy and programmatic questions.

HARVARD-CC models cervical cancer screening by individually programming in complex screening algorithms. These algorithms are very specific, with every possible result from a screening procedure having a detailed set of instructions on the next step to take.

To start at the beginning, there are four pieces of population-level information required to implement screening in the model: 1.) screening start age (what age to being screening), 2.) screening end age (what age to end screening), 3.) screening frequency (the amount of time between screens), and 4.) screening algorithm (the screening strategy itself).

Different screening algorithms vary in complexity, but at their core, they contain more or less the same pieces of information. These pieces of information are:

1. What is the primary screening procedure? In HARVARD-CC, the potential procedures are either a cytology, an HPV DNA test, or a combination co-test where both cytology and HPV test results are collected. In the past, the model has looked at VIA (visual inspection with acetic acid) for lower income countries. The model is also equipped to be able to handle future screening technologies.

2. For every potential result of the primary screening procedure, what is the next step? This includes defining the next procedure and the interval until that next procedure. For a negative screening result, the next procedure is usually returning for a primary screening procedure at the usual screening interval. For a positive screening result, the next procedure is usually an immediate follow-up confirmatory screen or a colposcopy to verify the presence of cervical lesions.

3. What is the follow-up procedure, and what is the next step for each potential result from the follow-up screen? The follow-up procedure could be a repeat cytology, HPV test, or co-test.

4. If a colposcopy is needed to verify a positive screening test, and the colposcopy is negative (indicating there are no cervical lesions), what is the subsequent surveillance procedure and interval to ensure an individual remains free of lesions?

5. If a colposcopy is positive (indicating the presence of cervical lesions), and the lesions are treated and removed, what is the subsequent surveillance procedure and interval to ensure an individual remains free of lesions?

6. Is there an age where the primary and follow-up screening procedures switch to different procedures?

Below is a snapshot of a portion of a “Microsoft Excel flow diagram” used to program a screening algorithm into HARVARD-CC. Note that for each procedure, every possible result has clear instructions on what the next step is and when to do it.

Strategy	Us6
Original Name	Us6 (HPV Primary; Cyto Reflex for any HR HPV)
Base	--

		Cytology		
		If result is...	*then do...*	*with screening schedule...*
Before Switch Age	PrimaryScreen1	NonCompliant	PrimaryScreen1	Routine 1. Keep to Regular screening schedule, or 2. Continue a SuperScreen schedule until X consecutive negative tests, or 3. Start a SubScreen schedule
		Fail	PrimaryScreen1	RescreenWait=0
		Negative	PrimaryScreen1	Routine
		ASCUS	FollowUpScreen1	FollowUpWait=0
		ACIN23	Verification1	VerifyWait=0
		LSIL	Verification1	VerifyWait=0
		HSIL	Verification1	VerifyWait=0

		HPV Test (Reflex)		
		If result is...	*then do...*	*with screening schedule...*
Before Switch Age	FollowUpScreen1	NonCompliant	PrimaryScreen1	Routine
		Fail	FollowUpScreen1	RescreenWait=0
		Negative	PrimaryScreen1	Routine
		LowRisk	PrimaryScreen1	Routine
		HighRisk	Verification1	VerifyWait=0
		HighRisk16	Verification1	VerifyWait=0
		HighRisk18	Verification1	VerifyWait=0

		HPV Test		
		If result is...	*then do...*	*with screening schedule...*
After Switch Age	PrimaryScreen2	NonCompliant	PrimaryScreen2	Routine
		Fail	PrimaryScreen2	RescreenWait=0
		Negative	PrimaryScreen2	Routine
		LowRisk	PrimaryScreen2	Routine
		HighRisk	FollowUpScreen2	FollowUpWait=0
		HighRisk16	FollowUpScreen2	FollowUpWait=0
		HighRisk18	FollowUpScreen2	FollowUpWait=0

		Cytology (Reflex)		
		If result is...	*then do...*	*with screening schedule...*
After Switch Age	FollowUpScreen2	NonCompliant	PrimaryScreen2	Routine
		Fail	FollowUpScreen2	RescreenWait=0
		Negative	SuperScreen2	CytoNeg SuperScreen=12, 1
		ASCUS	Verification2	VerifyWait=0
		ACIN23	Verification2	VerifyWait=0
		LSIL	Verification2	VerifyWait=0
		HSIL	Verification2	VerifyWait=0

Additionally, implementing screening in the model requires other pieces of information. On an individual level, there is screening compliance at every step in the algorithm (primary screen, follow-up screen, colposcopy, treatment). On a screening procedure level, the test performance of the procedure is critical (i.e. test sensitivity and specificity), as is the adequacy of the test (i.e. the ability to receive an adequate sample for testing).

The following table summarizes all the questions asked by the model at each screening step, as well as the source parameter of the answer to each question. Questions indicated with the game die emoji indicate that a random draw occurs in the model to generate the answer to the question, leading to variation between individuals.

QUESTION	🎲	PARAMETER
What procedure will be performed?	.	Screening algorithm
Was the procedure attended?	🎲	Screening compliance
Was the screening sample adequate?	🎲	Test adequacy
What was the screening result?	🎲	Test performance
What is the next screening procedure?	.	Screening algorithm
When is the next screening procedure?	.	Screening frequency

The description in this document reflects screening in HARVARD-CC at its most basic level. Many screening algorithms are much more complex than what has been described thus far.

HARVARD-HPV

HARVARD-HPV is an agent-based model that only concentrates on the transitions between No HPV Infection and HPV Infection (of seven independent types: high risk types 16, 18, 31, 33, 45, 52, and 58, and low-risk

types 6 and 11). The “agents” in this model are heterogeneous individuals (simulated women and men with unique attributes) who interact with each other on a monthly timescale by forming (or dissolving) heterosexual partnerships. Disease acquisition in the model is characterized by transmission of HPV within a partnership between two agents. Due to the interactive and dynamically evolving nature of the model, both direct and indirect benefits of HPV vaccination can be captured (direct benefits affecting those directly vaccinated; indirect benefits affecting those not vaccinated but receiving protection from vaccinated individuals).

Agents in the model have both fixed and dynamic attributes.

Fixed attributes do not change within the course of the model, and include:

- Sex (female or male)
- Sexual activity class (SAC), a category ranging from 1 to 4 that determines level of sexual mixing (1 = lowest, 4 = highest)

Dynamic attributes of agents do change over time, and include:

- Age (in months)
- Number of current partners and the duration of the partnerships
- History of partnerships
- HPV infection status and the duration of any HPV infections
- HPV natural immunity status

There are three main components to HARVARD-HPV:

1. Sexual mixing (acquisition and dissolution of partnerships)
2. HPV transmission
3. Vaccination

HARVARD-HPV: Sexual Mixing

Sexual mixing in HARVARD-HPV is driven by male individuals – that is, men seek, form, and dissolve partnerships with women, and the model inputs are adjusted to reflect this (see Parameter Overview).

There are six questions that drive sexual mixing, each of which is informed by a specific parameter. Questions indicated with the game die emoji indicate that a random draw occurs in the model to generate the answer to the question.

QUESTION	🎲	PARAMETER
Is he looking for a partner at this month?	.	Number of partners for men (varies by age, SAC)
What kind of partner is he looking for?	🎲	Assortativity (varies by age, SAC)
Is the partner available?	.	Number of partners for women (varies by age, SAC)
Will partnership formation be successful?	🎲	Partnership probability
When will the partnership happen?	🎲	Partnerships start at random months during each age year
How long will the partnership last?	🎲	Partnership dissolution rates

Within the sexual mixing component, the model cycles through every male in the population in every month. The model first checks to see if any of his current partnerships will dissolve. Next, if the month happens to be his birthday month (e.g. the month at which his age increments), the model compares his current number of partners with his expected number of partners (a function of his age and SAC). Concurrent partnerships are allowed and necessary.

If his current number of partners is equal to his expected number of partners, then there is no further partner acquisition and he (and his current partners) return to the population pool.

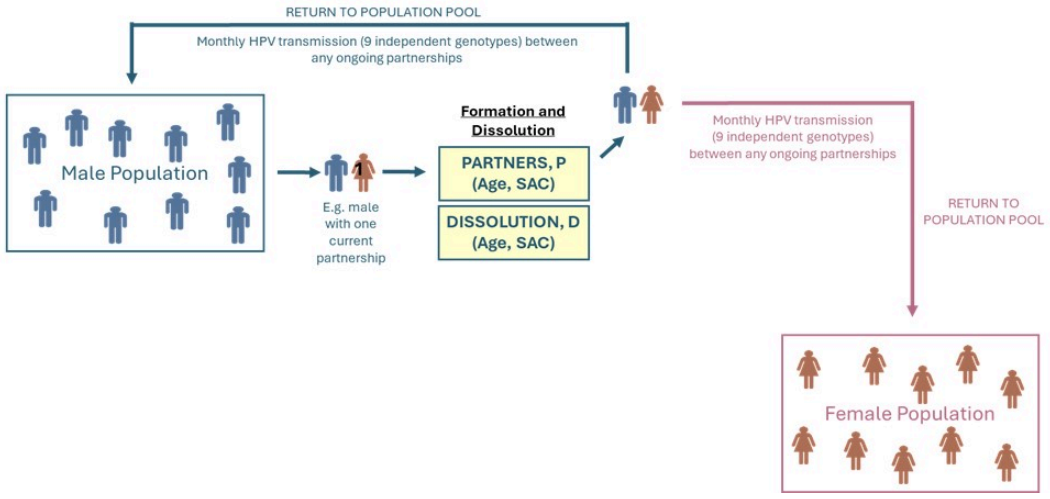
If the expected number of partners for his age is greater than the number of partners, the acquisition of partner(s) will be attempted. The model restricts the population to a pool of available women (i.e. women who have not reached their expected number of partners) who match the desired age and SAC of the partner he is seeking. Once a partner who meets all the criteria (availability, age, and SAC) is selected, the potential partnership is subjected to a partnership success probability before being formed. If the partnership formation is successful, the timing of the partnership formation will be randomly assigned to one of the next 12 months (before he increments in age).

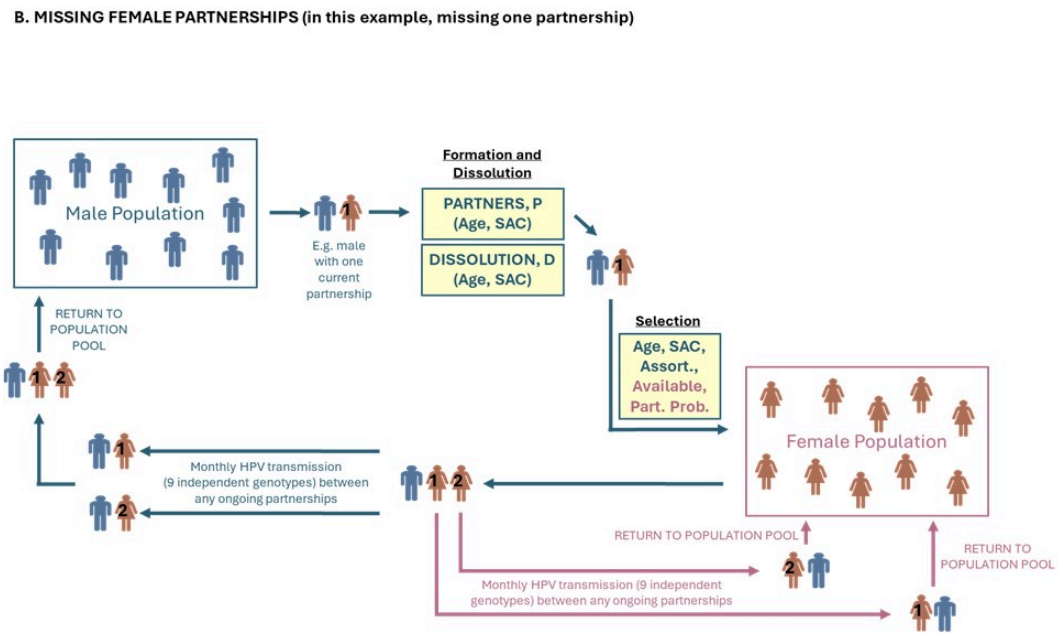
The following figures depict an example of the sexual mixing component in HARVARD-HPV. The first figure (A) shows an example of a male who is not missing any expected partnerships; the second figure (B) shows an example of a male who is seeking one additional partner.

In the first figure, a male individual has one current partner, and his expected number of partners based on his age and SAC is also one partner. If the partnership does not dissolve, then he does not need to find a new partner, and both the male and his female partner return to the population pool. The model then moves on to the next male.

In the second figure, a male individual has one current partner, and his expected number of partners based on his age and SAC is two partners. He then selects a partner from the pool of female individuals that matches his preference of age and SAC. If this female individual also has fewer current partners than expected partners, they could potentially form a partnership. If partnership formation is successful, the male individual now has two concurrent partnerships, and all individuals return to the population pool.

A. NOT MISSING FEMALE PARTNERSHIPS



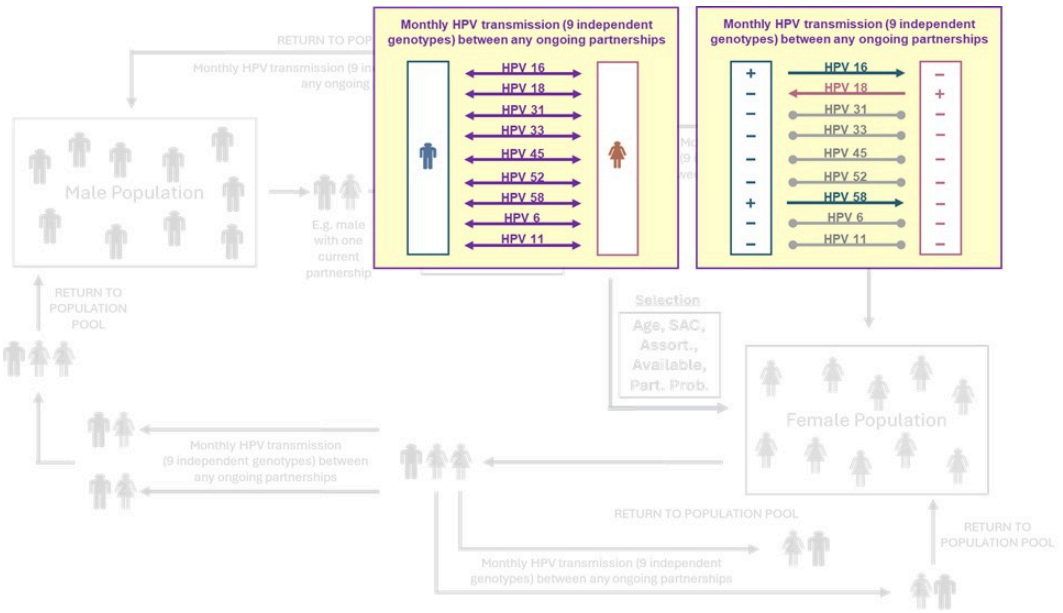


HARVARD-HPV: HPV Transmission

Disease in HARVARD-HPV is defined as high-risk types 16, 18, 31, 33, 45, 52, and 58, and low-risk types 6 and 11. Transmission of HPV occurs exclusively within partnerships, and each type acts independently of other types. Individuals can be infected with multiple types at the same time.

At each month, individuals with HPV can infect their partner based on HPV transmission probabilities for each HPV type. Thus, transmission in HARVARD-HPV is reflected as a per-partnership-per-month metric. Transmission probabilities can be adjusted to be higher at younger ages, reflecting potentially more sex acts per-partnership-per-month. Transmission probabilities are calibrated to fit setting-specific HPV data (e.g. prevalence).

The figure below shows an example of HPV transmission within a partnership. The male individual in infected with HPV types 16 and 58, while the female individual is infected with type 18. At each month they remain in a partnership, they could potentially infect their partner with the HPV type they have.

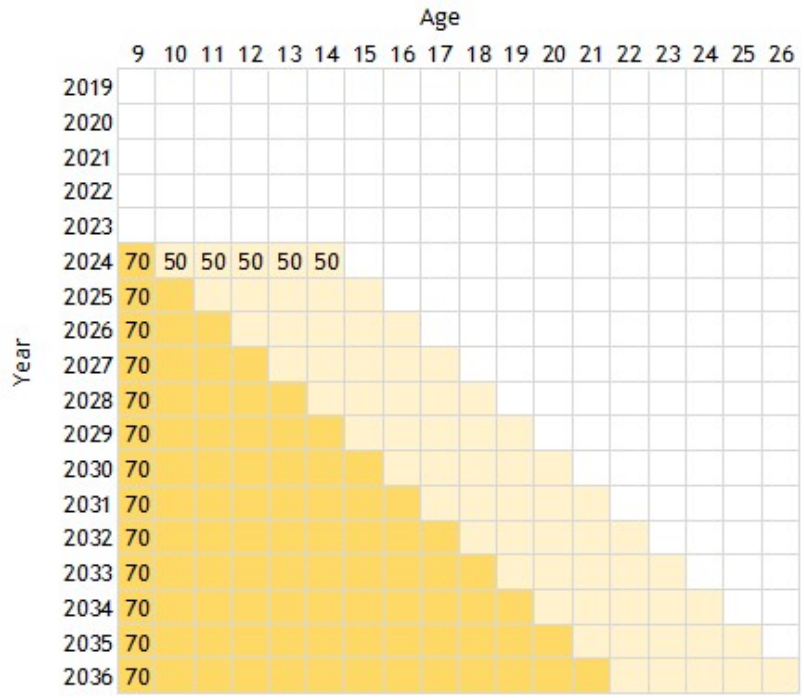


HARVARD-HPV: Vaccination

HARVARD-HPV allows routine vaccination programs to be implemented, as well as campaign vaccination programs. Females and males can have distinct vaccination programs.

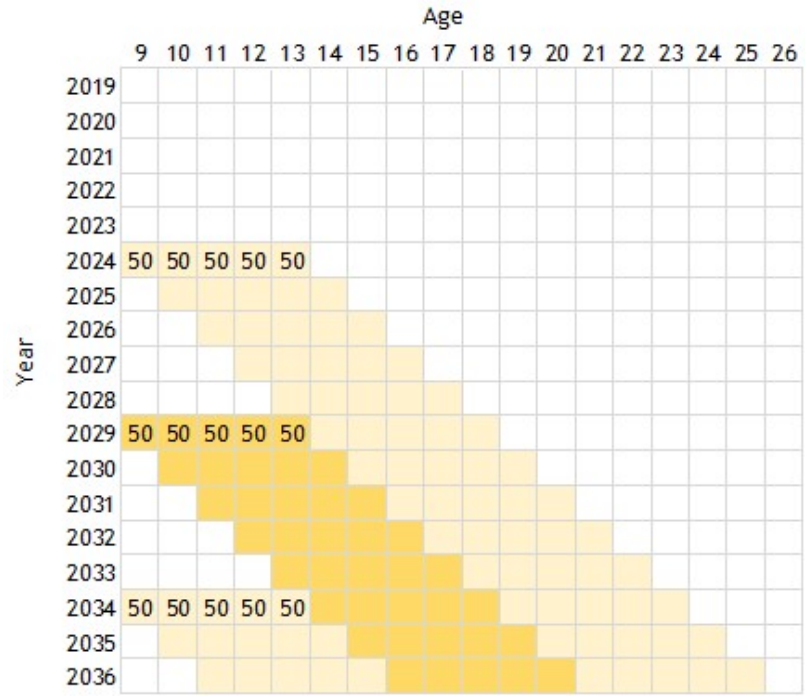
Most standard vaccination programs fall under the routine category. Under routine vaccination, the model can set coverage levels (among the unvaccinated) for every cohort at every age and every time. The most common scenario is to set coverage for incoming cohorts at a certain age, as well as set a catch-up coverage level for several prevalent cohorts.

The figure below shows a scenario where vaccination is introduced in 2024. Incoming 9-year olds receive the vaccine at a coverage level of 70%. In addition, 10- to 14-year olds in the first year of the program receive the vaccine at a coverage level of 50%. Shaded cells with values indicate the cohort was vaccinated at that coverage level at that year; shaded cells without values indicate the cohort was previously vaccinated. The figure follows multiple cohorts over time, with each individual cohort represented by a diagonal.



Under a campaign vaccination program, multiple cohorts are vaccinated during a point in time; however, there is no ongoing routine vaccination for incoming cohorts. Instead, another campaign would occur after several years.

The figure below shows a campaign vaccination scenario where five cohorts are vaccinated at once at a 50% coverage level, and the campaign cycle is every five years.

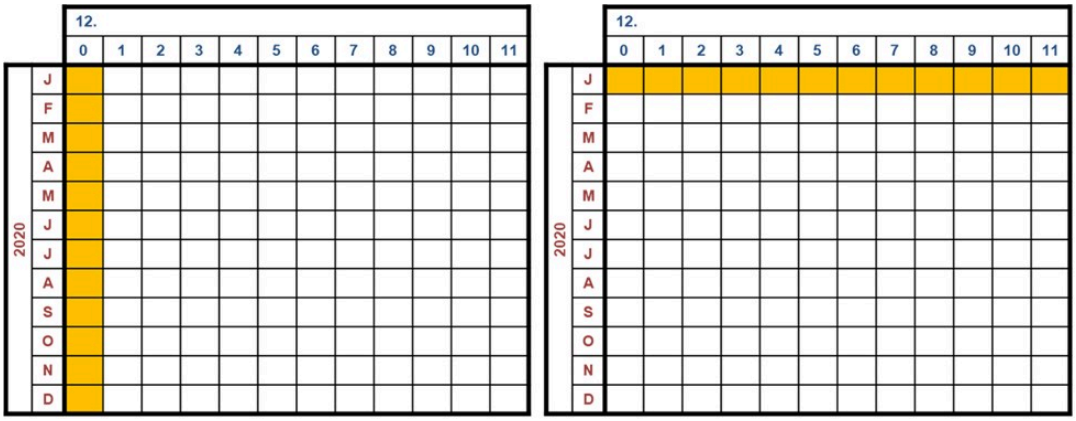


Aside from vaccine coverage over time, other characteristics of vaccination in HARVARD-HPV include:

- Number of vaccine doses
- Efficacy of vaccine, by HPV type and by number of doses
- Duration of vaccine (i.e. waning), by number of doses
- Targeted revaccination

On an individual level, vaccination in HARVARD-HPV can occur within a given year based on one of two rules Under “birthday” vaccination rules, vaccination occurs at the month an individual turns the vaccination age, regardless of which month during the calendar year it is. Under “timepoint” vaccination rules, vaccination occurs at a single month during the calendar year and covers everyone at the vaccination year, regardless of how many months they have been that age.

Consider the following grids in the panels below, with ages along the horizontal scale and calendar time along the vertical scale. The grid shows the 12 months of the 2020 calendar year as well as 12-year olds on a monthly scale (e.g. 12-years and 0-months old, 12-years and 1-month old, 12-years and 2-months old, etc). Each box represents a cohort, and cohorts along a diagonal are the same cohort (i.e. cohorts age along a diagonal every month; e.g. a 12-year 0-month old in January turns 12-year 1-month in February).



The left panel represents “birthday” vaccination for 12-year olds in 2020. The first cohort turns 12 in January and gets vaccinated. The second cohort turns 12 in February and gets vaccinated, and so on.

Ther right panel represents “timepoint” vaccination for 12-year olds in 2020. Here, vaccination occurs for all the cohorts in January. The cohort that just turned 12 (i.e. 12-years and 0-months) will get vaccinated, as will existing 12-year olds who turned 12 earlier.

Note that aside from the cohort that turns 12 in January, “birthday” and “timepoint” rules vaccinate different cohorts in the calendar year. But over time, every cohort has the opportunity to get vaccinated.

See Output Overview for a deeper description of how HARVARD-HPV handles its monthly timescale.

Output Overview

Summary

This document provides information on some of the more important outputs produced by HARVARD-CC and HARVARD-HPV. Both models produce total counts of model events (aggregated at the end of the simulation), as well as model events at each timepoint (aggregated during the course of the simulation). Specialized specific outputs unique to each model are also generated.

Overview

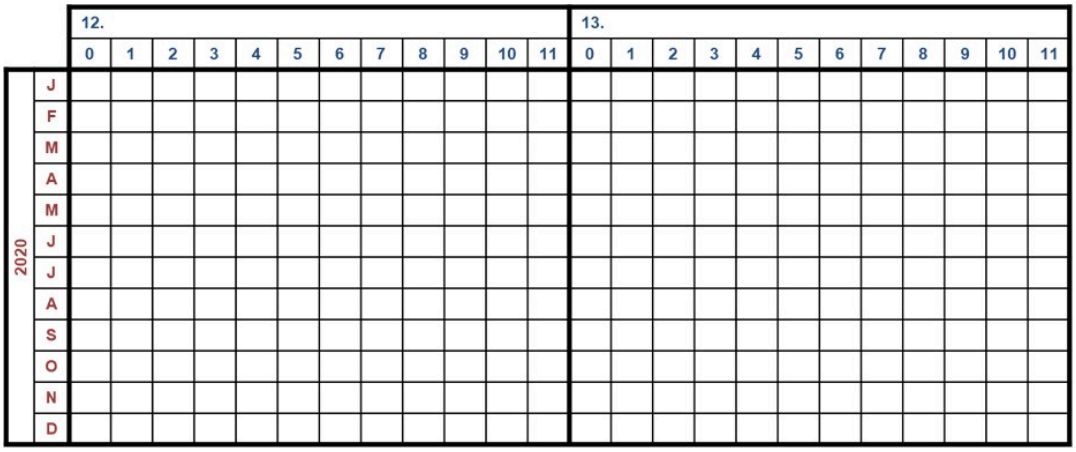
Both HARVARD-CC and HARVARD-HPV keep track of the health histories of simulated individuals. As such, aggregated counts of disease, interventions, and costs at the completion of a simulation can be output. Some model results are tracked as a function of time, and these monthly and yearly totals are arguably the most useful outputs from the model. Both models also produce specialized outputs, some of which will be described in the next section.

Since HARVARD-CC and HARVARD-HPV are structurally very different models, it follows that their outputs – while containing similar information – are also structurally very different.

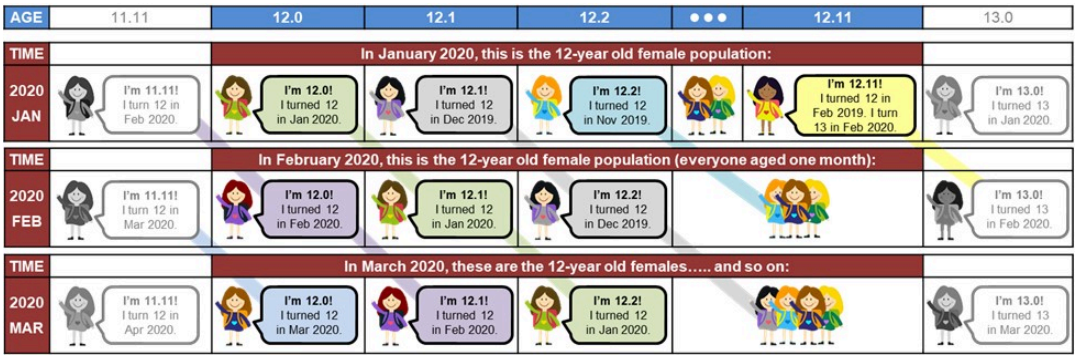
HARVARD-CC simulates one cohort; therefore, model output for HARVARD-CC is only for that single cohort. Outputs representing aggregate counts are out of the initial cohort size; for example, total number of detected cervical cancer cases out of one million. Outputs that are a function of time are also simultaneously a function of age since the outputs come from only a single cohort. In other words, for an output representing a certain calendar year, every simulated individual is the same age. For example, if the model is simulating a cohort born in the year 2000, then detected cervical cancer for 65-year olds is equivalent to detected cervical cancer in the year 2065. (Note that HARVARD-CC can generate multi-cohort results by "stacking" cohorts, i.e. running individual cohorts independently and then combining them into a single population.)

HARVARD-HPV simulates multiple cohorts at once; therefore model outputs that are a function of time can also have an age component. For example, for a single calendar year, say 2065, a single run of the model would be able to produce the number of HPV-16 cases for every single age in that year, instead of just a single age.

A tricky aspect of HARVARD-HPV is that it runs on a monthly timescale, and outputs are often reported on a yearly timescale. Combining monthly outputs from multiple cohorts into a single yearly output is not as straightforward as it might seem. Consider the following grid, with ages along the horizontal scale and calendar time along the vertical scale. The grid shows the 12 months of the 2020 calendar year as well as 12-year olds and 13-year olds on a monthly scale (e.g. 12-years and 0-months old, 12-years and 1-month old, 12-years and 2-months old, etc).



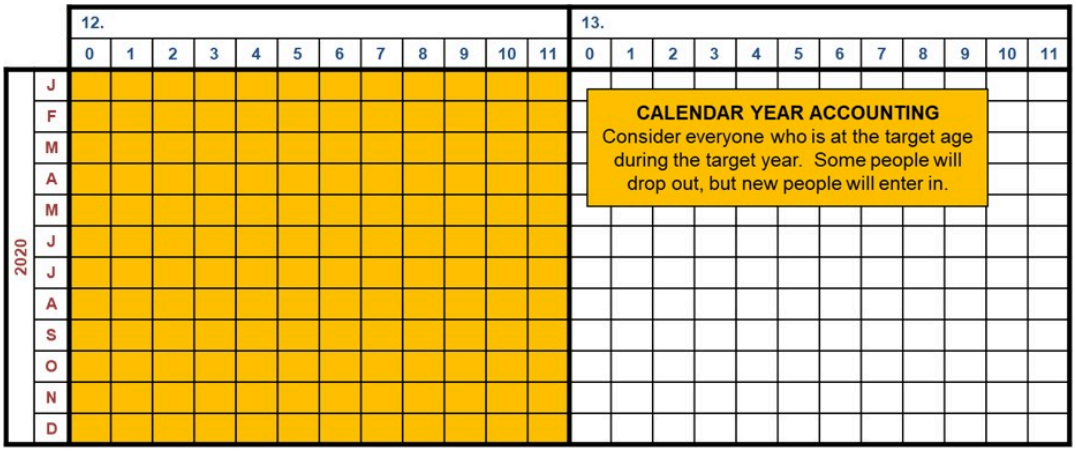
We can ask the question: who do we consider to be "12-year olds" in 2020? The following visualization may help clarify.



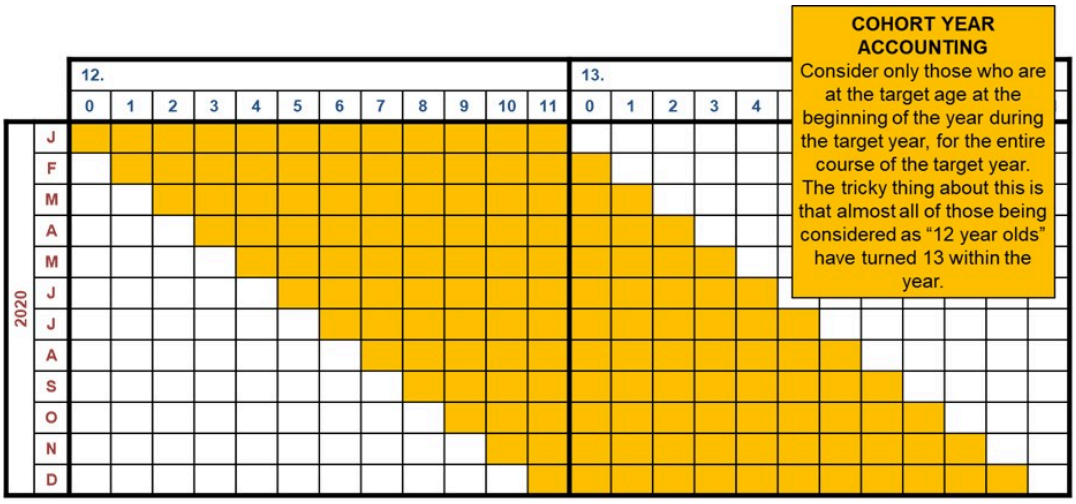
In January 2020, there are 12 cohorts of "12-year olds" – ranging from those who just turned 12 that month (i.e. 12.0, 12 years, 0 months), to those who are in their last month of being 12 (i.e. 12.11, 12 years, 11 months). In February 2020, everyone ages one month, and a group of 11.11-year olds in January turn 12.0 in February. Similarly, the 12.11 cohort in January turns 13.0 in February.

And so the question remains, in terms of accounting purposes, who is counted as a "12-year old" in 2020? HARVARD-HPV answers this question with two separate modes of accounting.

In "calendar year" accounting, only those who are the target age in the target year count. Some cohorts will drop out, but new cohorts will enter in, as shown in the shaded cells of the figure below.



In "cohort year" accounting, only those who are the target age at the beginning of the year count (as seen in the shaded cells of the figure below). The unintuitive thing about this is that almost all those being considered as "12-year olds" will have turned 13 within the calendar year.



Output Listing

HARVARD-CC

Harvard-CC outputs follow a fairly standard template.

First, there are the standard aggregated outputs at the end of a simulation. Below is a sample of some (but not all) of these outputs.

- Life expectancy
- Population life expectancy (discounted and undiscounted)
- Population quality-adjusted life expectancy (discounted and undiscounted)
- Screening counts
- Number of individuals screened
- Number of cytology tests
- Number of HPV tests
- Number of colposcopies
- Number of treatments
- Cost-effective analysis
- Total costs per individual (discounted and undiscounted)
- Total QALYs per individual (discounted and undiscounted)
- Disease counts
- Total individuals with CIN2 lesions
- Total individuals with CIN3 lesions
- Total individuals with undetected cancer
- Total individuals with detected cancer (i.e. total lifetime detected cancer risk)
- Total individuals with symptom-detected cancer

- Total individuals with screen-detected cancer
- Total undetected cancer deaths
- Total detected cancer deaths (i.e. total lifetime detected cancer mortality)
- Disease distributions
- Cancer stage distribution
- HPV type distribution in CIN2
- HPV type distribution in CIN3
- HPV type distribution in cancer
- Incidence
- Cancer incidence by age (unadjusted and adjusted for hysterectomy)
- Type-specific cancer incidence by age (unadjusted and adjusted for hysterectomy)
- Cancer mortality by age (unadjusted and adjusted for hysterectomy)
- Durations
- Average duration of HPV infection (no lesion) by type
- Average duration of CIN2
- Average duration of CIN3
- Average duration of CIN2 conditional on cancer
- Average duration of CIN3 conditional on cancer
- Also: median durations, and minimum, maximum, 25th and 75th percentiles

HARVARD-CC also has numerous outputs by age. Most of these are simply counts of model-related outputs at each age.

- Prevalence counts of each health state, i.e. the number of individuals in each health state (No HPV, HPV infection, CIN2, CIN3, undetected CA stages 1-4, detected CA stages 1-4, Hysterectomy, Dead, Dead from cancer) at every simulated month.
- Prevalence counts of each health state – further stratified by HPV type – at every simulated month. In other words, counts of the disease status for each HPV type, e.g. HPV-NL (no lesion) for each type, CIN2 for each type, CIN3 for each type, CA1-4 for each type, CA1d-4d for each type.
- Incidence counts of each health state at every simulated month.
- Incidence counts of each health state – further stratified by HPV type – at every simulated month.
- Cytology results at every simulated month (Untested, Non-compliant, Fail, Negative, ASC-US, LSIL, ASC-H, HSIL), even in months where no one gets screened (untested).
- HPV test results at every simulated month (Untested, Non-compliant, Fail, Negative, HR-16, HR-18, HR-31, HR-33, HR-45, HR-52, HR-58, OHR, LR).
- Colposcopy results at every simulated month (Untested, Non-compliant, Fail, Negative, CIN2, CIN3, CA1, CA2, CA3, CA4).
- Treatment results at every simulated month (Untreated, Treated).

Finally, HARVARD-CC can output specialized files, which don't fit a common template, but still provide very useful information. Some examples of these are:

- Screening validation file: counts number of individuals with specific results at every simulated month, and then looks ahead X years to see how many of those individuals (with that specific screening result)

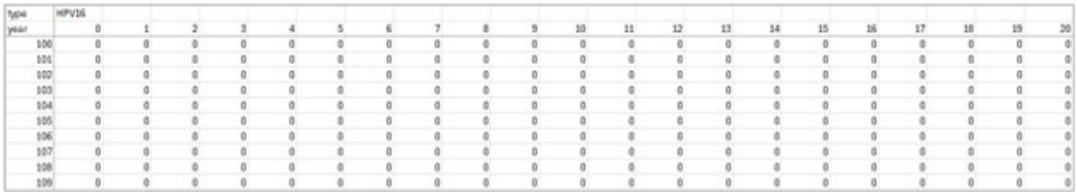
have progressed to CIN2, CIN3, and CA. Screening trials can easily produce this kind of data for the model to match to.

- Cancer history file: calculates dwell time for every simulated cancer case; outputs include the month of the insulting HPV infection, HPV dwell months, month of CIN progression, CIN dwell months, month of CA invasion, CA sojourn time, CA detection time, and CA detection stage.

HARVARD-HPV

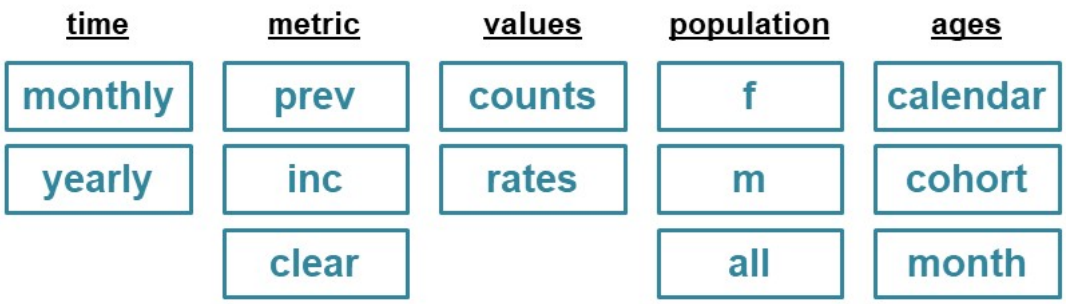
For disease outputs, HARVARD-HPV produces a generic three-dimensional output template, with age, time, and HPV type as the axes. To represent the output in a two-dimensional spreadsheet, age and HPV type are flattened and combined onto one axis, with time on the other axis.

In the image below, a snapshot of a generic output file is shown. The output displays year 100 to year 109 for the simulation on the vertical axis. The horizontal axis displays HPV-16 output for ages 0 to 20. If the entire file could be shown, the vertical axis would extend from year 0 to the end of the simulation. The horizontal axis would show all ages 0 to 89 for HPV-16, then it would repeat ages 0 to 89 for HPV-18, then HPV-31, and so on for all the HPV types included in HARVARD-HPV.



type	HPV16																				
year	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
101	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
104	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
107	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
108	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
109	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

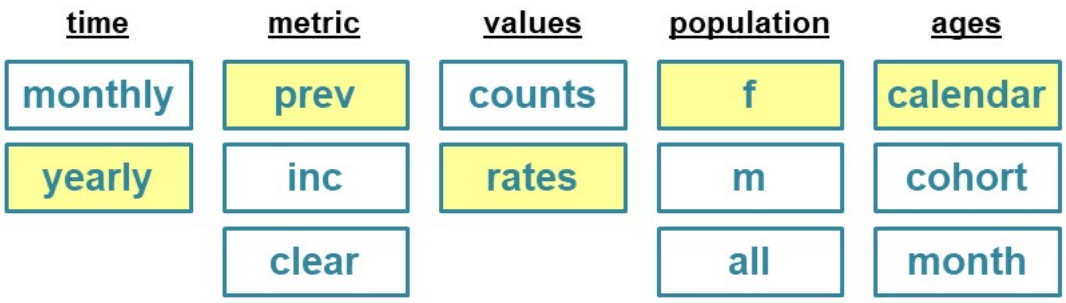
The main HARVARD-HPV outputs can be summarized by the following graphic:



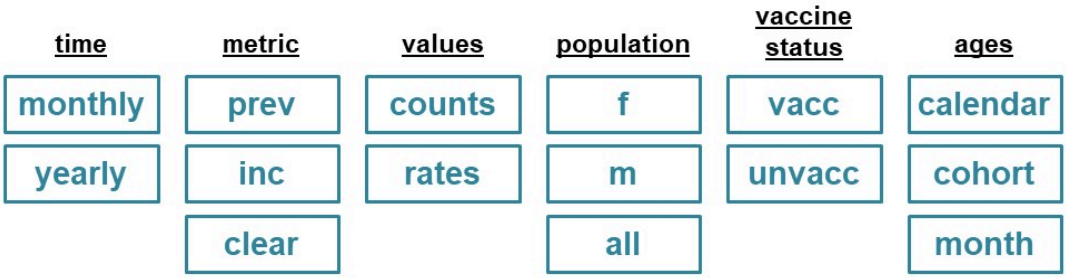
There are five components to an output file, and the model can output each possible combination.

1. Time: whether to display the vertical-axis time component in months or years (the years option will combine results over each 12-month period)
2. Metric: the output metric itself, whether it be prevalence, incidence, or clearance.
3. Values: how to display the metric, either in absolute counts, or as rates
4. Population: who to include in the output population, either just females, just males, or both females and males
5. Ages: whether to display the horizontal age component as “calendar age” or “cohort age”, or to output age in months instead of years.

For example, the shaded components below indicate that the output file generated will have yearly HPV prevalence values in females as rates, with female ages represented as calendar age.



The model can also further stratify by vaccine status or by SAC level. The corresponding graphic for further stratification by vaccine status is shown below.



Since sexual mixing is the critical component of HARVARD-HPV, naturally there are outputs that characterize the sexual behavior of the simulated population.

One metric is the number of lifetime partners, both mean, median, min, and max. An even more granular version of this metric is number of lifetime partners at every age (e.g. number of lifetime partners at age 30). The number of lifetime partners output is stratified by sex (female or male) or SAC (1 to 4).

Another format of representing number of lifetime partners is to show the distribution of the population with 0 lifetime partners, 1 lifetime partner, 2 lifetime partners, and so on.

The model outputs concurrency (i.e. individuals with multiple partners at the same time) in two ways. One way is by calculating the percentage of individuals who were concurrent in each month of the model, and then averaging across all months. The other way is by looking at only the final 12 months of a simulation, and determining the percentage of individuals who were concurrent at some point during that time. Concurrency is also stratified by sex or SAC.

Finally, since the model essentially creates a sexual mixing network, the model also outputs network characteristics. For example, the average degree of a node in a given month can be recorded (essentially the number of partners per individual) and converted into an output of mean monthly degree (i.e. average number of partners per individual in a month further averaged across all months in the model).

Results Overview

Summary

This section will document some calibration and validation results of HARVARD-CC and HARVARD-HPV. Summaries and references to selected key publications with policy-relevant results, both domestic and global, are also provided and will be updated routinely..

Overview

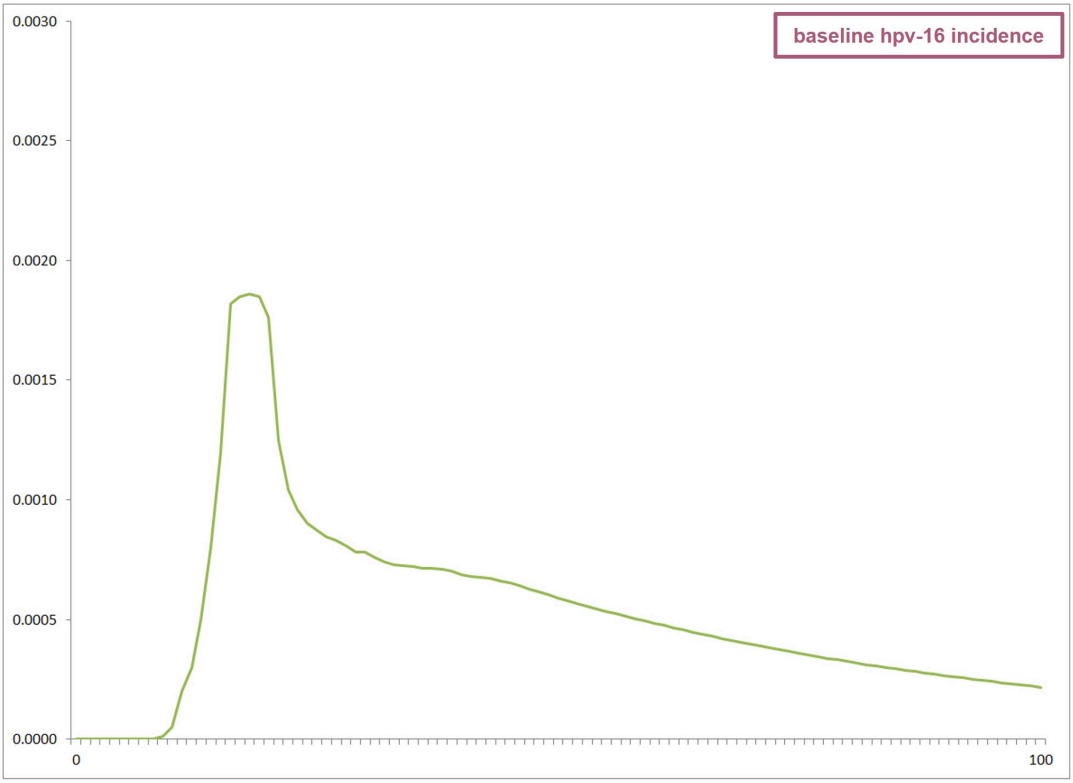
Model calibration for both HARVARD-CC and HARVARD-HPV involves adjusting values of unobservable variables, and then running the models with these values to fit setting-specific epidemiological targets.

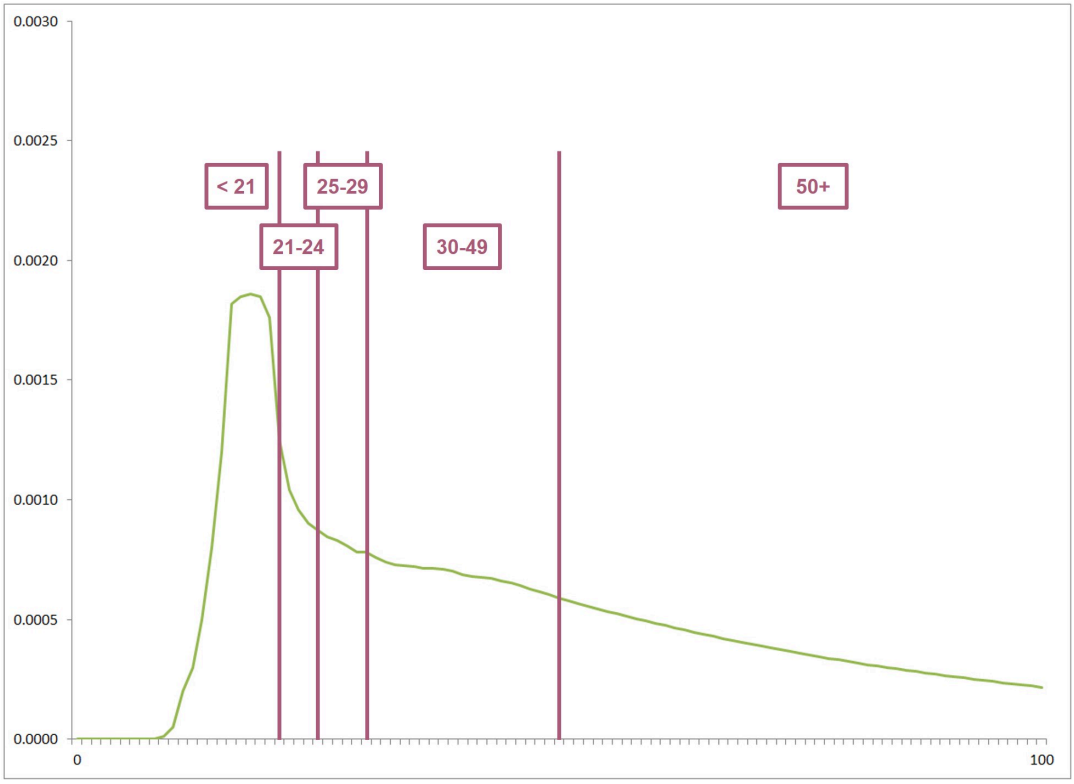
HARVARD-CC

HARVARD-CC currently calibrates the following parameters, all of which are HPV type-specific:

- HPV incidence
- Disease progression (e.g. HPV to CIN2, HPV to CIN3, CIN to cancer)
- Natural immunity

When possible, baseline values of these parameters are acquired and then multipliers are applied on top of baseline values to fit epidemiological targets. Multipliers can also be age-specific. For example, HARVARD-CC calibrates HPV-16 incidence by “hinging”, that is, taking baseline HPV-16 incidence by age (top figure) and dividing the incidence curve into five age ranges (bottom figure). Each age range can have multipliers applied onto their values, thereby increasing or decreasing the baseline value.





The search space for multiplier values are based on “reasonable ranges”. A repository of model runs using various multipliers is created, and then the goodness-of-fit of each run (i.e. each run is a parameter set) is scored to each target using random sampling and a likelihood-based approach.

The parameter sets are then ranked based on their likelihood scores. HARVARD-CC analyses are usually conducted using the top 50 parameter sets per setting.

HARVARD-HPV

The calibration process for HARVARD-HPV is similar to that of HARVARD-CC in that a repository is created, using multipliers to vary the values of unobservable inputs. The inputs being calibrated in HARVARD-HPV are (all of which are HPV type-specific):

- HPV transmission, separate for female-to-male and male-to-female
- Degree of natural immunity protection, separate for females and males

Results List

This section visualizes calibration results for HARVRD-CC and HARVARD-HPV in a U.S.-based setting. Some recent relevant publications and their summaries are also listed.

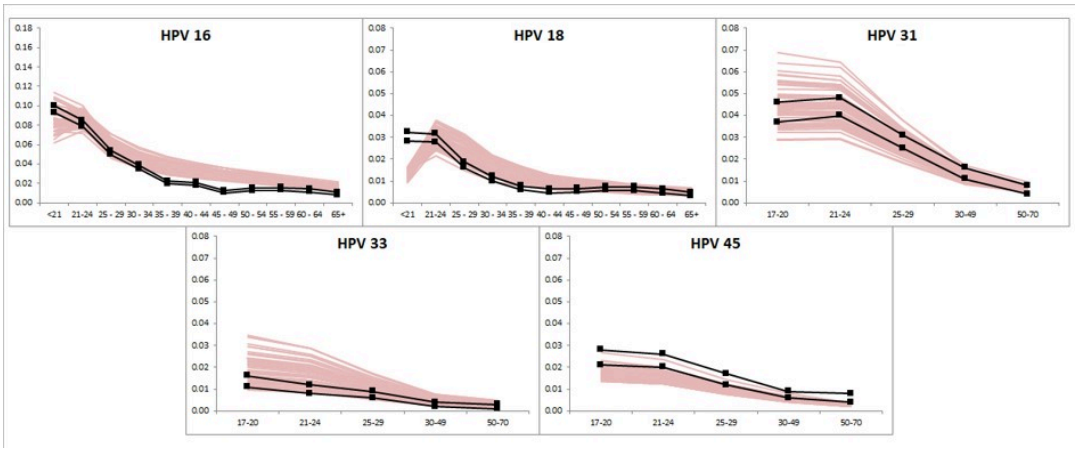
HARVARD-CC

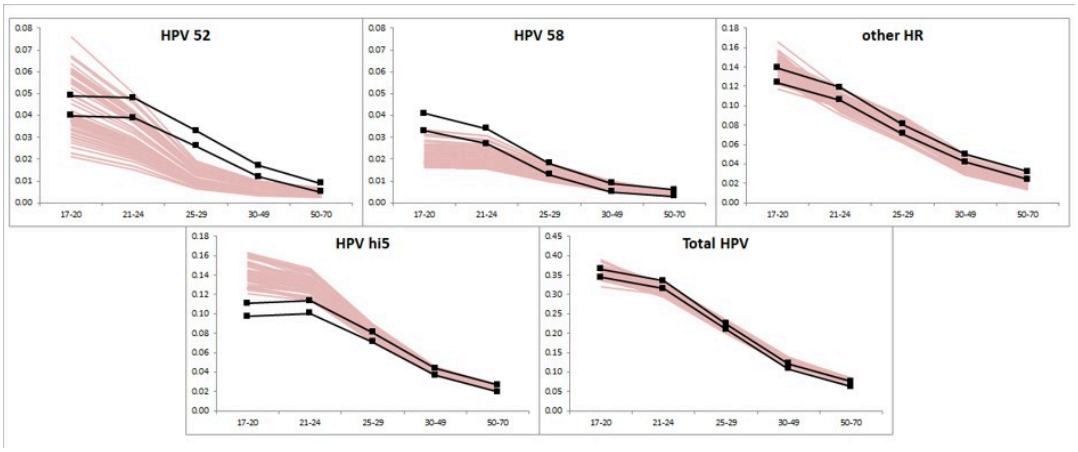
For a U.S.-based setting, calibration targets for HARVARD-CC include:

- HPV prevalence by age
- HPV type distribution in CIN2, CIN3, and cervical cancer, overall and by age’

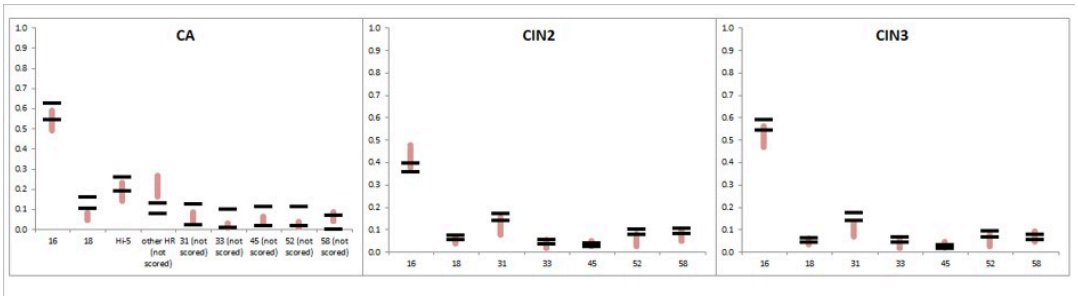
Below are graphs of the top 50 parameter sets (pink) to these targets (black).

HPV prevalence:

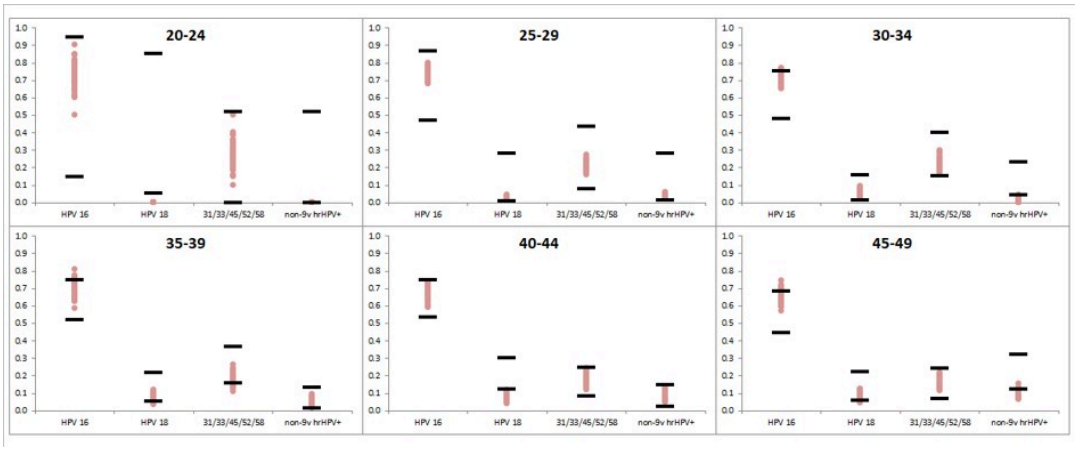


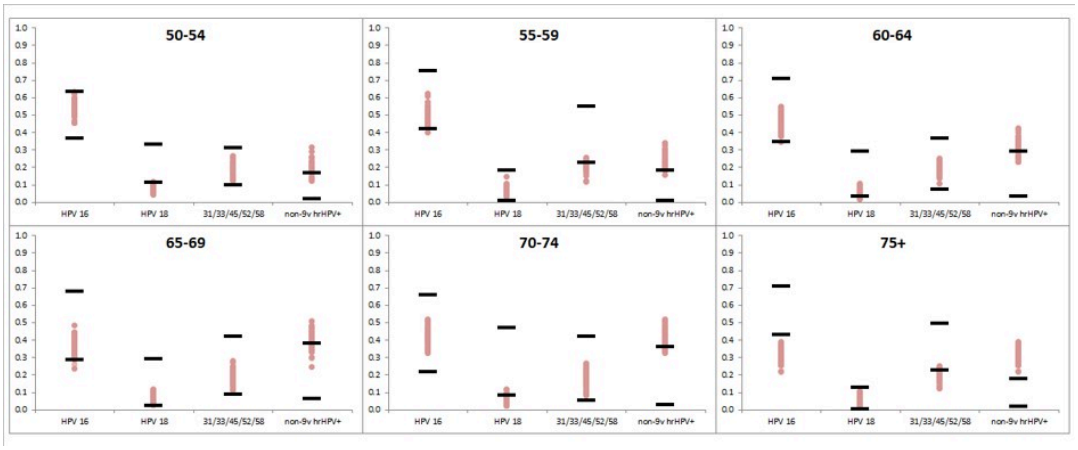


HPV type distribution (overall):



HPV type distribution (by age):

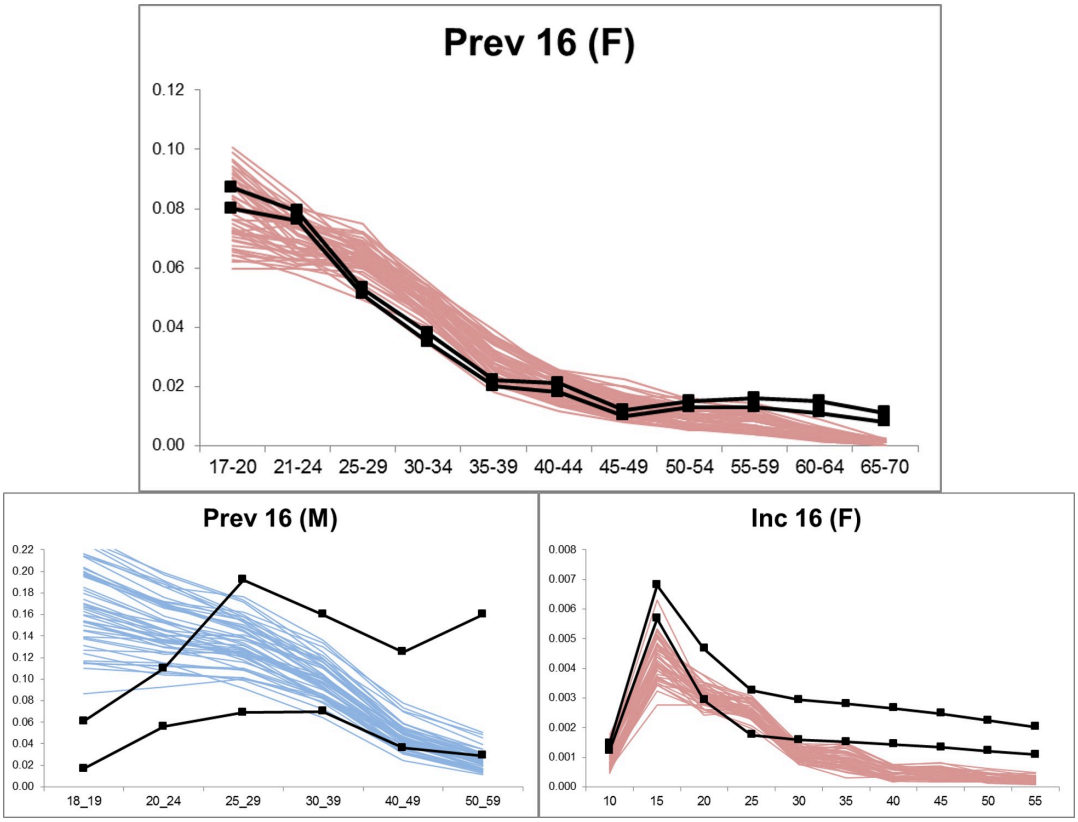




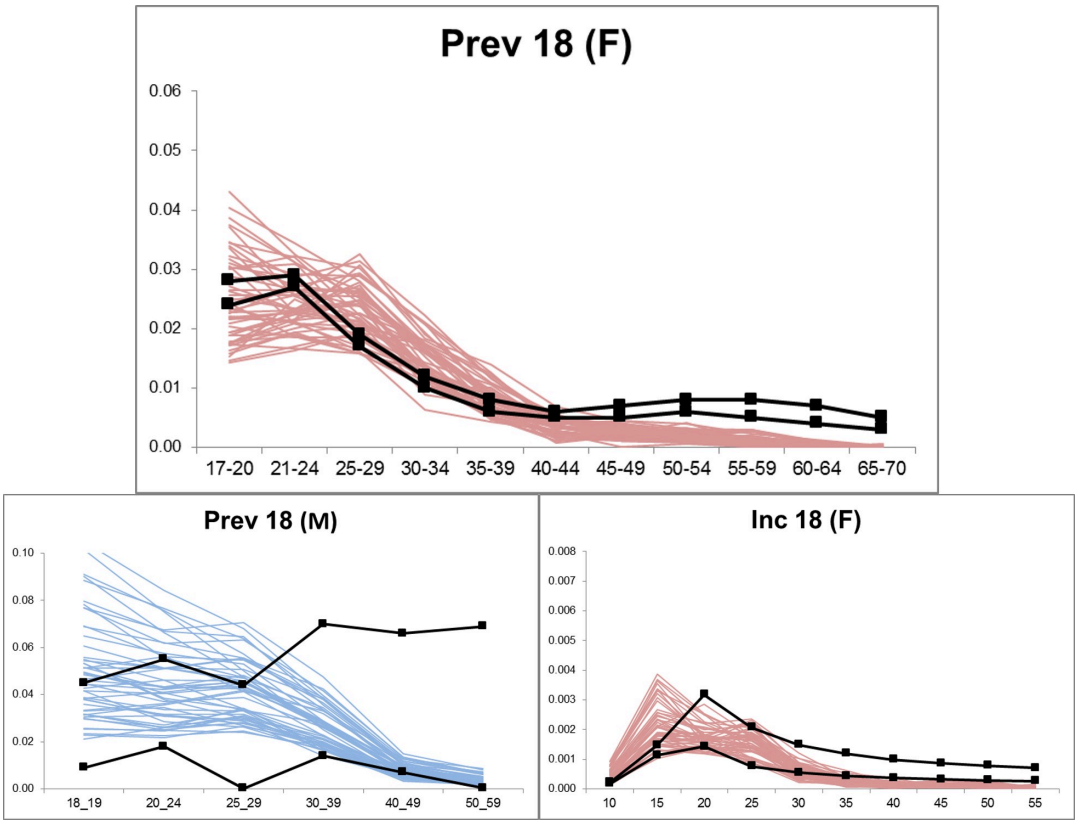
HARVARD-HPV

HARVARD-HPV uses the same HPV prevalence targets for the U.S.-based setting, and also adds HPV prevalence in males as a target. (In the graphs below, model-outputted HPV incidence is shown but is not formally calibrated to.)

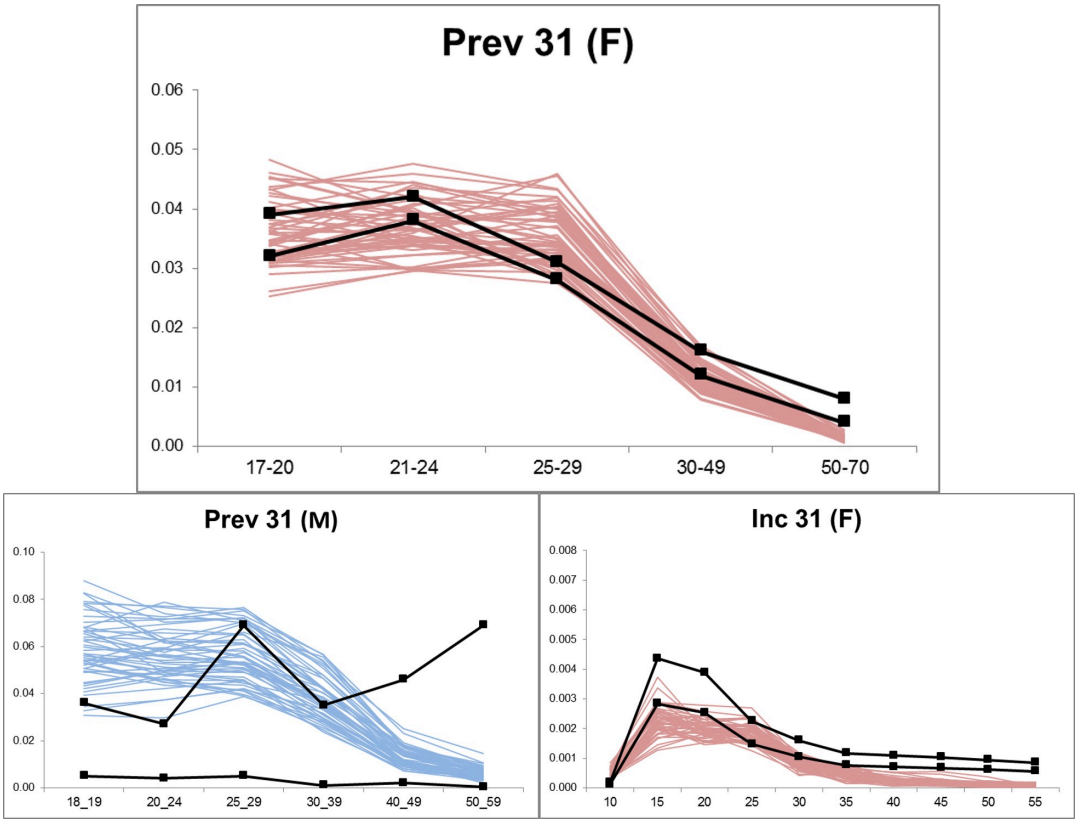
HPV-16:



HPV-18:


Prev 18 (F)
0.06
0.05
0.04
0.03
0.02
0.01
0.00
17-20 21-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-70
Prev 18 (M)
0.10
0.08
0.06
0.04
0.02
0.00
18_19 20_24 25_29 30_39 40_49 50_59
Inc 18 (F)
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0.000
10 15 20 25 30 35 40 45 50 55

HPV-31:


Prev 31 (F)
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0.04
0.03
0.02
0.01
0.00
17-20 21-24 25-29 30-49 50-70
Prev 31 (M)
0.10
0.08
0.06
0.04
0.02
0.00
18_19 20_24 25_29 30_39 40_49 50_59
Inc 31 (F)
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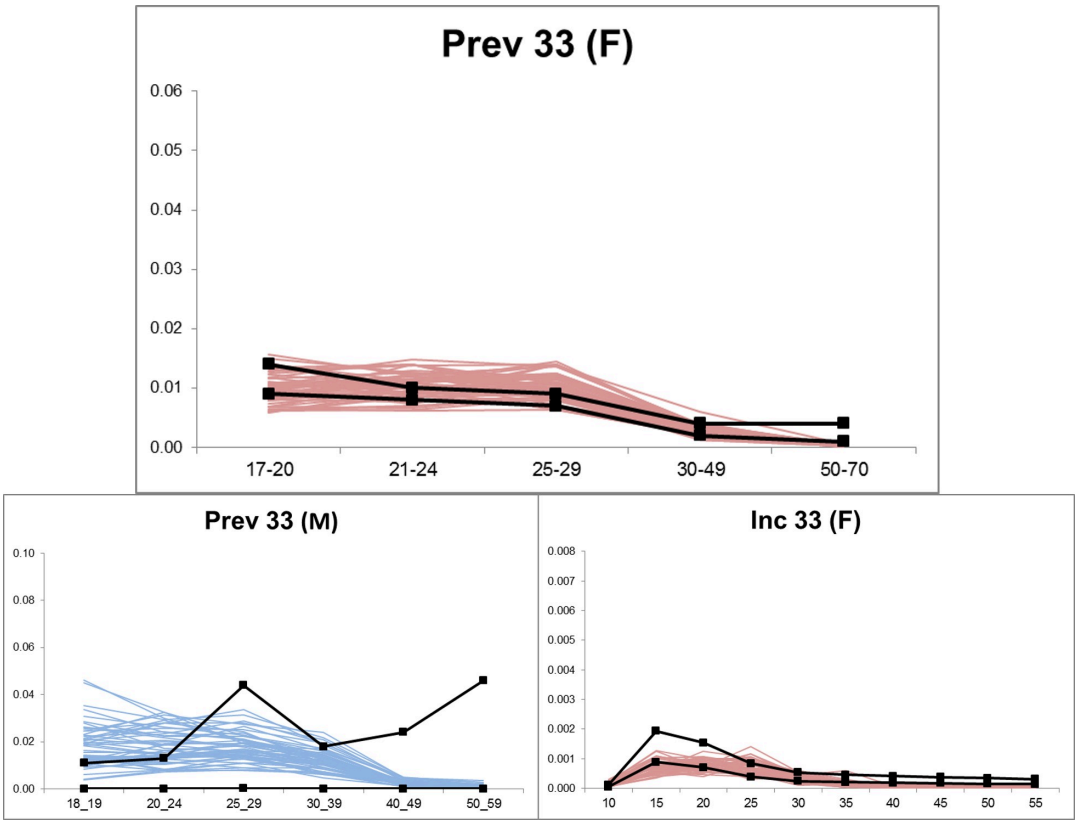
HPV-33: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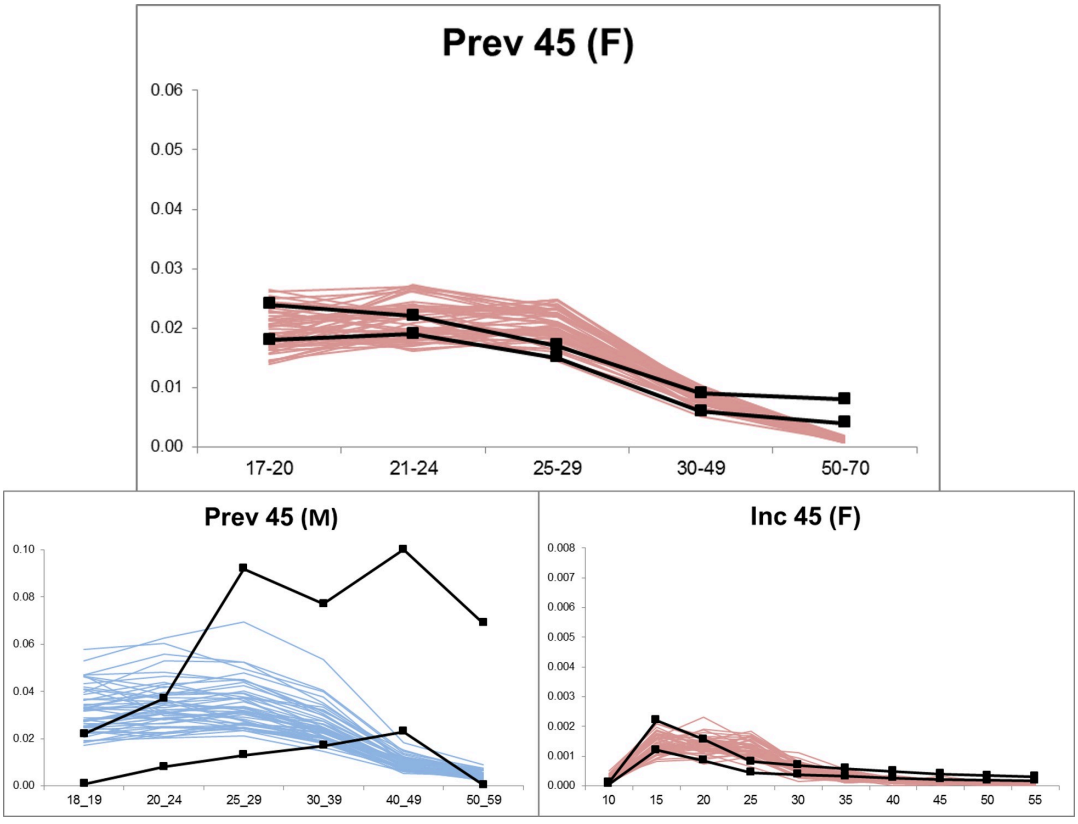
HPV-45: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30-49
50-70
Prev 45 (M)
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50_59
Inc 45 (F)
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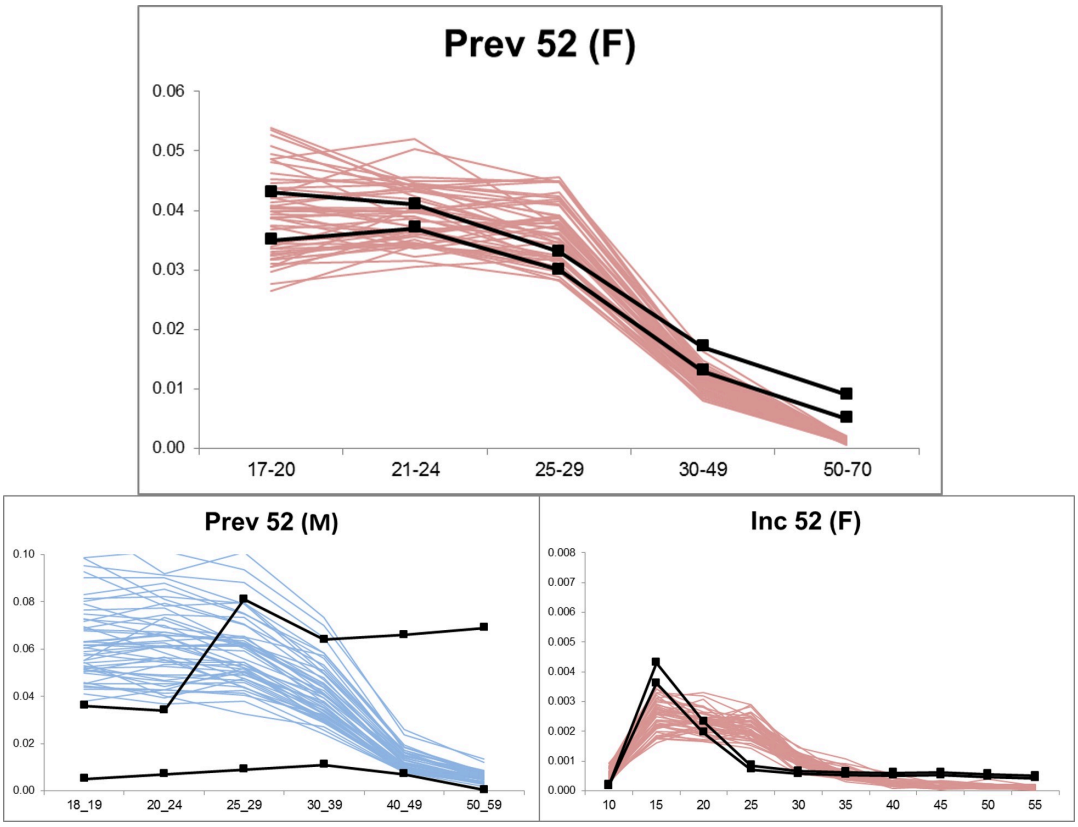
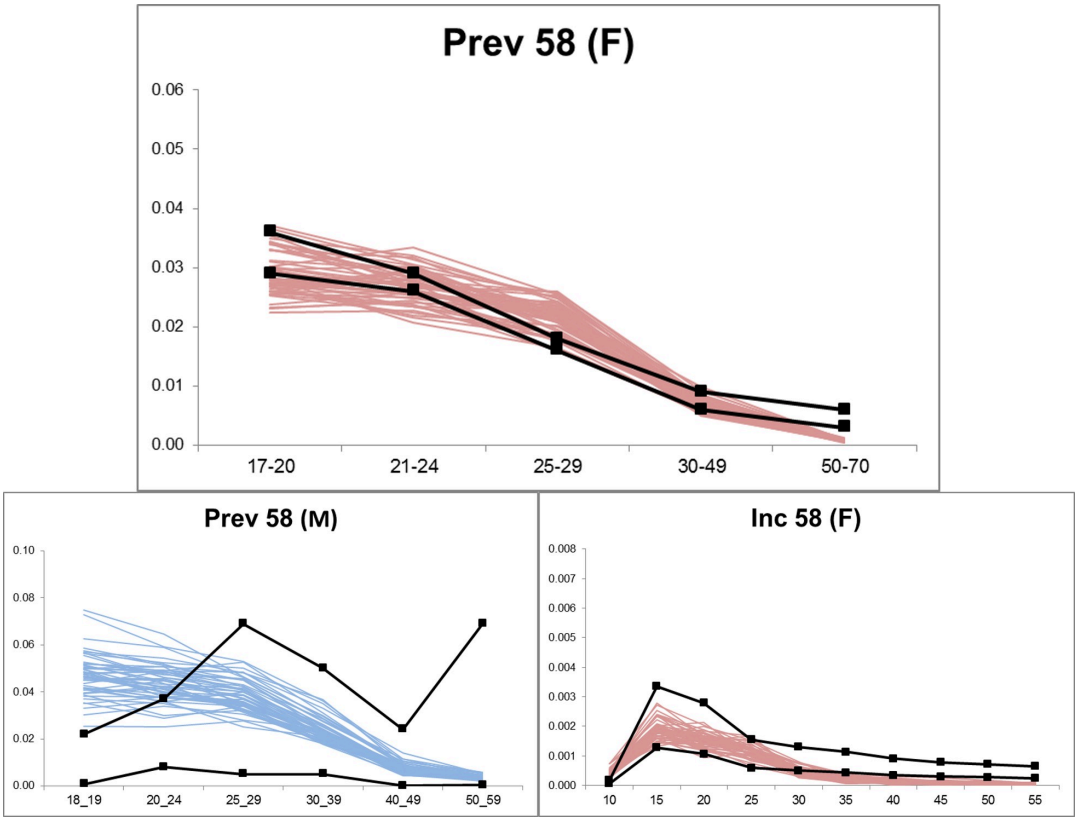
HPV-52:



HPV-58:



PUBLICATIONS

Below is a selected list of recent publications showcasing results from the Harvard cervical models.

Screening for Cervical Cancer in Primary Care: A Decision Analysis for the US Preventive Services Task Force[1]

Importance: Evidence on the relative benefits and harms of primary high-risk human papillomavirus (hrHPV) testing is needed to inform guidelines.

Objective: To inform the US Preventive Services Task Force by modeling the benefits and harms of various cervical cancer screening strategies.

Cost-Effectiveness of Cervical Cancer Screening in Women Living With HIV in South Africa: A Mathematical Modeling Study[2]

Background: Women with HIV face an increased risk of human papillomavirus (HPV) acquisition and persistence, cervical intraepithelial neoplasia, and invasive cervical cancer. Our objective was to determine the cost-effectiveness of different cervical cancer screening strategies among women with HIV in South Africa.

Estimating the Natural History of Cervical Carcinogenesis Using Simulation Models: A CISNET Comparative Analysis[3]

Background: The natural history of human papillomavirus (HPV)-induced cervical cancer (CC) is not directly observable, yet the age of HPV acquisition and duration of preclinical disease (dwell time) influences the effectiveness of alternative preventive policies. We performed a Cancer Intervention and Surveillance Modeling Network (CISNET) comparative modeling analysis to characterize the age of acquisition of cancer-causing HPV infections and implied dwell times for distinct phases of cervical carcinogenesis.

Projected time to elimination of cervical cancer in the USA: a comparative modelling study[4]

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

Human papillomavirus vaccination for adults aged 30 to 45 years in the United States: A cost-effectiveness analysis[5]

Background: A nonavalent human papillomavirus (HPV) vaccine has been licensed for use in women and men up to age 45 years in the United States. The cost-effectiveness of HPV vaccination for women and men aged 30 to 45 years in the context of cervical cancer screening practice was evaluated to inform national guidelines.

Impact of disruptions and recovery for established cervical screening programs across a range of high-income country program designs, using COVID-19 as an example: A modelled analysis[6]

Background: COVID-19 has disrupted cervical screening in several countries, due to a range of policy-, health-service and participant-related factors. Using three well-established models of cervical cancer natural history adapted to simulate screening across four countries, we compared the impact of a range of standardised screening disruption scenarios in four countries that vary in their cervical cancer prevention programs.

Impact of COVID-19-related care disruptions on cervical cancer screening in the United States[7]

Objectives: To quantify the secondary impacts of the COVID-19 pandemic disruptions to cervical cancer screening in the United States, stratified by step in the screening process and primary test modality, on cervical cancer burden.

A model-based analysis of the health impacts of COVID-19 disruptions to primary cervical screening by time since last screen for current and future disruptions[8]

Objectives: We evaluated how temporary disruptions to primary cervical cancer (CC) screening services may differentially impact women due to heterogeneity in their screening history and test modality.

Cost-effectiveness analysis of the 2019 American Society for Colposcopy and Cervical Pathology Risk-Based Management Consensus Guidelines for the management of abnormal cervical cancer screening tests and

cancer precursors[9]

Background: The guidelines for managing abnormal cervical cancer screening tests changed from a results-based approach in 2012 to a risk-based approach in 2019. We estimated the cost-effectiveness of the 2019 management guidelines and the changes in resource utilization moving from 2012 to 2019 guidelines.

Estimated US Cancer Deaths Prevented With Increased Use of Lung, Colorectal, Breast, and Cervical Cancer Screening[10]

Importance: Increased use of recommended screening could help achieve the Cancer Moonshot goal of reducing US cancer deaths.

Objective: To estimate the number of cancer deaths that could be prevented with a 10-percentage point increase in the use of US Preventive Services Task Force (USPSTF)-recommended screening.

Adapting a model of cervical carcinogenesis to self-identified Black women to evaluate racial disparities in the United States[11]

Background: Self-identified Black women in the United States have higher cervical cancer incidence and mortality than the general population, but these differences have not been clearly attributed across described cancer care inequities.

References

1. JJ Kim, EA Burger, C Regan, S Sy. Screening for Cervical Cancer in Primary Care: A Decision Analysis for the US Preventive Services Task Force. JAMA. 2018;320(7):706–714.
2. NG Campos, N Lince-Deroche, CJ Chibwesha, C Firnhaber, JS Smith, P Michelow, et al. Cost-Effectiveness of Cervical Cancer Screening in Women Living With HIV in South Africa: A Mathematical Modeling Study. Acquir Immune Defic Syndr. 2018;79(2):195–205.
3. EA Burger, IMCM de Kok, E Groene, J Killen, K Canfell, S Kulasingam, 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.
4. EA Burger, MA Smith, J Killen, S Sy, KT Simms, K Canfell, et al. Projected time to elimination of cervical cancer in the USA: a comparative modelling study. Lancet Public Health. 2020;5(4):e213–e222.
5. JJ Kim, KT Simms, J Killen, MA Smith, EA Burger, S Sy, et al. Human papillomavirus vaccination for adults aged 30 to 45 years in the United States: A cost-effectiveness analysis. PLoS Med. 2021;18(3):e1003534.
6. MA Smith, EA Burger, A Castanon, IMCM de Kok, SJB Hanley, M Rebolj, et al. Impact of disruptions and recovery for established cervical screening programs across a range of high-income country program designs, using COVID-19 as an example: A modelled analysis. Prev Med. 2021;151:106623.
7. EA Burger, EE Jansen, J Killen, IMCM de Kok, MA Smith, S Sy, et al. Impact of COVID-19-related care disruptions on cervical cancer screening in the United States. J Med Screen. 2021;28(2):213–216.
8. EA Burger, IMCM de Kok, JF O'Mahony, M Rebolj, EEL Jansen, DD de Bondt, et al. A model-based analysis of the health impacts of COVID-19 disruptions to primary cervical screening by time since last screen for current and future disruptions. Elife. 2022;11:e81711.
9. VN Munshi, RB Perkins, S Sy, JJ Kim. Cost-effectiveness analysis of the 2019 American Society for Colposcopy and Cervical Pathology Risk-Based Management Consensus Guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Am J Obstet Gynecol. 2022;226(2):228.e1-228.e9.
10. AB Knudsen, A Trentham-Dietz, JJ Kim, JS Mandelblatt, R Meza, AG Zauber, et al. Estimated US Cancer Deaths Prevented With Increased Use of Lung, Colorectal, Breast, and Cervical Cancer Screening. JAMA Netw Open. 2023;6(11):e2344698.
11. JC Spencer, EA Burger, NG Campos, MC Regan, S Sy, JJ Kim. Adapting a model of cervical carcinogenesis to self-identified Black women to evaluate racial disparities in the United States. J Natl Cancer Inst Monogr. 2023;62:188–195.

Key References

EA Burger, IMCM de Kok, E Groene, J Killen, K Canfell, S Kulasingam, 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.

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